Ther Adv Infectious Dis
2021, Vol. 8: 1–15
DOI: 10.1177/2049936121989548

Risk of infection associated with targeted therapies for solid organ and hematological malignancies

Isabel Ruiz-Camps and Juan Aguilar-Company

***Abstract*:** Higher risks of infection are associated with some targeted drugs used to treat solid organ and hematological malignancies, and an individual patient's risk of infection is strongly influenced by underlying diseases and concomitant or prior treatments. This review focuses on risk levels and specific suggestions for management, analyzing groups of agents associated with a significant effect on the risk of infection. Due to limited clinical experience and ongoing advances in these therapies, recommendations may be revised in the near future. Bruton tyrosine kinase (BTK) inhibitors are associated with a higher rate of infections, including invasive fungal infection, especially in the first months of treatment and in patients with advanced, pretreated disease. Phosphatidylinositol 3-kinase (PI3K) inhibitors are associated with an increased risk of *Pneumocystis* pneumonia and cytomegalovirus (CMV) reactivation. Venetoclax is associated with cytopenias, respiratory infections, and fever and neutropenia. Janus kinase (JAK) inhibitors may predispose patients to opportunistic and fungal infections; need for prophylaxis should be assessed on an individual basis. Mammalian target of rapamycin (mTOR) inhibitors have been linked to a higher risk of general and opportunistic infections. Breakpoint cluster region-Abelson (BCR-ABL) inhibitors are associated with neutropenia, especially over the first months of treatment. Anti-CD20 agents may cause defects in the adaptative immune response, hypogammaglobulinemia, neutropenia, and hepatitis B reactivation. Alemtuzumab is associated with profound and long-lasting immunosuppression; screening is recommended for latent infections and prevention strategies against CMV, herpesvirus, and *Pneumocystis* infections. Checkpoint inhibitors (CIs) may cause immune-related adverse events for which prolonged treatment with corticosteroids is needed: prophylaxis against *Pneumocystis* is recommended.

Keywords: checkpoint inhibitors, everolimus, ibrutinib, imatinib, rituximab, venetoclax

Received: 15 September 2020; revised manuscript accepted: 26 December 2020.

Introduction

Oncology and hematology are among the most dynamic and innovative fields in medicine. The therapeutic landscape is constantly being reshaped as new agents, often using formerly unknown therapeutic targets or innovative mechanisms, gain approval, or as new indications are defined for existing agents. Nevertheless, the amount and quality of data obtained from infection reporting in clinical studies is often hard to interpret and implement in daily practice. Furthermore, post-marketing case reports of uncommon infections make it difficult to keep track of the precise impact of these drugs on the risk of infection.

This review aims to analyze, from an infectious disease perspective, the safety profile of oral and parenteral targeted drugs used to treat solid organ and hematological malignancies and to establish specific recommendations. Unlike classic cytotoxic chemotherapy, targeted therapies exert their anti-tumor effect by modifying one or more cellular pathways, which may also be present in normal healthy cells, including cells and components of

Correspondence to:
Juan Aguilar-Company
Infectious Diseases Department and Oncology Department, Vall d'Hebron University Hospital, Barcelona, Spain.
juanaguilarcompany@gmail.com

Isabel Ruiz-Camps
Infectious Diseases Department, Vall d'Hebron University Hospital, Barcelona, Spain

the immune system.[1] Therefore, susceptibility to infections may be affected in different ways. In addition, the risk of infection will also be influenced by underlying diseases and by prior and concomitant treatments. All new drugs are initially tested in clinical trials with selected populations and the inherent limitations on the reporting of infectious complications.[2] Consequently, new and unexpected infections may be reported only after approval, when a larger and more diverse population of patients receives the drug. Post-marketing studies may also contribute new information. In view of the limited data available thus far for many of these agents, clinical reviews, expert recommendations, and scientific society guidelines become a key source of information.[3–10]

The suggestions and recommendations provided herein may be revised with ongoing and future clinical observations. Increased awareness by clinicians and constant reporting are, as previously mentioned, fundamental to identifying infections related to the use of these agents.

In this review we focus only on the groups of drugs with more significant impact on the risk of infection. Table 1 provides a summary of approved agents, indications and brief recommendations. Table 2 provides a brief description of relevant reviews on the risk of infection associated with selected groups of agents.[11–24]

Materials and methods

A PubMed search was performed to identify studies on agents currently used to treat solid organ and hematological malignancies that reported infectious events. The search focused on systematic reviews, meta-analyses, clinical trials, guidelines and case reports, looking mainly at the agents considered most relevant for clinicians and selecting drugs exhibiting a greater impact on the risk of infection. The agents were selected based on data described in previous articles, as well as on our clinical expertise with infectious disease consultants. Each group of agents was described with detail on current indications, biological impact on the immune system, available clinical data, and suggestions for managing infectious complications.

Bruton tyrosine kinase inhibitors

Ibrutinib, acalabrutinib, and zanubrutinib are oral drugs that irreversibly inhibit Bruton tyrosine kinase (BTK), acting on the signaling pathway of the B-cell receptor (BCR). Stimulation of the trans-membrane BCR protein leads to activation of different tyrosine kinases, including BTK and phosphatidylinositol 3-kinase (PI3K), which in turn activate proliferation and survival signals of B lymphocytes. BTK inhibitors bind to BTK irreversibly, thereby inducing apoptosis in B-cell tumors. The drugs in this group are currently approved for the treatment of several lymphoproliferative disorders, including mantle cell lymphoma, chronic lymphocytic leukemia (CLL), Waldenström macroglobulinemia, and marginal zone lymphoma.[25] Ibrutinib, as the first-in-class drug, is currently the most widely used agent, and more data are available on its effects. Nevertheless, it is difficult to establish the extent to which the risk of infection in patients receiving ibrutinib is attributable to the drug because patients often have other factors associated with a higher risk of infection,[26] and the underlying disease itself may be associated with immune defects, as occurs with CLL.[27] The most relevant studies reporting infections associated with ibrutinib are summarized in Table 2. In a systematic review of ibrutinib clinical trials that included 48 trials and 2119 patients, infection of any grade was reported in 56% of patients treated with the drug; the respiratory tract was the site most commonly involved.[11] The frequency and severity of these infections have been shown to be greater in patients with refractory or relapsed lymphoproliferative disease,[10] in patients with at least three previous lines of antineoplastic treatment, and in patients with concomitant neutropenia.[28]

Fungal infections, although rarely reported in clinical trials, have also been associated with the use of ibrutinib in several observational studies;[13,28–32] the most common causative agent was *Aspergillus* spp., although non-*Aspergillus* infections have also been reported.[33] Inhibition of the BTK pathway in macrophages involved in the defence against fungi may play a role.[32,34] Fungal infections typically appear during the first 6 months of treatment, in patients who have received previous antineoplastic treatment, and in those receiving glucocorticoids.[6] However, they are rare when ibrutinib is used as first-line treatment. Invasive aspergillosis often presents with extrapulmonary dissemination, with 25–40% of patients with central nervous system involvement.[6] At present, antifungal prophylaxis is not

Table 1. List of drugs and targeted molecules.

