Differentiating pulmonary hypertension associated with protein kinase inhibitors

Joshua A. Jacobs¹ | Eiman Jahangir² | John J. Ryan³

¹Department of Pharmacy, University of Utah Health, Salt Lake City, Utah, USA
²Division of Cardiovascular Medicine, Department of Medicine, Vanderbilt University, Nashville, Tennessee, USA
³Division of Cardiovascular Medicine, Department of Medicine, University of Utah, Salt Lake City, Utah, USA

Correspondence
John J. Ryan, Division of Cardiovascular Medicine, Department of Medicine, University of Utah Health, 30 North 1900 East, Room 4A100, Salt Lake City, UT 84132, USA.
Email: john.ryan@hsc.utah.edu

Funding information
The Reagan Corporation; NIH, Grant/Award Number: R01HL093081; The Gordon Family; The Cushman Family; VA Clinical Science Research & Development Service Merit Award.
Grant/Award Number: CX002152

Abstract
Protein kinase inhibitors (PKIs) have been implicated in pulmonary vascular toxicities including risk factors for at least three of the five World Health Organization groups of pulmonary hypertension (PH). These toxicities include direct drug-induced pulmonary arterial hypertension, an increase in cardiomyopathies, and an increase in interstitial lung disease. On- and off-target toxicities are common within multitargeted PKIs leading to cardiopulmonary toxicities. This review highlights the incidence, possible mechanisms, and management strategies for each group of possible PKI-induced PH. Future identification and clarification of protein kinase pathways for both mechanisms of toxicity and pathophysiology for PH could lead to improvements in patient care in oncology and pulmonary vascular diseases.

KEYWORDS
cancer, dasatinib, protein kinase, pulmonary arterial hypertension, tyrosine kinase

Abbreviations: ACE, angiotensin converting enzyme; ALK, anaplastic lymphoma kinase; ALL, acute lymphoblastic leukemia; ARB, angiotensin receptor blocker; ARTEMIS-IPF, Ambrisentan in Subjects with Pulmonary Hypertension Associated with Idiopathic Pulmonary Fibrosis; ATP, adenosine triphosphate; BCR-ABL1, breakpoint cluster region-Abelson leukemia gene; BMP, bone morphogenic protein; BNP, brain-natriuretic peptide; BTK, Bruton’s tyrosine kinase; CCL2, CC ligand chemokine 2; CDK, cyclin-dependent kinase; CML, chronic myeloid leukemia; CT, computed tomography; CTEPH, chronic thromboembolic pulmonary hypertension; EGFR, epidermal growth factor receptor; ET-1, endothelin-1; FDA, Food and Drug Administration; FGFR, fibroblast growth factor receptor; FLT3, FMS-like tyrosine kinase-3; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IGf1, insulin-like growth factor 1; ILD, interstitial lung disease; IMPRES, Imatinib in Pulmonary Arterial Hypertension, a Randomized, Efficacy Study; INCREASE, Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease; IPF, idiopathic pulmonary fibrosis; LV, left ventricular; LVEF, left ventricular ejection fraction; MAPK, mitogen activated protein kinases; mPAP, mean pulmonary artery pressure; NO, nitric oxide; PAH, pulmonary arterial hypertension; PDGFR, platelet-derived growth factor; PGI2, prostacyclin; PH, pulmonary hypertension; PI3K, phosphoinositide-3 kinase; PKI, protein kinase inhibitor; PVR, pulmonary vascular resistance; RCC, renal cell carcinoma; RHC, right heart catheterization; RISE-IIP, Riociguat for idiopathic interstitial pneumonia-associated pulmonary hypertension; ROS, reactive oxygen species; sE-selectin, soluble E-selectin; sICAM-1, soluble intercellular adhesion molecule; sVCAM-1, soluble vascular cell adhesion molecule; TGFB1, tumor growth factor-beta 1; VEGF, vascular endothelial growth factor; VTE, venous thromboembolism; WHO, World Health Organization.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2022 The Authors. Pulmonary Circulation published by John Wiley & Sons Ltd on behalf of Pulmonary Vascular Research Institute.
INTRODUCTION

Pulmonary hypertension (PH) is defined by the sixth World Symposium as a mean pulmonary artery pressure of greater than 20 mmHg.1 PH is classified into five different groups based on etiology and pathophysiology as defined by the World Health Organization (WHO). Over the last 30 years, advances in the understanding of pathophysiology, prognosis, and treatment paradigms have led to improved management of patients with PH.2 Similarly, innovations within cancer therapeutics have led to an improvement in progression-free survival for cancer survivors. Due to improvements in mortality among cancer survivors, complications from cancer treatment are more prevalent with cardiotoxicities as one of the leading causes of death.3

Protein kinases inhibitors (PKIs) have become ubiquitous in the field of oncology, being used for treating leukemias, lung cancer, and melanoma, among other forms of malignancy (Table 1). Protein kinases work by transferring phosphoryl groups from adenosine triphosphate (ATP) to proteins. Phosphorylation of these kinases is crucial in cell signaling, proliferation, and survival and disruption can lead to cell death. PKIs inhibit this pathway.95–97 Two classes of PKIs currently exist based on the binding properties and selectivity of the drug. Type I inhibitors inhibit phosphorylation via competitive binding within the ATP pocket of the substrate. Due to the ubiquity of ATP binding sites, Type I inhibitors exhibit low selectivity. Type II inhibitors demonstrate higher selectivity by binding to both the ATP pocket and an adjacent binding site.98,99

PKIs have been implicated in the development of PH. Different on-target and off-target toxicities of PKIs can lead to the development of PH through a variety of factors that contribute to one or multiple of the PH WHO groups.22,23 Therefore, when a patient develops PH having been treated with a PKI, it can be challenging to determine the group of PH they fall into and the underlying etiology. Specifically,1,100–103 In this review, we discuss the various PKIs, explore their role in the development of Group 1 pulmonary arterial hypertension (PAH), Group 2 PH due to left-sided heart disease, and Group 3 PH due to lung disease and/or hypoxia. In addition, we will offer guidance as to how to clinically approach patients who develop PH in the setting of PKI treatment, based on the WHO PH classification system, and discuss management strategies.

PULMONARY ARTERIAL HYPERTENSION

WHO Group 1 PAH accounts for <3%–14% of all cases of PH.104,105 The pathophysiology of PAH is an imbalance in endothelial proliferation, inflammation, and remodeling within the pulmonary vasculature via three main pathways: nitric oxide (NO), endothelin-1 (ET-1), and prostacyclin (PGI2) pathways.106 Prolonged disproportionality of these pathways leads to dysregulation of inflammation, apoptosis, and proliferation of the smooth muscle and endothelial cells of the pulmonary artery causing an increase in mean pulmonary artery pressure (mPAP).107 While the complexity of PAH pathophysiology extends beyond the NO, ET-1, and PGI2 pathways, PKIs can contribute to disparities in these pathways potentially leading to direct drug-induced PAH (Table 1).

