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FUNGAL GENOMICS AND PATHOGENESIS (S SHOHAM, SECTION EDITOR)

Fungal Infections with Ibrutinib and Other Small-Molecule Kinase Inhibitors

Marissa A. Zarakas[1] · Jigar V. Desai[1] · Georgios Chamilos[2,3] · Michail S. Lionakis[1]

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Abstract

Purpose of Review Small-molecule kinase inhibitors (SMKIs) have revolutionized the management of malignant and autoimmune disorders. Emerging clinical reports point towards an increased risk for invasive fungal infections (IFIs) in patients treated with certain SMKIs. In this mini-review, we highlight representative examples of SMKIs that have been associated with or are expected to give rise to IFIs.

Recent Findings The clinical use of the Bruton's tyrosine kinase inhibitor ibrutinib as well as other FDA-approved SMKIs has been associated with IFIs. The fungal infection susceptibility associated with the clinical use of certain SMKIs underscores their detrimental effects on innate and adaptive antifungal immune responses.

Summary The unprecedented development and clinical use of SMKIs is expected to give rise to an expansion of iatrogenic immunosuppressive factors predisposing to IFIs (and other opportunistic infections). Beyond increased clinical surveillance, better understanding of the pathogenesis of SMKI-associated immune dysregulation should help in devising improved risk stratification and prophylaxis strategies in vulnerable patients.

Keywords Invasive fungal infections · Small-molecule kinase inhibitors · Ibrutinib · Aspergillosis · *Pneumocystis jirovecii* pneumonia · Cryptococcosis

Introduction

With ~5 million species, fungi constitute a large and diverse eukaryotic lineage consisting of species that range from the ecologically important saprotrophs that facilitate nutrient cycling to fungi responsible for large-scale loss of amphibians and bats (i.e., *Batrachochytrium dendrobatidis*, *Geomyces destructans*) [1, 2]. Humans have evolved to resist infections by most fungi; however, a small fraction of fungal pathogens such as the dermatophytes, the commensal yeast *Candida*, and environmental fungi such as the inhaled molds (primarily *Aspergillus*), and *Cryptococcus* species are common causes of infections in humans [3]. Infections of skin and nails by dermatophytes and of oral and genital mucosal surfaces by *Candida* species are the most common human fungal diseases [4], accounting for an estimated ~8.6 million outpatient visits, with an associated cost of ~$460 million per year in the USA alone [5, 6•]. Of greater clinical concern, life-threatening invasive infections by *Candida*, *Aspergillus*, *Cryptococcus*, and *Pneumocystis* carry mortality rates that exceed 50% despite administration of antifungal therapy, leading to > 1 million deaths worldwide per year [4].

Fungi did not emerge as major human pathogens until the late twentieth century [7], concurrently with the HIV/AIDS epidemic and major advances in modern medicine that has led to a significant expansion of patient populations with iatrogenic immunodeficiency [8]. With the introduction of broad-spectrum antibiotics for bacterial infections, myeloablative chemotherapy for malignancies, glucocorticoids and other

Marissa A. Zarakas and Jigar V. Desai contributed equally to this work.

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✉ Michail S. Lionakis
lionakism@mail.nih.gov

[1] Fungal Pathogenesis Section, Laboratory of Clinical Immunology and Microbiology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 9000 Rockville Pike, Bethesda, MD 20892, USA

[2] Department of Clinical Microbiology and Microbial Pathogenesis, School of Medicine, University of Crete, Heraklion, Greece

[3] Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology, 71300 Heraklion, Crete, Greece

immunomodulatory regimens for autoimmune diseases, and the progress in solid-organ transplantation (SOT) and hematopoietic stem cell transplantation (HSCT), modern medicine succeeded to change the natural history of many previously incurable diseases and extend the lives of millions of patients, yet at the price of compromising innate and/or adaptive immune functions [3].

More recently, the advent of precision medicine therapies with novel small molecules targeting a variety of signaling kinases has revolutionized the treatment of malignancies and inflammatory diseases [9••]. However, many of these signaling kinase inhibitors also target key signaling pathways involved in host protection against fungi (and other pathogens) [9••]. Indeed, clinical reports describing an increased incidence of fungal infections associated with the clinical use of small-molecule kinase inhibitors (SMKIs) are now emerging [9••, 10••, 11••, 12••]. In light of the unprecedented rate of development of these compounds and their use in patients already at-risk for development of opportunistic infections, it is anticipated that we will witness an expansion of iatrogenic risk factors associated with invasive fungal (and other opportunistic) infections and new populations of patients with iatrogenic immunodeficiency in the coming years. In this mini-review, we highlight a few characteristic examples of SMKIs that have been associated with or are expected to give rise to fungal disease. A detailed review of all SMKIs leading to fungal disease and of non-fungal opportunistic infections that arise with SMKI treatment is beyond the scope of this report. Table 1 outlines the spectrum of reported SMKI-associated invasive fungal infections (IFIs) in humans.

