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## THERAPIES

### HEADING: Hemato-oncopharmacology

#### Pharmacology and pharmacovigilance of protein kinase inhibitors

##### *Pharmacology and pharmacovigilance of protein kinase inhibitors*

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## Abstract

Protein kinase inhibitors experienced their advent in the 2000s. Their market introduction made it possible to constitute the class of targeted therapies administered orally. This name was chosen to mark a break with conventional chemotherapy drugs, but it is important to stress that these are multi-target drugs with complex affinity profiles. Adverse effects can be explained by direct interactions with their targets of interest, chosen for their indications (on-target) but also interactions with other targets (off-target). The adverse effect profiles of these drugs are therefore varied and it is possible to identify common profiles related to inhibitions of common targets. Identification of these targets has improved the global understanding of the pathophysiological mechanisms underlying the onset of adverse drug reactions as well as of the related diseases, and makes it possible to predict the adverse effect profile of new protein kinase inhibitors based on their affinities. In this review, we describe the main adverse drug reactions associated with protein kinase inhibitors, their frequency and their plausible mechanisms of action.

## KEYWORDS

Protein kinases inhibitors; Pharmacovigilance; On- and off-target

## Abbreviations

ABL: Abelson proto-oncogene

ADR: adverse drug reaction

AGC: PKA, PKG, and PKC family kinases

ALK: anaplastic lymphoma kinase

ALP: alkaline phosphatase

ALT: alanine transaminase

aRR: adjusted rate ratio

AST: aspartate transaminase

ATP: adenosine triphosphate

BCR-ABL: breakpoint cluster region - Abelson

BTK: Bruton's tyrosine kinase

CDK4/CDK6: cyclin-dependent kinases

CMGC: CDK/MAPK/GSK/CDK-like kinase group

CSK: c-terminal Src kinase

EGFR: epidermal growth factor receptor

EMA: European Medicines Agency

FDA: Food and Drug Administration

FLT: fms-like tyrosine kinase

ILD: interstitial lung disease

JAK: Janus kinase

MAPK: mitogen-activated protein kinases

MEK1/MEK2: mitogen-activated protein kinase

mTOR: mammalian target of rapamycin

PAH: pulmonary arterial hypertension

PDGFR: platelet-derived growth factor receptors

PKC: protein kinase C

PKI: protein kinase inhibitor

SmPCs: summaries of product characteristics

STE: ste20 kinases

SyK: spleen tyrosine kinase

VEGFR: vascular endothelial growth factor receptor

WHO: World Health Organisation

## Protein kinases in the living world

Protein kinase enzymes are fundamental enzymes in the living world. The functions performed are ubiquitous and largely preserved in the different kingdoms of life, especially in plants and animals. For example, the number is: 1792 kinases in the genome of the rice grain (*Oryza sativa*), 454 for the nematode worm (*Caenorhabditis elegans*), 240 kinases for the fruit fly (*Drosophila melanogaster*) and 518 kinases for the human genome (*Homo sapiens*). Also, among the human genome representing 30,000 genes, around 1.7% codes for protein kinases. The biochemical principle of this class of enzyme is to catalyse the transfer of a phosphate radical from adenosine triphosphate (ATP) to a hydroxyl group of a protein to change its status from an inactive state to an active state. Enzymes catalysing this type of reaction are mostly substrates of another kinase, thus forming enzymatic cascades with an ability to mediate intracellular messages from the cytoplasmic membrane to the nucleus with the ability to modify the promotion of certain genes. Therefore, there are transmembrane proteins known as receptors (*e.g.* vascular endothelial growth factor [VEGFR], epidermal growth factor receptor [EGFR], platelet-derived growth factor receptors [PDGFR]) and intracytosolic proteins (*e.g.* mitogen-activated protein kinases [MAPK], Bruton's tyrosine kinase [BTK], anaplastic lymphoma kinase [ALK]). Protein kinases –that could be visualized on the kinome phylogenetic tree (Fig. 1)– are classified according to (i) the target amino acid they phosphorylate (*i.e.* serine, threonine or tyrosine) and (ii) the percentage of sequence homology of the amino acid sequences. Of the 518 kinases encoded within the human genome, 478 (92%) are classified as typical kinases –among which 388 (75%) are protein serine-threonine kinases and 90 (17%) are protein tyrosine kinases– and 40 (8%) are classified as atypical kinases [1]. Therefore, it is important to emphasize that kinase enzymes are not limited to tyrosine kinases but much more broadly to protein kinases.

## Pharmacological agents that inhibit protein kinases

Protein kinase inhibitor (PKI) drugs have been used for several decades, in particular in drugs that inhibit mTor (-rolimus). However, the advent of this family did not materialize until imatinib was marketed in the early 2000s. Over the past 20 years, in the region of 450 PKIs have at least one clinical trial registered in the clinicaltrials.gov register. Of these inhibitors, almost 100 molecules have been discontinued during their development, due in particular to toxicities, lack of efficacy or commercial reasons. A regulated and updated list of these medicines – with a known International Nonproprietary Name – can be found at <https://www.icoa.fr/pkldb> [2,3]. Currently, more than 60

drugs have been approved for marketing, primarily intended for the treatment of a variety of cancers but also directed against inflammatory diseases [4,5].