PKIs that have been implicated in Group 1 PAH are dasatinib, bosutinib, ponatinib, and nilotinib. These agents, along with imatinib, are breakpoint cluster region-Abelson leukemia gene (BCR-ABL1) inhibitors. They have been groundbreaking for the treatment of chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) and have varying cardiovascular profiles. Imatinib, the first Food and Drug Administration (FDA) approved BCR-ABL1 inhibitor, has been associated with improvements in hemodynamics of pulmonary pressures and was studied for the treatment of PAH in the IMPRES trial (Imatinib in Pulmonary Arterial Hypertension, a Randomized, Efficacy Study) demonstrating an improvement in functional capacity and hemodynamics.108–110 Although serious adverse events and study drug discontinuations were seen with imatinib in PAH, limiting its clinical use, the proposed mechanisms through which imatinib effects the pulmonary vasculature include, inhibition of platelet-derived growth factor-α/β (PDGFR-α/β), decrease proliferation of pulmonary artery smooth muscle cells, and a decrease in calcium influx resulting in pulmonary artery vasodilation.4,111,112

In contrast to imatinib, dasatinib, a second-generation BCR-ABL1 inhibitor has been associated with rare, but fatal PAH.22,23 Inflammation of the pulmonary artery smooth muscle cells and elevations of T lymphocytes, leukocytes, monocytes, and macrophages is thought to be the primary mechanism of dasatinib toxicity. Rat studies have demonstrated that dasatinib predisposes those with chronic hypoxia or monocrotaline with an exaggerated worsening of pulmonary pressures.23 Additionally, increased endothelial dysfunction as indicated by elevated levels of reactive oxygen species (ROS), soluble intercellular adhesion molecule (sICAM)-1, soluble vascular cell adhesion molecule (sVCAM)-1, and soluble E-selectin (sE-selectin) may be contributing.112,113 Furthermore, potential off-target inhibition of Src, a non-receptor tyrosine kinase family, can lead to pulmonary vascular remodeling.114 The Src kinase family is instrumental in phosphorylating and activating TWIK-related acid-sensitive potassium channel-1 (TASK-1) on
**TABLE 1**  FDA-approved PKIs with on- and off-target receptors, uses, and adverse drug effects according to WHO Group (as of February 2022)

| Drug | Receptors\(^{4,5}\) | Year approved | Uses | Group 1 risk factors | Group 2 risk factors | Group 3 risk factors |
|------|-------------------|--------------|------|-----------------------|----------------------|----------------------|
| **ALK inhibitors** | | | | | | |
| Alectinib\(^{6}\) | ALK | 2015 | NSCLC | | | ILD |
| Brigatinib\(^{7,8}\) | ALK, ErbB1 | 2017 | NSCLC | PAH | HTN | ILD |
| Ceritinib\(^{9,10}\) | ALK | 2014 | NSCLC | PAH | | ILD |
| Crizotinib\(^{11,12}\) | ALK, MET | 2011 | NSCLC | PAH | | ILD |
| Lorlatinib\(^{9,13}\) | ALK, ROS1 | 2018 | NSCLC | PAH | | ILD |
| **BTK inhibitors** | | | | | | |
| Acalabrutinib\(^{14}\) | BTK | 2017 | CLL, SLL, MCL | HTN, AF | | |
| Ibrutinib\(^{15}\) | BTK | 2013 | CLL, GVHD, MCL, MZL, SLL, WMG | HTN, AF, HFrEF | | |
| Zanubutinib\(^{16}\) | BTK | 2019 | MCL | HTN, AF | | |
| **BCR-ABL1 inhibitors** | | | | | | |
| Asciminib\(^{17}\) | BCR-ABL1, STAMP | 2021 | CML | | | HFrEF, HTN |
| Bosutinib\(^{18-21}\) | BCR-ABL1, Src, FGFR1-3, VEGFR1-2, FLT3, PDGFRα/β | 2012 | CML | PAH | | HFrEF, HTN |
| Dasatinib\(^{22-26}\) | BCR-ABL1, FGFR, KIT, PDGFRα/β, Src | 2006 | ALL, CML, GIST | PAH | | HFrEF, HTN |
| Imatinib\(^{27}\) | BCR-ABL1, FLT3, KIT, PDGFRα/β | 2001 | ALL, ASM, CEL, CML, DFSP, HES, GIST, MDS/MPD | | HTN, HFrEF | |
| Nilotinib\(^{28-30}\) | BCR-ABL1, FLT3, KIT, PDGFRα/β | 2007 | ALL, CML, GIST | PAH | AF | |
| Ponatinib\(^{29,31-33}\) | BCR-ABL1, FGFR, VEGFR1-3, FLT3, KIT, PDGFRα/β, Src, TIE2 | 2012 | ALL, CML | PAH | | HFrEF, HTN |
| **BRAF/MEK inhibitors** | | | | | | |
| Binimetinib\(^{34}\) | MEK1/2 | 2018 | Melanoma, CRC | | HFrEF, HTN | ILD |
| Cobimetinib\(^{35}\) | MEK1 | 2015 | Melanoma | | HFrEF, HTN | |
| Dabrafenib\(^{36}\) | BRAF | 2013 | Melanoma, NSCLC, TC | | HFrEF | |
| Encorafenib\(^{37}\) | BRAF | 2018 | CRC, Melanoma | | | |
| Selumetinib\(^{38}\) | MEK1/2 | 2020 | NF1 | | HFrEF, HTN | |
| Trametinib\(^{39}\) | MEK1/2 | 2013 | Melanoma, NSCLC, TC | | HTN, HFrEF | ILD |
| Vemurafenib\(^{40}\) | BRAF | 2011 | Melanoma, ECD, NSCLC | | AF, HTN | |
| **CDK-4/6 inhibitors** | | | | | | |
| Abemaciclib\(^{41}\) | CDK-4/6 | 2017 | BC | | | ILD |
| Palbociclib\(^{42}\) | CDK-4/6 | 2015 | BC | | | ILD |

(Continues)
### Table 1 (Continued)

| Drug          | Receptors | Year approved | Uses                      | Group 1 risk factors | Group 2 risk factors | Group 3 risk factors |
|---------------|-----------|---------------|---------------------------|----------------------|----------------------|----------------------|
| Ribociclib    | CDK-4/6   | 2017          | BC                        |                      |                      | ILD                  |
| Trilaciclib   | CDK-4/6   | 2021          | Chemo-induced myelosuppression |                      |                      | ILD                  |
| **ErbB inhibitors** |          |               |                           |                      |                      |                      |
| Arafatinib    | ErbB1, ErbB2, ErbB4 | 2013          | NSCLC                     |                      |                      | HFrEF, ILD           |
| Dacomitinib   | ErbB1, ErbB2, ErbB4 | 2018          | NSCLC                     |                      |                      | ILD                  |
| Erlotinib     | ErbB1     | 2004          | NSCLC, PC                 |                      |                      | ILD                  |
| Gefitinib     | ErbB1     | 2015          | NSCLC                     |                      |                      | ILD                  |
| Lapatinib     | ErbB1, ErbB2, ErbB4 | 2007          | BC                        |                      |                      | HFrEF, ILD           |
| Mobocertinib  | ErbB1, ErbB2, ErbB4 | 2021          | NSCLC                     |                      |                      | AF, HTN, HFrEF, ILD  |
| Neratinib     | ErbB1, ErbB2 | 2017          | BC                        |                      |                      |                      |
| Osimertinib   | ErbB1     | 2015          | NSCLC                     |                      |                      | HFrEF, ILD           |
| Tucatinib     | ErbB2     | 2020          | BC                        |                      |                      |                      |
| **FGFR inhibitors** |          |               |                           |                      |                      |                      |
| Erdafitinib   | FGFR      | 2019          | UC                        |                      |                      | HFrEF                |
| Infigratinib  | FGFR      | 2021          | Cholangio-carcinoma       |                      |                      |                      |
| Nintedanib    | FGFR, VEGFR1-3, Src, PDGFR, CSF1 | 2014          | ILD/IPF                   |                      |                      | HTN                  |
| Pemigatinib   | FGFR      | 2020          | Cholangio-carcinoma       |                      |                      |                      |
| **FLT3 inhibitors** |          |               |                           |                      |                      |                      |
| Gilteritinib  | FLT3, AXL, ALK | 2018          | AML                       |                      |                      | HFrEF, ILD           |
| Midostaurin   | FLT3, VEGFR2, KIT, PDGFR | 2017          | AML, MCL, ASM             |                      |                      | HTN, HFrEF, ILD      |
| **JAK inhibitors** |          |               |                           |                      |                      |                      |
| Abrocitinib   | JAK 1     | 2022          | Atopic dermatitis         |                      |                      | HTN                  |
| Baricitinib   | JAK1/2    | 2018          | RA                        |                      |                      |                      |
| Fedratinib    | JAK2, FLT3 | 2019          | Myelofibrosis             |                      |                      | HTN, HFrEF           |
| Ruxolitinib   | JAK1/2    | 2011          | Atopic dermatitis, GVHD, Myelofibrosis, PV | PAH |                      | HTN                  |
| Tofacitinib   | JAK1-3    | 2012          | RA, PsA, Ulcerative colitis |                      |                      | HTN, ILD             |
| **MET inhibitors** |          |               |                           |                      |                      |                      |
| Capmatinib    | MET       | 2020          | NSCLC                     |                      |                      | ILD                  |
| Tepotinib     | MET       | 2021          | NSCLC, thyroid cancer     |                      |                      |                      |
| **mTOR inhibitors** |          |               |                           |                      |                      |                      |
| Everolimus    | mTOR      | 2009          | BC, NT, RCC, TS, transplants, WMG |                      |                      | HTN, ILD             |
| Sirolimus     | mTOR      | 1999          | GVHD, LAM, transplants    |                      |                      | HTN, ILD             |
**TABLE 1** (Continued)