SMKIs as Novel Iatrogenic Risk Factors for IFIs

Fungi belonging to five genera (*Candida*, *Aspergillus*, *Cryptococcus*, *Pneumocystis*, *Mucorales*) are responsible for > 90% of IFIs in humans [4, 53]. The host risk factors associated with these infections vary greatly depending on the fungal species. As such, the presence of implanted medical devices, the use of central venous catheters, neutropenia, broad-spectrum antibiotic use, and intra-abdominal surgery are known predisposing factors for invasive candidiasis, underscoring the importance of myeloid phagocytes and intact mucosal barrier function in preventing this infection [54]. In addition, patients with neutropenia and/or corticosteroid use in the setting of hematological malignancies, SOT, or HSCT, and patients with neutrophil dysfunction-associated primary immunodeficiencies such as chronic granulomatous disease are at risk for aspergillosis and mucormycosis [53, 55–57]. In contrast to the critical role of neutrophils for the control of the aforementioned infections, quantitative and/or qualitative defects in $CD4^+$ T cells, such as with HIV infection, significantly enhance the risk for infections by *Cryptococcus* and *Pneumocystis jirovecii* [58–60]. Knowledge of these fungus-specific immune requirements for host defense is critical in understanding the pathogenesis and phenotypic expression of SMKI-associated IFIs in vulnerable patients.

Ibrutinib

An increasing number of clinical reports of IFIs have recently emerged with the use of inhibitors which target aberrantly active signaling pathways in patients with hematological malignancies or autoimmune diseases. A prominent example among these inhibitors is ibrutinib, a game-changing drug in the treatment of chronic lymphocytic leukemia (CLL). Beyond CLL, ibrutinib has also become a significant treatment modality for other B cell-targeted hematologic malignancies including mantle cell lymphoma, Waldenström macroglobulinemia, diffuse large B cell lymphoma, and primary central nervous system (CNS) lymphoma (PCNSL), as well as in HSCT recipients with graft-versus-host disease [9••, 61].

Ibrutinib is a covalent inhibitor of the Bruton's tyrosine kinase (BTK), which is critical for B cell receptor signaling and promotes B cell development and survival. In lymphomas, targeting BTK via ibrutinib leads to inhibition of pro-survival signals and drives elimination of malignant cells [62]. Its use, however, has been associated with an increased incidence of invasive infections by a broad range of opportunistic fungi such *Aspergillus*, *Fusarium*, *Mucorales*, *Cryptococcus*, and *Pneumocystis* [9••]. Strikingly, in an ibrutinib-based trial of patients with primary CNS lymphoma (PCNSL), 39% of treated patients developed invasive aspergillosis and 11% developed *Pneumocystis jirovecii* pneumonia (PCP) [12••]. In another clinical trial involving CLL patients, ibrutinib use led to PCP in 5% of them despite adequate CD4 counts (> 500/ul), with an estimated incidence of 2.05 cases per 100 patient years [63•]. Additional retrospective analyses at four different clinical centers have also shown occurrence of IFIs associated with ibrutinib use (Table 1) [10••, 11••, 13•, 15•]. In contrast, in other settings of ibrutinib use, there has not been a significant association with IFIs. In view of the lack of prospective epidemiological studies in large cohorts of different patient groups, the absolute risk of IFI associated with ibrutinib is difficult to quantify. Collectively, the available clinical data suggest that BTK may play a critical role in protection against various fungi, which becomes essential in the setting of additional (host or iatrogenic) immunocompromising factors; however, mechanistic details of BTK-dependent antifungal immunity remain less clear.

BTK is expressed on all the hematopoietic cell types except for T cells and plasma cells [64]. In the case of *Pneumocystis jirovecii*, as B cells have been shown to play an important role in protection during PCP via priming of anti-*Pneumocystis* T cell responses [65–67], a direct role of ibrutinib on inhibiting B cell-targeted BTK is plausible for the development of PCP.