Targeted molecule	Drugs	Currently approved indications	Prophylaxis and treatment suggestions
ALK	Crizotinib, ceritinib, alectinib, brigatinib, lorlatinib	ALK+, ROS1+ non-small cell lung cancer	No known increased risk of infection
BCL-2	Venetoclax	Chronic lymphocytic leukemia, acute myeloid leukemia	Prophylaxis for *Pneumocystis jirovecii* in patients receiving corticosteroids[8]
BRAF	Vemurafenib, dabrafenib, encorafenib	*BRAF*-mutated melanoma Dabrafenib, trametinib: *BRAF*-mutated thyroid cancer and non-small cell lung cancer	Associated with drug-induced pyrexia. No known increased risk of infection
Bruton tyrosine kinase	Ibrutinib, acalabrutinib, zanubrutinib	Mantle cell lymphoma, chronic lymphocytic leukemia, Waldenström macroglobulinemia, marginal zone lymphoma	Assess antifungal prophylaxis or screening for fungal infections if other risk factors. Prophylaxis for *Pneumocystis jirovecii* in patients receiving corticosteroids[8]
CCR4	Mogalizumab	Mycosis fungoides, Sézary syndrome	Hepatitis B virus reactivation screening and prophylaxis. Prophylaxis for *Pneumocystis jirovecii* in patients receiving corticosteroids[8]
CDK family	Palbociclib, ribociclib, abemaciclib	Estrogen receptor-positive breast cancer	Associated with higher risk of neutropenia. No known increased risk of infection
CD19	Blinatumomab	Acute lymphocytic leukemia	Hepatitis B virus reactivation screening and prophylaxis. Prophylaxis for *Pneumocystis jirovecii*[8]
CD20	Rituximab, obinotuzumab, ofatumumab	B-cell lymphoproliferative diseases	Hepatitis B virus reactivation screening and prophylaxis. Prophylaxis for *Pneumocystis jirovecii* in patients receiving R-CHOP every 14 days (optional) or with additional risk factors such as corticosteroids[8]
CD22	Inotozumab ozogamicin, moxetumomab pasudotox	B-cell acute lymphocytic leukemia, hairy cell leukemia	Hepatitis B virus reactivation screening and prophylaxis. Prophylaxis for *Pneumocystis jirovecii* in patients receiving corticosteroids[8]
CD30	Brentuximab vedotin	Hodgkin's lymphoma	Prophylaxis for *Pneumocystis jirovecii* in patients receiving corticosteroids[8]
CD33	Gentuzumab ozogamicin	CD33-positive acute myeloid leukemia	Hepatitis B virus reactivation screening and prophylaxis. Prophylaxis for *Pneumocystis jirovecii* in patients receiving corticosteroids[8]
CD38	Daratumumab	Multiple myeloma	Hepatitis B virus reactivation screening and prophylaxis. Prophylaxis for *Pneumocystis jirovecii* and varicella zoster infections in patients receiving corticosteroids or bortezomib[8]
CD52	Alemtuzumab	Anaplastic lymphoma, chronic lymphatic leukemia	Cytomegalovirus monitoring. Acyclovir prophylaxis for herpesvirus. Prophylaxis for *Pneumocystis jirovecii*.[8] Hepatitis B virus reactivation screening and prophylaxis

(Continued)

Table 1. (Continued)

Targeted molecule	Drugs	Currently approved indications	Prophylaxis and treatment suggestions
c-Kit, PDGF-R, BCR-ABL	Imatinib, dasatinib, nilotinib, bosutinib, ponatinib	Gastrointestinal stromal tumors, Philadephia positive chronic myeloid leukemia and acute lymphoblastic leukemia, dermatofibrosarcoma protuberans	Hepatitis B virus reactivation screening and prophylaxis
c-Met	Crizotinib, cabozantinib	Crizotinib: ALK-positive, ROS1-positive non-small cell lung cancer Cabozantinib: medullary thyroid cancer, hepatocellular carcinoma, renal cell carcinoma	No known increased risk of infection
EGFR/ HER1, ErbB2/ HER2 and other ErbB family members	Erlotinib, gefitinib, afatinib, neratinib, lapatinib, osimertinib, dacomitinib Cetuximab, panitumumab, trastuzumab, trastuzumab emtansine, pertuzumab	Neratinib, lapatinib: HER2-positive breast cancer Trastuzumab: HER2-positive breast cancer, HER2-positive gastroesophageal cancer Trastuzumab emtansine, pertuzumab: HER2-positive breast cancer Cetuximab, panitumumab: Head and neck cancer, colorectal cancer Remaining agents: EGFR-positive lung cancer	Small increase in the risk of infection with some agents (cetuximab, panitumumab). No expected benefit from universal use of antiviral, antifungal or anti-*Pneumocystis* prophylaxis
HDAC	Panobinostat, vorinostat, belinostat, romidepsin	Multiple myeloma, T-cell lymphomas	Hepatitis B virus reactivation screening and prophylaxis
JAK/STAT	Ruxolitinib	Polycythemia vera, myelofibrosis	Hepatitis B virus reactivation screening and prophylaxis. Prophylaxis for *Pneumocystis jirovecii* in patients receiving corticosteroids
mTOR	Temsirolimus, everolimus	Temsirolimus: kidney cancer, mantle cell lymphoma Everolimus: kidney cancer, neuroendocrine tumors, breast cancer	Hepatitis B virus reactivation screening and prophylaxis. Prophylaxis for *Pneumocystis jirovecii* in patients receiving corticosteroids and/or with lymphopenia.[8] Increased risk of herpes zoster infections: increased awareness and evaluate prophylaxis or vaccine in cases of recurrent zoster infections
FGFR	Erdafitinib	Urothelial carcinoma	No known increased risk of infection
MEK1/2	Trametinib, cobimetinib, binimetinib	BRAF-mutated melanoma	Associated with drug-induced pyrexia. No known increased risk of infection
PD-1, PD-L1, CTLA-4	Ipilimumab, tremelimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, cemiplimab, durvalumab	Ipilimumab, tremelimumab: melanoma Remaining agents: Melanoma, non-small cell lung carcinoma, urothelial carcinoma, renal cell carcinoma, tumors with microsatellite instability, head and neck cancer, hepatocellular carcinoma, breast cancer	In case of immune related adverse event: Hepatitis B virus reactivation screening and prophylaxis. Prophylaxis for *Pneumocystis jirovecii* in patients receiving corticosteroids[8,9]
PI3K	Idelalisib, rigosertib, duvelisib	Chronic lymphocytic leukemia, follicular lymphoma, myelodysplastic syndrome	Cytomegalovirus monitoring
RET	Vandetanib	Medullary thyroid cancer	No known increased risk of infection
TRK, ALK, ROS-1	Entrectinib, larotrectinib	NTRK-positive tumors Entrectinib: ROS1-positive non-small cell lung cancer	No known increased risk of infection
VEGFR/ VEGF	Axitinib, cabozantinib, lenvatinib, pazopanib, regorafenib, sorafenib, sunitinib, vandetanib Bevacizumab, aflibercept	Bevacizumab: colorectal cancer, gastric cancer, non-small cell lung cancer, renal cell carcinoma, breast cancer, ovarian cancer, cervical cancer Aflibercept: colorectal cancer Remaining agents: renal cell carcinoma, hepatocellular carcinoma, soft tissue sarcoma, gastrointestinal stromal tumors, colorectal cancer, neuroendocrine pancreatic cancer, differentiated thyroid cancer	Small increase in the risk of infections and increased risk of gastrointestinal perforation and fistulization with some agents (bevacizumab, aflibercept). No expected benefit from universal use of antiviral, antifungal or anti-*Pneumocystis* prophylaxis

R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone.

recommended for all patients.[35] Nevertheless, it is our opinion that periodic screening strategies or pharmacological prophylaxis should be considered in patients with other additional risk factors, such as concomitant treatment with fludarabine, alemtuzumab, other immunosuppressants, or previous invasive fungal infection.[26] Notably, ibrutinib interacts with potent CYP34A inhibitor drugs such as voriconazole, which are currently the mainstay of invasive aspergillosis therapy. If possible, these combinations should be avoided. Otherwise, the ibrutinib dose should be reduced to 140 mg/day.[13,36] A series of eight patients successfully treated with ibrutinib and isavuconazole (a newer antifungal agent with a lower risk of pharmacological interactions) has been reported.[37] In the case of *Pneumocystis jirovecii* pneumonia (PJP), data are more scarce but suggest an incidence of 1–3% in the absence of additional risk factors.[10,38] Other uncommon infections such as disseminated cryptococcosis, endemic fungal infections, miliary tuberculosis, and progressive multifocal leukoencephalopathy (PML) have also been reported.[39–43] Impaired responses to immunization have also been noted in patients under treatment with ibrutinib.[44] Latent hepatitis B virus (HBV) screening and prophylaxis are also advisable; cases of reactivation have been described.[45] Information on newer agents in this class is more limited, although a similar spectrum of effects on the susceptibility to infections is expected.[46]