| Drug               | Receptors                       | Year approved | Uses                     | Group 1 risk factors | Group 2 risk factors | Group 3 risk factors |
|--------------------|---------------------------------|---------------|--------------------------|----------------------|----------------------|----------------------|
| Temsirolimus⁷¹     | mTOR                            | 2007          | Endometrial cancer, RCC  |                       | HTN                  | ILD                  |
| PDGFR inhibitors   |                                 |               |                          |                      |                      |                      |
| Avapritinib⁷²      | PDGFRα, KIT                      | 2020          | GIST                     |                       |                      |                      |
| Ripretinib⁷³       | PDGFRα, KIT                      | 2020          | GIST                     |                       |                      |                      |
| PI3K-δ inhibitors  |                                 |               |                          |                      |                      |                      |
| Copanlisib⁷⁴       | PI3K-δ                           | 2017          | FL                       | HTN                  |                      | ILD                  |
| Idelalisib⁷⁵       | PI3K-δ                           | 2014          | CLL, FL, SLL             | ILD                  |                      |                      |
| Umbralisib⁷⁶       | PI3K-δ                           | 2021          | FL, MZL                  | ILD                  |                      |                      |
| RET inhibitors     |                                 |               |                          |                      |                      |                      |
| Pralsetinib⁷⁷      | RET, DDR1, JAK1/2, TRKA/C, PDGFRβ, FGFR | 2020          | NSCLC, TC                | HTN                  |                      | ILD                  |
| Selpercatinib⁷⁸    | RET, VEGFR1/3, FGFR              | 2020          | NSCLC, TC                |                      |                      |                      |
| Vandetanib⁷⁹       | RET, ErbB1, VEGFR2, TIE2, Src    | 2011          | TC                       |                      |                      |                      |
| TRK inhibitors     |                                 |               |                          |                      |                      |                      |
| Entrectinib⁸⁰      | TRKA/B/C, ROS1, ALK              | 2019          | NSCLC, NTRK + solid tumors |                      |                      |                      |
| Larotrectinib⁸¹    | TRKA/B/C                         | 2018          | NTRK + solid tumors      |                      |                      |                      |
| VEGF inhibitors    |                                 |               |                          |                      |                      |                      |
| Axitinib⁸²         | VEGF1-3, FGFR                     | 2012          | RCC, TC                  |                      |                      |                      |
| Cabozantinib⁸³     | VEGFR1-3, MET, RET, KIT, FLT3, TIE2, TRKB, AXL | 2012          | HCC, RCC, TC             |                      |                      |                      |
| Lenvatinib⁸⁴       | VEGFR1-3, FGFR, PDGFRα, KIT, RET | 2015          | Endometrial cancer, HCC, RCC, TC |                      |                      |                      |
| Pazopanib⁸⁵        | VEGFR1-3, KIT, PDGFRβ            | 2009          | RCC, Soft tissue sarcoma, TC |                      |                      |                      |
| Regorafenib⁸⁶      | VEGFR2/3, RET, KIT, PDFGR, BRAF  | 2012          | CRC, GIST, HCC, osteosarcoma |                      |                      |                      |
| Sorafenib⁸⁷        | VEGFR1-3, FLT3, PDGFRα/β, BCR-ABL1, FGFR | 2005          | Angiosarcoma, GIST, HCC, RCC, TC |                      |                      |                      |
| Sunitinib⁸⁸        | VEGFR1-3, FLT3, PDGFRα/β, BCR-ABL1, FGFR, Src | 2006          | GIST, PC, RCC             |                      |                      |                      |
| Tivozanib⁸⁹        | VEGF                             | 2021          | RCC                      | HTN                  |                      |                      |
| Other              |                                 |               |                          |                      |                      |                      |
| Belumosudil⁹⁰      | ROCK1, ROCK2                     | 2021          | GVHD                     | HTN                  |                      |                      |
| Fostamatinib⁹¹     | Syk                              | 2018          | ITP                      | HTN                  |                      |                      |

(Continues)
the pulmonary artery smooth muscle cells leading to vasodilation. Inhibition of the TASK-1 channels causes a depolarization of the smooth muscle cell leading to an increase in intracellular calcium via L-type voltage-gated calcium channels. This Src kinase inhibition could explain why imatinib might have a therapeutic effect in PAH, whereas dasatinib has been shown to cause PAH. (Figure 1) The PKI pathway continues to be explored therapeutically in PAH. One such example is with a novel inhaled PDGFR kinase inhibitor, seralutinib (Gb002), which in animal studies improved hemodynamics, NT-proBNP, and pulmonary vascular remodeling. Imatinib is also being explored in aerosolized forms. In theory, both of these agents will be expected to have less adverse events due to the localized delivery system and are currently being studied in

### TABLE 1 (Continued)

| Drug       | Receptors | Year approved | Uses                          | Group 1 risk factors | Group 2 risk factors | Group 3 risk factors |
|------------|-----------|---------------|-------------------------------|----------------------|----------------------|----------------------|
| Netarsudi  | Rho       | 2017          | Glaucoma                      |                      |                      |                      |
| Pexidartinib | CSF1, KIT, FLT3 | 2019     | Tenosynovial giant cell tumor | HTN                  |                      |                      |

