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VIEWPOINTS

Call for Action: Invasive Fungal Infections Associated With Ibrutinib and Other Small Molecule Kinase Inhibitors Targeting Immune Signaling Pathways

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Opportunistic infections caused by *Pneumocystis jirovecii*, *Cryptococcus neoformans*, and ubiquitous airborne filamentous fungi have been recently reported in patients with hematological cancers historically considered at low risk for invasive fungal infections (IFIs), after receipt of the Bruton tyrosine kinase inhibitor ibrutinib. The spectrum and severity of IFIs often observed in these patients implies the presence of a complex immunodeficiency that may not be solely attributed to mere inhibition of Bruton tyrosine kinase. In view of the surge in development of small molecule kinase inhibitors for treatment of malignant and autoimmune diseases, it is possible that there would be an emergence of IFIs associated with the effects of these molecules on the immune system. Preclinical assessment of the immunosuppressive effects of kinase inhibitors and human studies aimed at improving patient risk stratification for development of IFIs could lead to prevention, earlier diagnosis, and better outcomes in affected patients.

Keywords. ibrutinib; small molecule tyrosine kinase inhibitors; invasive fungal infections; opportunistic infections.

SMALL MOLECULE KINASE INHIBITORS: A BREAKTHROUGH IN THE TREATMENT OF HEMATOLOGICAL CANCERS

To overcome the bottleneck of toxicity and the lack of a specific mechanistic target with conventional chemotherapeutic agents [1–3], major emphasis has been placed on the development of precision "design" compounds that inhibit the signaling pathways implicated in the pathobiology of malignant and autoimmune diseases [4, 5]. The sophisticated mechanism-based design of these compounds has led to unprecedented treatment success in a range of hematological cancers [4, 5].

The most successful story has been the accelerated approval of ibrutinib by the US Food and Drug Administration in 2013. Ibrutinib, an irreversible inhibitor of Bruton tyrosine kinase (BTK) [4, 6, 7], is considered a "game-changing drug" for the treatment of B-cell cancers, including mantle cell lymphoma, chronic lymphocytic leukemia, Waldenström macroglobulinemia, diffuse large B-cell lymphoma, and primary central nervous system (CNS) lymphoma, with durable responses reported even in patients with refractory disease [4, 6–12].

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EMERGENCE OF IBRUTINIB-RELATED IFIS

Since the introduction of ibrutinib, there have been increasing reports of opportunistic fungal infections caused by *Pneumocystis jirovecii*, *Cryptococcus neoformans*, and ubiquitous airborne filamentous fungi (*Aspergillus*, *Fusarium*, and *Mucorales*); these often present with atypical manifestations, including CNS aspergillosis, extrapulmonary *P. jirovecii*, and disseminated cryptococcosis, and are associated with substantially increased mortality rates (Table 1) [6, 7, 9–25]. Although there is little information regarding the incidence of invasive fungal infections (IFIs) in patients with chronic lymphoproliferative disorders, such infections are considered uncommon in patients who have not undergone hematopoietic stem cell transplantation [26]. In contrast, in some studies of ibrutinib-based treatment for chronic lymphocytic leukemia [15] and primary CNS lymphoma [12], *P. jirovecii* pneumonia (PJP) and invasive aspergillosis (IA) occurred in 5% and 39% of patients, respectively. However, the frequency of IFIs in all other studies on patients with hematological cancer treated with ibrutinib was relatively low, ranging from 0% to 11% (Table 2).

Pneumocystis jirovecii pneumonia and Cryptococcosis

It is of interest that these opportunistic infections were unanticipated on the basis of the phenotype observed in patients with X-linked agammaglobulinemia, who display a genetic deficiency of BTK [27]. In fact, the only reported case of opportunistic IFI in X-linked agammaglobulinemia children is a case of PJP [28]. Because *Pneumocystis* infections occur sporadically in patients

Table 1. Reported Cases of IFI During Ibrutinib Therapy (n = 41)[a]