Based on data collected from the Cortellis database –a pharmaceutical pipeline database produced by Clarivate Analytics– all kinases targeted by at least one molecule have been represented using the kinome phylogenetic tree in Fig. 1. The tyrosine kinase family is the group for which there has been the most clinical development and the most drugs having obtained a marketing authorization. Kinase targeted by most of the approved drugs is VEGFR, EGFR, KIT, fms-like tyrosine kinase (FLT) and/or Abelson proto-oncogene (ABL). A few marketed drugs target the other groups such as CMGC, AGC and ste20 kinases (STE) family – the targeted kinases are the targeted kinases are cyclin-dependant kinases (CDK4/CDK6), protein kinase C (PKC) and mitogen-activated protein kinases MEK1/MEK2 respectively – but many small molecule kinase inhibitors targeting these families are currently under clinical development. Besides that, inhibition of some on-targets has so far not been successful. Indeed, inhibition of Aurora kinases (AGC family), under evaluation in clinical trials for a dozen molecules, led to many failures for the AKT targets.

Furthermore, small molecule kinase inhibitors are classified based on the region of interaction in the kinase and reversibility of the inhibition. This classification – that described interaction between drug and target(s) – is regularly updated. The drug can be fixed in a reversible orthosteric manner on the ATPase bag, either in an active form of the enzyme (type I) or in an inactive form (type II); some specific subtypes are also described. The interaction can be reversible allosteric on a pocket adjacent to the ATPase site (type III) or on a remote site (type IV). Bivalent inhibitors have been found and can interact on two domains from different regions (type V). Other types are described with irreversible bindings (type VI), especially on cysteine residues, or bindings on two different sites of the protein with the aim of increasing the selectivity of the inhibitor for its preferential target [6,7].

Depending on the modalities of interaction between the drug and its target(s), the notion of selectivity is quite relative. In fact, the ATPase catalytic site is common or even very close in its configuration for a good number of kinases. Finally, a PKI binding to a domain located at a distance from the ATPase catalytic site characterizing the kinases could probably bind to proteins other than the kinase family, but there is little data on this subject in the scientific literature. The affinity profile of PKIs on the human kinome is therefore complex and is now an integral part of the evaluation of drug candidates in the development process. Affinities for targets are quantified and graphical representations allow a better understanding of the ability of a drug to interact with multiple targets (Fig. 2) [8]. For example, dasatinib –a marketed drug for chronic myelogenous leukemia and acute lymphoblastic leukemia– has significant affinity for about 45 different kinases. Sunitinib – a marketed drug for renal adenocarcinoma, gastrointestinal stromal tumours and pancreatic cancer– has

significant affinity for about 69 different kinases. While dasatinib and sunitinib are marketed for very different indications (leukemia *versus* solid tumours), they have 21 protein kinases as common targets [9]. These two drugs not only bind to tyrosine kinase enzymes but also to serine-threonine kinase enzymes. This binding capacity on different targets reflects “on-target effects”, i.e. effects linked to the interaction of the identified target of interest in the management of a disease to be distinguished from the effects referred to as “off-target” which are related to interactions on targets other than that of interest. Several studies have linked the affinity profile of PKIs to adverse reaction profiles [10–14].

We have made the choice not to describe all the types of side effects associated with small molecule protein kinase inhibitors and we have restricted ourselves to the most frequent ones (Fig. 3).

### Cardiovascular and metabolic adverse drug reaction

The cardiovascular adverse effects of PKIs were first suggested in 2006 by Kerkela *et al.* They reported *in vitro* and murine experiments suggesting that imatinib caused toxic cardiomyopathy and a single-institution series of 10 patients who developed left ventricular dysfunction on imatinib [15]. However, subsequent prospective studies have not confirmed this first warning and have underlined the difficulty in distinguishing drug-dependent from drug-independent cardiovascular adverse drug reactions (ADRs) given the high incidence of cardiovascular disease in the general population, and even more so in patients suffering from cancer [16]. Indeed, imatinib is now considered to have a favourable metabolic and vascular safety profile [17]. Nevertheless, a number of later generations of PKI marketed in the following years have been linked to a variety of cardiovascular ADRs, from frequent ADRs such as thromboembolic ADRs or arterial hypertension identified in clinical trials, to extremely rare ADRs such as pulmonary arterial hypertension (PAH) identified after drug marketing. The cardio-vascular ADR of cancer therapies and notably from PKI constitute an active area of research because clinicians are faced with a large increase in the number of patients presenting with a combination of cancer, cancer treatment and cancer treatment-related cardiovascular adverse effects due to the longer life expectancy of patients [18,19].

### Arterial hypertension

Arterial hypertension is the most common cardio-vascular adverse event of PKI targeting VEGF receptors or their ligands such as pazopanib, sunitinib, sorafenib, ponatinib or apatinib [20,21]. Hypertension is a class effect of VEGF inhibitors and the incidence of hypertension varies depending on the agent used from 30% to 80% of patients [21,22]. Preclinical experiments have shown that the risk of blood pressure elevation with PKI is proportional to the amount of VEGFR2 inhibition [23]. Two main mechanisms for hypertension have been suggested: endothelial dysfunction leading to decreased NO production and stimulation of endothelin-1 pathway, and microvascular rarefaction [24,25]. As a potential consequence, the reporting risk of arterial dissection for which arterial hypertension is the main hypothesized mechanism was further correlated to VEGF inhibition in a pharmacovigilance study using the data from the Food and Drug Administration (FDA) adverse reporting system. This signal remains to be confirmed to date [26,27].