**Abbreviations:** ALK, anaplastic lymphoma kinase; ALL, acute lymphoblastic leukemia; ASM, aggressive systemic mastocytosis; AXL, AXL oncogene; BC, breast cancer; BCR-ABL1, breakpoint cluster region-Abelson leukemia gene; BTK, Bruton’s tyrosine kinase; Braf, b-Raf oncogene; CEL, chronic eosinophilic leukemia; CDK, cyclin-dependent kinase; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; CRC, colorectal cancer; CSF1, colony-stimulating factor 1; DPSP, dermatofibrosarcoma protuberans; ECD, Erdheim-Chester disease; ErbB1/EGFR, epidermal growth factor receptor; ErbB2/HER2, human epidermal growth factor receptor 2; ErbB4/HER4, human epidermal growth factor receptor 4; FGFR, fibroblast growth factor receptor; FL, follicular lymphoma; FLT3, Fms-like tyrosine kinase 3; GIST, gastrointestinal stromal tumor; GVHD, graft versus host disease; HTN, hypertension; HFrEF, heart failure with reduced left ventricular ejection fraction; HES, hypereosinophilic syndrome; HA, hemolytic anemia; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; ITP, immune thrombocytopenia; IAK, Janus kinase; KIT, c-KIT oncogene; LAM, lymphangioleiomyomatosis; MCL, mantle cell lymphoma; MEK1/MAPK, mitogen-activated protein kinase kinase 1; MET/HGHR, hepatocyte growth factor receptor; MDS/MPD, myelodysplastic/myeloproliferative disorder; mTOR, mechanistic target of rapamycin; MZL, marginal zone lymphoma; NF1, neurofibromatosis type 1; NSCLC, non-small cell lung cancer; NT, neuroendocrine tumor; NTRK, neurotrophic receptor kinase; PAH, pulmonary arterial hypertension; PC, pancreatic cancer; PDGFR, platelet-derived growth factor receptor; PI3K-δ, phosphoinositide-3 kinase delta; PsA, Psoriatic arthritis; PV, polycythemia vera; RA, rheumatoid arthritis; RET, rearranged during transfection oncogene; Rh, Rhodopsin oncogene; ROCK, rho-associated, coiled-coil containing protein kinase; ROS1, C-ros oncogene 1; SLL, small lymphocytic lymphoma; Src, Src oncogene; STAMP, specifically targeting the ABL myristoyl pocket; Syk, Spleen-associated tyrosine kinase; TC, thyroid cancer; TE, thromboembolic event; TIE2, tyrosine kinase with Ig and EGF homology domains 2; TRK, tropomyosin receptor kinase; TS, tuberous sclerosis; UC, urothelial carcinoma; VEGFR, vascular endothelial growth factor receptor; WMG, Waldenström macroglobulinemia.

*Denotes known Type I inhibitor.  

**FIGURE 1** Mechanism of dasatinib-induced PAH. PAH, pulmonary arterial hypertension; ROS, reactive oxygen species; sE-selectin, soluble E-selectin; sICAM-1, soluble intercellular adhesion molecule; sVCAM-1, soluble vascular cell adhesion molecule.
clinical trials. In addition, oral imatinib remains under consideration as a potential PAH therapy.

Bosutinib, ponatinib, and nilotinib have less evidence with only rare case reports or limited of worsening pre-existing PAH, some of which only found echocardiographic evidence of PH. A recent pharmacovigilance study supports the Src family kinase postulation indicating that the c-Src, c-yes, Lck, and Lyn genes (members of the Src kinase family) are implicated in a disproportionately high incidence of PAH within the BCR-ABL1 inhibitors that are dose-related.

Anaplastic lymphoma kinase (ALK)-inhibitors, brigatinib, ceritinib, crizotinib, lorlatinib are used in the treatment of non-small cell lung cancer and have also been implicated in the development of PAH, with lorlatinib being the most implicated. The causative mechanism of action of these agents in the development of pulmonary vascular disease is unknown although typical histologic findings of PAH are seen, namely intimal hyperplasia, medial hypertrophy, and angioproliferative plexiform lesions, plus sporadic peripheral arterial thrombosis in situ.

The difficulty of predicting the long-term effects of PKIs on pulmonary vascular toxicity may result in a failure to prevent adverse effects and may delay the use of life-saving PAH therapies. For example, several guidelines recommend regular monitoring for the development of cardiotoxicity with some chemotherapy drugs, but specific recommendations are not provided for pulmonary vascular toxicity. Within our program, the practice is to perform echocardiograms every 3 months on patients receiving PKIs. If patients have evidence of PH on echocardiogram, accompanied by rapid symptom onset or progression, they would be referred for urgent right heart catheterization (RHC) to evaluate for the presence of PAH. If PH is uncovered on echocardiogram and the patients are minimally symptomatic and display marginally progressive echocardiogram features, then these patients can be followed with serial echocardiograms to observe the development of early right ventricular failure or signs of early clinical decompensation. Patients are referred for RHC only if there is significant progression of disease or if there are questions regarding optimum oncological therapy. If patients have significant risk factors for Group 2 PH, then they are followed serially rather than referred for invasive hemodynamics, unless there is concern for the concomitant development of Group 1 PAH.

Early discontinuation of the culprit agent can lead to a reversal of the pulmonary vascular disease. Rapid clinical and hemodynamic improvements were noted within 4 months of discontinuation of dasatinib, although a more recent study found that PAH persisted in approximately one-third of patients.

The management of PKI-induced PAH varies depending on the long-term complications of the therapy. Pharmacotherapy for persistent PAH revolves around standard PAH-therapy protocols. In the absence of high-risk features, or the development of right heart failure, our practice is to start upfront dual combination therapy. This involves an endothelin receptor antagonist (ERA) combined with a phosphodiesterase 5 inhibitor (PDE5i). Within our program, we combine ambrisentan or macitentan with either sildenafil or tadalafil, once PAH is confirmed on RHC. If there is a concern regarding acute right heart failure, this requires initiation of parenteral prostacyclins. However, with the exception of dasatinib, most cases of PKI-induced PAH are low- to intermediate-risk, and cessation of the PKI combined with long-term use of dual combination therapy is sufficient to prevent or postpone clinical demise.

PH DUE TO LEFT HEART DISEASE

Group 2 PH is the most prevalent form of PH accounting for upwards of 68.5% of PH patients, encompassing heart failure with reduced ejection fraction (HFrEF), heart failure with preserved (HFpEF), and valvular heart disease. The association between PKI therapy and heart failure appears to be indirect and mediated by increase in left ventricular end-diastolic pressure from elevated blood pressure. Alternatively, a direct effect may be the antiangiogenesis in capillarization of the myocardium itself, which impairs the preservation of functional status. Of note, while bilateral pleural effusions may be associated with heart failure, certain PKIs, for example, dasatinib, have been shown to increase the permeability of endothelial cells leading to effusions independent of a heart failure diagnosis.

Hypertension remains the commonest modifiable risk factor for the development of heart failure and almost every group of PKIs is associated with the development of hypertension and heart failure (Table 1). The pathophysiology contrasts with Group 1 and these cases can be distinguished by an increased left ventricular end-diastolic pressure. In this setting, if there is concern for PH secondary to PKI therapies, an RHC is warranted to determine the optimum treatment strategy and a need to distinguish between Group 1 and Group 2 PH, although, combined pre- and post-capillary PH secondary to dasatinib has been reported. Select PKIs,
specifically VEGF inhibitors, such as sorafenib and sunitinib, and Bruton’s tyrosine kinase inhibitors (BTKs), such as ibrutinib and acalabrutinib, are known to increase hypertension and atrial fibrillation. VEGF inhibitor-induced hypertension is a multifactorial mechanism. First, vasodilation occurs from VEGFR2 activation of phosphoinositide-3 kinase (PI3K) increasing downstream endothelial NO synthase phosphorylation and thus NO release.\(^{130}\) VEGFR2 activation also leads to increases PGI2 via activation of mitogen-activated protein kinases (MAPKs).\(^{131}\) Antagonism of these pathways in addition to glomerular damage from increased ET-1 production lead to the on-target toxicity from VEGF inhibitors.\(^{130}\) Decreases in microvascular and myocardial capillary density could lead to increases in vascular resistance and endothelial dysfunction.\(^{131}\) Additionally, some PKIs, such as ponatinib, have off-target VEGF inhibition not related to their therapeutic target. The most effective blood pressuring lowering agent is unknown, but both calcium channel blockers and angiotensin-converting enzyme (ACE) inhibitors appear effective.\(^{132}\)

The BTK inhibitors, acalabrutinib, ibrutinib, and zanubrutinib. may increase the risk of HFpEF by elevating blood pressure, inducing atrial fibrillation, and other off-target effects involving C-terminal Src kinase inhibition causing left atrial inflammation, fibrosis, and enlargement.\(^{133}\) Ibrutinib can cause hypertension within a few months of treatment and is associated with upwards of 75% of patients developing or worsening hypertension.\(^{134}\) Atrial fibrillation has a 16% occurrence rate with ibrutinib.\(^{135}\) Of note, more selective BTK inhibitors, acalabrutinib and zanubrutinib, do not carry the same risk of hypertension or atrial fibrillation to the extent of ibrutinib.