Table 1 FDA-approved SMKIs and reported IFIs with their clinical use

Drug (trade name, manufacturer)	Molecular target(s)	Reported IFI(s)	Nature of study/indication	Reference(s)
Ibrutinib (Imbruvica, Pharmacyclics)	BTK	41 reports of IFIs IA ($n = 21$; *A. fumigatus* in 20, *A. nidulans* in 1); PCP ($n = 8$); cryptococcosis ($n = 7$), histoplasmosis ($n = 1$), mucormycosis ($n = 2$), mucormycosis concurrent with IA ($n = 1$), disseminated fusariosis ($n = 1$)	Review of IFI cases arising in ibrutinib-treated patients with CLL, MCL, PCNSL, and WM	Chamilos et al. [9••]
		33 cases of IFIs; IA ($n = 27$), disseminated cryptococcosis ($n = 4$), mucormycosis ($n = 1$), PCP ($n = 1$)	Retrospective analysis of patients with CLL, MCL, and WM (unknown denominator)	Ghez et al. [10••]
		17 cases of IFI; IA ($n = 12$) mucormycosis ($n = 2$), cryptococcosis ($n = 1$), blastomycosis ($n = 1$), and histoplasmosis ($n = 1$)	Retrospective analysis of 566 patients (417 CLL, 56 MCL, 46 indolent B cell malignancies, 35 DLBCL, 12 Richter's syndrome); 65 patients on prophylactic fluconazole	Rogers et al. [13•, 14]
		16 cases of IFIs; IA ($n = 8$), PCP ($n = 3$), concurrent IA and PCP ($n = 1$), pulmonary cryptococcosis ($n = 3$), candidemia ($n = 1$)	Retrospective analysis of 378 patients (165 CLL, 61 MCL, 52 DLBCL, and 34 WM)	Varughese et al. [11••]
		7 cases of IFIs; IA ($n = 5$)	Retrospective analysis of 200 patients (78 CLL, 30 DLBCL, 28 MCL, 19 WM, 15 marginal zone lymphoma, 7 T cell lymphoma, 2 PCNSL)	Barbosa et al. [15•]
		2 cases of cerebral cryptococcosis	MCL	Sun et al. [16]
		Pulmonary cryptococcosis	DLBCL	Swan et al. [17]
		Mucormycosis	CLL	Grossi et al. [18]
		IA	CLL	Nasir et al. [19]
		IA	CLL	Faisal et al. [20]
		Cranial aspergillosis caused by *Aspergillus felis*	CLL	Beresford et al. [21]
		IA	CLL	Stephens et al. [22](30642919)
		IA	Unclassifiable B cell lymphoma/leukemia	McCarter et al. [23]
		Concurrent IA and mucormycosis	CLL	Pouvaret et al. [24]
		Cryptococcosis	CLL treated with acalabrutinib	Wilson et al. [25]
Ruxolitinib (Jakafi, Incyte)	JAK1/2	Cryptococcosis	Myelofibrosis	Wysham et al. [26]
		PCP	Myelofibrosis	Lee et al. [27]
		Infection by *Talaromyces marneffei*	Myelofibrosis	Chan et al. [28]
		CNS cryptococcosis	Myelofibrosis	Chen et al. [29]
		Pulmonary cryptococcosis	Myelofibrosis	Hirano et al. [30]
		IA ($n = 2$) and esophageal/oral candidiasis ($n = 1$)	Retrospective study of 507 patients with myelofibrosis	Polverelli et al. [31]
		Cryptococcal pericarditis	Chronic myelomonocytic leukemia	Liu et al. [32]
		Aspergillus retinal necrosis	Myeloblastic leukemia and secondary myelodysplastic syndrome	Moruno-Rodriguez et al. [33]
		Cryptococcosis (9% of cases)	Retrospective analysis for infection burdens in patients with myelofibrosis	Dioverti et al. [34]
			Polycythemia vera	Prakash et al. [35]

Table 1 (continued)