### **Thromboembolic ADRs**

Although patients with malignancies display increased risks of thrombotic ADRs, several retrospective, prospective studies and meta-analyses have shown that arterial and venous thromboembolic ADRs are further increased in cancer patients treated with VEGF inhibitors or with some breakpoint cluster region-Abelson (BCR-ABL) inhibitors such as nilotinib [17,21]. The late onset of these ADRs, associated with the finding that cardiovascular risk factors were common in patients with vascular ADRs in clinical trials, have led to the hypothesis that some PKI may aggravate a pre-existing arteriosclerotic condition and may therefore impact all vascular beds [28]. Indeed, mechanistic studies have indicated that some of these drugs can produce proatherogenic changes, worsen dyslipidemia and hypertriglyceridemia (*e.g.* nilotinib), or have prothrombotic effect through increasing platelet adhesion (*e.g.* ponatinib) [29]. Overall, the higher rates of thrombotic ADRs in those with preexistent atherosclerotic risk factors have led to recommendations that risk factors be addressed in those receiving medications such as ponatinib [30]. For example, preventive strategies with n-acetylcysteine, have been tested in preclinical and early clinical studies but have yet to be prospectively tested in large clinical trials [30].

### **Bleeding ADRs**



On the other hand, bleeding has also been reported in patients with chronic myeloid leukemia using PKIs. Forty percent bleeding frequency was found in patients with chronic myeloid leukemia using dasatinib, with epistaxis and gastrointestinal bleeding as the most specific related bleeding ADRs [31]. Although, chronic myeloid leukemia may be associated with bleeding manifestations due to disease characteristics (platelet dysfunction, thrombocytopenia, acquired von Willebrand disease), it has been shown that some PKI, notably dasatinib, may impair platelet aggregation [32,33].

### **Cardiomyopathy**

PKI induced cardiac failure is one of the most serious cardiac ADR experienced by PKI exposed patients. It can lead to a decrease in left ventricular ejection fraction, contractile dysfunction, hypertensive cardiac remodelling and cardiac ischemia [34]. All the above-described vascular ADRs (*e.g.* arterial and venous thromboembolic ADRs, hypertension) may participate in the genesis of cardiac failure which, for example, has been observed in 2.3% of patients treated by VEGF inhibitors with an OR of 1.35 [1.06 – 1.70] (NNH = 139) in a meta-analysis including 77 phase 3 trials [35,36]. In addition, it has been shown in preclinical studies that inhibition of some protein kinase such as VEGFR or PDGFR may induce cardiotoxicity through a direct action on pericytes, endothelial cells and cardiomyocytes, notably impairing cardiac healing or compensatory mechanisms [36]. Moreover, a pharmacodynamic-pharmacovigilance study mixing disproportionality signals and affinity of PKI for their receptors highlighted the role of ABL protein kinases in cardiac homeostasis and cardiomyocytes survival [11].

### **Cardiac arrhythmia and QT prolongation**

QTc prolongation, have been described with some PKI, notably with pazopanib, sunitinib, imatinib, nilotinib and dasatinib [37]. Based on these observations, *in vitro* studies identified new pathways (non- $I_{Kr}$ -dependent pathways) to QT prolongation, notably with nilotinib through inhibition of the phosphoinositide 3-kinase [38]. Similar effects were observed with the multi-kinase inhibitors dasatinib and sunitinib; all three drugs are classified as ‘possible’ torsade de pointes risk at *crediblemeds.org* [39]. Nevertheless, torsade de pointes and sudden death remains very rare with these drugs [40].

Furthermore, ibrutinib, a Bruton PKI, has been associated with atrial fibrillation since the early drug development phases [41]. To explore the mechanism of ibrutinib related atrial fibrillation an elegant translational study mixing electrophysiology studies, chemoproteomic analysis and pharmacovigilance analysis identified CSK inhibition as a potential mechanism of ibrutinib mediated atrial fibrillation [42]. CSK inhibition is an off-target effect of ibrutinib and may lead to increased inflammation and fibrosis, predisposing the heart to atrial fibrillation [42]. Moreover, an analysis from the World Health Organization pharmacovigilance database described other potential cardiovascular toxicities related to ibrutinib including hypertension, heart failure, ventricular arrhythmias, and conduction disorders with ibrutinib which remains to be further explored [43].

### **Pulmonary arterial hypertension**

Dasatinib, a multi-PKI had been increasingly linked to PAH since 2009 and is now considered to be a definite cause of PAH by the 6<sup>th</sup> World symposium on pulmonary hypertension [44–46]. More recently, several cases have reported potential association with or deterioration of pre-existing PAH with other PKIs such as bosutinib, ponatinib and lapatinib [13]. Although the underlying mechanism of dasatinib related PAH is still unclear, evidence suggests that SRC and SRC independent mechanisms (through mitochondrial ROS production) are implicated [47–52]. A pharmacodynamics-pharmacovigilance study correlating affinities of PKI for a range of protein kinases and disproportionality values highlighted a possible role of SRC protein kinases as well as other targets, such as TEC whose role remains to be determined [13]. Indeed, given the probable influence of the PKI dosage on the onset of PAH, such secondary targets may also be significant in PAH onset.

