Title: Kinase Inhibitors FDA-Approved 2018-2023: Drug Targets, Metabolic Pathways, and Drug-Induced Toxicities

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Abbreviations Used: AUC, area under the plasma concentration-time curve; CYP, cytochrome P450; DDI, drug-drug interaction; DILI, drug-induced liver injury; EGFR, epidermal growth factor receptor; FDA, US Food and Drug Administration; FGFR, fibroblast growth factor receptor; HER, human epidermal growth factor receptor; JAK, Janus kinase; MET, mesenchymal-epithelial transition factor; MBI, mechanism-based inactivator; NSCLC, non-small cell lung cancer; TDI, time-dependent inhibitor; TKI, tyrosine kinase inhibitor; UGT, UDP-glucuronosyltransferase; VEGFR, vascular endothelial growth factor receptor

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Abstract

Small molecule kinase inhibitors are one of the fastest growing classes of drugs, which are approved by the US Food and Drug Administration (FDA) for cancer and non-cancer indications. As of September 2023, there were over 70 FDA-approved small molecule kinase inhibitors on the market, 42 of which were approved in the past five years (2018-2023). This minireview discusses recent advances in our understanding of the pharmacology, metabolism, and toxicity profiles of recently approved kinase inhibitors with a central focus on tyrosine kinase inhibitors (TKIs). In this minireview we discuss the most common therapeutic indications and molecular target(s) of kinase inhibitors FDA-approved 2018-2023. We also describe unique aspects of the metabolism, bioactivation, and drug-drug interaction (DDI) potential of kinase inhibitors; discuss drug toxicity concerns related to kinase inhibitors, such as drug-induced liver injury; and highlight clinical outcomes and challenges relevant to TKI therapy. Case examples are provided for common TKI targets, metabolism pathways, DDI potential, and risks for serious adverse drug reactions. The minireview concludes with a discussion of perspectives on future research to optimize TKI therapy to maximize efficacy and minimize drug toxicity.

Significance Statement

This minireview highlights important aspects of the clinical pharmacology and toxicology of small molecule kinase inhibitors FDA-approved 2018-2023. We describe key advances in the therapeutic indications and molecular targets of tyrosine kinase inhibitors (TKIs). The major metabolism pathways and toxicity profiles of recently approved TKIs are discussed. Clinically relevant case examples are provided that demonstrate the risk for hepatotoxic drug interactions involving TKIs and co-administered drugs.
Introduction and Brief Historical Perspective

Over the past two decades, small molecule kinase inhibitors have been one of the fastest growing classes of drugs. Given the important role of kinases in regulating cell signaling pathways for normal cell health and their dysregulation in various disease states, kinases are key targets for drug therapy (Krause and Van Etten, 2005). Today, kinase inhibitors are approved by the US Food and Drug Administration (FDA) for cancer and non-cancer indications (Roskoski, 2023; Ayala-Aguilera et al., 2022). The first small molecule tyrosine kinase inhibitor to receive FDA approval was imatinib, approved in 2001 for the treatment of chronic myeloid leukemia (Cohen et al., 2002). As of September 2023, there were over 70 FDA-approved small molecule kinase inhibitors on the market. Tyrosine kinase inhibitors (TKIs), which target receptor and non-receptor tyrosine kinases, represent the largest group of FDA-approved small molecule kinase inhibitors; other classes of kinases include serine/threonine kinases and lipid kinases. Several reviews have discussed the discovery, pharmacology, and clinical use of kinase inhibitors, including the safety and efficacy considerations (Roskoski, 2023; Ayala-Aguilera et al., 2022; Wu et al., 2016; Terada et al., 2015; de Wit et al., 2015; Krause and Van Etten, 2005). Further, there is extensive literature on the role of cytochrome P450 (CYP) enzymes in the metabolism and bioactivation of TKIs and the implications for drug-drug interactions (DDIs) and drug-induced toxicities (Duckett and Cameron, 2010; Teo et al., 2015; Filppula et al., 2018; Jackson et al., 2018; Tang and Chan, 2022; Zhao et al., 2022).

The scope of this minireview will focus on orally administered small molecule kinase inhibitors that received FDA approval from 2018-2023. Over the past five years (2018-2023), there have been 42 new small molecule kinase inhibitors approved by the FDA (Table 1). Although kinase inhibitors will be discussed broadly, TKIs will be the central focus of this minireview. The purpose of this minireview is to: 1) briefly review the most common therapeutic indications and molecular target(s) of TKIs FDA-approved 2018-2023; 2) describe unique
aspects of the metabolism and bioactivation pathways of TKIs as well as implications for DDIs; 3) discuss drug toxicity concerns related to TKIs, such as drug-induced liver injury (DILI); and 4) highlight clinical outcomes and challenges relevant to TKI therapy. This minireview is not meant to be a comprehensive review of all the TKIs, rather, we will highlight interesting case examples that illustrate advances in our understanding of selected TKI targets, metabolism pathways, DDI potential, and risks for serious adverse drug reactions. The minireview will conclude with a brief discussion of considerations for special populations and perspectives on the future landscape of TKIs in targeted therapy.

**Key Recent Advances: Kinase Inhibitors FDA Approved from 2018 to 2023**

**Therapeutic Indications & Molecular Targets**

Over the past two decades, TKIs have been predominately used in targeted cancer therapy; yet the list of non-cancer indications for TKIs continues to grow. The largest increase has been seen in the treatment of autoimmune disorders. The discussion here will focus on indications and targets of interest. Figure 1 shows selected molecular targets for small molecule kinase inhibitors FDA approved 2018-2023; Figure 2 provides a summary of the most common therapeutic indications and targets for recently approved kinase inhibitors.

**Autoimmune Disorders**

The non-cancer indications for TKIs include a variety of autoimmune disorders, such as rheumatoid arthritis, atopic dermatitis, and plaque psoriasis. Of these, rheumatoid arthritis is the most common indication. It is estimated that arthritis diagnoses will increase as the population grows and ages. By 2040, 78 million are predicted to have the immune disorder (CDC, 2023). This widespread disorder is an autoimmune disease that is characterized by inflammation of the tendon and can affect multiple joints on both sides of the body (Lin et al., 2020). Over time this
inflammation damages cartilage and eventually the bone, resulting in extreme pain for the patient (Lin et al., 2020). Advancements in arthritis treatment have been monumental with many individuals now able to manage and live with the disease. This is largely due to targeted disease-modifying anti-rheumatic drugs such as TKIs (Lin et al., 2020). The TKIs developed for various autoimmune and inflammatory conditions target Janus kinase (JAK).

**JAK Inhibitors**

JAK is one of the most common kinase targets of recent TKIs. This kinase family is ubiquitously expressed and has four members: JAK1, JAK2, JAK3, and Tyrosine kinase 2 (TYK2) (Kunihiro et al., 2004). JAK is closely associated with cytokine receptors localized to endosomes and the plasma membrane. However, *in vitro*, this kinase can be found in the cytosol (Kunihiro et al., 2004). Many cytokines rely upon JAK1 because they share receptor subunits, such as the interleukin (IL) cytokine family (Kunihiro et al., 2004). JAK2 is associated with hormone-like cytokines like prolactin and growth hormone. These kinases are located near the membrane of cytokine receptors, and interaction is increased upon ligand binding of the receptor (Kunihiro et al., 2004). This interaction results in cytokine signaling by conformational change of JAK, which allows autophosphorylation that phosphorylates the cytokine receptors (Kunihiro et al., 2004). Proteins are then able to bind to the phosphorylated receptor chains and become phosphorylated themselves and are then able to travel into the nucleus and influence gene expression (Kunihiro et al., 2004). JAK inhibitors for autoimmune and inflammatory conditions include baricitinib, upadacitinib, abrocitinib, and ritlecitinib. Two JAK inhibitors are for myelofibrosis treatment: fedratinib and pacritinib (Figure 1).
NSCLC

Of the 42 new small molecule kinase inhibitors approved by the FDA 2018-2023, 74% are indicated for various cancers with 26% of those specifically for non-small cell lung cancer (NSCLC) (Figure 2). Lung cancer has been the leading type of cancer in the US since the mid 1950’s; 85% of all lung cancer diagnoses are considered NSCLC (Bajbouj et al., 2021). Today, lung cancer remains the leading cause of cancer deaths, claiming an estimated 21% of cancer deaths in both men and women in 2023 (American Cancer Society, 2023). Due to the suboptimal results of platinum-based chemotherapies and targeted therapies, researchers are searching for novel approaches to treat NSCLC. One major key for treating this cancer is identifying its molecular signature, or the unique genetic and epigenetic characteristics of the tumor (Bajbouj et al., 2021). This is an exciting new opportunity to develop effective and safe therapies that are tailored to the individual patient. Here we discuss some of the novel TKIs, which target specific mutations in NSCLC. Of the small molecule TKIs FDA approved 2018-2023, eight are indicated for the treatment of NSCLC: dacomitinib, lorlatinib, entrectinib, capmatinib, pralsetinib, selpercatinib, tepotinib, and mobocertinib.