Drug (trade name, manufacturer)	Molecular target(s)	Reported IFI(s)	Nature of study/indication	Reference(s)
		Disseminated histoplasmosis with concurrent CNS cryptococcosis		
		CNS cryptococcosis	Myelofibrosis	Chakrabarti et al. [36]
Baricitinib (Olumiant, Lilly)	JAK1/2	Box warning indicating a risk for developing IFIs	Rheumatoid arthritis	FDA label
		4/18 cases with fungal infections including oral candidiasis and skin fungal infections	interferonopathies	Sanchez et al. [37•]
Tofacitinib (Xeljanz, Pfizer)	JAK3	Warning of IFIs on FDA label	Rheumatoid arthritis/psoriatic arthritis/ulcerative colitis	FDA label
Sorafenib (Nexavar, Onyx)	VEGFR1/2/3, B-/C-Raf, mutant B-Raf, Kit, Flt3, RET, and PDGFRß	IA ($n = 2$)	Phase II study for recurrent and/or metastatic salivary gland carcinomas	Locati et al. [38]
		IA	Hepatocellular carcinoma	Bazas et al. [39]
		IA	Phase II trial for relapsed thyroid cancer	Kloos et al. [40]
		Disseminated *Talaromyces marneffei* infection	Relapsed AML	Chan et al. [28]
Cobimetinib (Cotellic, Genentech)	MEK1/2	*Candida* infections (2% incidence rate)	Melanoma with BRAF mutations together with vemurafenib	Product monograph
Fostamatinib (Tavalisse, Rigel)	Syk	Vaginal yeast infection	Phase 1/2 trial in patients with B cell non-Hodgkin lymphoma	Friedberg et al. [41]
Bosutinib (Bosulif, Pfizer)	BCR-Abl, Src, Lyn, and Hck	FDA label for chronic and advanced phase CML indicates reports of fungal pneumonia and pulmonary fungal mycoses with unspecified incidence of specific fungal pneumonia and pulmonary mycoses	CML	FDA label
Dasatinib (Sprycel, Bristol-Myers Squibb)	BCR-Abl, EGFR, Src, Lck, Yes, Fyn, Kit, EphA2, PDGFRβ	3 IFI cases;	Retrospective study of 985 patients with chronic myeloid leukemia in chronic phase	Al-Ameri et al. [42]
		PCP ($n = 2$) and 1 unspecified fungal infection		
		3/82 incidence of *Candida* infections and coccidioidomycosis ($n = 1$)	Phase 2 results of a Clinical trial NCT01460160	Clinical trial: NCT01460160
		PCP ($n = 2$)	Acute lymphoblastic leukemia (1 patient) and chronic myeloid leukemia (1 patient)	Chang et al. [43]
Everolimus (Afinitor, Novartis)	FKBP12/mTOR	FDA label indicates a predisposition of patients to IFIs such as aspergillosis, candidiasis and PCP	Breast cancer, HER2-negative; PNET; RCC; renal angio-myolipoma; subependymal giant cell astrocytoma	FDA label
Afatinib (Giotrif, Boehringer Ingelheim)	EGFR, ErbB2, ErbB4	1% fungal infection incidence	NSCLC	BI product monograph
Crizotinib (Xalkori, Pfizer)	ALK, MET (HGFR), ROS1, MST1R	Pulmonary cryptococcosis	Lung adenocarcinoma	Su et al. [44]
		IA (concurrent corticosteroids)	NSCLC	Deiana et al. [45]
Gilteritinib (Xospata, Astellas)	Flt3	11/252 (4%) cases of fungal pneumonia, respiratory fungal infections ($n = 2$), fungemia ($n = 1$), and fungal laryngitis ($n = 1$)	Phase 1/2 trial for 252 patients with AML	Perl et al. [46]
		FDA label indicates fungal pneumonia as an adverse reaction	Relapsed or refractory AML with FLT3 mutation	FDA label
Imatinib (Gleevec, Novartis)	BCR-Abl, Kit, and PDGFR	Mucormycosis	Ph + acute lymphoblastic leukemia	Crisan et al. [47]
		IA	Gastrointestinal stromal tumor	Nasir et al. [19]
		FDA label indicates occurrence of fungal infections with frequency of 0.01–0.1%	CML and ALL, Ph+; aggressive systemic masto-cytosis; CEL; DFSP; HES; GIST; MDS/MDP	FDA label

Table 1 (continued)

Drug (trade name, manufacturer)	Molecular target(s)	Reported IFI(s)	Nature of study/indication	Reference(s)
Idelalisib (Zydelig, Gilead)	PI3Kδ	PCP ($n = 2$), additional cases of fungal pneumonia ($n = 2$), fungal sinusitis ($n = 1$)	54 patients with relapsed/refractory CLL	Brown et al. [48]
Loratinib (Lorbrena, Pfizer)	ALK	FDA label describes risk of upper respiratory infections, including fungal infections	ALK + NSCLC	FDA label
Midostaurin (Rydapt, Novartis)	FLT3, PDGFR, VEGFR2, PKC	FDA label indicates 7% incidence of fungal infections including IA, fungal pneumonia, splenic fungal infection, and hepatic candidiasis	AML, mastocytosis, mast cell leukemia	FDA label
Nilotinib (Tasigna, Novartis)	BCR-Abl, PDGFR, DDR1	1 death due to fungal pneumonia	Trial of 91 patients with Ph + ALL	Kim et al. [49]
Ponatinib (Iclusig, Ariad)	BCR-Abl, BCR-Abl T315I, VEGFR, PDGFR, FGFR, EphR, Src family kinases, Kit, RET, Tie2, Flt3	1 death due to fungal pneumonia	Trial of 270 patients with chronic phase CML	Cortes et al. [50]
Regorafenib (Stivarga, Bayer)	VEGFR1/2/3, BCR-Abl, B-Raf, B-Raf (V600E), Kit, PDGFRα/β, RET, FGFR1/2, Tie2, and Eph2A	FDA label indicates mucocutaneous and systemic fungal infection incidence of 3.3%	CRC, HCC, GIST	FDA label
Sunitinib (Sutent, Pfizer)	PDGFRα/β, VEGFR1/2/3, Kit, FLT3, CSF-1R, Axl, and RET	IA	Renal carcinoma	Visvardis et al. [51]
		Case of existing aspergilloma progressing to necrotizing pulmonary aspergillosis	Renal carcinoma	Kim et al. [52]
Vandetanib (Caprelsa, AstraZeneca)	RET, EGFRs, VEGFRs, Brk, Tie2, EphRs, and Src family kinases	EMA label contains incidence of fungal infections as "common" (> 1/10 to < 1/100)	Medullary thyroid cancer	EMA product information document