Pathogen or Type of IFI	Time After Treatment	Site of infection	Type and Status of Underlying Cancer	Age, y/Sex	Concomitant Use of Corticosteroids/ Prior Treatment	Outcome	Reference
Cryptococcosis	NA	NA	MCL/PD	NA	NA/NA	NA	Wang et al [7]
Cryptococcus neoformans	1 mo	Lungs, blood	CLL/PR	68/M	No/chlorambucil and prednisone	Alive	Okamoto et al [22]
C. neoformans	1 mo	CNS, lungs	Lymphoplasmacytic lymphoma/PD	88/M	No/rituximab, benadmustine	Alive	Messina et al [19]
C. neoformans	3 wk	CNS, lungs, blood	CLL/PD	54/M	No/fludarabine, ritiximab, cyclophosphamide	Dead	Messina et al [19]
C. neoformans	2 mo	CNS, skin	WM/PD	74/F	No/fludarabine, ritiximab, cyclophosphamide, dexamethasone, and idelasilib	Dead	Baron et al [18]
PJP	NA	NA	MCL/PD	NA	NA/yes (NA)	NA	Wang et al [7]
PJP	1.9 mo	Lungs	CLL/SD	69/M	No/no (frontline)	Alive	Ahn et al [15]
PJP	23.6 mo	Lungs	CLL/SD	68/M	Yes[b]/no (frontline)	Alive	Ahn et al [15]
PJP	1.9 mo	Lungs	CLL/SD	72/M	No/no (frontline)	Alive	Ahn et al [15]
PJP	6 mo	Lungs	CLL/PD	78/M	No/yes (NA)	Alive	Ahn et al [15]
PJP[b]	11.6 mo	Lungs	CLL/SD	70/M	No/no (frontline)	Alive	Ahn et al [15]
Histoplasmosis	NA	NA	MCL/PD	NA	NA/NA	NA	Wang et al [7]
IA[c]	1 month	CNS	CLL/PD	NA	Yes/NA	Dead	Ruchlemer et al [13]
IA	2 mo	CNS	CLL/PD	NA	Yes/NA	Alive	Ruchlemer et al [13]
IA	2 mo	CNS	CLL/PD	NA	Yes/NA	Alive	Ruchlemer et al [13]
IA	6 wk	Lungs	CLL/PD	62/M	No/fludarabine and rituximab	Alive	Arthus et al [14]
IA	2 wk	CNS, lungs	PCNSL	76/F	Yes/no (frontline)	Dead	Lionakis et al [12]
IA	2 wk	CNS, lungs	PCNSL	65/M	Yes/no (frontline)	Dead	Lionakis et al [12]
IA	3 mo	CNS, lungs	PCNSL	87/F	No/no (frontline)	Dead	Lionakis et al [12]
IA[d]	4 mo	Lungs	PCNSL	60/M	Yes/no (frontline)	Alive	Lionakis et al [12]
IA[d]	2 mo	Lungs	PCNSL	53/M	No/no (frontline)	Alive	Lionakis et al [12]
IA[d]	[1 mo	Lungs	PCNSL	64/M	Yes/no (frontline)	Alive	Lionakis et al [12]
IA	2 wk	CNS, lungs	PCNSL	49/M	Yes/no (frontline)	Alive	Lionakis et al [12]
Aspergillus nidulans	3 wk	Sinusitis, CNS	CLL/PD	75/F	No/fludarabine, ritiximab, cyclophosphamide	Alive	Baron et al [18]
Extensive aspergillosis	2.1 mo	Lungs, brain	CLL/PD	76/NA	No/rituximab	Dead	Jain et al [6]
Mucormycosis, aspergillosis	7 mo	Lungs	CLL/PD	67/M	No/rituximab, fludarabine	Dead	Kreiniz et al [23]
Mucormycosis	NA	Skin	CLL/NA	NA	NA/no	Dead[c]	Figuera Castro et al [17]
Fusarium solani	1.5 mo	Disseminated	CLL/PD	46/M	No/anti-CD20 mAb and bendamustin	Alive	Chan et al [20]

Abbreviations: CLL, chronic lymphocytic leukemia; CNS, central nervous system; F, female; IA, invasive aspergillosis; IFI, invasive fungal infection; M, male; mAb, monoclonal antibody; MCL, mantle cell lymphoma; NA, not available; PCNSL, primary central nervous system lymphoma; PD, progressive disease; PJP, *Pneumocystis jirovecii* pneumonia; PR, partial response; SD, stable disease; WM, Waldenström macroglobulinemia.

[a]Five additional cases of IFIs in patients with LLC and MCL were reported at a single university cancer center during a 1-year study period, including 2 cases of IA and 1 case each of mucormycosis, PJP, and cryptococcosis, all occurring within 3 months of ibrutinib therapy (Protin et al [16]). Dimopoulos et al [9] reported 1 case of IA in a patient with WM; Byrd et al [10], 2 cases of pulmonary IA; Byrd et al [11], 1 case of cryptococcal infection in a patient with CLL; O'Brien et al [21], 1 case of PJP in a patient with CLL; Choquet et al [24], 2 cases of pulmonary IA in patients with PCNSL; and Grommes et al [25], 1 case of CNS IA in a patient with PCNSL. Information on infectious disease outcome and patient clinical characteristics was not available for these cases.

[b]The patient received an intermittent course of low-dose oral corticosteroids.

[c]Death due to unrelated causes.

[d]Possible IA.

with acquired or congenital defects in B-cell function, selective inhibition of BTK in B lymphocytes could partially explain the association between ibrutinib and PJP [27, 29]. In fact, recent evidence suggests that immunocompetent mice treated with a BTK inhibitor become susceptible to PJP [30]. Nonetheless, PJP is typically observed in patients with acquired CD4 T-cell immunodeficiency (human immunodeficiency virus [HIV]/AIDS), severe lymphopenia due to high doses of corticosteroids, idiopathic CD4 lymphopenia, severe combined immunodeficiency, X-linked recessive anhidrotic ectodermal dysplasia with immunodeficiency caused by NF-kappa-B essential modulator (NEMO) or IKBA deficiency, X-linked CD40L deficiency, or GATA2 deficiency, indicating that defective CD4 T-lymphocyte–macrophage crosstalk has an important role in the pathogenesis of PJP [27, 29].