Overcoming EGFR Resistance

Epidermal growth factor receptor (EGFR) is a common target for NSCLC therapy; nonetheless, overcoming EGFR resistance in NSCLC has been a driving force for new drug discovery and development. Other targets for TKIs used to treat NSCLC include anaplastic lymphoma kinase (ALK), tropomyosin receptor tyrosine kinases (TRK), proto-oncogene tyrosine-protein kinase (ROS1), mesenchymal-epithelial transition factor (MET), as well as other kinases. Although progression-free survival rates for EGFR targeting drugs are adequate, patients taking EGFR targeting TKIs often develop drug resistance through various mechanisms (Dong et al., 2021). One mechanism by which this resistance occurs is by mutations in EGFR. The most common mutations occur in exons 18-21 (Dong et al., 2021). Approximately 60% of
cases of resistance to first- and second-generation TKIs occur due to the EGFR T790M. Prior
third generation TKIs target this specific mutation, preventing resistance through this
mechanism. Two TKIs in the last five years target other EGFR mutations (Figure 1).
Mobocertinib is an irreversible, third generation TKI for exon 20 insertions (Wang et al., 2022).
The structure of this drug is similar to the structure of another third generation TKI, osimertinib,
approved in 2015. Their structures only differ by an additional C5-carboxylate isopropyl ester
group on mobocertinib, which increases it’s specificity (Wang et al., 2022). Another EGFR
mutation targeting TKI, dacomitinib, targets exon 19 deletion or exon 21 L858R. Dacomitinib is
an irreversible EGFR/HER1, human epidermal growth factor receptor 2 (HER2), and HER4
inhibitor approved in 2018 (Engelman et al., 2007; Gonzales et al., 2008). When compared to
gefitinib in a German clinical study, dacomitinib showed higher life expectancy, less back pain,
and less signs of liver damage (Institute for Quality and Efficiency in Health Care, 2019).

There are several mechanisms of EGFR-TKI resistance of which the vast majority are
acquired resistance (Dong et al., 2021). These acquired mechanisms are altered EGFR
signaling, activation of aberrant bypassing pathways, downstream pathway activation, and
histological/phenotypic transformation (He et al., 2021). Altered EGFR signaling is caused by
tertiary mutations, which are mutations that develop after treatment with a TKI. The C797S
mutation is the most common tertiary EGFR mutation. Some patients also develop EGFR signal
amplification as a resistance mechanism. Another mechanism of resistance is caused by
activating nearby abnormal pathways (He et al., 2021). These pathways include receptors in the
EGFR family such as HER2 and FGFR, as well as other receptors and kinases like insulin-like
growth factor 1 receptor (IGF1R), anexelekto (AXL), phosphoinositide 3 kinase (PI3K), and the
activation of downstream pathways like RAS, RAF, MEK, and ERK.
FGFR Inhibitors

Fibroblast growth factor receptors (FGFRs) are another common target for recently approved TKIs. FGFRs are a family of tyrosine kinases that are expressed on the cell membrane (Dai et al., 2019). These receptors are responsible for regulating developing cells along with mature, adult cells. Similar to other receptor tyrosine kinases, FGFRs are activated by extracellular stimuli (Dai et al., 2019). This receptor family is responsible for the development and advancement of various types of cancers throughout the body (Dai et al., 2019). Four FGFR inhibitors are among the list of TKIs FDA approved 2018-2023: erdafitinib, pemigatinib, futibatinib, and infigratinib (Figure 1), which are indicated for urothelial carcinoma, cholangiocarcinoma, intrahepatic cholangiocarcinoma, and metastatic cholangiocarcinoma, respectively.

FGFR inhibitors can be divided into two groups, type I and type II (Figure 3) (Dai et al., 2019; Schröder et al., 2020). Type I binds to FGFR in the DFG-in enzymatic active conformation, while type II binds to the flipped DFG-out state, which is inactive (Dai et al., 2019). Erdafitinib, a type I pan-FGFR reversible inhibitor (FGFR 1-4), was the first approved FGFR targeting drug. In an open-label, phase 2 study, the response rate to the therapy was 40% of patients (Loriot et al., 2019). Although there were treatment related adverse events in about half of the treated patients, there were no treatment related deaths in this study (Loriot et al., 2019). Futibatinib, a type I pan-FGFR irreversible inhibitor, had a similar response rate of 42% with 2% of patients discontinuing treatment, but no treatment related deaths were reported (Goyal et al., 2023). Unlike the previous examples, pemigatinib selectively inhibits FGFR 1, 2, and 3 (Abou-Alfa et al., 2020). Pemigatinib is also a type I FGFR reversible inhibitor (Dai et al., 2019). An open-label phase 2 trial found that 64% of patients had grade 3 or higher adverse events. Though almost half the patients died during the trial, no treatment related deaths were
reported (Abou-Alfa et al., 2020). These trials model the safety and effectiveness of recently approved FGFR targeting therapeutics.

**PI3K Inhibitors**

The intracellular kinase PI3K is responsible for controlling various cellular responses, including growth, cytoskeletal remodeling, survival, differentiation, and organelle trafficking (Koyasu, 2003). Four of the recently approved kinase inhibitors are PI3K inhibitors (Figure 1). Duvelisib, a PI3K inhibitor, was approved to treat relapsed or refractory chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), and follicular lymphoma (FL). Although the overall response rate warranted accelerated approval, fatal or serious infections occurred in 31% of duvelisib treated patients (FDA, 2018b). Alpelisib also targets PI3K and was approved for treatment of hormone receptor (HR) positive, HER2 negative, PIK3CA-mutated, advanced or metastatic breast cancer. Adverse reactions were seen in patients, notably severe cutaneous reactions and severe hyperglycemia (FDA, 2019d). Another PI3K inhibitor approved for cancer treatment was umbralisib, approved for treatment of marginal zone lymphoma (MZL) and FL. Umbralisib caused infections in some patients, but adverse events as severe as other PI3K inhibitors were not seen (FDA, 2021b). Interestingly, leniolisib was approved for an immune disorder: activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS). This therapeutic was approved in adults and pediatric patients over 12 years of age. Warnings associated with this drug include embryo-fetal toxicity, and the drug may cause vaccinations to be less effective (FDA, 2023d).

**Metabolism & Bioactivation Pathways**

Most of the small molecule kinase inhibitors approved 2018-2023 are metabolized by human CYP enzymes (Figure 4). UDP-glucuronosyltransferases (UGTs) are also involved in the metabolism of some kinase inhibitors, but generally to a lesser extent. Although many kinase
inhibitors interact with membrane transporters as substrates and/or inhibitors, the role of transporters in the disposition of kinase inhibitors is beyond the scope of this review. The discussion below will focus on metabolism by CYP enzymes.

**Cytochrome P450 Enzymes**

CYP enzymes are membrane-bound hemoproteins expressed in the liver as well as extra-hepatic tissues; CYP enzymes are responsible for cellular metabolism, homeostasis, and detoxication of both endogenous compounds and xenobiotics (Zhao et al., 2021). Xenobiotic-metabolizing CYP enzymes influence the mechanism of action, bioactivation, toxicity, and resistance properties of a drug. Both genetic polymorphisms and epigenetic marks influence the activity and abundance of CYP enzymes. The activity of CYP enzymes can be inhibited or induced by other xenobiotics, as well as foods (Zhao et al., 2021). These phenomena result in interindividual variability in both the pharmacokinetics and pharmacodynamics of drugs metabolized by CYP enzymes. The influence of pharmacogenetics on a patient’s ability to metabolize a drug can be described in categories: poor metabolizers, intermediate metabolizers, normal metabolizers, rapid metabolizers, and ultrarapid metabolizers for a given CYP enzyme (Caudle et al., 2017). This is known as their drug-metabolizing phenotype, which influences the patient’s exposure to the drug.

As shown in Figure 4, the majority of TKIs are metabolized by CYP3A4, the most abundant CYP in the adult human liver and intestine (Guengerich, 1999). CYP3A4 can metabolize a vast range of structures and in some cases can bind two substrates at once (Zhao et al., 2021). The other most common CYP3A subfamily member in adults is CYP3A5, which shares much of its sequence identity with CYP3A4 (Zanger and Schwab, 2013), resulting in these two subfamily members working together to metabolize some substrates. However, they do have independent pathways and selectively metabolize other substrates (Zanger and Schwab, 2013). Of particular interest are the polymorphisms associated with CYP3A5. These
polymorphisms seem to be population-specific and have been found in different frequencies between populations. For example, a study found that patients of African descent had higher expression of CYP3A5 than those of European descent (Kuehl et al., 2001). The functional CYP3A5*1 allele is rarely found in people of European descent but is more frequently expressed in people of African descent (45-70%), East and South Asian descent (25-40%), as well as in other global populations (Kuehl et al., 2001; Zhou et al., 2017). CYP3A5*3 is the most common nonfunctional allele, which many people of European descent possess (frequency 82-95%) (Kuehl et al., 2001; Lamba et al., 2012; Zhou et al., 2017). Other nonfunctional alleles, CYP3A5*6 and *7, are found predominately in people of African descent (Kuehl et al., 2001; Lamba et al., 2012). These variant alleles (CYP3A5*3, *6, *7) cause a premature stop codon or protein truncation and result in nonfunctional CYP3A5 protein; the CYP3A5*2 allele is not fully functional and has been less studied (Kuehl et al., 2001; Lamba et al., 2012).