### **Metabolic disorders**

Induction of metabolic dysregulation by PKI may largely contribute to the increased risk of cardiovascular diseases. For example, 36% of patients on nilotinib 300 mg twice-a-day experienced hyperglycemia compared with 20% on imatinib [53]. A study of 27 patients also showed a significant increase in total, low-density lipoprotein, and high-density lipoprotein cholesterol within 3 months of treatment [54]. These metabolic ADRs are observed to a lesser extent with all BCR-ABL kinase inhibitors (imatinib, dasatinib, nilotinib, bosutinib, and ponatinib), while conversely PKI that target VEGF and PDGF signalling pathways (*e.g.* sunitinib and sorafenib) seem to improve glycemia

[55,56]. Although the pathophysiology of these ADRs remains unclear some evidence suggests PI3K inhibition inducing upregulation of the glucose transporter, GLUT4, may be involved [55].

Taken together, the cardiovascular ADRs studies with PKIs made it possible to identify different safety profiles regarding this type of ADRs, probably due to different target profiles [57,58]. These studies have also provided important new insights into vascular biology, physiology, and pathology [59].

## Pulmonary ADRs

Pulmonary side effects associated with PKIs are relatively frequent and represent 12.7% of all ADR recorded in Vigibase® with this large drug class (request of April 9, 2021). Pleural effusions and interstitial/parenchymal lung disease are the two main pulmonary disorders reported with PKIs.

### Pleural effusion

The incidence of pleural effusion with PKIs varies greatly depending on the molecule, with the most data in the literature being for BCR-ABL protein kinase inhibitors (PKIs).

Between 10% and 27% of patients treated with dasatinib in clinical trials developed pleural effusions, most often exudative and lymphocyte predominant with an increased incidence between the 24<sup>th</sup> and 36<sup>th</sup> months of treatment [60–63]. Dasatinib dose schedule is a risk factor for pleural effusion and posology of 100 mg once daily had a better safety profile with the same efficacy of higher doses (*i.e.* 70 mg twice-a-day). In a clinical trial with chronic myeloid leukemia patients, drug-related pleural effusion was more common with dasatinib (28%) than with imatinib (0.8%), with a higher incidence in patients over 65 years of age [60].

Most of the lung ADRs reported during imatinib therapy are related to fluid retention, a common side effect [64]. However, peripheral and periorbital oedema are far more frequent manifestations of fluid retention than are pleural or pericardial effusions and pulmonary oedema. Imatinib-induced pleural effusion appears to be dose dependent, with higher incidence in patients treated with 400 mg twice-a-day.

For the other BCR-ABL PKIs, the incidence of pleural effusion in clinical trials ranged from 9 to 12% for bosutinib [65], 2.1 to 9% for ponatinib [66] and less than 1% for nilotinib [67]. A

disproportionality analysis through data registered in the World Health Organization (WHO) safety report database (VigiBase<sup>®</sup>) showed that 29 of 33 PKIs included have significant RORs for pleural effusion with a highest value for dasatinib, bosutinib and ponatinib [12]. Besides, the study highlighted the role of Lyn (an off-target) in pleural effusion caused by PKIs through an immune-mediated process. Inhibition of Lyn could destabilize endothelial barrier leading to an increased endothelial permeability in pulmonary tissue [68].

In clinical trial with avapritinib, a PDGFR- $\alpha$  inhibitor, pleural effusions occurred in 12% of patients (2% grade 3 or worse) [69]. Cases of pleural effusion, some fatal, were reported during post-marketing surveillance with sunitinib, another PDGFR- $\alpha$  inhibitor [66].

### **Interstitial/parenchymal lung disease**

Although it is uncommon, drug-induced interstitial lung disease (ILD) is one of the most serious off-target adverse reactions of PKIs and reported in many summaries of product characteristics (SmPCs) with varying frequency. The major concern is with PKIs indicated for non-small cell lung cancer cells such as anti-EGFR agents (*e.g.* erlotinib, gefitinib) and ALK inhibitors (*e.g.* crizotinib, ceritinib).

In a meta-analysis, the incidences of all-grade and high-grade ILD associated with EGFR-PKIs (gefitinib, erlotinib, and afatinib) in advanced non-small cell lung cancer cells were 1.6% and 0.9%, respectively, with a mortality rate of 13% [70]. Risk factors for EGFR-associated ILD include older age, male sex, smoking, history of pulmonary fibrosis, prior radiotherapy and anti-PD-1 monoclonal antibodies. The frequency of ILD-type ADRs in Japanese patients is much higher than in the rest of the world (broadly reported as 1.6–4.3 vs. 0.3–1.0%) suggesting a specific increased genetic susceptibility to ILD in the Japanese population [71]. The interval to onset of ILD is unpredictable, and its onset could be acute or insidious, and clinical manifestations are often severe enough to be potentially life-threatening. The molecular mechanism of PKI-induced pulmonary toxicity is currently unknown, and it appears increasingly likely that multiple factors are involved. Available evidence suggests that ILD is not an on-target effect resulting from inhibition of EGFR and not confined to a specific chemical structure of the PKI, especially in the lack of cross reactivity between EGFR-PKIs.

All drugs in the ALK family have been associated with ILD. The overall incidence of ALK inhibitor pneumonitis was 2.14% in patients with advanced non-small cell lung cancer cells. The

patients from Japanese cohorts had a higher incidence of ALK-inhibitor pneumonitis [72]. In clinical trials, crizotinib and ceritinib were associated with ILD by 3% and 4% respectively, and 1.5% and 3% with high grade. For brigatinib, incidence is higher with 9% all grade and close to 4% for severe grades. The clinical presentation differs from other ALK with a more rapid onset in the first one to nine days of treatment, and after suspension of brigatinib until pneumonitis resolution, approximately one-half are able to resume therapy [73]. Several hypotheses have been put forward to better clarify mechanisms responsible for this family with particular regard to crizotinib. It was hypothesized that crizotinib-associated ILD could emerge as a drug-related hypersensitivity pneumonitis, considering the relatively late onset potentially necessary for compound sensitization, the resolution after crizotinib discontinuation, and the reoccurrence after crizotinib reintroduction. The ILD could be interpreted as an effective immune antitumor response that was favoured or elicited by ALK inhibitor treatment [74].