PI3K inhibitors

PI3K inhibitors include idelalisib, rigosertib and duvelisib, small molecules that, given orally, are able to inhibit the PI3K signaling pathway, which plays a central role in the development of B lymphocytes and is overexpressed in many lymphoproliferative diseases. These drugs are currently approved for use in patients with CLL, follicular lymphoma, and myelodysplastic syndrome. Adverse events caused by immune dysregulation, most notably colitis, hepatitis, and pneumonitis[26] often requiring treatment with high-dose glucocorticoids, may carry an increased risk of infection.[47] PJP has been reported in up to 3.5% of patients not receiving prophylaxis.[48] In pivotal studies, cytomegalovirus (CMV) reactivation occurred in 2.4% of patients during the first 6 months; this percentage was even higher if idelalisib was combined with bendamustine (6.3%). Based on available clinical data, the European Conference on Infections in Leukaemia and the European Medicines Agency recommend that CMV serology be performed before the start of treatment and that CMV viral load be determined at least monthly. In CMV-seronegative patients, blood products should be treated or preferably sourced from CMV-negative donors.[10,49] Prophylaxis against PJP is also recommended from the start of treatment and for 2–6 months after completion.[3,10,50]

Antiapoptotic protein BCL-2 inhibitors

Venetoclax is a potent and selective oral inhibitor of BCL-2 antiapoptotic protein, which is overexpressed by tumor cells. It is used as a single agent or associated with anti-CD20 monoclonal antibodies in CLL patients with unfavorable cytogenetics (CD17 deletion) or previously treated CLL, and for the treatment of acute myeloid leukemia (AML) in frail patients or in the relapsed/refractory setting in combination with hypomethylating agents. The immunosuppressive effect of venetoclax is related to cytopenia. Neutropenia occurred in approximately 40–50% of patients in pivotal trials, and 15% of patients with grade 3 or 4 neutropenia experienced a serious infection.[51,52] In a safety analysis including 350 CLL patients from three early-phase studies, infections of any grade occurred in 72% of patients; respiratory infections and fever with neutropenia were the most commonly reported infectious complications. Two cases of PJP and two cases of *Aspergillus* lung infection were also reported.[51] Rates of severe infection varied depending on the profile of patients included in each study (underlying diseases, frequency of neutropenia, association with rituximab, etc.).[53] The impact on latent viral infections, such as hepatitis B, is yet to be clarified although it does not seem to be superior to that of the underlying disease. Rates of invasive fungal infection in AML patients are reported to be low and are associated with uncontrolled disease in pretreated patients.[54] In view of the limited data, we recommend that infection risk should be assessed at an individual level and based on previous infections, underlying diseases, and previous or concomitant therapies. Venetoclax is metabolized *via* CY3A4 and, therefore, has interactions with many drugs, including azoles.

Janus kinase inhibitors

The Janus kinase (JAK) family phosphorylates sites on the cytoplasmic tail of a variety of hematopoietic and inflammatory cytokine receptors (i.e. erythropoietin or thrombopoietin receptors), activating downstream targets *via* the signal transducer and activator of transcription (STAT) pathway. Through these mechanisms, JAKs play a significant role in hematopoiesis and immune cell signaling and differentiation. Drugs from this group are approved for use in different conditions including autoimmune diseases and hematological malignancies. Currently, ruxolitinib is approved for the treatment of patients with myelofibrosis,[55] polycythemia vera,[56] and graft-*versus*-host disease in some countries.[57] Ruxolitinib targets JAK1 and JAK2, producing downregulation of the T-helper cell type 1 (Th1) response and of cytokines such as interleukin (IL)-1, IL-6 and tumor necrosis factor-α (TNF-α). The effects of ruxolitinib on the adaptive immune system can be profound. A systematic review and meta-analysis of randomized clinical trials, post-marketing studies and case reports found that ruxolitinib was associated with a higher frequency of herpes zoster infections[14] (see Table 2). Cases of opportunistic infections such as PML, *Toxoplasma* retinitis, fungal infections, PJP, mycobacterial infections (including tuberculosis), and HBV reactivation have been documented.[3]

In view of these data, we suggest considering screening and therapy for latent tuberculosis and for chronic HBV infection before starting treatment. During treatment, clinicians should be aware of the increased risk of overall and opportunistic infections, especially in those with additional risk factors (i.e. prior or concomitant corticosteroid therapy, low lymphocyte counts, or high-dose therapy with JAK inhibitors). The administration of antiviral and anti-*Pneumocystis* prophylaxis should be considered, especially in patients with additional risk factors.

Mammalian target of rapamycin inhibitors

The Ras/PI3K/Akt/mTOR pathway plays a crucial role in cell survival, growth, and proliferation. Mammalian target of rapamycin (mTOR) is a serine/threonine kinase and a member of the PI3K-related kinase superfamily. mTOR inhibitors possess both immunosuppressive and anticancer activity and, therefore, are used in various situations: as immunosuppressors in solid organ transplantation, for example, or as antineoplastic drugs. Basic research shows that mTORC1-mediated functions result in both immunosuppressive and immune-activating effects.[58] Patients receiving mTOR inhibitors may have an impaired immune status not due to selective neutropenia or lymphopenia, but to an altered immune response. Nevertheless, due to high toxicity rates and the emergence of therapeutic alternatives, the use of these drugs is gradually declining. A retrospective analysis of patients treated with mTOR pathway inhibitors showed a higher risk of infections when compared with patients treated with other targeted therapies in phase I trials.[59] Three meta-analyses of trials evaluating fatal adverse events in patients treated with mTOR inhibitors in trials found sepsis was the cause of death reported most often.[60–62] Non-infectious pneumonitis is a common adverse event of mTOR inhibitors, with a reported rate of 2–9.9%, and should be included in the differential diagnosis of patients receiving these agents who develop pulmonary infiltrates.[63] A recent meta-analysis utilizing data from 12 trials comparing everolimus or temsirolimus *versus* placebo in cancer patients also reported a significantly higher risk of infection with mTOR inhibitors, with rates of all-grade and severe mTOR inhibitor-attributable infection of 9.3% and 2.3%, respectively[15] (see Table 2). Respiratory and urinary tract infections are among the most frequently reported infections, with some examples of opportunistic infection (i.e. tuberculosis, PJP, and herpes zoster) and HBV reactivation mentioned in case reports.[64–67] Therefore, infection risk associated with mTOR inhibitors seems to be relevant and, in our opinion, an individualized risk evaluation is suggested, as some patients may benefit from targeted prophylaxis (e.g. prophylaxis against *Pneumocystis jirovecii* in patients with lymphopenia and/or concomitant treatment with corticosteroids, and screening for latent HBV infection).

Breakpoint cluster region-Abelson tyrosine kinase inhibitors

The main target of these multikinase inhibitors (imatinib, dasatinib, nilotinib, bosutinib and ponatinib) is the adenosine triphosphate-binding pocket of the breakpoint cluster region-Abelson (BCR-ABL) protein. Other kinases [e.g. c-kit, stem-cell factor receptor, platelet-derived growth factor receptors (PDGFR) or the vascular endothelial growth factor receptor (VEGFR)] may also be

Table 2. Reviews evaluating infectious events associated to new agents.