The largest family of CYPs is the CYP2 family; of this family CYP2C8, CYP2C9, CYP2C19, and CYP2D6 are involved in the metabolism of TKIs. CYP2C9 is the most abundant member of the CYP2C subfamily; CYP2C8 is the second most abundant and the most inducible (Zanger and Schwab, 2013). There are three alleles that have potential for clinical relevance and are the most common polymorphisms of CYP2C8. These are: CYP2C8*2, *3, and *4 (Backman et al., 2016). Interestingly, these alleles are distributed differently around the world. For example, the reduced function CYP2C8*2 variant is seen in high frequency in people from Western and Sub-Saharan Africa but is found in low frequency in some other populations (Backman et al., 2016). The CYP2C8*3 variant is unique due to its substrate dependance; for some substrates this variant shows increased function while for other substrates the variant shows reduced function. CYP2C8*3 is seen in high frequency in European populations and in lower frequency throughout other regions of the world (Backman et al., 2016). The reduced function CYP2C8*4 allele is seen less frequently overall, but it’s frequency is highest in
European populations (Backman et al., 2016). It is possible that the possession of a CYP2C8 variant allele could influence the exposure of a TKI in which CYP2C8-mediated metabolism is the major route of elimination.

Another member of the CYP2 family, CYP2D6, is the only protein-coding gene within the CYP2D subfamily. This CYP is known not to be inducible or influenced by sex; however, it is known to be prone to inhibition by numerous substrates (Zanger and Schwab, 2013). CYP2D6 metabolizes many clinically used medications from virtually all therapeutic areas. Genetic variants of CYP2D6 have been extensively studied and are highly impactful on CYP2D6-mediated metabolism. This is interesting due to the negligible impact that environmental and nongenetic factors play in CYP2D6 activity. Like CYP2C8, the frequencies of CYP2D6 variants differ around the world. For example, the CYP2D6*4 variant is seen in European populations and is practically absent in other populations (Zanger and Schwab, 2013). Conversely, the reduced function CYP2D6 *10 and *17 variants are seen in African and Asian populations (Zanger and Schwab, 2013). There are also common variants found throughout the world, such as CYP2D6*5. CYP2D6 metabolism is highly dependent on genetic variants. This makes CYP2D6 an important and interesting case in drug metabolism, including in the metabolism of TKIs. For example, reduced CYP2D6 function was associated with increased risk for adverse reactions by the first-generation EGFR TKI gefitinib (Suzumura et al., 2012; Kwok et al., 2022). The implication of CYP2D6 variants in interindividual variation in pharmacokinetics is important to understand to ensure each patient is provided with optimal and equitable care.

Among the recently approved kinase inhibitors, at least five are primarily metabolized by CYP2 family enzymes. Tucatinib is primarily metabolized by CYP2C8 to the hydroxylated metabolite ONT-993, and to a lesser extent by CYP3A4 to other metabolites (Sun et al., 2022) (Figure 5). The impact of CYP2C8 genotype on tucatinib metabolic clearance is unknown. Erdafitinib and umbralisib are metabolized by CYP2C9; the CYP2C9*3/*3 genotype (poor
metabolizer phenotype) is predicted to result in increased erdafitinib exposure compared to CYP2C9 normal metabolizers (FDA 2019a; FDA 2021b). Abrocitinib is metabolized largely by CYP2C19 (~53%) and to a lesser extent by CYP2C9 (~30%) (Bauman et al., 2022). CYP2C19 polymorphism impacts systemic exposure (area under the plasma concentration-time curve, AUC) to abrocitinib (FDA 2022a). CYP2C19 poor metabolizers have reduced metabolic clearance of abrocitinib and increased AUC compared to CYP2C19 normal metabolizers. Dacomitinib is metabolized by CYP2D6 via O-demethylation to form the major circulating active metabolite PF-05199265 (Bello et al., 2013) (Figure 6a). Compared to the CYP2D6 wild-type protein, recombinantly expressed CYP2D6 variants showed reduced metabolic clearance of dacomitinib to the O-demethylated metabolite in vitro (Han et al., 2022). Other pathways of dacomitinib metabolism in vivo include glutathione conjugation at the electrophilic α,β-unsaturated carbonyl moiety and oxidation of the piperazine ring, resulting in reactive metabolite formation and other oxidative metabolites (Figure 6b) (Bello et al., 2013; Attwa et al., 2018b).

**TKIs and Reactive Intermediates**

Several TKIs have been shown to undergo metabolic activation by CYP enzymes to form chemically reactive metabolites. The bioactivation pathways may be relevant for better understanding the mechanisms of metabolism-dependent CYP inactivation and/or the mechanisms of drug toxicity (e.g., DILI). While the mechanisms for DILI are not fully understood, the formation of reactive intermediates by CYP enzymes is proposed to be a key initiating event in the development of DILI (Park et al., 2005; Duckett and Cameron, 2010; Teo et al., 2015; Jackson et al., 2018; Tang and Chan, 2022; Zhao et al., 2022). Other proposed mechanisms of DILI include mitochondrial dysfunction, accumulation of bile acids via bile salt export pump (BSEP) inhibition (Mosedale and Watkins, 2017), altered bile acid homeostasis via CYP7A1 and sodium taurocholate co-transporting polypeptide (NTCP) upregulation (Saran et al., 2022), and
activation of the adaptive immune response via the interaction of parent drug or drug-modified peptides with human leukocyte antigen (HLA) leading to subsequent immune-mediated injury (Andrade et al., 2019).

Evidence for the generation of reactive metabolites is often provided by the detection of trapped adducts in vitro. For example, entrectinib metabolism in liver microsomes formed iminium and quinone methide reactive metabolites trapped as potassium cyanide adducts and glutathione (GSH) conjugates, respectively (Attwa et al., 2018a). Tepotinib bioactivation produced iminium intermediates trapped as cyano adducts in vitro (Abdelhameed et al., 2020). Pemigatinib bioactivation produced reactive iminium intermediates, which may be involved in mechanism-based inactivation of CYP3A (Tang et al., 2022). Infigratinib produced a 1,4-benzoquinone iminium intermediate and a reactive epoxide (Tang et al., 2021a; Attwa et al., 2018b) also characterized the bioactivation of dacomitinib in vitro. Using potassium cyanide and methoxylamine as trapping agents, an iminium ion intermediate was trapped as a cyano adduct, and a reactive aldehyde was trapped as a methoxylamine conjugate (Attwa et al., 2018b). The bioactivation pathway of dacomitinib leading to the iminium ion intermediate is proposed to involve oxidation of the piperidine ring (Figure 6b). Iminium ions can be converted to lactams (Kalgutkar et al., 2020), which is consist with the lactam metabolite of dacomitinib observed in vivo (Bello et al., 2013). It should be noted that the generation of reactive intermediates does not always result in hepatotoxicity. Several drugs are known to form reactive metabolites but are not associated with hepatotoxicity. Chemically reactive metabolites are also involved in mechanism-based inactivation of CYP enzymes, potentially leading to DDIs.

Drug-drug Interactions and Time-dependent Inhibition
Pharmacokinetic DDIs are common types of DDIs associated with kinase inhibitors approved by the FDA from 2018-2023. Based on review of the drug prescribing information, interactions with inhibitors and inducers of drug-metabolizing enzymes and transporters are among the most frequent kinase inhibitor DDIs. In addition, some kinase inhibitors are perpetrators of DDIs as inhibitors or inducers of CYP enzymes. Of the 42 small molecule kinase inhibitors FDA approved 2018-2023, at least 10 have been reported as time-dependent inhibitors (TDIs) of CYP enzymes. Eight were CYP3A TDIs (encorafenib, lorlatinib, erdafitinib, avapritinib, pralsetinib, tucatinib, pemigatinib, infigratinib); one was a CYP1A2 TDI (leniolisib); and one was a TDI of both CYP1A2 and CYP3A (pacritinib). Although encorafenib and pralsetinib were reported as CYP3A TDIs, kinetic parameters for inactivation ($K_i$ and $k_{\text{inact}}$) have not been published. The reported $K_i$ and $k_{\text{inact}}$ values are shown in Table 2.

Tucatinib is a strong inhibitor of CYP3A; however, the mechanisms of CYP3A TDI/metabolism-dependent inhibition by tucatinib have not been reported. In a clinical DDI study by Topletz-Erickson et al. (2022), tucatinib was shown to increase the AUC of the CYP3A sensitive substrate midazolam in healthy volunteers by 5.7-fold. This DDI observation supports the recommendation that concomitant use of narrow therapeutic window CYP3A substrates with tucatinib should be avoided or the dose of the CYP3A substrate should be reduced (FDA 2023b).

The mechanisms of CYP3A TDI by erdafitinib were extensively studied by Tang et al. (2021b). Erdafitinib was identified as a mechanism-based inactivator (MBI) of both CYP3A4 and CYP3A5 (Tang et al., 2021b). The efficiency of inactivation ($k_{\text{inact}}/K_i$) was approximately 6-fold higher for CYP3A4 compared to CYP3A5 (Tang et al., 2021b). The mechanism was reported to involve irreversible covalent modification of CYP3A by a reactive metabolite of erdafitinib. Evidence from GSH trapping studies showed that erdafitinib undergoes bioactivation by CYP3A enzymes to an epoxide via the quinoxaline ring; a GSH adduct of the reactive metabolite was
characterized by high resolution mass spectrometry (Tang et al., 2021b). Tang and colleagues have also investigated the mechanisms of MBI by other FGFR inhibitors (Tang and Chan, 2022). Additional studies are needed to determine the mechanisms of TDI by other recently approved kinase inhibitors.