Table 2. Frequency of Reported IFIs in Clinical Studies of Ibrutinib Treatment for Hematological Cancer

Type and Status of Cancer	Type of IFI (No. of Cases)	Frequency of IFI, %	Patients, No.	Median Follow-up, mo	Study Timing, Month/Year	Reference
Relapsed CLL	Cryptococcosis (1)	1.2	85	20.9	5/2010–2/2013	Byrd et al [11]
Relapsed CLL/SLL	IA (2)	0.5	391	9.4	6/2012–11/2013	Byrd et al [10]
Relapsed WM	IA (1)	3.2	31	18.1	8/2014–2/2015	Dimopoulos et al [9]
Relapsed MCL	Cryptococcosis (1), PJP (1), histoplasmosis (1)	2.7	111	26.7	2/2011–1/2014	Wang et al [7]
CLL	1 multifocal IA, 1 fungal pneumonia	1.6	127	13	7/2010–5/2014	Jain et al [6]
Relapsed/refractory DLBCL	None	0	80	11.5	5/2012–5/2013	Wilson et al [8]
Refractory CLL/SLL	PJP (1)	0.7	145	27.6	1/2013–6/2013	O'Brien et al [21]
Refractory PCNSL[a]	IA (7), PJP (1)	44	18	15.5	8/2014–3/2016	Lionakis et al 12]
Refractory PCNSL	IA (2)	11	18	NA	9/2015–8/2016	Choquet et al [24]
Refractory PCNSL	IA (1)	5	20	NA	NA	Grommes et al [25]

Abbreviations: CLL, chronic lymphocytic leukemia; CNS, central nervous system; DLBCL, diffuse large B cell lymphoma; IA, invasive aspergillosis; IFI, invasive fungal infection; MCL, mantle cell lymphoma; NA, not available; PCNSL, primary central nervous system lymphoma; PJP, *Pneumocystis jirovecii* pneumonia; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

[a]Of enrolled patients, 28% were previously untreated.

Similarly, although cryptococcosis has been reported in a broad range of patients with acquired immunodeficiency (eg, solid organ or stem cell transplant recipients, patients with hematological cancer, and patients receiving corticosteroids), debilitated patients with metabolic abnormalities (eg, cirrhosis), and isolated patients with no apparent acquired or genetic immune defects, this IFI has been classically associated with acquired CD4 T-cell immune defects in the setting of HIV/AIDS or idiopathic CD4 lymphopenia [27]. In addition, cryptococcosis develops in patients with X-linked CD40L deficiency or interleukin 12 receptor mutations and those with autoantibodies to interferon-γ and granulocyte macrophage colony-stimulating factor, revealing an important role for CD4 T-cell–macrophage cross-talk in the host's defense against this intracellular pathogen [27]. Notably, BTK is expressed in all bone marrow cell lineages, with the exception of T cells and plasma cells [31].

Therefore, given the importance of the T cell-macrophage axis in the pathogenesis of cryptococcosis/PJP, it is plausible that ibrutinib has off-target effects on other kinases that affect CD4 T-cell function. Alternatively, in view of the major role of macrophage activation defects in non-HIV cryptococcosis [32], a direct inhibitory effect of ibrutinib on BTK signaling in monocytes and macrophages could affect susceptibility to infection. In support of this hypothesis, BTK signaling regulates the development and a range of effector functions of myeloid cells, including chemotaxis, adhesion, transmigration, reactive oxygen species production, cytokine response, and inflammasome activation [33–37].

Invasive Mold Infections

There have been sporadic reports of invasive mold infections in patients receiving ibrutinib, either alone or in combination with other immune modulators, raising important questions about the interplay of events that underlie this observation. In particular, IFIs caused by molds, including *Aspergillus* spp., are typically observed in patients with severe and complex quantitative or qualitative innate immune defects; so far, they have not been associated with B- or T-cell acquired or congenital immunodeficiency [26, 38]. IA typically occurs in patients with hematological cancers and chemotherapy-related prolonged neutropenia or those receiving high-dose corticosteroids and other immunosuppressive regimens for graft-vs-host disease [38]. Indeed, mice with neutrophil or mononuclear phagocyte depletion, but not those with lymphocyte deficiency, are susceptible to IA [39].

In the setting of primary immunodeficiency, IA occurs almost exclusively in patients with genetic defects that affect effector mechanisms, numbers, or chemotaxis of phagocytes, including (1) patients with chronic granulomatous disease and genetic defects in NADPH oxidase-dependent reactive oxygen species production; (2) patients with autosomal-dominant mutations in the transcription factor *GATA2* (monoMAC syndrome) who display profound monocytopenia, B-cell and natural killer cell lymphocytopenia, decreased numbers of circulating and tissue-resident dendritic cells, and various neutrophil functional abnormalities; and (3) rarely, patients with severe congenital neutropenia and type I leukocyte adhesion deficiency [27, 38]. Importantly, in the congenital immunodeficiency setting, cases of extrapulmonary IA with CNS involvement that resemble ibrutinib-associated IA have been reported only in patients with a deficiency in caspase recruitment domain-containing protein 9 (CARD9), a key downstream signaling component of C-type lectin receptors that is critical for neutrophil recruitment and effector function [40, 41].