Study	Study characteristics	Indication	Relevant conclusions
Ibrutinib			
Tillman *et al*.[11]	Systematic review of clinical trials. Included 48 study cohorts, 2119 patients. 44 of them reported infectious complications.	All hematological malignancies	Any grade infections/grade 3–4 infections: reported in 56%/26% of patients treated with ibrutinib as single agent and 52%/20% of patients treated with ibrutinib in combination with other drugs, respectively. Grade 3–4 pneumonia: reported in 13% of patients treated with ibrutinib as single agent (reported in 22 trials) and 18% of patients treated with ibrutinib in combination with other drugs (reported in 15 trials). Fatal infections: 2% in all groups
Ball *et al*.[12]	Systematic review and meta-analysis of randomized controlled trials. Included 7 studies, 2167 patients.	B-cell malignancies (chronic lymphocytic leukemia, Waldenström macroglobulinemia, mantle cell lymphoma)	Ibrutinib associated with increased risk of infection; any grade and grade 3–5: RR 1.34, 95% CI 1.06–1.69, $p=0.015$, and RR 1.35, 95% CI 1.05–1.74, $p=0.018$, respectively Not associated with higher risk of grade 3–5 pneumonia; RR 1.25, 95% CI 0.85–1.84 $p=0.260$
Bechman *et al*.[13]	Review of risk of fungal infections associated with small-molecule protein kinase inhibitors	Hematological malignancies	Collects 269 cases of fungal infection associated with ibrutinib reported in the literature from retrospective studies, reviews and case reports
Ruxolitinib			
Lussana *et al*.[14]	Systematic review and meta-analysis including 5 RCTs and 1009 patients, 6 post-marketing studies and 28 case reports	Myelofibrosis, polycythemia vera	Data on infections not systematically reported in RCTs. Increased risk of herpes zoster infection in a pooled analysis of RCT PV patients (OR 7.39, 95% CI 1.33–41.07) and extended-phase RCT publications (OR 5.20, 95% CI 1.27–21.18). Reported rates of infection 16–38% in post-marketing studies.
Everolimus, temsirolimus			
Garcia and Wu[15]	Meta-analysis of RCTs, including 12 RCTs and 4097 patients	Pancreatic neuroendocrine tumor, angiomyolipoma, mantle cell lymphoma, renal cell carcinoma, giant cell astrocytoma, breast cancer	Overall incidence of all-grade and grade 3–4 infection in mTOR inhibitor arms: 25%, 95% CI 16.7–35.9% and 4%, 95% CI 2.2–7%, respectively. Increased RR of all-grade and grade 3–4 infection compared to control arms: 1.96, 95% CI 1.42–32.77 ($p<0.001$) and 2.86, 95% CI 1.73–4.72 ($p<0.001$) respectively. Summary incidence of all-grade and 3–4 grade infection attributable to mTOR inhibitors: 9.3, 95% CI 5.8–14.6% and 2.3%, 95% CI 1.2–4.4% respectively
Rituximab			
Aksoy *et al*.[16]	Systematic review and meta-analysis evaluating the risk of infection in patients treated with rituximab as maintenance therapy in RCTs and phase II trials, including 9 studies and 637 patients	B-cell non-Hodgkin's lymphoma	Increased risk of infection and neutropenia in rituximab-treated patients in 5 RCTs: RR 2.8, 95% CI 1.3–6.2, $p=0.01$ and RR 2.4, 95% CI 1.5–3.9, $p=0.001$, respectively
Lanini *et al*.[17]	Systematic review and meta-analysis evaluating the risk of infection in patients treated with rituximab-containing regimens in RCTs, including 17 RCTs and 5259 patients	B-cell non-Hodgkin's lymphoma	No increased risk of infection in patients receiving rituximab-containing regimens (RR 1, 95% CI 0.87–1.14 $p=0.943$); risk of death as a consequence of infection (RR 1.6, 95% CI 0.68–3.75 $p=0.279$); or febrile neutropenia (RR 1.14, 95% CI 0.8–1.63, $p=0.478$)

(Continued)

Table 2. (Continued)

Study	Study characteristics	Indication	Relevant conclusions
Hua *et al.*[18]	Meta-analysis evaluating severe and fatal events in patients treated with rituximab, including 8 RCTs and 3363 patients	B-cell non-Hodgkin's lymphoma	No increased risk of infection. Slightly increased risk of leukocytopenia [6.4% *versus* 31%, RR 1.13, 95% CI 1.01–1.27 ($p = 0.03$)]
Jiang *et al.*[19]	Systematic review and meta-analysis evaluating the risk of PJP in patients treated with rituximab-containing regimens in trials, including 7 trials and 1919 patients, and the benefit of prophylaxis including 4 trials and 1208 patients	B-cell non-Hodgkin's lymphoma	Increased risk of PJP (RR 3.65, 95% CI 1.65–8.07, $p = 0.001$) Decreased risk associated with the use of prophylaxis (RR 0.28, 95% CI 0.09–0.94, $p = 0.039$)
Anti-EGFR			
Funakoshi *et al.*[20]	Systematic review and meta-analysis evaluating the risk of infection in patients treated with anti-EGFR monoclonal antibodies cetuximab and panitumumab, including 14,957 patients from 28 trials	Colorectal cancer, non-small cell lung carcinoma, head and neck squamous cell cancer and others	Increased risk of severe infections (RR 1.34, 95% CI 1.33–1.66, $p < 0.001$) and of fever and neutropenia (RR 1.27, 95% CI, 1.09–1.48, $p = 0.002$)
Qi *et al.*[21]	Systematic review and meta-analysis evaluating the risk of infection in patients treated with anti-EGFR monoclonal antibodies cetuximab and panitumumab, including 14,066 patients from 26 trials	Colorectal cancer, non-small cell lung carcinoma, head and neck squamous cell cancer and others	Severe infections: RR 1.49, 95% CI 1.1–1.62, $p = 0.003$
Wang *et al.*[22]	Systematic review and meta-analysis evaluating the risk of infection in patients treated with anti-EGFR kinase inhibitors gefitinib and erlotinib, including 13,436 patients from 25 trials	Non-small cell lung cancer	All-grade infections: OR 1.48, 95% CI: 1.12–1.96, $p = 0.006$ No differences in severe infections
Anti-VEGF			
Qi *et al.*[23]	Systematic review and meta-analysis evaluating the risk of infection in patients treated with bevacizumab, including 33,526 patients from 41 trials	Colorectal cancer, non-small cell lung carcinoma, breast cancer, ovarian cancer and others	Increased risk of all-grade (RR 1.45, 95% CI 1.27–1.66, $p < 0.001$) and high-grade (RR 1.59, 95% CI 1.42–1.79, $p < 0.001$) infection, and of fistulae/abscesses (RR 2.13, 95% CI 1.06–4.27, $p = 0.033$)
Zhang *et al.*[24]	Systematic review and meta-analysis evaluating the risk of infection in patients treated with aflibercept, including 4310 patients from 10 trials	Lung cancer, colorectal cancer and others	Increased risk of high grade (RR 1.87, 95% CI 1.52, 2.30, $p < 0.001$) and fatal (OR 2.16, 95% CI 1.14–4.11, $p = 0.018$) infections

95% CI, 95% confidence interval; EGFR, endothelial growth factor receptor; mTOR, mammalian target of rapamycin, OR, odds ratio; PJP, *Pneumocystis jirovecii* pneumonia; PV, polycythemia vera; RCT, randomized clinical trials; RR, relative risk.

inhibited depending on the specific profile of each drug. These drugs are used to treat chronic myeloid leukemia and relapsed or refractory Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL), among other hematological conditions, as well as for gastrointestinal stromal tumors (GISTs).[3]

Infections associated with the use of these drugs are uncommon, and most are the result of neutropenia which occurs within the first months of treatment. Imatinib is the most widely used drug in this group; long-term data suggest that infections occur almost exclusively during the first year of treatment.[7,68] Long-term data on ponatinib show higher rates of neutropenia and severe infection; however, the drug is used in patients with more advanced stage, previously treated disease.[69]

Reactivation of HBV has been repeatedly described in case reports in patients undergoing treatment with BCR-ABL inhibitors; therefore, screening and treatment are advisable.[70,71]