SMKI, small-molecule kinase inhibitor; *IFI*, invasive fungal infection; *BTK*, Bruton's tyrosine kinase; *IA*, invasive aspergillosis; *PCP*; *Pneumocystis jirovecii* pneumonia; *CLL*, chronic lymphocytic leukemia; *MCL*, mantle cell lymphoma; *PCNSL*, primary central nervous system lymphoma; *WM*, Waldenström macroglobulinemia; *DLBCL*, diffuse large B cell lymphoma; *JAK*, Janus kinase; *VEGFR*, vascular endothelial growth factor receptor; *PDGFR*, platelet-derived growth factor receptor; *EGFR*, epidermal growth factor receptor; *AML*, acute myeloid leukemia; *NSCLC*, non-small-cell lung cancer; *MEK*, mitogen-activated protein kinase; *ALK*, anaplastic lymphoma kinase; *HGFR*, hepatocyte growth factor receptor; *ROS*, reactive oxygen species; *MST1R*, macrophage-stimulating protein receptor aka RON; *FKBP12*, FK506-binding protein; *mTOR*, mammalian target of rapamycin; *PNET*, progressive neuroendocrine tumors of pancreatic origin; *RCC*, renal cell carcinoma; *CEL*, chronic eosinophilic leukemia; *DFSP*, dermatofibrosarcoma protuberans; *HES*, hypereosinophilic syndrome; *GIST*, gastrointestinal stromal tumor; *MDS/MPD*, myelodysplastic/myeloproliferative diseases; *PI3K*, phosphoinositide 3-kinase; *PKC*, protein kinase C; *FGFR*, fibroblast growth factor; *CRC*, colorectal cancer; *HCC*, hepatocellular carcinoma

Moreover, considering the central role of $CD4^+$ T cells in protection against PCP, an off-target inhibition of T cell-targeted kinases such as ITK (interleukin-2-inducible T cell kinase) by ibrutinib is also possible in driving PCP susceptibility. Additionally, it is likely that BTK exerts functions on myeloid antigen-presenting cells such as dendritic cells (DCs) and macrophages for protective anti-*Pneumocystis* immunity, given the crucial role that DCs play in $CD4^+$ T cell priming and that macrophages play in efficient intracellular *Pneumocystis* clearance [68]. Therefore, further investigation is required to fully understand the immunopathogenesis behind PCP infection susceptibility in the context of BTK pharmacological inhibition.

Similar to PCP, $CD4^+$ T cells are also of central importance for orchestrating protection against cryptococcosis, as evident by the emergence of cryptococcal infections during the HIV/AIDS epidemic [69]. Cryptococcosis is also prevalent in patients in other acquired immunodeficiencies that affect T cell function such as in patients receiving SOT or HSCT, in hematological malignancies, or in patients on systemic corticosteroid therapy [70]. Studies using mouse models of subacute or chronic cryptococcal infections have also revealed the important roles of monocyte-derived DCs in $CD4^+$ T cell priming, their skewing towards a Th1-phenotype, and consequently the roles of Th1 cytokines in macrophage activation towards the M1 phenotype for effective fungal clearance [71–73]. Consistently, patients with mutations in IL12 or the IL12 receptor, in CD40L, or those carrying neutralizing autoantibodies against IFN-γ and granulocyte-macrophage colony-stimulating factor (GM-CSF) have also been reported to develop cryptococcosis [74], highlighting a critical role for the cross-talk between T cells and macrophages in sterilizing cryptococcal immunity. It is therefore possible that ibrutinib-associated development of cryptococcosis may arise from either off-target effects on BTK-related kinases expressed on T cells and/or a direct effect of ibrutinib on BTK signaling on myeloid phagocytes. Indeed, reduced phagocytosis by alveolar macrophages, decreased levels of anti-*Cryptococcus* IgM, and increased susceptibility to *Cryptococcus* infection has also been reported in studies using X-linked immunodeficient mice carrying a mutation in BTK [75]. Ultimately, it is apparent that host defense against *Cryptococcus* requires the intricate and synchronized interplay of both cell-mediated and humoral immunity, with both myeloid phagocytes as well as T cells and even B cells critical for clearance of the fungus [76]. In view of BTK's almost universal expression among immune cells and its major role in regulating development and multiple effector functions, direct inhibition with ibrutinib could indeed affect susceptibility to infection and more studies are needed to elucidate the cell type-specific effects on ibrutinib in inhibiting anticryptococcal host defense.