Several lines of evidence, including the variability in frequency of reported infections across different studies (Table 2), indicate that ibrutinib-associated IFIs result from a complex immunodeficiency that affects a broad range of immune cells

in the adaptive and innate immune systems. Therefore, disease-related factors, including type and status of underlying cancer, aging, and other comorbid conditions, seem to play a critical role in the ibrutinib-related risk for the development of IA and other IFIs. The "net state of immunosuppression" in such patients is differentially influenced by (1) environmental exposures to fungal conidia; (2) synergistic effects of ibrutinib with other immunosuppressive therapies, especially corticosteroids [42], as shown elsewhere with mucormycosis in patients with chronic granulomatous disease [43]; (3) BTK-independent immunogenetic factors associated with an increased risk of IA in some patients [44, 45]; (4) direct effects of acute pharmacological inhibition of BTK on macrophages and monocytes [12, 46, 47]; and (5) off-target effects of ibrutinib on other kinases [35, 48, 49], especially when the drug is given at higher doses [12], or theoretically excessive ibrutinib exposure resulting from drug-drug interactions or pharmacogenetic differences in ibrutinib metabolism.

For example, TLR-9/BTK signaling in murine macrophages regulates calcineurin-nuclear factor of activated T cells-mediated tumor necrosis factor production and neutrophil chemotaxis and partially accounts for the increased susceptibility to IA in solid organ transplant recipients receiving calcineurin inhibitors [48]. The increased risk of mold infections with pharmacological BTK inhibition is not evident in the context of the genetic deficiency of BTK in patients with X-linked agammaglobulinemia; this could be related to residual BTK activity on myeloid cells [31, 33–37] or the development of compensatory immune mechanisms over the course of long-term (congenital) immunodeficiency.

With regard to its potential off-target effects, ibrutinib binds covalently to several other homologous cysteine-containing kinases of the TEC family, including ITK, BMX, TXK, and TEC [49–51]. In fact, ibrutinib BTK-independent actions that are associated with off-target effects on ITK and other kinases of the TEC family result in the activity of this inhibitor in a wide range of cancers, including breast cancer and T-cell and acute myelogenous leukemia [52–54]. Furthermore, ibrutinib has a very broad kinome [55] and binds noncovalently to several other kinases that have pivotal roles in normal immune signaling and malignant B-cell signaling, including kinases of the Src family [52–54]. In fact, off-target binding to other kinases has been already implicated in noninfectious toxic effects, including cardiac arrhythmias (PI3K/Akt signaling) and bleeding [56–58], consistent with the important role of SRC family kinases on platelet activation. Specifically, platelet signaling through phospho-SRC/spleen tyrosine kinase (SYK) signaling downstream of C-type lectin-like receptor 2 (CLEC-2) receptor is required for stable platelet adhesion to lymphatic endothelial cells and is inhibited by ibrutinib [56]. Notably, platelets participate in immune responses against *Aspergillus fumigatus* [59].

PRECLINICAL EVALUATION OF THE INFECTIOUS RISK OF SMALL MOLECULE KINASE INHIBITORS: A CALL TO ACTION

We have been witnessing an unprecedented rate of development of compounds that target immune-signaling pathways in malignant and autoimmune diseases (Table 3 and Table 4) [60, 61]. In fact, some of these molecules target the essential pathways of antifungal innate immunity, including C-type lectin receptor signaling (Src and SYK inhibitors), reactive oxygen species production in phagocytes (NOX inhibitors), Janus kinase-signal tranducer and activator of transcription (JAK-STAT) signaling, interleukin 17 signaling, and other proinflammatory cytokine pathways (tumor necrosis factor and interleukin 6) with a prominent role in antifungal immunity [59, 60].

There is a paucity of preclinical data on the immunosuppressive potential of small molecule kinase inhibitors (SMKIs). Knockout mice have been bred with selective genetic defects on these pathways and molecular targets [3]. However, pathogenesis studies of the role of SMKIs in targeting immune signaling pathways in clinically relevant models of fungal diseases and cross-validation in knockout mice is needed; such findings would complement the information on the predisposition of patients with congenital immunodeficient to opportunistic IFIs in various components of the corresponding pathway. They would also help predict the excess risk for IFIs that are associated with the clinical use of compounds that block these pathways. As an example, increased susceptibility to PJP [30] and cryptococcosis [62] has been observed in mice with BTK deficiency. The authors of one of these studies study insightfully predicted that the use of BTK inhibitors would result in cryptococcosis in humans [62]. In addition, recent preclinical studies have confirmed the direct impact of BTK inhibition on susceptibility to IA [12].

Another interesting conclusion from the ibrutinib story is that the effects of SMKIs on the immune system and the associated risk for the development of IFIs cannot always be predicted on the basis of the drug target or the phenotype of the related congenital immunodeficiency in humans. This is probably related to a constellation of predisposing factors that are implicated in the pathogenesis of IFIs in cancer patients receiving SMKIs and are virtually impossible to predict (Box 1) [1–3, 44, 45, 60, 63–67].

Overall, in view of the relative rarity of IFIs in patients receiving SMKIs, it is likely that genetic predisposition has a critical role in the development of infection [45, 46]. Lately, significant progress has been made in characterizing the genetic defects that predispose patients to the development of IFIs. In addition, polymorphisms in immune-related genes may predispose patients to IFIs, even patients with severe acquired immunodeficiencies [44, 45].