Monoclonal agents targeting hematological cells

CD20-directed agents

Monoclonal anti-CD20 antibodies are currently a cornerstone in the therapeutic approach to CD20-positive malignancies. Their action is exerted through the depletion of B lymphocytes. Patients receiving prolonged treatment with these agents may develop hypogammaglobulinemia. Nevertheless, the most relevant effect caused by these drugs on the immune response is related to the modulation of B and T-cell interactions, and infections related to cellular immunity defect have been reported.[72]

Neutropenia is reported in 10–33% of patients receiving non-conjugated anti-CD20 monoclonal antibodies (including patients receiving concomitant chemotherapy) and in more than 50% of patients receiving conjugated antibodies.[73] A peculiar condition is late-onset neutropenia, probably immune-mediated, that occurs between 1 and 5 months after the end of therapy in 5–15% of patients treated with rituximab. This kind of neutropenia can persist for months and eventually resolves spontaneously, but its impact on the risk of infections is unclear.[74]

Meta-analyses including patients with lymphoma treated with rituximab-containing regimens have not shown an increased overall rate of reported infections,[17,18,75] although an increased risk of infection was seen in lymphoma patients receiving rituximab as maintenance therapy[16] (Table 2). More importantly, HBV reactivation has been extensively reported and estimated to be increased more than five-fold; screening for latent infection is recommended.[76] Hepatitis C exacerbation, herpesvirus infections, and PML cases have also been described.[77,78] The risk of PJP has also been shown to rise with the addition of rituximab to chemotherapy regimens, and prophylaxis has been shown to be highly effective.[19] However, the overall incidence seems to be low (less than 3%).[19,79] In view of these data, the European Conference on Infections in Leukaemia currently considers PJP prophylaxis optional in patients receiving biweekly rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP), in the absence of additional risk factors.

There seems to be a reduced response to immunization during treatment with anti-CD20;[80] therefore, any vaccinations should be delayed until at least 6 months after the end of treatment. After this period, evidence suggests that pneumococcal and *Haemophilus influenzae* type B vaccines are beneficial.[81]

CD30-directed agents

Brentuximab vedotin is a conjugated antibody directed against CD30, approved for the treatment of adult patients with Hodgkin's lymphoma, relapsed or refractory anaplastic lymphoma, and cutaneous T-cell lymphoma. Although associated with neutropenia, fever episodes are rare. Infection rates are 0.1–1% for PJP and 1–10% for herpesvirus. PML cases have been reported in both pivotal and post-marketing studies, and patients should be monitored for neurological manifestations.[82,83]

CD52-directed agents

Alemtuzumab is an anti-CD52 monoclonal antibody approved for the treatment of CLL and multiple sclerosis. Off-label uses include other lymphoproliferative diseases, prevention of graft rejection in solid organ transplantation, and prevention or treatment of graft-*versus*-host disease. Nevertheless, its use in hematological malignancies has been replaced in the past few years by newer drugs with more favorable safety profiles. Alemtuzumab produces serious immune defects (with involvement of B, T, and natural killer [NK] lymphocytes) that persist up to 9 months after the end of treatment. Use of the drug has been correlated with a higher risk of viral hepatitis B and C reactivation and opportunistic infections (herpesvirus infections, CMV disease, PJP, mycobacterial infections, human papillomavirus infections).[84,85] Data available from trials on hematological malignancies support screening for latent tuberculosis, HBV, and hepatitis C infection before starting treatment as well as prophylaxis for herpesvirus and *Pneumocystis*. Prevention strategies for CMV infection (mainly preemptive therapy) are also advisable for CMV-seropositive patients.[77]

Other agents used in hematological malignancies

Blinatumomab is a bispecific anti-CD19/anti-CD3 monoclonal antibody causing depletion of CD19+ circulating cells and is currently approved for the treatment of relapsed or refractory B-cell precursor ALL. Therapy with CD19-targeted agents has not been proved to be associated with a meaningful increase in the risk of infection compared with conventional chemotherapy, with overall rates comparable to those expected in patients undergoing treatment for relapsed or refractory ALL or non-Hodgkin lymphoma in clinical trials.[86] Nevertheless, an increase has been reported in catheter-associated infections, probably arising from the need for continuous intravenous infusion; hypogammaglobulinemia is common and may require monitoring.[77,87]

Inotuzumab ozogamicin is an anti-CD22 antibody–drug conjugate approved for the treatment of refractory B-cell precursor ALL. An increased risk of infection has not been reported in clinical trials.[88] Prophylaxis should be individualized, and like rituximab, screening for chronic HBV infection is advisable.[78,89]

Gemtuzumab ozogamicin is another antibody–drug conjugate that binds to the CD33 antigen, which is expressed on the surface of normal and leukemic myeloid cells, as well as leukemic blasts in more than 80% of cases of AML, but is not expressed on normal hematopoietic stem cells. The expected impact on the risk of infection seems to be similar to that observed with other standard AML treatments that induce severe and long-lasting neutropenia (e.g. cytotoxic chemotherapy).[89,90]

Daratumumab is an anti-CD38 antibody approved for the treatment of multiple myeloma in adult patients, either in monotherapy or in combination with other agents. The risk of neutropenia and infections reported in clinical trials was similar to that of the comparator arms; therefore, in view of available data on therapy with CD38-targeted agents, daratumumab does not seem to increase the risk of infection meaningfully.[91,92] However, an increased rate of varicella-zoster virus infections (2–5%) has been observed in clinical trials that included patients treated with combination therapy; prophylaxis is recommended in seropositive patients.[89]

Immune checkpoint inhibitors

Immune checkpoint inhibitors (CIs) comprise monoclonal antibodies whose objective is to restore or enhance the action of the immune system against tumor cells. Cancer cells can develop the ability to evade immunological identification and elimination through the usurpation of various signaling pathways or immune checkpoints. The most relevant of these are the C4 protein pathway of the T lymphocyte (CTLA-4) and the programmed cell death (PD-1) pathway. Neoplastic cells are able to exploit them, mainly by overexpression of ligands, to induce a decrease in T-cell proliferation, cytotoxicity, and cytokine production, contributing to generating and maintaining an immunotolerant microenvironment. The pharmacological blockade of these signaling mechanisms allows reactivation of the antitumoral activity of the immune system. Anti-CTLA4 and anti-PD1/PDL-1 are now part of the standard of care in many solid tumors and some hematological malignancies.[93]

CIs can have the unwelcome adverse effect of triggering immune-mediated adverse events in multiple organs. The most important and frequent forms of toxicity are cutaneous, endocrinological, digestive, hepatic, and pulmonary. In most cases, the treatment of these adverse inflammatory reactions involves the use of systemic glucocorticoids or other immunosuppressants such as infliximab or mycophenolate. Data on the risk of infections associated with the use of CIs are mainly derived from studies conducted in patients with solid organ cancer. A study conducted in more than 740 patients with malignant melanoma who received CIs showed that 7.3% of patients had a serious bacterial, viral, fungal, or PJP infection; the main factor associated with the development of infections was the use of glucocorticoids and infliximab.[94] Another study evaluating the prevalence of infections among 200 patients treated with CIs reported 18% of patients experienced an infection, usually mild. Treatment with glucocorticoids (present in 21% of patients at the onset of infection) was not associated with a higher risk. In addition, opportunistic infections were not reported, but no data were available on the use of prophylactic strategies (e.g. cotrimoxazole).[95] Cases of CMV enterocolitis have been reported in relation to immunosuppressive therapy in patients with immune-mediated enterocolitis.[96] Pulmonary tuberculosis has also been

described,[97] probably due to an immune reconstitution mechanism. Some data indicate that the use of CIs is safe in patients with chronic viral infections such as HBV or HIV infection.[98] At present, CIs are being investigated in combination with other therapies such as chemotherapy, monoclonal antibodies, chimeric antigen receptor T-cells (CARTs), or hematopoietic stem cell transplantation.[99] The extended use of these combinations in the future may lead to a wider array of adverse effects including effects on the immune system and infection susceptibility. Most likely, the most relevant preventable infection is PJP in patients treated with glucocorticoids, a condition with a dismal prognosis in non-HIV patients.[100] Prophylaxis according to current recommendations should be considered.[9]

Conclusion

The advent of targeted therapies has changed the landscape of many hematological and solid organ malignancies. New treatments often result in significant changes in prognosis, with toxic effects unlike those of conventional chemotherapy. Nevertheless, the extent of adverse events is not yet known. Screening for latent infections and individualized prophylaxis may be advisable. Due to the limited clinical experience available, these recommendations may evolve in the near future.