More recently, PKIs have been related to the development of valvular dysfunction. One culprit is the BCR-ABL1 inhibitor, nilotinib which has been associated with rapid progression of aortic valve stenosis. The mechanism behind this is theorized to be related to an increase in BMP2 related valvular interstitial cell calcification.\(^{136}\)

VEGF inhibiting PKIs have also been associated with the development of HFrEF. While the incidence is difficult to estimate, two meta-analyses described a higher risk of developing cardiomyopathy among people treated with VEGF inhibitors (odds ratio: 1.35 (95% confidence interval [CI]: 1.06–1.70) and 2.53 (95% CI: 1.79–3.57)).\(^{137,138}\) Sunitinib treats renal cell carcinoma and targets the VEGF receptors to produce antiproliferative and antiangiogenesis effects (RR: 2.96; 95% CI: 1.93–4.53) and has the highest risk of causing cardiomyopathy (prevalence of ~10%).\(^{137,138}\) Due to its wide selectivity, sunitinib also inhibits PDGFR-α/β, FMS-like tyrosine kinase-3 (FLT3), fibroblast growth factor receptors (FGFR), and multiple other receptors. While the exact mechanism of left ventricle (LV) dysfunction from sunitinib is unknown and is likely multifactorial; it could be a sequel of hypertension associated with VEGF inhibition (on-target) or due to inhibition of FGFR, which are important to LV functionality (off-target).\(^{139−141}\)

Fortunately, in patients who develop LV dysfunction from sunitinib, withdrawal of the medication appears to lead to improvement in LV dysfunction and heart failure symptoms.\(^{141}\)

Management of PKI-induced Group 2 PH includes screening left ventricular ejection fraction (LVEF) and blood pressure along with management of any baseline cardiovascular risk factors.\(^{142}\) For hypertension, ACE inhibitors and angiotensin receptor blockers (ARBs) are the preferred agents, as calcium channel blockers (specifically verapamil and diltiazem) can cause CYP3A4 interactions. A recent publication compiled the recommendations from European and American guidelines for the management of cardiotoxicities in cancer patients.\(^{142}\) Laboratory screening of biomarkers such as brain-natriuretic peptide (BNP)/NT-proBNP and troponin can also be considered. After initial evaluation, follow-up screening can be considered every 3 months during treatment or sooner if symptoms develop. In patients who experience a decrease in LVEF, a referral for a cardio-oncological evaluation and the initiation of ACE inhibitors and β-blockers are recommended (Figure 2), in addition to other guideline-directed medical therapy for cardiomyopathy as needed. If the patient is symptomatic and/or the LVEF is <40%, discontinuation of the therapy is recommended. If the patient is asymptomatic with an LVEF ≥ 40%, continuation of therapy can be considered with close monitoring. Consultation from an expert cardio-oncology center is recommended to navigate the complex treatment environment associated with Group 2 PH and cancer.\(^{143}\)

**PH DUE TO CHRONIC LUNG DISEASE AND HYPOXIA**

PH due to chronic lung disease and hypoxia is the second most common form of PH.\(^{105,144}\) PKIs are implicated in interstitial lung disease (ILD) and idiopathic pulmonary fibrosis (IPF), purely in the parenchymal space.\(^{145}\) ILD was first noted as a complication of gefitinib, an epidermal growth factor receptor (EGFR) inhibitor in
the early 2000s.\textsuperscript{146} ILD developed typically within days of initiation, but could occur up to 3 months after starting therapy. The prevalence of ILD with gefitinib was <1%, but with a high mortality of up to 35%.\textsuperscript{48,145} In IPF, a PH has been reported in 8%–15% of patients upon initial diagnosis with increasing prevalence up to >60% in advanced and end-stage disease.\textsuperscript{147–149} Additionally, a high prevalence of PH in ILD was noted in an echocardiographic study.\textsuperscript{150} In this manner, it is reasonable to assume that PKI-induced ILD could be associated with PH, no least through hypoxic pulmonary vasoconstriction alone.

Cyclin-dependent kinase (CDK)-4/6 inhibitors, ErbB inhibitors, and FLT3 inhibitors are the commonest causes of PKI-induced ILD (Table 1), but can also occur with the use of ALK inhibitors, such as brigatinib.\textsuperscript{151} Contrary to most forms of ILD, PKI-induced ILD has nonspecific changes with the parenchymal tissue on high-resolution computed tomography (CT) that is difficult to diagnose.\textsuperscript{152} Nonspecific areas with ground-glass opacities without loss of lung volume are the most common pattern accounting for 50% of PKI-induced ILD. The toxicity does not appear to be dose related, and the mechanism remains largely unknown.\textsuperscript{153} Recent bioinformatics studies indicate that the four genes with the highest association with ILD development include EGFR, tumor growth factor β-1 (TGFβ1), insulin-like growth factor 1 (IGF1), and CC ligand chemokine 2 (CCL2).\textsuperscript{154} Further investigation into the exact mechanism of these pathways may elucidate the on- and off-target toxicities of PKIs that lead to ILD.

For patients on PKIs that develop pulmonary symptoms or suspected ILD, the PKI should be held.\textsuperscript{145} Furthermore, switching to another PKI appears to be safe with no recurrence of ILD, indicating a lack of cross-reactivity between agents.\textsuperscript{145} Also, as symptoms improve, one can consider rechallenging the person with the PKI after discussing the risk versus benefit of treatment.\textsuperscript{155} The use of high-dose corticosteroids has been used in other forms of drug-induced ILD (i.e., taxanes and gemcitabine) and may be useful in PKI-induced ILD.\textsuperscript{146} Otherwise, there is conflicting evidence in using PAH-specific therapies Group 3 PH in this population.\textsuperscript{144} Riociguat and ambrisentan have been shown to be harmful in patients with idiopathic interstitial pneumonia as noted in the RISE-IIP and ARTEMIS-IIP studies.\textsuperscript{156,157} There is evidence that inhaled treprostinil (INCREASE trial) improves symptoms in ILD-associated PH.\textsuperscript{158} Although not specifically studied in PKI-induced ILD, inhaled treprostinil could be considered in this group, especially if withdrawal of the offending agent does not result in clinical improvement.
CONCLUSION

Targeted PKI therapies for malignancies have revolutionized treatment for many patients with cancer. However, increasing cardiotoxicities are being identified as both on- and off-target effects, including effects on the pulmonary vasculature. Cardiac screening and cardio-oncology programs have typically focused on the effects of cancer therapeutics on the left ventricle and systemic vasculature. Growing awareness of PH and the risks associated with PKIs and other novel targeted therapies is important in this population, as is understanding which agents are implicated in the different forms of PH (Figure 3). This review provides a roadmap for the management of PH in the setting of PKI therapy and highlights the ongoing challenges that these patients face.