Due to their interactions with CYP3A, several kinase inhibitors are reported to cause CYP3A-mediated DDIs with Paxlovid™, a drug containing the CYP3A inhibitor ritonavir co-packaged with the CYP3A substrate nirmatrelvir, used to treat COVID-19 (Anwar et al., 2023). Examples of TKI DDIs with Paxlovid™ include tucatinib, a strong CYP3A inhibitor, and pralsetinib, also a CYP3A inhibitor (Anwar et al., 2023). Paxlovid™ was shown to increase exposure to encorafenib (FDA 2023a).

**Case Example: Lorlatinib**

Some kinase inhibitors are both CYP3A inducers and CYP3A TDIs. For example, lorlatinib is a moderate CYP3A inducer via PXR (pregnane X receptor) and CAR (constitutive active/androstane receptor) activation and a CYP3A TDI; the net in vivo effect is CYP3A induction (FDA 2021a). Coadministration of lorlatinib with a strong CYP3A inducer is contraindicated due to the risk for severe hepatotoxicity (Chen et al., 2020). Grade 2-4 transaminase elevations, which are clinical signals for liver injury, were observed with concomitant use of lorlatinib with strong CYP3A inducers, such as rifampin (Chen et al., 2020). Lorlatinib has been shown to form an N-oxide metabolite (M6) through \[^{14}\text{C}]\text{lorlatinib}

absorption, distribution, metabolism, and excretion studies (Stypinski et al., 2020). Interestingly, two radiolabel positions were used in this study to fully characterize lorlatinib metabolism. This was because there was no single metabolically stable position to place the radiolabel, and therefore two positions were required. The M6 N-oxide accounted for 4.5% and 6.0% of total radioactivity in each study, respectively. However, unchanged lorlatinib was the major circulating...
drug-related material, accounting for 80% and 97% of circulating radioactivity in each study, respectively. The metabolic scheme in Figure 7 shows the circulating metabolites M6, M1a, and M2a, as well as M8, an unexpected circulating metabolite that was formed in humans and not in vitro. A recent study was conducted in a nonhuman primate model to elucidate the mechanisms of hepatotoxicity observed from lorlatinib coadministration with rifampin and other CYP3A inducers; however, no definitive mechanism was identified (Hu et al., 2021). Therefore, the molecular basis for the hepatotoxic drug interaction between lorlatinib and CYP3A inducers warrants further investigation.

Case Example: Dacomitinib

Beyond CYP3A-mediated DDIs, a CYP2D6-mediated DDI was reported with dacomitinib, an irreversible EGFR, HER2, and HER4 inhibitor, and metoprolol, a beta-blocker; both drugs are CYP2D6 substrates (Qui et al., 2023). Dacomitinib is also a strong CYP2D6 inhibitor (Bello et al., 2012). In a case report involving a patient with NSCLC, dacomitinib coadministration with metoprolol caused acute liver injury, marked by elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (Qui et al., 2023). The proposed mechanism for the hepatotoxic drug interaction was CYP2D6 inhibition by dacomitinib resulting in increased metoprolol exposure. Although the plasma concentrations of metoprolol were not measured in the study, the authors indicated that decreased heart rate and blood pressure were observed in the patient after starting dacomitinib with metoprolol, and the heart rate recovered after discontinuing dacomitinib, suggesting that increased metoprolol exposure may have been the cause (Qui et al., 2023). Moreover, ALT and AST continued to rise even after dacomitinib was discontinued and did not recover until metoprolol was stopped, implicating metoprolol as the probable cause for the liver injury; however, whether dacomitinib was the DILI causative agent cannot be ruled out (Qui et al., 2023). A proposed pathway leading to DILI from concomitant use of dacomitinib with metoprolol is shown in Figure 8. Another case report
described severe cholestatic liver injury in a patient taking dacomitinib with metoprolol and loratadine, a CYP2D6 and CYP3A substrate (Qiao et al., 2022). In an additional case report involving a patient treated with dacomitinib for NSCLC, dacomitinib was identified as the probable cause for cholestatic liver injury, marked by elevations in alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT); however, the possible mechanism(s) of dacomitinib-induced liver injury are unknown (Wang et al., 2022). The mechanisms of dacomitinib-induced liver injury with and without concomitant drugs warrant further investigation.

In addition to DDIs with CYP enzymes, the DDI potential of kinase inhibitors with UGT enzymes has been described previously (Zhang et al., 2015). The first-generation EGFR inhibitor erlotinib is a known inhibitor of UGT1A1 \( (K_i 0.64\text{ to }1.23\ \mu M) \) (Cheng et al., 2017; Liu et al., 2010; Zientek and Youdim, 2015). Moreover, inhibition of UGT1A1 by the earlier kinase inhibitors regorafenib and sorafenib may contribute to hyperbilirubinemia (Miners et al., 2017). Among the recent kinase inhibitors FDA-approved 2018-2023, at least seven have been reported as UGT inhibitors: dacomitinib, encorafenib, fostamatinib major active metabolite R406, pexidartinib, belumosudil, asciminib, and quizartinib (Table 3). All seven of these drugs inhibit UGT1A1; pexidartinib also inhibits UGT1A4 and UGT2B7; and belumosudil also inhibits UGT1A9. Belumosudil and asciminib may inhibit UGT1A1 at clinically relevant concentrations (Przepiorka et al., 2022; belumosudil NDA 2020; asciminib NDA 2021). The belumosudil metabolite KD025-M2 was also shown to inhibit UGT1A1 and UGT1A9, although less potently (belumosudil NDA 2020). UGT1A1 inhibition by the fostamatinib active metabolite R406 can result in hyperbilirubinemia (FDA 2018a).

As shown in Table 3, the IC\(_{50}\) values have been reported for UGT inhibition by encorafenib, pexidartinib, belumosudil, and the belumosudil metabolite KD025-M2. An unbound \( K_{iu} \) value of 0.35 \( \mu M \) was reported for UGT1A1 inhibition by asciminib (asciminib NDA 2021). The mean maximum steady-state plasma concentrations (\( C_{\text{max}} \)) of asciminib with recommended
doses of 80 mg once daily and 200 mg twice daily were 3.96 and 12.54 \( \mu \text{M} \), respectively (FDA 2021). This indicates that asciminib is a potent inhibitor of UGT1A1 at therapeutic concentrations. Additional studies are needed to determine the \( K_{i,u} \) values for UGT inhibition by other kinase inhibitors.

**Toxicities: Drug-Induced Liver Injury & Other Toxicities**

DILI, or hepatotoxicity, has been associated with many of the kinase inhibitors. Although rare, DILI is a significant health complication. In a multi-center observational study of hepatotoxicity occurrence in cancer patients, 5.5% of patients experienced high grade hepatotoxicity after TKI usage (Han et al., 2020). Compared to earlier kinase inhibitors (approved 2001-2017), six of which had boxed warnings for hepatotoxicity, only one kinase inhibitor approved from 2018-2023 has a boxed warning for potentially severe DILI. Nonetheless, hepatotoxicity remains a concern in the clinical use of kinase inhibitors.

**Kinase Inhibitors with Warnings for Hepatotoxicity**

Pexidartinib is currently the only kinase inhibitor approved from 2018-2023 that has a boxed warning for hepatotoxicity (FDA 2019c). Pexidartinib (commercially available as Turalio®) is only available via a restricted program known as the Turalio Risk Evaluation and Mitigation Strategy (REMS) due to the risk and severity of hepatotoxicity (Dharmani et al., 2022). The type of liver injury has been determined as mixed or cholestatic; however, the mechanism of injury is unknown (Tap et al., 2019; Gelderblom and de Sande, 2020). Cholestatic liver injury is characterized by ALP and bilirubin elevations following the use of medication (Liver Tox, 2012). Pexidartinib is metabolized by CYP3A4 and UGT1A4 (FDA 2019c). Inhibitors of CYP3A4 and UGT1A4 can increase pexidartinib serum levels and possibly lead to hepatotoxicity (Monestime
and Lazaridis, 2020). Additionally, taking pexidartinib with a high fat meal can increase serum concentrations of the drug and increase the chance of a hepatotoxic event (FDA 2019c).

In the phase 3 ENLIVEN study for pexidartinib, 61 patients received pexidartinib. ALP, ALT, and AST levels were assessed as a measurement of liver function. AST and ALT levels (any grade) increased for 39% and 28% of patients enrolled in the study, respectively (Tap et al., 2019). The percentage of grade 3/4 liver enzyme elevations was 10% for AST, 10% for ALT, and 7% for ALP (Tap et al., 2019). Additionally, seven patients discontinued pexidartinib due to liver-related adverse events (Tap et al., 2019). In a separate study of Asian patients, ALT and AST elevations were observed at three times the upper limit of normal (ULN) in four to five patients (36-45%) out of 11 total patients (Lee et al., 2020). In a meta-analysis of long-term hepatic safety of pexidartinib, the elevation in serum ALT levels was shown to be common and occurred in 50-90% of patients (Lewis et al., 2021).