Table 3. FDA-Approved SMKIs Associated With Severe Bacterial Infections and/or OIs[a]

Compound (Trade name; Manufacturer)	Mode of Action	Targets	Indication	Year of Approval	Comments
Sunitinib (Sutent; Pfizer)	Multiple TKIs	PDGFRα/β, VEGFR1/2/3, Kit, Flt3, CSF-1R, RET	RCC, GIST, PNET	2006	Postmarketing reports of severe bacterial infections (sepsis, UTI, SSTI, respiratory); no evidence of OI
Dasatinib (Sprycel; Bristol-Myers Squibb)	TKI	BCR-Abl, Src, Lck, Yes, Fyn, Kit, EphA2, PDGFRβ	Ph^+ CML, ALL	2006	**Bacterial infections, including sepsis, pneumonia, several cases of PJP, possible fungal pneumonia, candidemia, and CMV reactivation**
Pazopanib (Votrient; GlaxoSmithKline)	Multiple TKIs	VEGFR1/2/3, PDGFRα/β, FGFR1/3, Kit, Lck, Fms, Itk	RCC, soft-tissue sarcomas	2009	**Warnings for serious bacterial infections; no evidence of OI**
Ruxolitinib (Jakafil; Incyte)	TKI	JAK1/2	Myelofibrosis, PV	2011	**Warning box: serious bacterial (UTI), mycobacterial, fungal, viral (VZV, PML) infections**
Tofacitinib (Xeljanz; Pfizer)	TKI	JAK 1/3	Rheumatoid arthritis	2012	**Warning box: serious infections, including significant risk for OIs; significant risk for disseminated tuberculosis and IFIs, including cryptococcosis, PJP, *Candida* esophagitis; disseminated VZV; CMV**
Cabozantinib (Cometriq/ Cabometyx; Exelixis)	TKI	RET, Met, VEGFR1/2/3, Kit, TrkB, Flt3, Axl, Tie2	Metastatic medullary thyroid cancer, advanced RCC	2012, 2016	No evidence of OI; sepsis reported
Ponatinib (Iclusig; Ariad)	Multiple TKIs	BCR-Abl, BCR-Abl T315I, VEGFR, PDGFR, FGFR, EphR, Src family kinases, Kit, RET, Tie2, Flt3	Ph^+ CML or ALL	2012	No evidence of OI; occasional febrile neutropenia and sepsis
Dabrafenib (Tafinar; GSK)	Serine/threonine kinase inhibitor	B-Raf	Melanoma with *BRAF* mutations	2013	UTI, cellulitis; no evidence of OI
Ibrutinib (Imbruvica; Pharmacyclics and Johnson & Johnson)	TKI	Bruton kinase	MCL, CLL, WM	2013	**Reported SSTIs; no evidence of OI**b
Idelalisib (Zydelig; Gilead)	Lipid kinase inhibitor	PI3Kδ	Small lymphocytic lymphoma, NHL, CLL	2014	**Black-box warning for serious infections in 21% of patients receiving monotherapy, including CMV reactivation, PJP**

Abbreviations: ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; CMV, cytomegalovirus; FDA, Food and Drug Administration; FGFR, fibroblast growth factor; GIST, gastrointestinal stromal tumor; MCL, mantle cell lymphoma; NHL, non-Hodgkin lymphoma; OI, opportunistic infection; PDGFR, platelet-derived growth factor receptor; Ph^+, Philadelphia chromosome positive; PJP, *Pneumocystis jirovecii* pneumonia; PML, progressive multifocal leukoencephalopathy; PNET, progressive neuroendocrine tumors of pancreatic origin; PV, polycythemia vera; RCC, renal cell carcinoma; SMKIs, small molecular kinase inhibitors; SSTI, skin and soft-tissue infection; TKI, tyrosine kinase inhibitor; UTI, urinary tract infection; VEGFR, vascular endothelial growth factor receptor; VZV, varicella zoster virus; WM, Waldenström macroglobulinemia.

[a]Major infectious complications of SMKIs associated with OI and black-box warnings are presented in bold. The full list of FDA-approved SMKIs and associated infectious episodes is presented in Table 4. Temsirolimus (Torsiel; Wyeth, 2007) and everolimus (Afinitor; Novartis, 2009) are 2 recently approved inhibitors of mechanistic target of rapamycin (mTOR) serine/threonine kinase approved for the treatment of RCC and human epidermal growth factor receptor 2–negative breast cancer, PNET, RCC, renal angiomyolipoma, and subependymal giant cell astrocytoma, respectively. Both mTOR inhibitors are immunosuppressive agents associated with an increased risk for severe infections and OIs, including VZV and herpes simplex virus reactivation, PJP, and invasive aspergillosis.

All FDA-approved SMKIs were retrieved from the FDA's official Web site (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/NDAandBLAApprovalReports/ucm373420.htm). Information on the pharmacological targets of SMKIs was obtained from the Web site of the Blue Ridge Institute for Medical Research (http://www.brimr.org/PKI/PKIs.htm).