FUTURE DIRECTIONS

The ongoing identification of PKI toxicities plays a crucial role in determining treatment options for patients who develop PH while undergoing cancer treatment. Advancements in bioinformatics and genomics research, in conjunction with large electronic databases, improve detection of PKI toxicities, as it pertains to the pulmonary vasculature. Such advances may also help identify PKIs with therapeutic potential.

AUTHOR CONTRIBUTIONS

Joshua A. Jacobs contributed by designing the concept, writing, correcting the manuscript, and creating tables. John J. Ryan contributed by designing the concept, writing, correcting the manuscript, and creating figures. Eiman Jahangir contributed by writing and correcting the manuscript. All authors have reviewed and acknowledged the accuracy of this review paper.

ACKNOWLEDGMENTS

Dr. John J. Ryan and his research team would like to thank The Reagan Corporation, The Gordon Family, and The Cushman Family for their support and funding from R01HL093081.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.
ETHICS STATEMENT
The ethics statement is not available.

ORCID
Joshua A. Jacobs https://orcid.org/0000-0002-9621-9060

REFERENCES
1. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53(1):1801913.
2. Galile N, McLaughlin VV, Rubin LJ, Simonneau G. An overview of the 6th World Symposium on Pulmonary Hypertension. Eur Respir J. 2019;53(1):1802148.
3. Henson KE, Reulen RC, Winter DL, Bright CJ, Fidler MM, Frohisher C, Guha C, Wong KF, Kelly J, Edgar AB, McCabe MG, Whelan J, Cutter DJ, Darby SC, Hawkins MM. Cardiac mortality among 20000 five-year survivors of cancer diagnosed at 15 to 39 years of age: the teenage and young adult cancer survivor study. Circulation. 2016;134(20):1519–31.
4. Moslehi JJ, Deininger M. Tyrosine kinase inhibitor-associated cardiovascular toxicity in chronic myeloid leukemia. J Clin Oncol. 2015;33(35):4210–8.
5. National Center for Biotechnology Information. 2021. Available from: https://pubchem.ncbi.nlm.nih.gov/compound.
6. Alecensa (alectinib) [prescribing information]. South San Francisco, CA: Genentech USA Inc; 2021.
7. Tabbò F, D’Aveni A, Tota D, Pignataro D, Bironzo P, Carnio S, Cappia S, Cortese G, Righi L, Novello S. Pulmonary arterial hypertension in ALK receptor tyrosine kinase-positive lung cancer patient: adverse event or disease spread? J Thorac Oncol. 2019;14(2):e38–40.
8. Alunbrig (brigatinib) [prescribing information]. Cambridge, MA: Aria Pharmaceuticals Inc; 2021.
9. Khouri C, Hlavaty A, Roustit M, Cracowski JL, Chaumais MC, Humbert M, Montani D. Investigating the association between ALK receptor tyrosine kinase inhibitors and pulmonary arterial hypertension: a disproportionality analysis from the WHO pharmacovigilance database. Eur Respir J. 2021;58.
10. Xalkori (crizotinib) [prescribing information]. New York, NY: Pfizer Labs; 2021.
11. Awada A, Grobs Y, Wu WH, Habbout K, Romanet C, Breuil-Bonnet S, Tremblay E, Martineau S, Paulin R, Bonnet S, Provencher S, Potus F, Boucherat O. R-Crizotinib predisposes to and exacerbates pulmonary arterial hypertension in animal models. Eur Respir J. 2021;57(5):2003271.
12. Xalkori (crizotinib) [package insert]. New York City, NY: Pfizer Inc; 2021.
13. Lorbrerna (lorlatinib) [prescribing information]. New York, NY: Pfizer Labs; 2021.
14. Calquence (acalabrutinib) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2019.
15. Imbruvica (ibrutinib) [prescribing information]. South San Francisco, CA: Pharmacyclics LLC; 2021.
16. Brukinsa (zanubrutinib) [prescribing information]. San Mateo, CA: BeiGene USA Inc; 2021.
17. Scemblix (asciminib) tablets [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2021.
18. Yo S, Thenganatt J, Lipton J, Granton J. Incident pulmonary arterial hypertension associated with Bosutinib. Pulm Circ. 2020;10(3):2045894020936913.
19. Hickey PM, Thompson AA, Charalampopoulos A, Elliot CA, Hamilton N, Kiely DG, Lawrie A, Sabroe I, Condliffe R. Bosutinib therapy resulting in severe deterioration of pre-existing pulmonary arterial hypertension. Eur Respir J. 2016;48(5):1514–6.
20. Riou M, Seferian A, Savale L, Chaumais MC, Guignabert C, Canuet M, Magro P, Rea D, Sitbon O, Jais X, Humbert M, Montani D. Deterioration of pulmonary hypertension and pleural effusion with bosutinib following dasatinib lung toxicity. Eur Respir J. 2016;48(5):1517–9.
21. Bosulif (bosutinib) [prescribing information]. New York, NY: Pfizer; 2021.
22. Montani D, Bergot E, Günther S, Savale L, Bergeron A, Bourdin A, Bouvaist H, Canuet M, Pison C, Macro M, Poubeau P, Girerd B, Natali D, Guignabert C, Perros F, O’Callaghan DS, Jais X, Tubert-Bitter P, Zalcman G, Sitbon O, Simonneau G, Humbert M. Pulmonary arterial hypertension in patients treated by bosutinib. Circulation. 2012;125(17):2128–37.
23. Guignabert C, Phan C, Seferian A, Huertas A, Tu L, Thuillet R, Sattler C, Le Hiress M, Tamura Y, Jutant EM, Chaumais MC, Bouchet S, Manéglier B, Molimard M, Rousselot P, Sitbon O, Simonneau G, Montani D, Humbert M. Dasatinib induces lung vascular toxicity and predisposes to pulmonary hypertension. J Clin Invest. 2016;126(9):3207–18.
24. Morishita S, Hagihara M, Itabashi M, Ishii Y, Yamamoto W, Numata A, Motohashi K, Matsumoto K, Fujisawa S, Nakajima H. Development of pulmonary arterial hypertension during oral dasatinib therapy for chronic myelogenous leukemia. Rinsho Ketsueki. 2016;57(8):999–1003.
25. Weatherald J, Chaumais MC, Savale L, Jais X, Seferian A, Canuet M, Bouvaist H, Magro P, Bergeron A, Guignabert C, Sitbon O, Simonneau G, Humbert M, Montani D. Long-term outcomes of dasatinib-induced pulmonary arterial hypertension: a population-based study. Eur Respir J. 2017;50(1):1700217.
26. Sprycel (dasatinib) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; 2021.
27. Gleevec (imatinib) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals; 2020.
28. Zakrzewski D, Seferynska I, Warzocha K, Hryniewiecki T. Elevation of pulmonary artery pressure as a complication of dasatinib therapy resulting in severe deterioration of pre-existing pulmonary arterial hypertension. Eur Respir J. 2016;134(20):1519–6.
29. Cornet L, Khouri C, Roustit M, Guignabert C, Chaumais MC, Humbert M, Revol B, Despas F, Montani D, Cracowski JL. Pulmonary arterial hypertension associated with protein kinase inhibitors: a pharmacovigilance-pharmacodynamic study. Eur Respir J. 2019;55(5):1802472.
30. Tasigna (nilotinib) [prescribing information]. East Hanover, NJ: Novartis; 2021.
31. Quilot FM, Georges M, Favrot N, Beltramo G, Foignet C, Grandvuillemien A, Montani D, Bonniaud P, Camus P. Pulmonary hypertension associated with ponatinib therapy. Eur Respir J. 2016;47(2):676–9.