While the mechanisms for TKI-associated hepatotoxicity are not fully understood, several mechanisms have been proposed; and it is possible that multiple pathways are involved. Pexidartinib hepatotoxicity may be due to CSF1R (colony stimulating factor receptor 1) inhibition on Kupffer cells, which are involved in maintaining liver functions (Tap et al., 2019).

Very few studies have been conducted to determine the mechanisms of hepatotoxicity by pexidartinib and other recently approved TKIs as these compounds are relatively new to the market.

Three recently approved kinase inhibitors have a warning for hepatotoxicity, as well as a boxed warning for other toxicities. Duvelisib, a PI3K inhibitor, includes a boxed warning for infections, diarrhea or colitis, cutaneous reactions, and pneumonitis, but also has a warning for hepatotoxicity, specifically when in combination with ibrutinib (Paul et al., 2023; FDA 2018b). Immune-mediated hepatotoxicity from duvelisib exposure may be caused by a decrease in regulatory T cells, which was first investigated as a mechanism of toxicity for another PI3K
inhibitor, idelalisib (Lampson and Brown, 2021). However, further investigation is required to elucidate duvelisib-specific toxicity mechanisms. Fedratinib has a boxed warning for encephalopathy, including Wernicke’s, as well as hepatotoxicity (FDA 2019b). A specific mechanism of toxicity for fedratinib has not been identified. As shown in Table 4, there are additional kinase inhibitors with warnings and precautions regarding hepatotoxicity. Although there are not boxed warnings for hepatotoxicity for most of these drugs, these warnings are available on the prescribing information for the medication and should be seriously considered by the prescribing physician.

Kinase Inhibitors with Non-Hepatic Related Toxicities

In addition to hepatotoxicity, kinase inhibitors are also associated with other clinically significant toxicities. Figure 9 shows the distribution of toxicities with boxed warnings associated with kinase inhibitors FDA-approved 2018-2023. Cardiovascular toxicities are the most common cause for boxed warnings for kinase inhibitors approved between 2018-2023 as well as for kinase inhibitors approved earlier (2001-2017). Among the newer TKIs, abrocitinib, baricitinib, ritletinenib, and upadacitinib all have boxed warnings for serious infections, thrombosis, and major adverse cardiovascular events (MACE) (FDA 2022a; FDA 2022b; FDA 2022c; FDA 2023c). Cardiovascular events are associated specifically with JAK inhibitors, which may be related to slower cholesterol ester breakdown (Wei et al., 2023). Dacomitinib is associated with skin toxicity, which can lead to dose reduction and treatment discontinuation (Iwasaku et al., 2023). These drug toxicities may arise from on-target and off-target effects. Serious adverse drug reactions remain a challenge for the clinical management of patients treated with kinase inhibitors. Moreover, QTc prolongation is another cardio-related toxicity relevant to these therapeutics. Both mobocertinib and quizartinib caused life-threatening QTc prolongation in patients. The mechanism for this toxicity, like previously studied kinase inhibitors, may be
related to prolonged action potentials in ventricular cells due to increased inward currents through sodium channels or decreased outward currents through potassium channels (Roden, 2019). Although several mechanisms have been proposed, the exact mechanisms of QT prolongation by these kinase inhibitors are unknown. Therefore, further studies are needed to define the mechanisms of cardiovascular and other serious toxicities associated with the newer kinase inhibitors.

**Clinical Outcomes**

Recently FDA-approved kinase inhibitors have shown significant clinical benefits in their respective therapeutic areas, such as increased progression-free survival in cancer therapy (Yu et al., 2023; Li et al., 2023; Singh et al., 2022). Briefly discussed below is a case example of the clinical outcomes with tucatinib.

**Case Example: Tucatinib**

Tucatinib, a HER2-selective inhibitor, is approved for use in combination with trastuzumab (a humanized IgG1 kappa monoclonal antibody); and capecitabine (a fluoropyrimidine carbamate with antineoplastic activity). Tucatinib is indicated for HER2-positive breast cancer, including patients with brain metastases (FDA 2023b). It is also indicated for unresectable or metastatic colorectal cancer that has progressed following more traditional chemotherapy methods: fluoropyrimidine-, oxaliplatin-, and irinotecan-based therapies. Dose modifications are recommended to those patients who experience adverse events, such as diarrhea which led to dehydration, hypotension, acute kidney injury, and hepatotoxicity (FDA 2023b). During the HER2CLIMB study for HER2-positive breast cancer, 81% of patients experienced diarrhea; 12% Grade 3 and 0.5% Grade 4. The same study also found that 1.5% of patients had to discontinue due to hepatotoxicity (Murthy et al., 2020). Overall, serious adverse reactions occurred in 26% of patients of which 6% discontinued the drug, and 12 patients (2%)
experienced fatal adverse effects (Murthy et al., 2020). The outcomes of this study show that tucatinib was able to increase progression-free survival and overall survival compared to the placebo group; however, tucatinib-treated patients were at a higher risk for deadly adverse reactions, such as diarrhea and DILI (Murthy et al., 2020).

During the MOUNTAINEER study for HER2-positive colorectal cancer, serious adverse events occurred in 22% of patients, which included intestinal obstruction, urinary tract infection, pneumonia, abdominal pain, and rectal perforation (Stickler et al., 2023). Permanent discontinuation of tucatinib due to adverse reactions occurred in 6% of patients (Stickler et al., 2023). Therefore, the risk-benefit profile remains an important consideration for the treatment of patients with tucatinib, even in late stages of disease. However, unlike HER2CLIMB, no deaths were attributed to tucatinib adverse reactions, showing its relative safety in this patient population (Stickler et al., 2023). This trial consisted of a patient population that was 77% “White” and 5% “Black”, providing an example of underrepresentation of non “White” individuals in the cancer clinical trial space. It should be noted that “race” is not a proxy for biological differences or genetic variation; we do not assume that population groups are homogenous, distinctively categorized, or stable over periods of time, as recommended by the National Academy of Sciences (National Academy of Sciences, 2023). Implementing inclusive research strategies, in which clinical trial populations reflect real-world patient populations, is critical to ensure the equitable efficacy and safety of cancer therapeutics now and in the future.

Current Challenges and Knowledge Gaps: Population Differences

Resistance to targeted therapies continues to be a challenge in cancer therapy. Treatment of cancer is dependent on the assumption that the cancer will not acquire resistance to the medication. As described earlier, resistance to TKIs can develop due to acquired
mutations in the target kinase (e.g., EGFR). Common EGFR mutations in exon 19 and 21 showed greater frequency in self-reported Asian patients compared to self-reported non-Hispanic White patients (Riley et al., 2006; Chung, 2016). Resistance from cancer therapeutics can also develop due to pharmacokinetic mechanisms when the therapeutic concentration is not reached. This can be caused by both intrinsic and extrinsic factors, which alter the metabolism and disposition of the drug. Because TKIs are prescribed as a standard fixed dose, interindividual variability in metabolism and disposition can alter the plasma concentrations and efficacy of the drug (de Wit et al., 2015). The variability in drug metabolism can be attributed to the individual’s environment and genetics. Due to this, “inter-ethnic differences” in TKI pharmacokinetics and pharmacodynamics have been noted in the literature (Touma et al., 2017). This variation in the systematic exposure to TKIs may be caused by genetic and non-genetic factors, such as ancestral origins, lifestyle, and other environmental factors.

While there is limited data on population-specific pharmacokinetics for recently approved TKIs, previous studies have shown inter-ethnic differences in the pharmacokinetics of imatinib, the first approved TKI. In a recent study, imatinib showed inter-ethnic differences between patients of European and African descent (Adiwidjaja et al., 2022). This group successfully built a physiologically-based pharmacokinetic (PBPK) model to predict imatinib pharmacokinetics and the impact of ethnicity on imatinib dosing. They found that populations of European, Japanese, and Chinese ancestry individuals required a similar dose to achieve the desired trough concentration while populations of African ancestry individuals required a higher dose to reach the same trough concentration (Adiwidjaja et al., 2022). This model suggests that patients of African ancestry would benefit from a higher initial dose of imatinib, adding to evidence that inter-ethnic differences in pharmacokinetics occur with TKIs. A population pharmacokinetic study in Nigerian patients found that various factors, including whole blood cell count, ethnicity (Yoruba, Husa, Igbo), CYP3A5 genotype, and ABCB1 genotype (which codes for ATP-binding
cassette subfamily B member 1, P-glycoprotein), influenced imatinib apparent clearance (Adeagbo et al., 2017). The authors concluded that the standard dose of imatinib may not achieve the desired therapeutic benefit in most Nigerian patients, and treatment resistance may result from drug underexposure. Additional studies are needed for the newer TKIs to evaluate inter-population variability in drug exposure and drug response in ethnically diverse populations.