Unlike *Pneumocystis* and *Cryptococcus*, anti-*Aspergillus* host defense primarily relies on myeloid phagocytes [56, 77]. Instead, cells of the lymphoid lineage are dispensable for host protection as mice or patients lacking lymphoid cells are not susceptible to invasive aspergillosis [56, 78••]. Owing to the expression of BTK on myeloid cells, inhibition of BTK-dependent effector functions of myeloid cells by ibrutinib may compromise anti-*Aspergillus* defense. Indeed, we have demonstrated that myeloid phagocyte-specific conditional BTK knockout mice are susceptible to invasive pulmonary aspergillosis and phenocopy the susceptibility to the infection observed in global BTK-deficient mice (Desai and Zarakas et al., in preparation) [12••]. Furthermore, it has been shown that, in murine and human monocyte-derived macrophages, BTK functions downstream of Dectin-1 and TLR9 fungal sensing to promote NFAT/NFκB-dependent TNF production in the setting of ex vivo challenge with *A. fumigatus* [79••, 80•]. NFAT signaling in myeloid phagocytes also regulates pentraxin production and anti-*Aspergillus* host defense [81]. However, the precise myeloid cellular subsets and the molecular mechanisms responsible for BTK-dependent *Aspergillus* clearance in vivo remain unclear and are a subject of ongoing research investigation.

These collective data indicate a crucial role for BTK in antifungal defense; however, patients with X-linked agammaglobulinemia (XLA), who harbor mutations in BTK rarely develop fungal infections. In fact, only two cases of fungal infections have been reported in XLA patients thus far; one with PCP and one with invasive aspergillosis [82, 83]. These observations indicate that a constellation of predisposing factors, in addition to the acute pharmacological inhibition by ibrutinib per se, may impact the incidence of IFIs in ibrutinib-treated patients. Such factors include, but are not limited to, the underlying lymphoid malignancy and its status (active versus in remission), additional genetic predisposition via polymorphisms in immune-related genes, pharmacogenetic variation that may result in greater ibrutinib exposures, co-administration of other pharmacological agents and their impacts on the immune status, the age of the patient [84•], and the extent of fungal exposure including the inoculum and fungal strain. In addition, compensatory mechanisms may be operational in XLA patients to overcome long-term, early-onset BTK-dependent inhibition of antifungal immune effector mechanisms, as opposed to the acute pharmacological BTK inhibition conferred by ibrutinib. With the advent of second-generation BTK inhibitors that are expected to have greater specificity for BTK over other non-BTK kinases, it will be important to carefully define the incidence of IFIs relative to that of ibrutinib.

Ruxolitinib

Ruxolitinib, an inhibitor of Janus-associated kinases (JAK) 1 and 2, was initially approved by the FDA in 2011 for the treatment of myelofibrosis and was later approved for

polycythemia vera in 2014 [85]. The pathogenesis of myelofibrosis involves dysregulation of signaling through JAK1/2-signal transducer and activator of transcription (STAT) pathways, leading to reactive bone marrow fibrosis, splenomegaly, extramedullary hematopoiesis, and increased risk for leukemia progression and decreased survival [86–88]. Ruxolitinib-mediated JAK1/2 inhibition has shown marked and durable clinical benefits in terms of reductions in splenomegaly and disease-related symptoms [89–92].

In the initial randomized clinical trials, ruxolitinib treatment exerted hematological side effects, mainly dose-related anemia, thrombocytopenia, and neutropenia [90, 93], while data on infections were not initially systematically captured [89, 90, 94–96], with the exception of a signal for herpes zoster virus infections [94]. Since ruxolitinib came into the market, multiple case reports have surfaced detailing infectious complications caused by viruses and bacteria [34, 96–103]. As outlined in Table 1, reports of opportunistic fungal infections have also emerged with ruxolitinib (and other JAK/STAT inhibitor) use.