Acknowledgements

The authors would like to thank Helen Casas and Laura Casas for language support.

Author contribution

IRC and JAC conceived, structured and wrote the manuscript. IRC and JAC reviewed available literature in the process. Both authors contributed equally.

Conflict of interest

The authors declare that there is no conflict of interest.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Isabel Ruiz-Camps https://orcid.org/0000-0003-3743-2379

References

1. Bhullar KS, Lagarón NO, McGowan EM, *et al.* Kinase-targeted cancer therapies: progress, challenges and future directions. *Mol Cancer* 2018; 17: 48.
2. Tau N, Shargian-Alon L, Reich S, *et al.* Reporting infections in clinical trials of patients with haematological malignancies. *Clin Microbiol Infect* 2019; 25: 1494–1500.
3. Reinwald M, Silva JTT, Mueller NJJ, *et al.* ESCMID Study Group for Infections in Compromised Hosts (ESGICH) consensus document on the safety of targeted and biological therapies: an infectious diseases perspective (intracellular signaling pathways: tyrosine kinase and mTOR inhibitors). *Clin Microbiol Infect* 2018; 24: S53–S70.
4. Aguilar-Company J, Fernández-Ruiz M, García-Campelo R, *et al.* ESCMID Study Group for Infections in Compromised Hosts (ESGICH) consensus document on the safety of targeted and biological therapies: an infectious diseases perspective (cell surface receptors and associated signaling pathways). *Clin Microbiol Infect* 2018; 24: S41–S52.
5. Reinwald M, Boch T, Hofmann WK, *et al.* Risk of infectious complications in hemato-oncological patients treated with kinase inhibitors. *Biomark Insights* 2015; 10s3: 55–68.
6. Chamilos G, Lionakis MS and Kontoyiannis DP. Call for action: invasive fungal infections associated with ibrutinib and other small molecule kinase inhibitors targeting immune signaling pathways. *Clin Infect Dis* 2018; 66: 140–148.
7. Kin A and Schiffer CA. Infectious complications of tyrosine kinase inhibitors in hematological malignancies. *Infect Dis Clin North Am* 2020; 34: 245–256.
8. Maertens J, Cesaro S, Maschmeyer G, *et al.* ECIL guidelines for preventing *Pneumocystis jirovecii* pneumonia in patients with haematological malignancies and stem cell transplant recipients. *J Antimicrob Chemother* 2016; 71: 2397–2404.
9. Baden LR, Swaminathan S, Angarone M, *et al.* Prevention and treatment of cancer-related infections, version 2.2016, NCCN clinical practice guidelines in oncology. *J Natl Compr Cancer Netw* 2016; 14: 882–913.
10. Maschmeyer G, De Greef J, Mellinghoff SC, *et al.* Infections associated with immunotherapeutic and molecular targeted

agents in hematology and oncology. A position paper by the European Conference on Infections in Leukemia (ECIL). *Leukemia* 2019; 33: 844–862.

11. Tillman BF, Pauff JM, Satyanarayana G, *et al*. Systematic review of infectious events with the Bruton tyrosine kinase inhibitor ibrutinib in the treatment of hematologic malignancies. *Eur J Haematol* 2018; 100: 325–334.

12. Ball S, Das A, Vutthikraivit W, *et al*. Risk of infection associated with ibrutinib in patients with B-cell malignancies: a systematic review and meta-analysis of randomized controlled trials. *Clin Lymphoma Myeloma Leuk* 2020; 20: 87–97.e5.

13. Bechman K, Galloway JB and Winthrop KL. Small-molecule protein kinases inhibitors and the risk of fungal infections. *Curr Fungal Infect Rep* 2019; 13: 229–243.

14. Lussana F, Cattaneo M, Rambaldi A, *et al*. Ruxolitinib-associated infections: a systematic review and meta-analysis. *Am J Hematol* 2018; 93: 339–347.

15. Garcia CA and Wu S. Attributable risk of infection to mTOR inhibitors everolimus and temsirolimus in the treatment of cancer. *Cancer Invest* 2016; 34: 521–530.

16. Aksoy S, Dizdar Ö, Hayran M, *et al*. Infectious complications of rituximab in patients with lymphoma during maintenance therapy: a systematic review and meta-analysis. *Leuk Lymphoma* 2009; 50: 357–365.

17. Lanini S, Molloy AC, Fine PE, *et al*. Risk of infection in patients with lymphoma receiving rituximab: systematic review and meta-analysis. *BMC Med* 2011; 9: 36.

18. Hua Q, Zhu Y and Liu H. Severe and fatal adverse events risk associated with rituximab addition to B-cell non-Hodgkin's lymphoma (B-NHL) chemotherapy: a meta-analysis. *J Chemother* 2015; 27: 365–370.

19. Jiang X, Mei X, Feng D, *et al*. Prophylaxis and treatment of *Pneumocystis jiroveci* pneumonia in lymphoma patients subjected to rituximab-contained therapy: a systemic review and meta-analysis. *PLoS One* 2015; 10: e0122171.

20. Funakoshi T, Suzuki M and Tamura K. Infectious complications in cancer patients treated with anti-EGFR monoclonal antibodies cetuximab and panitumumab: a systematic review and meta-analysis. *Cancer Treat Rev* 2014; 40: 1221–1229.

21. Qi W-X, Fu S, Zhang Q, *et al*. Incidence and risk of severe infections associated with anti-epidermal growth factor receptor monoclonal antibodies in cancer patients: a systematic review and meta-analysis. *BMC Med* 2014; 12: 203.

22. Wang Y, Wang M, Wang Q, *et al*. Incidence and risk of infections associated with EGFR-TKIs in advanced non-small-cell lung cancer: a systematic review and meta-analysis of randomized controlled trials. *Oncotarget* 2017; 8: 29406–29415.

23. Qi W-X, Fu S, Zhang Q, *et al*. Bevacizumab increases the risk of infections in cancer patients: a systematic review and pooled analysis of 41 randomized controlled trials. *Crit Rev Oncol Hematol* 2015; 94: 323–336.

24. Zhang X, Ran Y, Shao Y, *et al*. Incidence and risk of severe infections associated with aflibercept in cancer patients: a systematic review and meta-analysis. *Br J Clin Pharmacol* 2016; 81: 33–40.

25. da Cunha-Bang C and Niemann CU. Targeting Bruton's tyrosine kinase across B-cell malignancies. *Drugs* 2018; 78: 1653–1663.

26. Teh BW, Tam CS, Handunnetti S, *et al*. Infections in patients with chronic lymphocytic leukaemia: mitigating risk in the era of targeted therapies. *Blood Rev* 2018; 32: 499–507.

27. Ravandi F and O'Brien S. Immune defects in patients with chronic lymphocytic leukemia. *Cancer Immunol Immunother* 2006; 55: 197–209.

28. Varughese T, Taur Y, Cohen N, *et al*. Serious infections in patients receiving ibrutinib for treatment of lymphoid cancer. *Clin Infect Dis* 2018; 67: 687–692.

29. Teh BW, Chui W, Handunnetti S, *et al*. High rates of proven invasive fungal disease with the use of ibrutinib monotherapy for relapsed or refractory chronic lymphocytic leukemia. *Leuk Lymphoma* 2019; 60: 1572–1575.