Health disparities in understudied and underserved populations are a well-established issue in the United States. In general, cancer outcomes between people of African and European descent favor those with European heritage. A recent study investigated if “race” was an independent predictor of overall survival in patients with renal cell carcinoma treated with vascular endothelial growth factor receptor (VEGFR) TKIs (e.g., sunitinib and axitinib); the study found that “race” was not an independent predictor of overall survival, but the African American patients had more risk factors and worse outcomes using TKIs than their European American counterparts (Bosse et al., 2020). This study shows that understanding the social and biological determinants of survival outcomes in non-European cancer patients is important and a key missing piece in the advancement and implementation of precision oncology. In another study investigating differences in survival between Black and non-Black patients with EGFR-mutated NSCLC, researchers found that Black patients in the study had shorter survival times than their non-Black counterparts (Cheng et al., 2020). Black patients with EGFR mutations treated with EGFR TKIs (e.g., erlotinib, afatinib) also had worse survival compared to non-Black patients (Cheng et al., 2020). The authors suggest that these survival disparities warrant a more tailored approach to treating these patients. Although the precise mechanisms of interindividual differences in clinical outcomes are not completely clear, both genetic and environmental factors combine to determine a patient’s metabolism, disposition, and response to small molecules therapeutics like kinase inhibitors. Mutation specific TKIs aimed toward mutations seen in
underrepresented populations may be needed. This begins with inclusive research in the oncology clinical trial space.

**Perspective on Future Directions**

Despite the recent advances in the development of kinase inhibitors and the clinical success of kinase inhibitors in targeted therapy, several questions remain to be addressed in the future. For example: 1) What is the role of small molecule TKIs in the cancer treatment landscape with the increasing use of immunotherapies and other therapeutic modalities? 2) What molecular strategies are needed to overcome treatment resistance to TKIs? 3) How can dosing of small molecule TKIs be optimized for the individual patient to maximize drug efficacy and minimize drug toxicity? 4) Given that drug cost is a major barrier to medication access for some patients, what can be done to ensure that all patients have access to therapeutically relevant TKIs for disease treatment?

From a drug metabolism and disposition perspective, future opportunities to advance the science and clinical use of TKIs will rely on both: 1) increasing our mechanistic understanding of the causes for serious DDIs and adverse drug reactions, such as DILI, related to TKIs; and 2) developing practical and clinically actionable approaches to optimize drug dosing for the individual patient to maximize drug efficacy and minimize drug toxicity. Advances in precision medicine and precision dosing strategies that include diverse populations (Gonzalez et al., 2017; Jackson et al., 2023; Chothe et al., 2023) should aid in efforts to improve the clinical use of targeted therapies, including small molecule TKIs, for all patients.

**Summary and Conclusions**
In this review, we have highlighted several aspects of the clinical and molecular pharmacology of small molecule kinase inhibitors FDA-approved 2018-2023. While TKIs are mostly used in targeted cancer therapy, there is a growing list of TKIs approved for non-cancer indications. JAK inhibitors have been an important class of new TKIs for the treatment of autoimmune disorders. The most common cancer indication for FDA-approved TKIs is NSCLC, with eight TKIs approved for NSCLC over the past five years. Selected TKIs, such as EGFR targeted covalent inhibitors, have been designed to overcome issues of treatment resistance due to specific mutations in NSCLC. FGFR inhibitors are also a growing class of TKIs indicated for the treatment of different types of carcinomas.

The metabolism and toxicity profiles of recently FDA-approved TKIs were also reviewed. Drug metabolism by CYP3A is the major route of elimination for most of the small molecule kinase inhibitors FDA-approved 2018-2023. CYP2C8, CYP2C9, CYP2C19, and CYP2D6 also play a primary role in the metabolism of some kinase inhibitors, such as tucatinib, erdafitinib, abrocitinib, and dacomitinib, respectively, which may have implications for pharmacogenomics (Reizine et al., 2022). Metabolic activation of TKIs by CYP enzymes has important implications for DDIs and toxicity risks. Several of the recently approved TKIs are time-dependent inhibitors of CYP enzymes, particularly CYP3A. The DDI potential of some TKIs, such as tucatinib, has been demonstrated in vivo with CYP3A sensitive substrates; therefore, care should be given when treating patients with polypharmacy involving these TKIs. In addition, clinical case examples were presented in which dacomitinib, a strong CYP2D6 inhibitor, was associated with severe DILI likely due to interaction with metoprolol. Additional studies are needed to identify the mechanisms of liver injury associated with this and other recently FDA-approved TKIs to ensure their safe use in patients. Several kinase inhibitors also inhibit UGT enzymes, which may have implications for DDIs and adverse drug reactions.

The risk-benefit profile remains an important consideration for the treatment of patients with kinase inhibitors. Future research aimed at increasing our understanding of the drug toxicity...
mechanisms and risk factors should provide greater insight into reducing serious adverse
reactions related to kinase inhibitors. Moreover, identifying factors that contribute to variability in
drug exposure and drug response will aid in optimizing drug dosing for the individual patient.

Data Availability Statement

The authors declare that all the data supporting the information presented in this minireview are
contained within the paper. References to literature sources of data are cited.

Authorship Contributions

Participated in research design: Not applicable (minireview)

Conducted experiments: Not applicable (minireview)

Contributed new reagents or analytic tools: Not applicable (minireview)

Performed data analysis: Not applicable (minireview)

Wrote or contributed to the writing of the manuscript: Latham, Geffert, and Jackson

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Footnotes

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Conflict of Interest Statement

The authors declare no conflict of interest with the contents of this article.
Figure legends

**Figure 1.** Overview of selected targets for small molecule kinase inhibitors FDA-approved 2018-2023. Receptor tyrosine kinases are shown in the membrane, and non-receptor tyrosine kinases are shown below. Targets include epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), mesenchymal-epithelial transition factor (MET), fibroblast growth factor receptor (FGFR), Janus kinase (JAK), and phosphoinositide 3 kinase (PI3K). Figure created with Biorender.com.

**Figure 2.** Common indications and targets of small molecule kinase inhibitors FDA-approved 2018-2023. A) Indications and B) molecular targets of small molecule kinase inhibitors are shown. Information regarding indication and targets of kinase inhibitors is from drug prescribing information. (Immune disorders include autoimmune disorders, activated PI3K delta syndrome, and Graft-versus-host disease). Targets shown are Janus kinase (JAK), fibroblast growth factor receptor (FGFR), phosphoinositide 3 kinase (PI3K), epidermal growth factor receptor (EGFR), Bruton’s tyrosine kinase (BTK), mesenchymal-epithelial transition factor (MET), tropomyosin receptor kinase (TRK), rearranged during transfection (RET), KIT, and fms like tyrosine kinase 3 (FLT3). Only targets with two or more drugs FDA approved 2018-2023 are shown.

**Figure 3.** Types of fibroblast growth factor receptor (FGFR) inhibitors. Type 1 kinase inhibitors target the active state of the receptor and are bound by hydrogen bonds to kinase hinge and occupy the ATP binding pocket. Type 2 inhibitors target the inactive conformation and also occupy the ATP binding pocket; however, they induce a conformation change in DFG to turn from “IN” to “OUT” which is a 180° flip. This binding creates a pocket accessible to inhibitors that mimic ATP. Figure created with Biorender.com.

**Figure 4.** Drug-metabolizing enzymes involved in the metabolism of small molecule kinase inhibitors FDA-approved 2018-2023. A) Primary enzyme involved. B) All enzymes involved.
Information regarding drug-metabolizing enzyme involvement in the metabolism of kinase inhibitors is from drug prescribing information.

**Figure 5.** Tucatinib metabolic scheme, as described by Sun et al. (2022). Adapted to show only the most abundant circulating metabolite (M1, ONT-993) as well as other characterized metabolites M20 and M23. Figure adapted with permission from Sun et al. (2022). ©2022 Springer Nature.

**Figure 6.** Proposed pathways of dacomitinib metabolism. A) Major pathway of dacomitinib metabolism via O-demethylation by CYP2D6. B) Other proposed sites of dacomitinib metabolism. Figure adapted with permission from Bello et al. (2013) ©2013 Springer Nature; and Attwa et al. (2018b) ©2018 The Royal Society of Chemistry.

**Figure 7.** Lorlatinib metabolic scheme, as described in Stypinski et al. (2020). Adapted to show only the most abundant circulating metabolites. Figure adapted with permission from Stypinski et al. (2020). ©2020 John Wiley and Sons.

**Figure 8.** Proposed mechanism for DDI with dacomitinib and metoprolol leading to DILI. Dacomitinib is a strong CYP2D6 inhibitor. In a clinical case report, coadministration of dacomitinib with metoprolol resulted in acute liver failure. The proposed mechanism for the liver injury was increased hepatic exposure to metoprolol due to CYP2D6 inhibition by dacomitinib. The actual molecular basis for the liver injury is unknown (case report by Qui et al., 2023). Figure created with Biorender.com.