32. Iclusig (ponatinib) [prescribing information]. Lexington, MA: Takeda Pharmaceuticals America Inc; 2021.

33. Spina E, Renna R, Lanterna LA, Colleoni ML, Andreone V. Progressive thrombosis of cervical and intracranial arteries related to Ponatinib treatment for Chronic Myeloid Leukemia. J Stroke Cerebrovasc Dis. 2020;29(9):105085.

34. Mektoni (binimetinib) [prescribing information]. Boulder, CO: Array BioPharma Inc; 2020.

35. Cotellic (cobimetinib) [prescribing information]. South San Francisco, CA: Genentech USA, Inc; 2018.

36. Tafinlar (dabrafenib) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2021.

37. Braftovi (encorafenib) [prescribing information]. Boulder, CO: Array BioPharma Inc; 2020.

38. Koselugo (selumetinib) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2021.

39. Mekinist (trametinib) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2021.

40. Zelboraf (vemurafenib) [prescribing information]. South San Francisco, CA: Genentech USA Inc; 2020.

41. erzenio (abemaciclib) [prescribing information]. Indianapolis, IN: Lilly USA, LLC; 2021.

42. Brance (palbociclib) [prescribing information]. New York, NY: Pfizer Labs; 2019.

43. Isqali (ribociclib) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2021.

44. Cosela (trilaciclib) [prescribing information]. Durham, NC: G1 Therapeutics Inc; 2021.

45. Gilotrif (afatinib) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals Inc; 2019.

46. Vizimpro (dacomitinib) [prescribing information]. New York, NY: Pfizer Labs; 2020.

47. Tarceva (erlotinib) [prescribing information]. South San Francisco, CA: Genentech USA Inc; 2016.

48. Cohen MH, Williams GA, Sridhara R, Chen G, McGuinn WD Jr, Morse D, Abraham S, Rahman A, Liang C, Lostritto R, Baird A, Pazdur R. United States Food and Drug Administration Drug Approval summary: Gefitinib (ZD1839; Iressa) tablets. Clin Cancer Res. 2004;10(4):1212–8.

49. Iressa (gefitinib) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2021.

50. Tykerb (lapatinib) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2021.

51. Exkivity (mocobertinib) [prescribing information]. Lexington, MA: Takeda Pharmaceuticals America Inc; 2021.

52. Nerlynx (neratinib) [prescribing information]. Los Angeles, CA: Puma Biotechnology Inc; 2021.

53. Tagrisso (osimertinib) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2020.

54. Tukysa (tucatinib) [prescribing information]. Bothell, WA: Seattle Genetics Inc; 2020.

55. Balversa (erdafitinib) [prescribing information]. Horsham, PA: Janssen Products, LP; 2020.

56. Truseltiq (infigratinib) [prescribing information]. Brisbane, CA: QED Therapeutics Inc; 2021.

57. Ofev (nintedanib) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals Inc; 2020.

58. Pemazyre (pemigatinib) [prescribing information]. Wilmington, DE: Incyte Corporation; 2021.

59. Xospata (gilteritinib) [prescribing information]. Northbrook, IL: Astellas Pharma US, Inc; 2019.

60. Rydapt (midostaurin) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2021.

61. Cibinqo (abrocitinib) [prescribing information]. New York, NY: Pfizer Labs; 2022.

62. Olumiant (baricitinib) [prescribing information]. Indianapolis, IN: Lilly USA LLC; 2021.

63. Inrebic (fedratinib) [prescribing information]. Summit, NJ: Celgene Corporation; 2021.

64. Jakafi (ruxolitinib) [prescribing information]. Wilmington, DE: Incyte Corporation; 2021.

65. Opzelura (ruxolitinib) [prescribing information]. Wilmington, DE: Incyte Corporation; 2021.

66. Xeljanz/Xeljanz XR (tofacitinib) [prescribing information]. New York, NY: Pfizer Inc; 2021.

67. Tabrecta (capmatinib) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2020.

68. Tepmetko (tepotinib) [prescribing information]. Rockland, MA: EMD Serono Inc; 2021.

69. Zortress (everolimus) [prescribing information]. East Hanover, NJ: Novartis Pharmaceutical Corporation; 2021.

70. Rapamune (sirolimus) [prescribing information]. Philadelphia, PA: Wyeth Pharmaceuticals LLC; 2021.

71. Torisel (temsirolimus) [prescribing information]. Philadelphia, PA: Pfizer Inc; 2018.

72. Ayvakit (avapritinib) [prescribing information]. Cambridge, MA: Blueprint Medicines Corporation; 2021.

73. Qinlock (ripretinib) [prescribing information]. Waltham, MA: Deciphera Pharmaceuticals LLC; 2021.

74. Aliqopa (copanlisib) [prescribing information]. Whippany, NJ: Bayer Healthcare Pharmaceuticals Inc; 2021.

75. Zydelig (idelalisib) [prescribing information]. Foster City, CA: Gilead Sciences Inc; 2020.

76. Ukoniq (umbralisib) [prescribing information]. Edison, NJ: TG Therapeutics Inc; 2021.

77. Gavreto (pralsetinib) [prescribing information]. South San Francisco, CA: Genentech Inc; 2021.

78. Retevmo (selpercatinib) [prescribing information]. Indianapolis, IN: Lilly USA LLC; 2021.

79. Caprelsa (vandetanib) [prescribing information]. Cambridge, MA: Genzyme Corporation; 2021.

80. Rozlytrek (entrectinib) [prescribing information]. South San Francisco, CA: Genentech USA Inc; 2021.

81. Vitracki (larotrectinib) [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; 2021.

82. Inlyta (axitinib) [prescribing information]. New York, NY: Pfizer Inc; 2020.

83. Cabometyx (cabozantinib) tablet [prescribing information]. Alameda, CA: Exelixis Inc; 2021.

84. Lenvima (lenvatinib) [prescribing information]. Woodcliff Lake, NJ: Eisai Inc; 2021.

85. Votrient ( pazopanib) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2021.
86. Stivarga (regorafenib) [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; 2020.
87. Nexavar (sorafenib) [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals; 2020.
88. Sutent (sunitinib) [prescribing information]. New York, NY: Pfizer Labs; 2021.
89. Fotidiva (tivazanib) [prescribing information]. Boston, MA: AVEO Pharmaceuticals Inc; 2021.
90. Rezurock (belumosudil) [prescribing information]. Warrendale, PA: Kadmon Pharmaceuticals LLC; 2021.
91. Tavalisse ( fostamatinib) [prescribing information]. South San Francisco, CA: Rigel Pharmaceuticals, Inc; 2020.
92. Rhopressa (netarsudil) [prescribing information]. Irvine, CA: Aerie Pharmaceuticals; 2019.
93. Turalio (pexidartinib) [prescribing information]. Basking Ridge, NJ: Daiichi Sankyo Inc; 2021.
94. Zhao Z, Bourne PE. Overview of current type i/ii kinase inhibitors. In: Shapiro P, editor. Next generation kinase inhibitors: moving beyond the ATP binding/catalytic sites. Cham: Springer International Publishing; 2020. p. 13–28.
95. Wang Z, Cole PA. Catalytic mechanisms and regulation of protein kinases. Methods Enzymol. 2014;548:1–21.
96. Roskoski RJr. Properties of FDA-approved small molecule protein kinase inhibitors: A 2020 update. Pharmacol Res. 2020;152:104609.
97. Davis MI, Hunt JP, Herrgard S, Ciceri P, Wodicka LM, Pallares G, Hocker M, Treiber DK, Zarrinkar PP. Comprehensive analysis of kinase inhibitor selectivity. Nat Biotechnol. 2011;29(11):1046–51.
98. Ferguson FM, Gray NS. Kinase inhibitors: the road ahead. Nat Rev Drug Discov. 2018;17(5):353–77.
99. Chen MH, Kerkelä R, Force T. Mechanisms of cardiac dysfunction associated with tyrosine kinase inhibitor cancer therapeutics. Circulation. 2008;118(1):84–95.
100. Taichman DB, Ornelas J, Chung L, Klinger JR, Lewis S, Klinger JR, Elliott CG, Levine DJ, Bossone E, Duvall L, Fagan K, Frantsve-Hawley J, Kawut SM, Ryan JJ, Rosenzweig EB, Sederstrom N, Steen VD, Badesch DB. Therapy for pulmonary arterial hypertension in adults: update of the CHEST Guideline and Expert Panel Report. Chest. 2019;155(3):565–86.
101. Rosenzweig EB, Abman SH, Adatia I, Beghetti M, Bonnet D, Haworth S, Ivy DD, Berger R. Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. Eur Respir J. 2019;53(1):180916.
102. Strange G, Playford D, Stewart S, Deague JA, Nelson H, Kent A, Gabbay E. Pulmonary hypertension: prevalence and mortality in the Armadale echocardiography cohort. Heart. 2012;98(24):1805–11.
the Su5416 hypoxia rat model of pulmonary arterial hypertension (PAH). Circulation. 2019;140(Suppl 1):A11102.