30. Ghez D, Calleja A, Protin C, *et al*. Early-onset invasive aspergillosis and other fungal infections in patients treated with ibrutinib. *Blood* 2018; 131: 1955–1959.

31. Ruchlemer R, Ben-Ami R, Bar-Meir M, *et al*. Ibrutinib-associated invasive fungal diseases in patients with chronic lymphocytic leukaemia and non-Hodgkin lymphoma: an observational study. *Mycoses* 2019; 62: 1140–1147.

32. Zarakas MA, Desai JV, Chamilos G, *et al*. Fungal infections with ibrutinib and other small-molecule kinase inhibitors. *Curr Fungal Infect Rep* 2019; 13: 86–98.

33. Anastasopoulou A, DiPippo AJ and Kontoyiannis DP. Non-*Aspergillus* invasive

mould infections in patients treated with ibrutinib. *Mycoses* 2020; 63: 787–793.

34. Bercusson A, Colley T, Shah A, *et al*. Ibrutinib blocks Btk-dependent NF-kB and NFAT responses in human macrophages during *Aspergillus fumigatus* phagocytosis. *Blood* 2018; 132: 1985–1988.

35. Lindsay J, Teh BW, Micklethwaite K, *et al*. Azole antifungals and new targeted therapies for hematological malignancy. *Curr Opin Infect Dis* 2019; 32: 538–545.

36. Facchinelli D, Marchesini G, Nadali G, *et al*. Invasive mold infections in patients with chronic lymphoproliferative disorders. *Curr Fungal Infect Rep* 2018; 12: 179–186.

37. Cummins KC, Cheng MP, Kubiak DW, *et al*. Isavuconazole for the treatment of invasive fungal disease in patients receiving ibrutinib. *Leuk Lymphoma* 2019; 60: 527–530.

38. Ryan CE, Cheng MP, Issa NC, *et al*. Pneumocystis jirovecii pneumonia and institutional prophylaxis practices in CLL patients treated with BTK inhibitors. *Blood Adv* 2020; 4: 1458–1463.

39. Messina JA, Maziarz EK, Spec A, *et al*. Disseminated cryptococcosis with brain involvement in patients with chronic lymphoid malignancies on ibrutinib. *Open Forum Infect Dis*. Epub ahead of print 1 January 2017. DOI: 10.1093/ofid/ofw261

40. Wang S-Y, Ebert T, Jaekel N, *et al*. Miliary tuberculosis after initiation of ibrutinib in chronic lymphocytic leukemia. *Ann Hematol* 2015; 94: 1419–1420.

41. Stankowicz M, Banaszynski M and Crawford R. Cryptococcal infections in two patients receiving ibrutinib therapy for chronic lymphocytic leukemia. *J Oncol Pharm Pract* 2019; 25: 710–714.

42. Mok TS, Wu Y-L, Thongprasert S, *et al*. Gefitinib or carboplatin–paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009; 361: 947–957.

43. Hsiehchen D, Arasaratnam R, Raj K, *et al*. Ibrutinib use complicated by progressive multifocal leukoencephalopathy. *Oncology* 2018; 95: 319–322.

44. Douglas AP, Trubiano JA, Barr I, *et al*. Ibrutinib may impair serological responses to influenza vaccination. *Haematologica* 2017; 102: e397–e399.

45. Hammond SP, Chen K, Pandit A, *et al*. Risk of hepatitis B virus reactivation in patients treated with ibrutinib. *Blood* 2018; 131: 1987–1989.

46. Furman RR, Byrd JC, Owen RG, *et al*. Safety of acalabrutinib (Acala) monotherapy in hematologic malignancies: pooled analysis from clinical trials. *J Clin Oncol* 2020; 38: 8064–8064.

47. Cuneo A, Barosi G, Danesi R, *et al*. Management of adverse events associated with idelalisib treatment in chronic lymphocytic leukemia and follicular lymphoma: a multidisciplinary position paper. *Hematol Oncol* 2019; 37: 3–14.

48. Sehn LH, Hallek M, Jurczak W, *et al*. A retrospective analysis of *Pneumocystis jirovecii* pneumonia infection in patients receiving idelalisib in clinical trials. *Blood* 2016; 128: 3705–3705.

49. European Medicines Agency. *Procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data*. https://www.ema.europa.eu/documents/variation-report/zydelig-h-c-003843-a20-1439-0023-epar-assessment-report-article-20_en.pdf. Accessed September 1, 2020.

50. European Medicines Agency. *Annex IV scientific conclusions*. https://www.ema.europa.eu/en/documents/referral/xeljanz-article-20-procedure-annex-iv_en.pdf. Accessed September 1, 2020.

51. Davids MS, Hallek M, Wierda W, *et al*. Comprehensive safety analysis of venetoclax monotherapy for patients with relapsed/refractory chronic lymphocytic leukemia. *Clin Cancer Res* 2018; 24: 4371–4379.

52. DiNardo CD, Pratz KW, Letai A, *et al*. Safety and preliminary efficacy of venetoclax with decitabine or azacitidine in elderly patients with previously untreated acute myeloid leukaemia: a non-randomised, open-label, phase 1b study. *Lancet Oncol* 2018; 19: 216–228.

53. Coutre S, Choi M, Furman RR, *et al*. Venetoclax for patients with chronic lymphocytic leukemia who progressed during or after idelalisib therapy. *Blood* 2018; 131: 1704–1711.

54. Aldoss I, Dadwal S, Zhang J, *et al*. Invasive fungal infections in acute myeloid leukemia treated with venetoclax and hypomethylating agents. *Blood Adv* 2019; 3: 4043–4049.

55. Harrison C, Kiladjian J-J, Al-Ali HK, *et al*. JAK Inhibition with ruxolitinib versus best available therapy for myelofibrosis. *N Engl J Med* 2012; 366: 787–798.

56. Vannucchi AM, Kiladjian JJ, Griesshammer M, *et al*. Ruxolitinib versus standard therapy for the

treatment of polycythemia vera. *N Engl J Med* 2015; 372: 426–435.

57. Zeiser R, Burchert A, Lengerke C, *et al.* Ruxolitinib in corticosteroid-refractory graft-versus-host disease after allogeneic stem cell transplantation: a multicenter survey. *Leukemia* 2015; 29: 2062–2068.

58. Pollizzi KN and Powell JD. Regulation of T cells by mTOR: the known knowns and the known unknowns. *Trends Immunol* 2015; 36: 13–20.

59. Rafii S, Roda D, Geuna E, *et al.* Higher risk of infections with PI3K-AKT-mTOR pathway inhibitors in patients with advanced solid tumors on phase I clinical trials. *Clin Cancer Res* 2015; 21: 1869–1876.

60. Qi W-X, Huang Y-J, Yao Y, *et al.* Incidence and risk of treatment-related mortality with mTOR inhibitors everolimus and temsirolimus in cancer patients: a meta-analysis. *PLoS One* 2013; 8: e65166.

61. Choueiri TK, Je Y, Sonpavde G, *et al.* Incidence and risk of treatment-related mortality in cancer patients treated with the mammalian target of rapamycin inhibitors. *Ann Oncol* 2013; 24: 2092–2097.

62. Wesolowski R, Abdel-Rasoul M, Lustberg M, *et al.* Treatment-related mortality with everolimus in cancer patients. *Oncologist* 2014; 19: 661–668.

63. Albiges L, Chamming's F, Duclos B, *et al.* Incidence and management of mTOR inhibitor-associated pneumonitis in patients with metastatic renal cell carcinoma. *Ann Oncol* 2012; 23: 1943–1953.

64. Mizuno S, Yamagishi Y, Ebinuma H, *et al.* Progressive liver failure induced by everolimus for renal cell carcinoma in a 58-year-old male hepatitis B virus carrier. *Clin J Gastroenterol* 2013; 6: 188–192.