Given the prominent role of JAK/STAT signaling downstream of diverse cytokine receptors, increasing evidence suggests that ruxolitinib-dependent JAK1/2 inhibition exerts immunosuppressive effects [104], leading to enhanced susceptibility to infection. In the case of fungal infections, the importance of JAK-STAT signaling downstream of type I–III interferons and other cytokines in host immune defense is beginning to unravel. For example, in neutrophils, cell-intrinsic STAT1 activation via IFN-λ/IFNLR1 signaling leads to reactive oxygen species production for efficient *Aspergillus* clearance [78••]. Additionally, *C. neoformans*-dependent transcriptional activation of JAK/STAT signaling in monocytes has been reported [105]. Furthermore, given the central role of JAK-STAT signaling in T cell and macrophage physiology [106] and effector functions [107•], direct ruxolitinib-derived functional impairment of the T cell-macrophage cross-talk leading to cryptococcosis and PCP is likely. More research is required to elucidate the detrimental antifungal immune effects conferred by ruxolitinib and other JAK-STAT inhibitors leading to opportunistic (including fungal) infections. In addition, expanded use of JAK/STAT inhibitors in patients with additional immunosuppressive factors (e.g., transplant recipients) could result in higher number of IFIs.

Sorafenib

Sorafenib is an oral multi-kinase inhibitor of cell surface tyrosine kinase receptors and intracellular serine/threonine kinases in the RAS/mitogen-activated protein kinase (MAPK) cascade. Sorafenib was approved by the FDA for the treatment of advanced renal cell carcinoma in 2005, unresectable hepatocellular carcinoma in 2007, and metastatic differentiated thyroid cancer in 2013 [108–110]. By blocking the activity of Raf-1, BRAF and kinases in the RAS/ extracellular signal-regulated kinase (ERK), and mitogen-activated kinase/ERK (RAS/RAF/MEK/ERK) signaling pathway, sorafenib inhibits tumor proliferation and survival and induces tumor cell apoptosis [109–111]. In addition, sorafenib inhibits angiogenesis through vascular endothelial growth factor receptor (VEGFR) 1, 2, and 3; platelet-derived growth factor receptor β (PDGFR-β); and other tyrosine kinases [109–111]. Currently, multiple ongoing clinical trials are examining the therapeutic potential of sorafenib for a plethora of cancers (clinicaltrials.gov). Potential beneficial outcomes of sorafenib in the treatment of acute myelogenous leukemia [112, 113] and salivary tumors have also been reported [38].

Adverse events in sorafenib-treated patients are predominantly gastrointestinal, constitutional, or dermatologic in nature, including diarrhea, weight loss, and hand–foot skin reactions [109]. More recently, cases of sorafenib-induced acute interstitial pneumonia [114] and other cutaneous side effects were reported [115] [116]. As summarized in Table 1, IFIs have been associated with the use of sorafenib, including three cases with invasive aspergillosis [28, 38–40]. Notably, two cases appeared in the absence of concurrent immunosuppressive treatment with chemotherapy or corticosteroids within the last month prior to the fungal infection diagnosis, implicating sorafenib alone for the increased susceptibility of infection [28, 38]. Furthermore, sorafenib-treated patients were reported to develop mucocutaneous fungal infections caused by *Candida* and *Rhodotorula mucilaginosa* yeasts [117, 118]. In the context of acute myeloid leukemia treated with sorafenib, fungal lung nodules and fungal pneumonia have also been reported [112, 113].

Multiple immune modulating functions of sorafenib can potentially account for the increased risk for mucosal fungal disease and IFIs. The RAS associated with diabetes (RAD)/MAPK/ERK signaling pathway, a major target of sorafenib, is important for antifungal effector functions in phagocytes against fungal species [119, 120]. In addition, ERK signaling regulates killing of *Aspergillus* by macrophages independently of TLR signaling [119]. Moreover, by interfering with phosphoinositide 3-kinase (PI3), MAP kinases and NF-kB signaling, sorafenib inhibits DC function by inducing apoptosis, and by impairing antigen presentation, it results in decreased T cell responses, which may underlie the mucosal fungal susceptibility [121]. In addition, RAF-dependent activation of JAK/STAT signaling may also be inhibited by sorafenib [122], with potential negative effects on antifungal immunity, as mentioned above.