In clinical a trial with idelalisib, a PI3K inhibitor, pneumonitis was reported in 4% of patients, including serious and fatal cases. Clinical manifestations included interstitial infiltrates and organizing pneumonia, and time to onset ranged from less than 1 month to 15 months. For alpelisib, incidence was 1.8%, and in patients with new or worsening respiratory symptoms or who are suspected of having pneumonitis, it is recommended to stop treatment immediately to evaluate the patient. In those with confirmed pneumonitis, treatment should be discontinued.

Post-marketing surveillance has revealed a small risk of potentially severe lung inflammation in patients treated with CDK4/6 inhibitors. A recent study using US pharmacovigilance data investigated the reporting of ILD with these drugs [75]. The results revealed a consistent increased reporting of ILD with CDK4/6 inhibitors as a class, which was consistent across the various sensitivity analyses, accounting for major biases and confounders, especially for abemaciclib.

ILD is a known side effect of inhibitors of mTOR. Mostly, ILD remains asymptomatic or mildly symptomatic with nonspecific clinical features, but infrequent fatal issues are reported [76]. In a meta-analysis of trials in which temsirolimus and everolimus were used to treat solid malignancies, the incidence rates of high grade and overall pulmonary toxicity were 3 and 12% respectively [77]. The exact mechanism or interplay of mechanisms leading to the development of ILD remains to be defined. Suggested mechanisms are either a direct toxic effect or immune-mediated mechanisms, considering mTOR inhibitors have several effects on the immune system [78].

ILD may have been underdiagnosed because it requires diagnostic testing, which may not have been undertaken in patients who developed respiratory symptoms during PKI therapy, possibly because the symptoms were assumed to be due to advanced non-small cell lung cancer cells. Furthermore, it can be difficult to distinguish progressive cancer from drug-induced ILD.

## Other lung conditions

Cases of pneumothorax have been reported in patients treated with pazopanib, a PKI directed against the VEGF receptors [79].

PKIs used for autoimmune disease, comprised mostly of Janus kinase (JAK) and to a lesser extent, spleen tyrosine kinase (SyK) inhibitors, are associated with respiratory tract infections and increase the risk of non-opportunistic respiratory infections (upper and lower respiratory tract infections, influenza and pneumonia) when compared with placebo [80].

Overall, pulmonary ADRs with PKIs are relatedly frequent. The absence of specific signs and symptoms, as well as the absence of any clearly defined criteria for drug induced lung disease, makes diagnosis a real challenge. A better understanding of the underlying mechanisms will allow us to better prevent this risk and to adapt treatments according to the situation. In general, suspicion of significant drug-induced pulmonary complication justifies discontinuation of the PKI.

## Hepatobiliary disorders

### Hepatitis

PKIs have some degree of hepatotoxicity and many have been linked to cases of clinically apparent liver injury which can be severe and even fatal. Confirmation of PKI-induced hepatotoxicity can present challenges in the presence of hepatic metastasis and potential drug interactions. Onset of PKI-induced hepatotoxicity is usually within the first 2 months of initiating treatment, but may be delayed, and is usually reversible [81]. Some of the cases of liver injury attributed to the protein kinase antagonists had features of autoimmunity, suggesting that the liver injury may be caused by an immunologic reaction to metabolic products of the agent itself, rather than off-target activity of the inhibitor [82].

The incidence and severity of hepatotoxicity varies widely among PKI, but overall it is uncommon. Ghatalia *et al.* conducted a meta-analysis to determine the relative risk (RR) of hepatotoxicity with VEGFR PKI [83]. They found a statistical increase in RR of all-grade ALT, AST, ALP and bilirubin elevations (RR varying from 1.20 to 1.57) compared to the arm in the non-PKI

group. However, the incidence of liver failure was only 0.8%. The mechanism of VEGFR PKI induced hepatotoxicity has not been described but some hypothesize that the signal transduction pathways activated/inhibited during oxidative stress play a key role in drug-induced liver injury.

### **Hepatitis B virus reactivation and BCR-ABL PKIs**

Several case reports and small studies have suggested that the use of BCR-ABL PKIs may be associated with an increased risk of hepatitis B virus reactivation in patients with the virus. Based on this initial data, in 2016, the European Medical Agency (EMA) highlighted the potential risk of hepatitis B virus reactivation associated with BCR-ABL PKI treatment and required that the product information be amended as reactivation of hepatitis B in patients who are chronic carriers of this virus has occurred after these patients received BCR-ABL PKI. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome. Recently, a nested case-control study which included patients who entered a hepatitis B carrier cohort in Taiwan confirmed this risk [84]. This analysis revealed that BCR-ABL PKIs use during the previous 90 days was independently associated with a 56% higher risk of hepatitis B flare (adjusted rate ratio [aRR], 1.56, CI95% [1.11–2.20]). These results also showed a gender-specific difference, with a significantly increased risk of flare among women (aRR, 3.20, CI95% [1.70–6.03]) when the BCR-ABL PKI was used during the 60 days previous to the start of the study. Among the hypotheses raised, IPKs could target different pathways involved in the immune activation and the lymphocytes proliferation, leading to hepatitis B virus reactivation.