On the other hand, an analysis of the infectious complications of Food and Drug Administration–approved SMKIs (Table 3) reveals that opportunistic infections, including IFIs, have been almost exclusively related to compounds that target immune signaling pathways, including BTK, JAK/STAT, and PI3K signaling [61]. Because clinical trials typically enroll carefully selected patients with fewer comorbid conditions and immunosuppressive conditions than average patients, the true incidence of IFIs associated with the introduction of a new SMKI is anticipated to be higher in clinical practice, especially in view of the expanding indications of these compounds in patients with severe underlying immunodeficiency [68, 69]. Therefore, an important research priority is increased surveillance for the early capturing and reporting of cases of IFIs in clinical studies of compounds that target the immune system. Importantly, the toxicity associated with IFIs must be clearly discriminated from sepsis episodes or other bacterial infections because the former diseases have different natural histories and prognoses.

Table 4. Full List of FDA-Approved SMKIs and Relative Risk for Development of IFIs[a]

Compound (Trade Name; Manufacturer)	Mode of Action	Targets	Indication	Year of Approval	Comments
Imatinib (Gleevec; Novartis)	TKI	BCR-abl, Kit, PDGFR	Ph^+ CML or ALL, aggressive systemic mastocytosis, CEL, DFSP, HES, GIST, MDS/MPD	2001	No evidence of OI
Gefitinib (Iressa; Astrazeneca)	TKI	EGFR	NSCLC	2003–2005, 2015	No evidence of infection
Erlotinib (Tarceva; OSI Pharmaceuticals)	TKI	EGFR	NSCLC, pancreatic cancer	2004	No evidence of OI; minimal risk for infection
Sorafenib (Nexavar; Bayer)	Dual TKIs	B/C-Raf, B-Raf (V600E), Kit, Flt3, RET, VEGFR1/2/3, PDGFRβ	Hepatocellular carcinoma, RCC, DTC	2005	No evidence of infection
Sunitinib (Sutent; Pfizer)	Multiple TKIs	PDGFRα/β, VEGFR1/2/3, Kit, Flt3, CSF-1R, RET	RCC, GIST, PNET	2006	Postmarketing reports of severe bacterial infections (sepsis, UTI, SSTI, respiratory); no evidence of OI
Dasatinib (Sprycel, Bristol-Myers Squibb)	TKI	BCR-Abl, Src, Lck, Yes, Fyn, Kit, EphA2, PDGFRβ	Ph^+ CML, ALL	2006	**Bacterial infections, including sepsis, pneumonia, several cases of PJP, possible fungal pneumonia, candidemia, and CMV reactivation**
Lapatinib (Tykerb; GlaxoSmithKline)	Dual TKIs	EGFR, ErbB2	Breast cancer	2007	No evidence of infection
Nilotinib (Tasigna; Novartis)	TKI	BCR-Abl, PDGFR, DDR1	Ph^+ CML	2007	URTIs, no evidence of OI
Pazopanib (Votrient; GlaxoSmithKline)	Multiple TKIs	VEGFR1/2/3, PDGFRα/β, FGFR1/3, Kit, Lck, Fms, Itk	RCC, soft-tissue sarcomas	2009	**Warnings for serious bacterial infections;** no evidence of OI
Vandetanib (Caprelsa; IPR Pharms)	Multiple TKIs	EGFRs, VEGFRs, RET, Brk, Tie2, EphRs, Src family kinases	Medullary thyroid cancer	2011	URTIs, no evidence of OI
Vemurafenib (Zelboraf; Hoffmann–La Roche)	TKI	A/B/C-Raf, B-Raf (V600E), SRMS, ACK1, MAP4K5, FGR	Melanoma with *BRAF*V600E mutation	2011	No evidence of infection
Crizotinib (Xalkori; Pfizer)	Multiple TKIs	ALK, c-Met (HGFR), ROS, MST1R	ALK-positive NSCLC (2011), ROS-1–positive NSCLC (2016)	2011, 2016	URTIs, no evidence of OI
Ruxolitinib (Jakafi; Incyte)	TKI	JAK1/2	Myelofibrosis, PV	2011	**Warning box: serious bacterial (UTI), mycobacterial, fungal, viral (VZV, PML) infections**
Axitinib (Inlyta; Pfizer)	TKI	VEGFR1/2/3, PDGFRβ	RCC	2012	No evidence of infection
Bosutinib (Bosulif; Wyeth)	TKI	BCR-Abl, Src, Lyn, Hck	CML	2012	Respiratory tract infections; no evidence of OI
Regorafenib (Stivarga; Bayer)	Multiple TKIs	VEGFR1/2/3, BCR-Abl, B-Raf, B-Raf (V600E), Kit, PDGFRα/β, RET, FGFR1/2, Tie2, Eph2A	CRC	2012	No evidence of OI
Tofacitinib (Xeljanz; Pfizer)	TKI	JAK 1/3	Rheumatoid arthritis	2012	**Warning box: serious infections, including significant risk for OIs; significant risk for disseminated tuberculosis and IFIs, including cryptococcosis, PJP,** ***Candida*** **esophagitis; disseminated VZV; CMV**
Cabozantinib (Cometriq/ Cabometyx; Exelixis)	TKI	RET, Met, VEGFR1/2/3, Kit, TrkB, Flt3, Axl, Tie2	Metastatic medullary thyroid cancer, advanced RCC	2012, 2016	No evidence of OI; sepsis reported