Fostamatinib

Fostamatinib is an oral spleen tyrosine kinase (Syk) inhibitor developed for the treatment of immune thrombocytopenic purpura (ITP), autoimmune hemolytic anemia (AHA), and

IgA nephropathy. It was recently approved by the FDA for the treatment of adult treatment-refractory ITP in 2018, as it was shown to inhibit platelet destruction and achieve durable clinical responses [123, 124]. Syk is a principal regulatory kinase that acts downstream of multiple fungal-sensing pattern recognition receptors of the C-type lectin receptor family [77]. Upon activation, Syk-dependent signaling engages the adaptor caspase recruitment domain family member 9 (CARD9), which assembles with B cell CLL/lymphoma 10 (BCL10) and mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1) to relay downstream antifungal responses, ultimately leading to the induction of ERK and NF-kB and the production of inflammatory mediators such as IL-6, IL-12, GM-CSF, TNFa, and IL-1β [77].

Patients with inherited CARD9 deficiency develop specific and severe susceptibility to fungal infections [125•]. Specifically, CARD9-deficient patients suffer from spontaneous fungal infections, predominantly localized to the oral mucosa, central nervous system (CNS), bone, and subcutaneous tissues, caused by *Candida*, *Aspergillus*, *Exophiala*, *Phialophora*, and other phaeohyphomycetes [125•]. The mechanisms of Syk-CARD9-dependent antifungal immunity are now being elucidated. In the CNS, CARD9-dependent signaling is necessary for protective neutrophil recruitment via mechanisms that relate to induction of protective factors within the CNS, not neutrophil-intrinsic survival or chemotaxis [126••]. We recently showed that the secreted fungal secreted toxin candidalysin acts on brain-resident microglia, in a CARD9-dependent manner to induce transcriptional activation and inflammasome-dependent production of IL-1β, which in turn drives microglial CXCL1 production to recruit protective $CXCR2^+$ neutrophils in the *Candida*-infected brain [127••]. Indeed, CARD9-deficient patients have absent CXCL1 in the *Candida*-infected cerebrospinal fluid and do not mobilize neutrophils in the fungal-infected CNS [126••]. Additional detrimental effects of CARD9 deficiency on neutrophil effector function include a selective defect in killing of unopsonized *Candida* yeast forms, which may also contribute to the patient fungal susceptibility, by compromising the function of the few neutrophils that traffic into the infected CNS [128].

CARD9-deficient patients were also reported to develop extrapulmonary aspergillosis, associated with a defect in neutrophil accumulation in the infected tissue [129•]. CARD9-dependent induction of IL-17 may underlie the susceptibility to mucocutaneous fungal disease [130]. Thus, owing to the central role of Syk-CARD9 signaling in antifungal host defense, careful surveillance of fostamatinib-treated patients for the development of fungal disease is warranted. So far, a case of vaginal yeast infection in a fostamatinib-treated woman was described [41]. There are currently 44 clinical trials of fostamatinib treatment registered in clinicaltrials.gov, including in the management of conditions that already predispose patients to fungal disease (e.g., leukemia, graft-versus-host disease). Besides the potential direct effects of fostamatinib in compromising antifungal immune responses, neutropenia can occur in a small proportion of fostamatinib-treated patients, further increasing the risk for fungal infections [124]. Data from the ongoing clinical trials and post-market surveillance will shed light on the degree by which fostamatinib treatment in humans may pose a risk of increased susceptibility to IFIs, as it would be predicted based on the inherited CARD9 deficiency.

Conclusions

A recent surge in the development and clinical use of SMKIs has undoubtedly changed the treatment paradigm of serious, often fatal, human diseases. Some of these molecules can also target critical immune surveillance pathways, creating a permissive environment for fungi (and other opportunistic pathogens) to cause disease. With the expanding indications and the unprecedented rate of development of these compounds, new populations of patients with predicted or unpredicted iatrogenic immunosuppression may develop, requiring increased clinical surveillance for opportunistic infections and timely reporting. Real-time epidemiological data and case-control studies to identify the true risk of individual SMKIs for IFIs in the real world, out of the setting of selected patients participating in phase II/III trials, are missing and are urgently needed. More research into the physiological antifungal effector signaling pathways and the detrimental effects that SMKIs have on the innate and adaptive immune system should allow for better risk stratification and prophylaxis of susceptible patients. Finally, there is an unmet need for development of functional immune assays that will allow for an estimate of the net state of immunodeficiency of the individual patient who is a candidate for or is receiving SMKI therapy.

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Compliance With Ethical Standards

Conflict of Interest Marissa Zarakas, Jigar Desai, Georgios Chamilos, and Michail Lionakis declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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