**Figure 9.** Distribution of boxed warning toxicities from small molecule kinase inhibitors FDA approved from 2018-2023. Toxicities are grouped by toxicity type. The graph represents 11 drugs that have 16 total toxicities in boxed warnings. Five drugs have two toxicities indicated (baricitinib, duvelisib, upadacitinib, abrocitinib, and ritlectinib). Each other drug (gilteritinib, glasdegib, fedratinib, pexidartinib, mobocertinib, and quizartinib) has only one toxicity indicated.
in the boxed warning. Information regarding boxed warning toxicities is from drug prescribing information.
### Table 1. Small Molecule Kinase Inhibitors FDA-Approved 2018-2023

<table>
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<th>Drug</th>
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<th>Therapeutic Indication(s)</th>
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<td>Baricitinib</td>
<td>2018</td>
<td>JAK</td>
<td>Rheumatoid arthritis</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Binimetinib</td>
<td>2018</td>
<td>MEK1,2</td>
<td>Melanoma</td>
<td>UGT1A1, CYP1A2, CYP2C19</td>
</tr>
<tr>
<td>Dacomitinib</td>
<td>2018</td>
<td>EGFR, HER2</td>
<td>NSCLC</td>
<td>CYP2D6, CYP3A4</td>
</tr>
<tr>
<td>Duvelisib</td>
<td>2018</td>
<td>PI3K</td>
<td>CLL, SLL, FL</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Encorafenib</td>
<td>2018</td>
<td>BRAF, CRAF</td>
<td>Melanoma, CRC</td>
<td>CYP3A4, CYP2C19, CYP2D6</td>
</tr>
<tr>
<td>Fostamatinib</td>
<td>2018</td>
<td>STK</td>
<td>Thrombocytopenia, ITP</td>
<td>CYP3A4, UGT1A9</td>
</tr>
<tr>
<td>Gilteritinib</td>
<td>2018</td>
<td>FLT3</td>
<td>AML</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Glasdegib</td>
<td>2018</td>
<td>Hedgehog pathway</td>
<td>AML</td>
<td>CYP3A4, CYP2C8, UGT1A9</td>
</tr>
<tr>
<td>Ivosidenib</td>
<td>2018</td>
<td>IDH1</td>
<td>AML</td>
<td>CYP3A4</td>
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<tr>
<td>Larotrectinib</td>
<td>2018</td>
<td>TRK (NTRK gene fusion)</td>
<td>Solid tumors</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Lorlatinib</td>
<td>2018</td>
<td>ALK, ROS1</td>
<td>ALK-positive NSCLC</td>
<td>CYP3A4, UGT1A4, minor CYP2C8, CYP2C19, CYP3A5, UGT1A3</td>
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<tr>
<td>Alpelisib</td>
<td>2019</td>
<td>PI3K</td>
<td>HR+, HER2- Breast cancer</td>
<td>chemical and enzymatic hydrolysis</td>
</tr>
<tr>
<td>Entrectinib</td>
<td>2019</td>
<td>TRK</td>
<td>NSCLC</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Erdafitinib</td>
<td>2019</td>
<td>FGFR1,2,3,4</td>
<td>Urothelial carcinoma</td>
<td>CYP2C9, CYP3A4</td>
</tr>
<tr>
<td>Fedratinib</td>
<td>2019</td>
<td>JAK2, FLT3</td>
<td>Myelofibrosis</td>
<td>CYP3A4, CYP2C19</td>
</tr>
<tr>
<td>Pexidartinib</td>
<td>2019</td>
<td>CSF1R, KIT, FLT3</td>
<td>TGCT</td>
<td>CYP3A4, UGT1A4</td>
</tr>
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<td>Upadacitinib</td>
<td>2019</td>
<td>JAK</td>
<td>Rheumatoid arthritis</td>
<td>CYP3A4, CYP2D6</td>
</tr>
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<td>Zanubrutinib</td>
<td>2019</td>
<td>BTK</td>
<td>MCL</td>
<td>CYP3A4</td>
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<td></td>
<td>Drug Name</td>
<td>Year</td>
<td>Target(s)</td>
<td>Indication(s)</td>
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<td>Avapritinib</td>
<td>2020</td>
<td>KIT, PDGFRA</td>
<td>GIST, AvdSM</td>
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<td>20</td>
<td>Capmatinib</td>
<td>2020</td>
<td>MET</td>
<td>NSCLC</td>
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<td>21</td>
<td>Pemigatinib</td>
<td>2020</td>
<td>FGFR1,2,3</td>
<td>Cholangiocarcinoma</td>
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<td>22</td>
<td>Pralsetinib</td>
<td>2020</td>
<td>RET</td>
<td>NSCLC</td>
</tr>
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<td>23</td>
<td>Ripretinib</td>
<td>2020</td>
<td>KIT, PDGFRA</td>
<td>GIST</td>
</tr>
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<td>24</td>
<td>Selpercatinib</td>
<td>2020</td>
<td>RET, VEGFR1, 3</td>
<td>NSCLC</td>
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<td>25</td>
<td>Selumetinib</td>
<td>2020</td>
<td>MEK1,2</td>
<td>Neurofibromatosis type 1, plexiform neurofibromas</td>
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<td>Tucatinib</td>
<td>2020</td>
<td>HER2,3</td>
<td>HER2+ breast cancer</td>
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<td>27</td>
<td>Asciminib</td>
<td>2021</td>
<td>ABL/BCR-ABL1</td>
<td>CML</td>
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<td>28</td>
<td>Belumosudil</td>
<td>2021</td>
<td>ROCK - rho-associated, coiled-coil containing protein kinase</td>
<td>GVHD</td>
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<td>29</td>
<td>Futibatinib</td>
<td>2021</td>
<td>FGFR1,2,3,4</td>
<td>Intrahepatic cholangiocarcinoma, FGFR2 gene fusions</td>
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<td>Infigratinib</td>
<td>2021</td>
<td>FGFR2</td>
<td>Metastatic cholangiocarcinoma</td>
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<td>Mobocertinib</td>
<td>2021</td>
<td>EGFR</td>
<td>NSCLC</td>
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<td>32</td>
<td>Tepotinib</td>
<td>2021</td>
<td>MET</td>
<td>NSCLC</td>
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<td>33</td>
<td>Tivozanib</td>
<td>2021</td>
<td>VEGFR1,2,3</td>
<td>Renal cell carcinoma</td>
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<td>34</td>
<td>Trilaciclib</td>
<td>2021</td>
<td>Transient inhibitor of Chemotherapy-induced</td>
<td></td>
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<td></td>
<td>CDK4,6</td>
<td>myelosuppression</td>
<td></td>
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<td>Abrocitinib</td>
<td>2022</td>
<td>JAK</td>
<td>Atopic dermatitis</td>
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<td>Deucravacitinib</td>
<td>2022</td>
<td>TYK2</td>
<td>Plaque psoriasis</td>
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<td>Pacritinib</td>
<td>2022</td>
<td>JAK2</td>
<td>Myelofibrosis</td>
</tr>
<tr>
<td>38</td>
<td>Umbralisib</td>
<td>2022</td>
<td>PI3K, CK1</td>
<td>MZL, FL</td>
</tr>
<tr>
<td>39</td>
<td>Leniolisib</td>
<td>2023</td>
<td>PI3K-delta</td>
<td>APDS</td>
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<td>40</td>
<td>Quizartinib</td>
<td>2023</td>
<td>FLT3</td>
<td>AML</td>
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<td>41</td>
<td>Ritlecinitib</td>
<td>2023</td>
<td>JAK3</td>
<td>Severe alopecia areata</td>
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<td>42</td>
<td>Pirtobrutinib</td>
<td>2023</td>
<td>BTK</td>
<td>MCL</td>
</tr>
</tbody>
</table>

*Data adapted from the drug prescribing information for FDA approval year, target(s), therapeutic indication(s), and metabolic pathway(s).

Abbreviations: AML, acute myeloid leukemia; AO, aldehyde oxidase; APDS, activated PI3K-delta syndrome; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; CYP, cytochrome P450; FL, follicular lymphoma; FMO, flavin-containing monooxygenase; GIST, gastrointestinal stromal tumor; GST, glutathione S-transferase; GVHD, Graft-versus-host disease; ITP, immune thrombocytopenia; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NSCLC, non-small cell lung cancer; SLL, small lymphocytic lymphoma; TGCT, Tenosynovial giant cell tumors; UGT, UDP-glucuronosyltransferase
Table 2. CYP Inactivation Kinetic Parameters by Kinase Inhibitors (FDA approved 2018-2023)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Enzyme (probe substrate)</th>
<th>$K_i$, $\mu$M</th>
<th>$k_{inact}$, min$^{-1}$</th>
<th>$k_{inact}/K_i$ min$^{-1}$ mM$^{-1}$</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infgratinib</td>
<td>CYP3A4 (testosterone)</td>
<td>3.26 ± 0.61</td>
<td>0.027 ± 0.002</td>
<td>8.4</td>
<td>(Tang et al., 2021a)</td>
</tr>
<tr>
<td></td>
<td>CYP3A4 (midazolam)</td>
<td>9.03 ± 2.85</td>
<td>0.088 ± 0.011</td>
<td>9.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CYP3A4 (rivarozaban)</td>
<td>4.17 ± 0.93</td>
<td>0.068 ± 0.005</td>
<td>16.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CYP3A4 (testosterone)</td>
<td>1.14 ± 0.35</td>
<td>0.039 ± 0.002</td>
<td>34.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CYP3A4 (midazolam)</td>
<td>6.35 ± 0.57</td>
<td>0.150 ± 0.004</td>
<td>23.6</td>
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</tr>
<tr>
<td></td>
<td>CYP3A4 (rivarozaban)</td>
<td>4.01 ± 0.42</td>
<td>0.120 ± 0.003</td>
<td>29.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CYP3A5 (testosterone)</td>
<td>2.87 ± 0.73</td>
<td>0.019 ± 0.001</td>
<td>6.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CYP3A5 (midazolam)</td>
<td>26.80 ± 2.40</td>
<td>0.052 ± 0.002</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CYP3A5 (rivarozaban)</td>
<td>10.04 ± 1.91</td>
<td>0.045 ± 0.003</td>
<td>4.9</td>
<td></td>
</tr>
<tr>
<td>Erdafitinib</td>
<td>CYP3A4 (rivarozaban)</td>
<td>8.69 ± 1.62</td>
<td>0.108 ± 0.008</td>
<td>12.4</td>
<td>(Tang et al., 2021b)</td>
</tr>
<tr>
<td></td>
<td>CYP3A5 (rivarozaban)</td>
<td>11.95 ± 4.41</td>
<td>0.042 ± 0.007</td>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td>Pemigatinib</td>
<td>CYP3A4 (rivarozaban)</td>
<td>8.69 ± 1.62</td>
<td>0.108 ± 0.008</td>
<td>12.4</td>
<td>(Tang et al., 2022)</td>
</tr>
<tr>
<td></td>
<td>CYP3A5 (rivarozaban)</td>
<td>11.95 ± 4.41</td>
<td>0.042 ± 0.007</td>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td>Lorlatinib</td>
<td>CYP3A$^d$</td>
<td>7.92</td>
<td>0.081</td>
<td>10.2</td>
<td>(Lorlatinib NDA, 2018)$^c$</td>
</tr>
<tr>
<td>Avapritinib</td>
<td>CYP3A$^d$</td>
<td>12.3</td>
<td>0.03</td>
<td>2.4</td>
<td>(Avapritinib NDA, 2020)$^c$</td>
</tr>
<tr>
<td>Tucatinib</td>
<td>CYP3A (midazolam)</td>
<td>0.54</td>
<td>0.011</td>
<td>20.4</td>
<td>(Tucatinib NDA, 2020)$^c$</td>
</tr>
<tr>
<td>Pacritinib</td>
<td>CYP1A2 (phenacetin)</td>
<td>0.95$^b$</td>
<td>0.041</td>
<td>43.2</td>
<td>(Pacritinib NDA, 2022)$^c$</td>
</tr>
<tr>
<td></td>
<td>CYP3A4 (midazolam)</td>
<td>1.6$^b$</td>
<td>0.0096</td>
<td>6.0</td>
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</tr>
<tr>
<td>Leniolisib</td>
<td>CYP1A2$^d$</td>
<td>303</td>
<td>0.017</td>
<td>0.06</td>
<td>(Leniolisib NDA, 2023)$^c$</td>
</tr>
</tbody>
</table>