### **Pancreatitis**

Cases of vemurafenib (a BRAF inhibitor) induced pancreatitis have been reported and a safety signal was published by the Word Health Organization in 2014. The reactions generally occurred during the first two weeks of treatment. A retrospective French pharmacovigilance study found 22 cases of acute pancreatitis with anti-BRAF molecules [vemurafenib (n = 8), dabrafenib (n = 11) and encorafenib (n = 3)], suggesting a potential class effect [85,86]. This study highlights a dose-dependent mechanism with three cases of negative reintroduction with reduced dose.

Moreover, VEGF may play a role in regulating the cell cycle of acinar cells and maintaining adult pancreatic fenestrated capillaries; inhibition of VEGF leading to acinar cell apoptosis and



release of autodigestive enzymes. This hypothesis is reinforced by the cases described in the literature with VEGF inhibitory PKIs such as sorafenib or sunitinib [87]. Ghathalia *et al.* conducted a metanalysis and found a significant 1.95-fold increase ( $p = 0.042$ , CI95% [1.02–3.70]) in the risk of all grades of pancreatitis with VEGFR PKIs compared to controls not receiving PKIs [88].

## Musculoskeletal disorders

Musculoskeletal pain is well described during clinical trial with PKIs and up to 80% of chronic myeloid leukemia using PKIs reports this disorder [89]. Recently, it has been described that these pains, mainly the upper body joints, may occur upon discontinuation of the treatment constituting PKI withdrawal syndrome [90,91]. Indeed, over the past decade, many clinical trials in chronic myeloid leukemia have shown that the cessation of PKIs was achievable and safe. This withdrawal syndrome is a BCR-ABL inhibitor class effect and has been reported in 20 to 40% of patients attempting treatment free remission [91]. The syndrome appeared within two months after PKI discontinuation and lasted for several months (median: 7 months), although some patients experienced these pains for longer. The duration of PKI treatment and history of osteoarticular symptoms have been identified as risk factors for the occurrence of this withdrawal syndrome.

Rhabdomyolysis is an adverse effect to be watchful for. Cases have been reported in clinical trials and post-marketing with MEK inhibitors (*e.g.* cobimetinib, tramatenib), used in the treatment of melanoma [92].

This overview of the ADRs associated with PKIs is obviously not exhaustive and the safety profile of these drugs is still being actively monitored.

## Conclusion

Overall, almost 20 years after the development of first PKIs, preclinical, clinical and epidemiological research on their ADRs made it possible to identify a different safety profile, probably due to different target profiles. Identification of these targets, on- and off-targets, has improved the global understanding of the pathophysiological mechanisms underlying the onset of ADRs with these drugs. However, knowledge of the safety profile of PKIs is not fully complete and active



pharmacosurveillance of this large class of drugs should be continued. This is supported by the drug safety communications about PKIs, regularly issued by the drug agencies of various countries; for example in 2021 regarding increased risk of serious heart-related ADRs, cancer, blood clots, and death for tofacitinib, JAK inhibitor that treat certain chronic inflammatory conditions. Further collaboration between basic and translational scientists will permit investigations to elucidate the mechanism of the ADRs and to define patients at risk, such that preventive and treatment efforts can be focused on these high-risk patients.

#### **Disclosure of interest**

Authors have no competing interest to declare.