Table 4. Continued

Compound (Trade Name; Manufacturer)	Mode of Action	Targets	Indication	Year of Approval	Comments
Ponatinib (Iclusig; Ariad)	Multiple TKIs	BCR-Abl, BCR-Abl T315I, VEGFR, PDGFR, FGFR, EphR, Src family kinases, Kit, RET, Tie2, Flt3	Ph^+ CML or ALL	2012	No evidence of OI; occasional febrile neutropenia and sepsis
Trametinib (Mekinist; GlaxoSmithKline)	Serine/threonine kinase inhibitor	MEK1/2	Melanoma	2013	No evidence of OI; secondary skin infections
Dabrafenib (Tafinar; GlaxoSmithKline)	Serine/threonine kinase inhibitor	B-Raf	Melanoma with *BRAF* mutations	2013	UTI, cellulitis, no evidence of OI
Afatinib (Gilotrif; Boehringer Ingelheim)	TKI	EGFR, ErbB2, ErbB4	NSCLC, squamous NSCLC	2013, 2016	No evidence of OI
Ibrutinib (Imbruvica; Pharmacyclics and Johnson & Johnson)	TKI	Bruton kinase	MCL, CLL, WM	2013	**Reported SSTIs, no evidence of OI**[b]
Ceritinib (Zykadia; Novartis)	TKI	ALK, IGF-1R, InsR, ROS1	ALK-positive NSCLC after crizotinib resistance	2014	No evidence of infection
Idelalisib (Zydelig; Gilead)	Lipid kinase inhibitor	PI3Kδ	Small lymphocytic lymphoma, NHL, CLL	2014	**Black-box warning for serious infections in 21% of patients receiving monotherapy, including CMV reactivation, PJP**
Nintedanib (Ofev; Boehringer Ingelheim)	TKI	FGFR1/2/3, PDGFRα/β, VEGFR1/2/3, Flt3	Idiopathic pulmonary fibrosis	2014	No evidence of infection
Palbociclib (Ibrance; Park Davis)	Serine/threonine kinase	CDK 4/6	ER^+ and $HER2^-$ breast cancer as first-line (2015) and second-line (2016) therapy	2015	URTIs; less commonly, pneumonia, UTIs; no evidence of OI
Lenvatinib (Lenvima; Easai)	TKI	VEGFRs, FGFRs, PDGFR, Kit, RET	Thyroid cancer	2015	Dental/oral infections, UTIs, no evidence of OI
Cobimetinib (Cotellic; Genetech)	TKI	MEK	Melanoma with *BRAF* V600E/K mutations with vemurafenib	2015	No evidence of infection
Osimetinib (Tagrisso; AstraZeneca)	TKI	EGFRT790M	NSCLC	2015	Pneumonia; no evidence of other infections, including OI
Alectinib (Alecensa; Hoffman–La Roche)	TKI	ALK, RET	ALK-positive NSCLC	2015	No evidence of infection

Abbreviations: ALK, anaplastic lymphoma kinase; ALL, acute lymphoblastic leukemia; CDK, cyclin-dependent kinase; CEL, chronic eosinophilic leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; CMV, cytomegalovirus; CRC, colorectal cancer; DDR1, discoidin domain receptor family, member 1; DFSP, dermatofibrosarcoma protuberans; DTC, differentiated thyroid carcinoma; EGFR, epidermal growth factor receptor; ER, estrogen receptor; FDA, Food and Drug Administration; FGFR, fibroblast growth factor; GIST, gastrointestinal stromal tumor; HER, human epidermal growth factor receptor; HES, hypereosinophilic syndrome; HGFR, hepatocyte growth factor receptor; IFIs, invasive fungal infections; IGF, insulinlike growth factor; MCL, mantle cell lymphoma; MDS/MPD, myelodysplastic/myeloproliferative diseases; MEK, mitogen-activated protein kinase; MST1R, macrophage-stimulating protein receptor aka RON; NHL, non-Hodgkin lymphoma; NSCLC, non–small cell lung cancer; OI, opportunistic infection; PDGFR, platelet-derived growth factor receptor; Ph^+, Philadelphia chromosome positive; PI3K, phosphoinositide 3-kinase; PJP, *Pneumocystis jirovecii* pneumonia; PML, progressive multifocal leukoencephalopathy; PNET, progressive neuroendocrine tumors of pancreatic origin; PV, polycythemia vera; RCC, renal cell carcinoma; ROS, reactive oxygen species; SMKIs, small molecular kinase inhibitors; SSTI, skin and soft-tissue infection; TKI, tyrosine kinase inhibitor; URTIs, upper respiratory tract infections; UTI, urinary tract infection; VEGFR, vascular endothelial growth factor receptor; VZV, varicella zoster virus; WM, Waldenström macroglobulinemia.

[a]Major infectious complications of SMKIs associated with OI and black-box warnings are presented in bold. Temsirolimus (Torsiel; Wyeth, 2007) and everolimus (Afinitor; Novartis, 2009) are 2 recently approved inhibitors of mechanistic target of rapamycin (mTOR) serine/threonine kinase approved for the treatment of RCC and HER2-negative breast cancer, PNET, RCC, renal angiomyolipoma, and subependymal giant cell astrocytoma, respectively. Both mTOR inhibitors are immunosuppressive agents associated with an increased risk for severe infections and OI, including VZV and herpes simplex virus reactivation, PJP, and invasive aspergillosis.