$^a$Values shown are the mean ± standard deviation as reported by Tang et al., 2021a; Tang et al., 2021b; Tang et al., 2022. Reprinted with permission from: Tang LWT, Teng JW, Koh SK, Zhou L, Go ML and Chan ECY (2021) Mechanism-Based Inactivation of Cytochrome P450 3A4 and 3A5 by the Fibroblast Growth Factor Receptor Inhibitor Erdafitinib. Chem Res Toxicol 34:1800-

*Values shown are the reported $K_{i,u}$ values.*

*Values shown are reported in the New Drug Applications (NDA) for the respective drugs.*

*Probe substrate not reported*
**Table 3. UGT Inhibition by Kinase Inhibitors (FDA approved 2018-2023)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>UGT Enzyme(s) Inhibited</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt;, µM&lt;sup&gt;a&lt;/sup&gt;</th>
<th>K&lt;sub&gt;i,u&lt;/sub&gt; µM&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Reference(s)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dacomitinib</td>
<td>UGT1A1</td>
<td>-</td>
<td>-</td>
<td>FDA 2018</td>
</tr>
<tr>
<td>Encorafenib</td>
<td>UGT1A1</td>
<td>5.9</td>
<td>-</td>
<td>FDA 2020; Encorafenib NDA 2017</td>
</tr>
<tr>
<td>Fostamatinib (major active metabolite R406)</td>
<td>UGT1A1</td>
<td>-</td>
<td>-</td>
<td>FDA 2018</td>
</tr>
<tr>
<td>Pexidartinib</td>
<td>UGT1A1</td>
<td>6.9</td>
<td>-</td>
<td>FDA 2019; Pexidartinib NDA 2018</td>
</tr>
<tr>
<td></td>
<td>UGT1A4</td>
<td>22</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UGT2B7</td>
<td>26</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Belumosudil</td>
<td>UGT1A1</td>
<td>0.06</td>
<td>-</td>
<td>FDA 2021; Belumosudil NDA 2020; Przepiorka et al., 2022</td>
</tr>
<tr>
<td></td>
<td>UGT1A9</td>
<td>0.86</td>
<td>-</td>
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<tr>
<td>Belumosudil metabolite KD025-M2</td>
<td>UGT1A1</td>
<td>0.63</td>
<td>-</td>
<td>Belumosudil NDA 2020</td>
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<tr>
<td></td>
<td>UGT1A9</td>
<td>11.2</td>
<td>-</td>
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<tr>
<td>Asciminib</td>
<td>UGT1A1</td>
<td>-</td>
<td>0.35</td>
<td>FDA 2021; Asciminib NDA 2021</td>
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<tr>
<td>Quizartinib</td>
<td>UGT1A1</td>
<td>-</td>
<td>-</td>
<td>FDA 2023</td>
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</table>

<sup>a</sup>*In vitro* IC<sub>50</sub> values reported in the NDA for the respective drugs; dash (-) indicates value not reported. The IC<sub>50</sub> value for encorafenib is the unbound IC<sub>50</sub> corrected for microsomal protein binding (encorafenib NDA 2017).

<sup>b</sup>*In vitro* unbound K<sub>i,u</sub> value reported in the NDA for asciminib; dash (-) indicates value not reported.

<sup>c</sup>UGT inhibition data adapted from drug prescribing information and from the NDA for the respective drugs.
Table 4. Small Molecule Kinase Inhibitors FDA-Approved 2018-2023 with Warnings and Precautions for Toxicities

<table>
<thead>
<tr>
<th>Drug</th>
<th>Boxed Warning</th>
<th>Warning and Precautions for Hepatotoxicity</th>
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<tr>
<td>Abrocitinib</td>
<td>Serious infections, MACE, thrombosis</td>
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<tr>
<td>Adagrasib</td>
<td>-</td>
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</tr>
<tr>
<td>Baricitinib</td>
<td>Serious infections, MACE, thrombosis</td>
<td>-</td>
</tr>
<tr>
<td>Binimetinib</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>Capmatinib</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>Duvelisib</td>
<td>Infections, diarrhea or colitis, cutaneous reactions, pneumonitis</td>
<td>Yes</td>
</tr>
<tr>
<td>Entrectinib</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>Fedratinib</td>
<td>Encephalopathy including Wernicke’s</td>
<td>Yes</td>
</tr>
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<td>Fostamatinib</td>
<td>-</td>
<td>Yes</td>
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<td>Gilteritinib</td>
<td>Differentiation Syndrome</td>
<td>-</td>
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<tr>
<td>Glasdegib</td>
<td>Embryo Fetal Toxicity</td>
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<td>Larotrectinib</td>
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<td>Yes</td>
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<tr>
<td>Lorlatinib</td>
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<td>Yes</td>
</tr>
<tr>
<td>Mobocertinib</td>
<td>QTc Prolongation and Torsades de Pointes</td>
<td>-</td>
</tr>
<tr>
<td>Pexidartinib</td>
<td>Hepatotoxicity</td>
<td>-</td>
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<td>Pralsetinib</td>
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<td>Yes</td>
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<tr>
<td>Quizartinib</td>
<td>QTc Prolongation and Torsades de Pointes</td>
<td>-</td>
</tr>
<tr>
<td>Rittlecitinib</td>
<td>Serious infections, MACE, thrombosis</td>
<td>-</td>
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<tr>
<td>Selpercatinib</td>
<td>-</td>
<td>Yes</td>
</tr>
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<td>Tepotinib</td>
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<td>Yes</td>
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<td>Tucatinib</td>
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<td>Umbralisib</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>Upadacitinib</td>
<td>Serious infections, MACE, thrombosis</td>
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</table>

Data adapted from drug prescribing information for warnings and precautions.

Abbreviation: MACE, major adverse cardiovascular events
A. 

Number of Drugs

Indication

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<th>Number of Drugs</th>
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</tr>
<tr>
<td>Breast cancer</td>
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<tr>
<td>Myelofibrosis</td>
<td>2</td>
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<td>Thromocytopenia</td>
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</table>

B. 

Number of Drugs

Target

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<td>PI3K</td>
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<td>EGFR</td>
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<td>MET</td>
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<td>2</td>
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<tr>
<td>RET</td>
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<td>KIT</td>
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<tr>
<td>FLT3</td>
<td>2</td>
</tr>
</tbody>
</table>

Figure 2

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Figure 3

Type 1 Inhibitors

Type 2 Inhibitors
A. B. 

Figure 4
Figure 5
Figure 6

A. Dacomitinib

B. PF-05199265
(major metabolite)

Iminium ion intermediate; lactam formation

Piperidine ring oxidation; ring opening

Glutathione conjugation

Oxidation
Figure 9

- Cardiovascular: 38% (6 drugs)
- Hematologic/Neutropenia: 6%
- Hepatic: 25% (4 drugs)
- Differentiation Syndrome: 6%
- Gastointestinal: 6%
- Hypersensitivity: 6%
- Encephalopathy: 6%
- Reproductive/Embryo-Fetal: 6%

1 drug each