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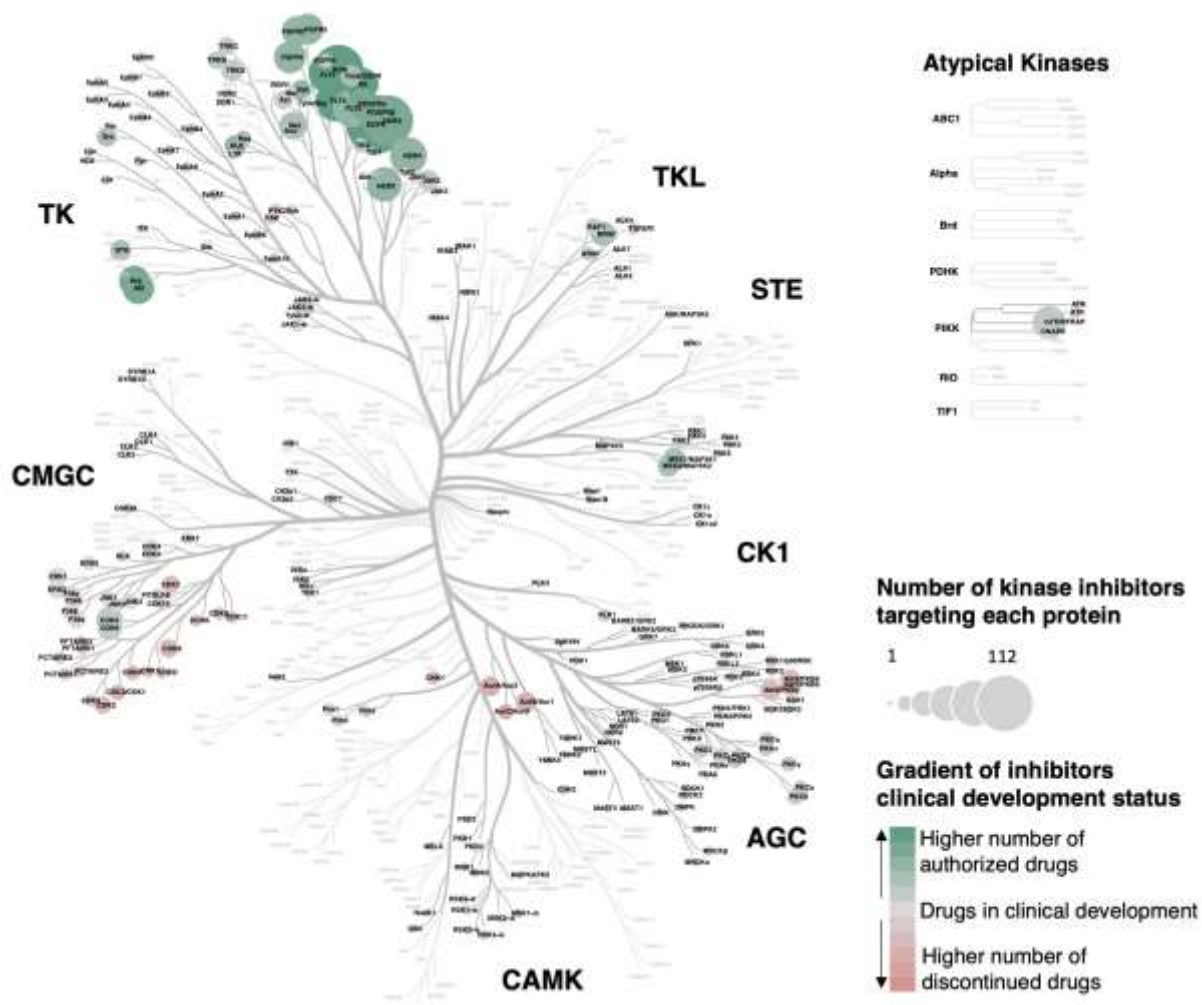
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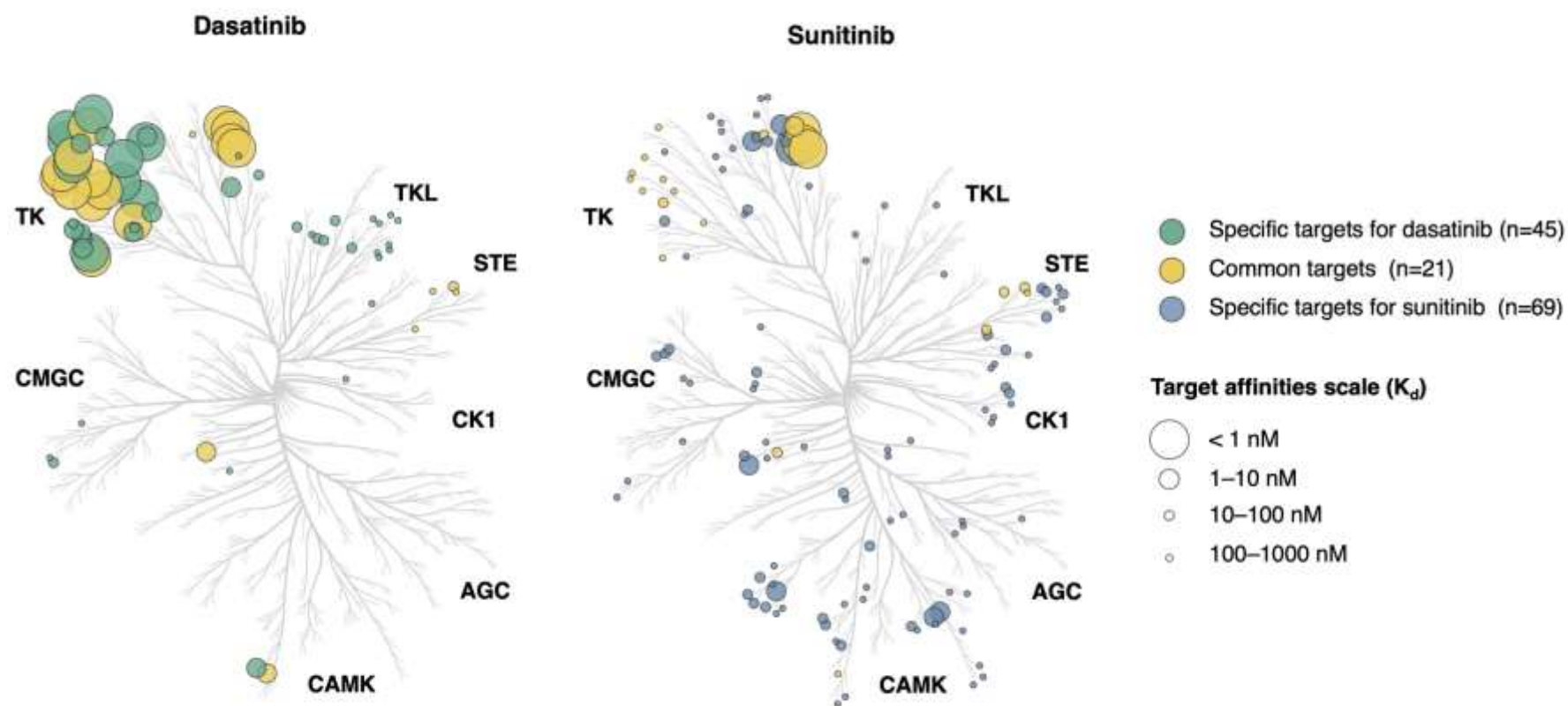