All FDA-approved SMKIs were retrieved from the FDA's official Web site (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/NDAandBLAApprovalReports/ucm373420.htm). Information on the pharmacological targets of SMKIs was obtained from the Web site of the Blue Ridge Institute for Medical Research (http://www.brimr.org/PKI/PKIs.htm).

[b]Information obtained from the official Web site of FDA.

To that end, the diagnosis of an IFI in the context of a clinical trial should trigger a mandatory report, early notification of the medical community via a timely report in the public access health databases and implementation of preemptive diagnostic measures for IFIs.

With a more standardized approach for capturing IFIs and immunogenetic and immunophenotyping strategies that allow for the accurate assessment of infection risk in individual patients, we can provide personalized approaches to prevent opportunistic fungal diseases associated with SMKIs. We hope that the lessons being learned from ibrutinib will pave the way for new strategies to prevent IFIs in these patients and will increase our insight into the nuances of the immunopathogenesis of human fungal diseases.

Box 1. Potentially Predisposing Factors Associated With an Increased Risk of IFIs in Patients Receiving SMKIs

Factor	Comments
Immunodeficiency related to status and type of underlying cancer	Certain cancers (eg, B-cell CLL) induce a broad spectrum of immune defects that worsen during progression of the underlying disease [63]; anecdotal observations suggest that disease remission has a positive effect on the infectious complications associated with treatment with SMKIs, whereas clinical studies of frontline ibrutinib-based therapy have not revealed any associations between remission and major infectious complications [64]
Patient-specific environmental exposure	Complex epidemiological factors that are associated with climatic variables, travel, occupation, nosocomial exposures, and previous lung colonization with molds (eg, *Aspergillus*) or other fungi (eg, PJP) have an effect on the fungal inoculum's effect on individual patients [1, 3]
Broad inhibitory effects of SMKIs on the immune system	In contrast to patients with primary immunodeficiency, who may have cell-specific residual activity of the affected gene [47], pharmacological inhibition of the corresponding signaling pathway typically affects a broader range of immune cells that could result in a more severe immunosuppressive phenotype
Acute-onset effects of SMKIs on the immune system	Immune restoration mechanisms with a protective role against infectious insults are less likely to operate in the acute setting of pharmacologically induced immunodeficiency than in the long-term course of congenital immunodeficiency
Potential off-target effects of SMKIs	The off-target effects of kinase inhibitors depend on the structure, dosage, type of action (covalent binding vs noncompetitive inhibition of the target), and possibly other host-related factors that are difficult to assess (eg, PK/PD properties, metabolism, drug-drug interactions, and synergistic effects with other immunosuppressive medications) and could result in broad immunosuppressive effects
Genetic predisposition to IFI	Certain polymorphisms in innate immunity genes are associated with an increased risk for the development of IFI in hematopoietic stem cell transplant recipients and patients with hematological cancer and severe underlying immunodeficiency [44, 45]
Immune defects related to previous infectious episodes	IFIs are increasingly observed in patients recovering from sepsis or following infections with certain immunosuppressive viruses (eg, influenza and CMV) [1–3]; the complex underlying mechanisms of sepsis-induced immunodeficiency in these patients are incompletely understood [65]
Immunosuppressive effects of other drugs	Corticosteroids and other immunosuppressive medications (eg, purine analogues) markedly increase the risk for the development of IFIs [1–3]; previous, concomitant, or sequential receipt of immunosuppressive therapies makes it challenging to assess the relative risk of IFI in patients treated with SMKIs
Pharmacogenomics and drug-drug interactions on compound metabolism	The clinical efficacy, development of resistance, and toxicity associated with SMKI treatment largely depend on the PK/PD parameters of these compounds [60]; genetic variation in drug-metabolizing enzymes or transporters involved in the absorption, metabolism, and elimination of these SMKIs are influenced by a constellation of genetic and nongenetic factors (eg, disease, drugs, comorbid conditions, and exposures) [66, 67]
Net state of immunodeficiency related to aging and underlying comorbid conditions	Aging, structural lung disease, iron overload, diabetes mellitus or other metabolic abnormalities, chronic inflammatory disease, and comorbid conditions affect systemic and local antifungal host defense mechanisms; collectively, all these factors profoundly affect the net state of immunodeficiency of individual patients and increase the colonization risk for certain fungi (eg, *Aspergillus*, and PJP) [3]
Uncharacterized pathogen-associated risk factors	Dissecting the complex pathogenetic mechanisms of IFIs in immunocompromised patients will require understanding the molecular interactions among fungal virulence attributes and (1) the microbiome, (2) other copathogens, (3) local and systemic host defense pathways, and (4) immunosuppression related to underlying diseases, medications, and incompletely characterized environmental factors

Abbreviations: CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; IFI, invasive fungal infection; PJP, *Pneumocystis jirovecii* pneumonia; PK/PD, pharmacokinetic/pharmacodynamic; SMKIs, small molecule kinase inhibitors.

Notes

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