116. https://clinicaltrials.gov/ct2/show/NCT05036135 clinicaltrials.gov: National Institute of Health U.S. National Library of Medicine. 2022. Available from: https://clinicaltrials.gov/ct2/show/NCT04456998

117. https://clinicaltrials.gov/ct2/show/NCT05036135 clinicaltrials.gov: National Institute of Health U.S. National Library of Medicine. 2022. Available from: https://clinicaltrials.gov/ct2/show/NCT01179737

118. clinicaltrials.gov: National Institute of Health U.S. National Library of Medicine. 2014. https://clinicaltrials.gov/ct2/show/NCT01179737

119. Lenihan DJ, Kowey PR. Overview and management of hypertension (PAH). Circulation. 2019;140(Suppl_1):A11102.

120. Manouchehri A, Kanu E, Mauro MJ, Aday AW, Lindner JR, De Marco T, Dabelea D, Wolpert C, Reguart N, Vachiéry JL, Tedford RJ, Rosenkranz S, Palazzini M, Lang I, Zile MR, Kass DA, Paulus WJ. Phenotype-specific treatment of heart failure with preserved ejection fraction: a multiorgan roadmap. Circulation. 2016;134(1):73–90.

121. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Aledort L, Andrade D, Angiolillo DJ, Bax JJ, Benetos A, Cheema K, Charron P, et al. ESC guidelines on the management of cardiovascular diseases in patients with cancer: the Task Force for the Management of Cardiovascular Diseases in Patients With Cancer of the European Society of Cardiology (ESC). Eur Heart J. 2019;40(25):2443–55.

122. Dickerson T, Wiczer T, Waller A, Philippon J, Porter K, Haddad D, Guha A, Rogers KA, Bhat S, Byrd JC, Woyach JA, Awan F, Addison D. Hypertension and incident cardiovascular events following ibritinib initiation. Blood. 2019;134(22):1919–28.

123. Totzeck M, Mincu RI, Mrotzek S, Schadendorf D, Rassaf T. Tyrosine kinase inhibitors in leukemia and lymphoma: a review. Leukemia. 2018;32(1):58–75.

124. Angiolillo DJ, Lancellotti P, Zamorano J, Vachiéry JL, Tedford RJ, Feld PA, et al. ESC guidelines on the management of cardiovascular diseases in patients with cancer: the Task Force for the Management of Cardiovascular Diseases in Patients With Cancer of the European Society of Cardiology (ESC). Eur Heart J. 2014;35(38):2768–801.

125. Dickerson T, Wiczer T, Waller A, Philippon J, Porter K, Haddad D, Guha A, Rogers KA, Bhat S, Byrd JC, Woyach JA, Awan F, Addison D. Hypertension and incident cardiovascular events following ibritinib initiation. Blood. 2019;134(22):1919–28.
140. Catino AB, Hubbard RA, Chirinos JA, Townsend R, Keefe S, Haas NB, Puzanov I, Fang JC, Agarwal N, Hyman D, Smith AM, Gordon M, Pappert T, Englefeld V, Narayan V, Ewer S, ElAmm C, Lenihan D, Ky B. Longitudinal assessment of vascular function with sunitinib in patients with metastatic renal cell carcinoma. Circ Heart Fail. 2018;11(3):e004408.

141. Chu TF, Rupnick MA, Kerkela R, Dallabrida SM, Catino AB, Hubbard RA, Chirinos JA, Townsend R, Keefe S, PULMONARY CIRCULATION.

142. Alexandre J, Cautela J, Ederhy S, Damaj GL, Salem JE, Alexandre J, Cautela J, Ederhy S, Damaj GL, Salem JE, Catino AB, Hubbard RA, Chirinos JA, Townsend R, Keefe S, PULMONARY CIRCULATION.

143. Raghu G, Nathan SD, Behr J, Brown KK, Egan JJ, Kawut SM, Shorr AF, Wainright JL, Cors CS, Lettieri CJ, Nathan SD. Idiopathic pulmonary fibrosis with mild restriction. Eur Respir J. 2019;53:1.

144. Nathan SD, Barbera JA, Gaine SP, Harari S, Martinez FJ, Collard HR, Cottin V, Hoeper MM, Waxman A, Restrepo A, Montani D. Pulmonary complications of Bcr-Abl tyrosine kinase inhibitors. Eur Respir J. 2020;56(4).

145. Nathan SD, Behr J, Collard HR, Cottin V, Hoeper MM, Martinez FJ, Corte TJ, Keogh AM, Leuchte H, Mogulkoc N, Ulrich S, Wuyts WA, Yao Z, Boaeng F, Wells AU. Riociguat for idiopathic interstitial pneumonia-associated pulmonary hypertension (RISE-IIP): a randomised, placebo-controlled phase 2b study. Lancet Respir Med. 2019;7(9):780–90.

146. Raghu G, Behr J, Brown KK, Egan JJ, Kawut SM, Flaherty KR, Martinez FJ, Nathan SD, Wells AU, Collard HR, Costabel U, Richeldi L, deAndrade J, Khalil N, Morrison LD, Lederer DJ, Shao L, Li X, Pedersen PS, Montgomery AB, Chien JW, O’Riordan TG, ARTEMIS-IPF I. Treatment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomized controlled trial. Ann Intern Med. 2013;158(9):641–9.

147. Waxman A, Restrepo-Jaramillo R, Thenappan T, Ravichandran A, Engel P, Bajwa A, Allen R, Feldman J, Argula R, Smith P, Rollins K, Deng C, Peterson L, Bell H, Tapson V, Nathan SD. Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. N Engl J Med. 2021;384(4):325–34.

148. Gujral DM, Lloyd G, Bhattacharyya S. Provision and clinical utility of cardio-oncology services for detection of cardiac toxicity in cancer patients. J Am Coll Cardiol. 2016;67(12):1499–500.

149. Beck EM, Hatton ND, Ryan JJ. Novel techniques for advancing our understanding of pulmonary arterial hypertension. Eur Respir J. 2019;53(5).

150. How to cite this article: Jacobs JA, Jahangir E, Ryan JJ. Differentiating pulmonary hypertension associated with protein kinase inhibitors. Pulmonary Circulation. 2022;12:e12075. https://doi.org/10.1002/pul2.12075.