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**Figure 1. Kinome phylogenetic tree representing the pharmacological targets of clinically developed kinase inhibitors.**

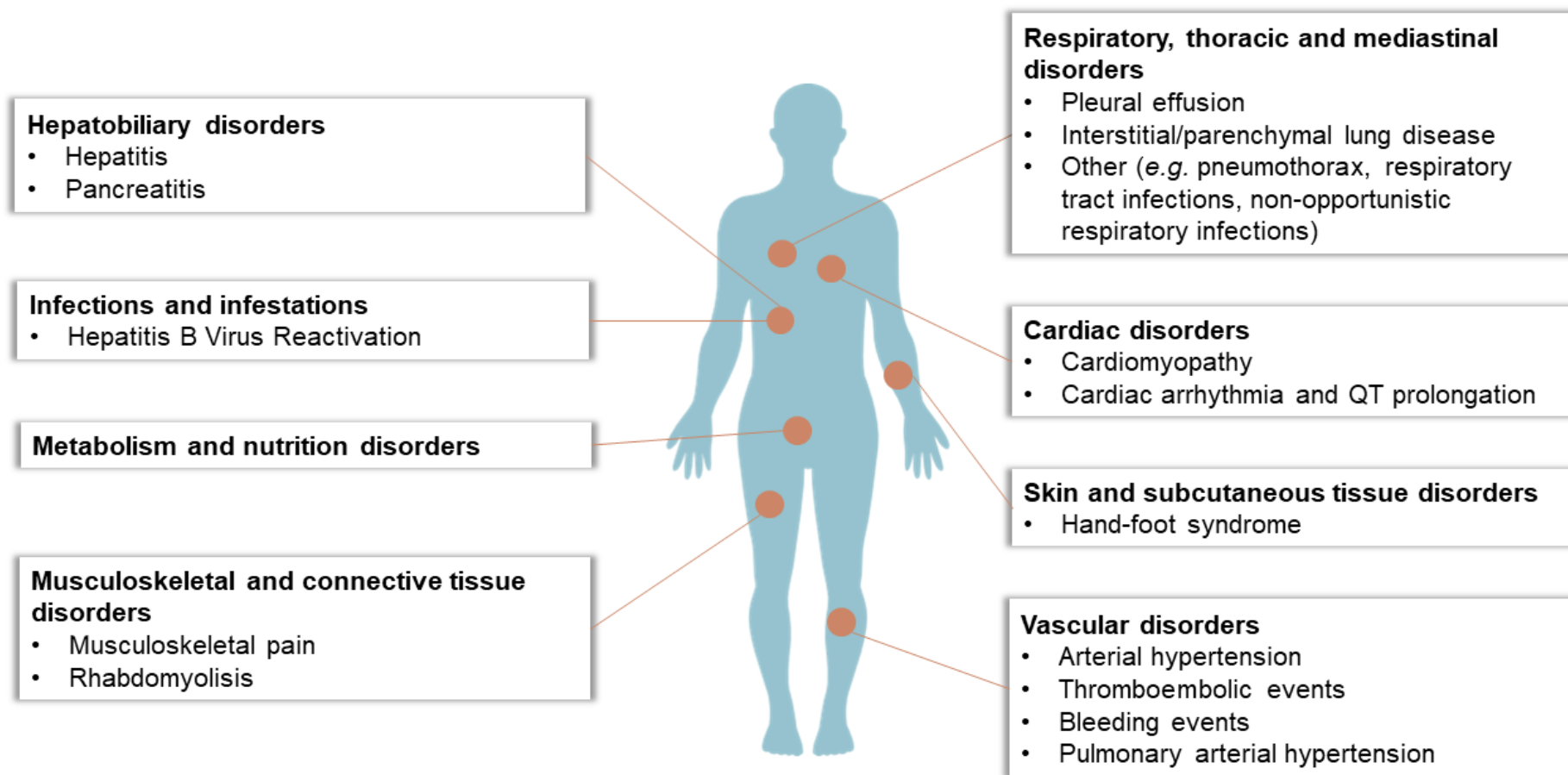
According to Cortellis database, all of the kinases being targeted by at least one inhibitor have been highlighted. Each circle for each protein kinase reflects the total number of inhibitors known to have an action on this target. All the drugs' mechanisms have been taken into account, i.e. for multiple mechanisms, the molecule has been assigned to each of its targets as well as its state of development. The greener the circle, the greater the number of inhibitors granted marketing authorisation. Conversely, the redder the circle is, the more inhibitors there are that have failed during clinical development. Grey circles represent targets for which inhibitors are all under development. *This kinase dendrogram were created using the interactive web application CORAL.*



**Figure 2. Kinome phylogenetic tree representing the target profiles of dasatinib and sunitinib.**

Each circle for each protein kinase represents the interactions observed for the two kinase inhibitors based on data from Karaman *et al.*. Only affinities less than 1000 nM are shown. Larger circles indicate higher affinity for the kinase. The yellow circles represent common targets while the green and blue circles correspond to the specific targets of dasatinib and sunitinib respectively. *This kinase dendrogram were created from the interactive web application CORAL.*

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**Figure 3.** Major adverse drug reactions (ADRs) induced by protein kinase inhibitors.