65. Göksu SS. Hepatitis B reactivation related to everolimus. *World J Hepatol* 2013; 5: 43.

66. Carbonnaux M, Molin Y, Souquet P-J, *et al. Pneumocystis jirovecii* pneumonia under everolimus in two patients with metastatic pancreatic neuroendocrine tumors. *Invest New Drugs* 2014; 32: 1308–1310.

67. Saito Y, Nagayama M, Miura Y, *et al.* A case of *Pneumocystis* pneumonia associated with everolimus therapy for renal cell carcinoma. *Jpn J Clin Oncol* 2013; 43: 559–562.

68. Hochhaus A, Larson RA, Guilhot F, *et al.* Long-term outcomes of imatinib treatment for chronic myeloid leukemia. *N Engl J Med* 2017; 376: 917–927.

69. Cortes JE, Kim D-W, Pinilla-Ibarz J, *et al.* Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia: final 5-year results of the phase 2 PACE trial. *Blood* 2018; 132: 393–404.

70. Benjamini O, Zlotnick M, Ribakovsky E, *et al.* Evaluation of the risk of hepatitis B reactivation among patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors. *Blood* 2016; 128: 5429–5429.

71. Kim S-H, Kim HJ, Kwak J-Y, *et al.* Hepatitis B virus reactivation in chronic myeloid leukemia treated with various tyrosine kinase inhibitors: multicenter, retrospective study. *Blood* 2012; 120: 3738–3738.

72. Kamel S, O'Connor S, Lee N, *et al.* High incidence of *Pneumocystis jirovecii* pneumonia in patients receiving biweekly rituximab and cyclophosphamide, adriamycin, vincristine, and prednisone. *Leuk Lymphoma* 2010; 51: 797–801.

73. Emmanouilides C, Witzig TE, Wiseman GA, *et al.* Safety and efficacy of yttrium-90 ibritumomab tiuxetan in older patients with non-Hodgkin's lymphoma. *Cancer Biother Radiopharm* 2007; 22: 684–691.

74. Dunleavy K, Tay K and Wilson WH. Rituximab-associated neutropenia. *Semin Hematol* 2010; 47: 180–186.

75. Rafailidis PI, Kakisi OK, Vardakas K, *et al.* Infectious complications of monoclonal antibodies used in cancer therapy. *Cancer* 2007; 109: 2182–2189.

76. Evens AM, Jovanovic BD, Su Y-C, *et al.* Rituximab-associated hepatitis B virus (HBV) reactivation in lymphoproliferative diseases: meta-analysis and examination of FDA safety reports. *Ann Oncol* 2011; 22: 1170–1180.

77. Ippolito G, Drgona L, Mikulska M, *et al.* ESCMID Study Group for Infections in Compromised Hosts (ESGICH) consensus document on the safety of targeted and biological therapies: an infectious diseases perspective (agents targeting lymphoid cells surface antigens [I]: CD19, CD20 and CD52). *Clin Microbiol Infect* 2018; 24: S71–S82.

78. Leandro MJ. Infections related to biologics: agents targeting B cells. *Infect Dis Clin North Am* 2020; 34: 161–178.

79. Barreto JN, Ice LL, Thompson CA, *et al.* Low incidence of *Pneumocystis* pneumonia utilizing PCR-based diagnosis in patients with B-cell lymphoma receiving rituximab-containing combination chemotherapy. *Am J Hematol* 2016; 91: 1113–1117.

80. de Lavallade H, Garland P, Sekine T, *et al*. Repeated vaccination is required to optimize seroprotection against H1N1 in the immunocompromised host. *Haematologica* 2011; 96: 307–314.

81. Moulis G, Lapeyre-Mestre M, Palmaro A, *et al*. Infections in non-splenectomized persistent or chronic primary immune thrombocytopenia adults: risk factors and vaccination effect. *J Thromb Haemost* 2017; 15: 785–791.

82. Carson KR, Newsome SD, Kim EJ, *et al*. Progressive multifocal leukoencephalopathy associated with brentuximab vedotin therapy: a report of 5 cases from the Southern Network on Adverse Reactions (SONAR) project. *Cancer* 2014; 120: 2464–2471.

83. Jalan P, Mahajan A, Pandav V, *et al*. Brentuximab associated progressive multifocal leukoencephalopathy. *Clin Neurol Neurosurg* 2012; 114: 1335–1337.

84. Thursky KA, Worth LJ, Seymour JF, *et al*. Spectrum of infection, risk and recommendations for prophylaxis and screening among patients with lymphoproliferative disorders treated with alemtuzumab⋆. *Br J Haematol* 2006; 132: 3–12.

85. Martin SI, Gribben JG, Fiumara K, *et al*. Infectious complications associated with alemtuzumab use for lymphoproliferative disorders. *Clin Infect Dis* 2006; 43: 16–24.

86. Yu J, Wang W and Huang H. Efficacy and safety of bispecific T-cell engager (BiTE) antibody blinatumomab for the treatment of relapsed/refractory acute lymphoblastic leukemia and non-Hodgkin's lymphoma: a systemic review and meta-analysis. *Hematology* 2019; 24: 199–207.

87. Wilke AC and Gökbuget N. Clinical applications and safety evaluation of the new CD19 specific T-cell engager antibody construct blinatumomab. *Expert Opin Drug Saf* 2017; 16: 1191–1202.

88. Kantarjian HM, DeAngelo DJ, Stelljes M, *et al*. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. *N Engl J Med* 2016; 375: 740–753.

89. Drgona L, Gudiol C, Lanini S, *et al*. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) consensus document on the safety of targeted and biological therapies: an infectious diseases perspective (agents targeting lymphoid or myeloid cells surface antigens [II]: CD22, CD30, CD33. *Clin Microbiol Infect* 2018; 24: S83–S94.

90. Hills RK, Castaigne S, Appelbaum FR, *et al*. Addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia: a meta-analysis of individual patient data from randomised controlled trials. *Lancet Oncol* 2014; 15: 986–996.

91. Dimopoulos MA, Oriol A, Nahi H, *et al*. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med* 2016; 375: 1319–1331.

92. Palumbo A, Chanan-Khan A, Weisel K, *et al*. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. *N Engl J Med* 2016; 375: 754–766.

93. Esfahani K, Roudaia L, Buhlaiga N, *et al*. A review of cancer immunotherapy: from the past, to the present, to the future. *Curr Oncol* 2020; 27: 87–97.

94. Del Castillo M, Romero FA, Argüello E, *et al*. The spectrum of serious infections among patients receiving immune checkpoint blockade for the treatment of melanoma. *Clin Infect Dis* 2016; 63: 1490–1493.

95. Karam JD, Noel N, Voisin AL, *et al*. Infectious complications in patients treated with immune checkpoint inhibitors. *Eur J Cancer* 2020; 141: 137–142.

96. Uslu U, Agaimy A, Hundorfean G, *et al*. Autoimmune colitis and subsequent CMV-induced hepatitis after treatment with ipilimumab. *J Immunother* 2015; 38: 212–215.

97. Fujita K, Terashima T and Mio T. Anti-PD1 antibody treatment and the development of acute pulmonary tuberculosis. *J Thorac Oncol* 2016; 11: 2238–2240.

98. Ostios-Garcia L, Faig J, Leonardi GC, *et al*. Safety and efficacy of PD-1 inhibitors among HIV-positive patients with non-small cell lung cancer. *J Thorac Oncol* 2018; 13: 1037–1042.

99. Alatrash G, Daver N and Mittendorf EA. Targeting immune checkpoints in hematologic malignancies. *Pharmacol Rev* 2016; 68: 1014–1025.

100. Mundo W, Morales-Shnaider L, Tewahade S, *et al*. Lower mortality associated with adjuvant corticosteroid therapy in non-HIV-infected patients with *Pneumocystis jirovecii* pneumonia: a single-institution retrospective us cohort study. *Open Forum Infect Dis*. Epub ahead of print 13 August 2020. DOI: 10.1093/ofid/ofaa354