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)

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Narrative review

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)

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ABSTRACT

Background: The present review is part of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biologic therapies.
Aims: To review, from an infectious diseases perspective, the safety profile of therapies targeting different intracellular signaling pathways and to suggest preventive recommendations.
Sources: Computer-based Medline searches with MeSH terms pertaining to each agent or therapeutic family.
Content: Although BCR-ABL tyrosine kinase inhibitors modestly increase the overall risk of infection, dasatinib has been associated with cytomegalovirus and hepatitis B virus reactivation. BRAF/MEK kinase inhibitors do not significantly affect infection susceptibility. The effect of Bruton tyrosine kinase inhibitors (ibrutinib) among patients with B-cell malignancies is difficult to distinguish from that of previous immunosuppression. However, cases of *Pneumocystis jirovecii* pneumonia (PCP), invasive fungal infection and progressive multifocal leukoencephalopathy have been occasionally reported. Because phosphatidylinositol-3-kinase inhibitors (idelalisib) may predispose to opportunistic infections, anti-*Pneumocystis* prophylaxis and prevention strategies for cytomegalovirus are recommended. No increased rates of infection have been observed with venetoclax (antiapoptotic protein Bcl-2 inhibitor). Therapy with Janus kinase inhibitors markedly increases the incidence of infection. Pretreatment screening for chronic hepatitis B virus and latent tuberculosis infection must be performed, and anti-*Pneumocystis* prophylaxis should be considered for patients with additional risk factors. Cancer patients receiving mTOR inhibitors face an increased incidence of overall infection, especially those with additional risk factors (prior therapies or delayed wound healing).

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Implications: Specific preventive approaches are warranted in view of the increased risk of infection associated with some of the reviewed agents. **M. Reinwald, Clin Microbiol Infect 2018;24:S53**

Introduction

The present review is part of a larger effort launched by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Infections in Compromised Hosts (ESGICH) and aims to analyse, from an infectious diseases perspective, the safety profile of biologic and targeted therapies. By means of a set of unrestricted computer-based Medline searches based on the MeSH terms appropriate for each agent or therapeutic family, we identified literature pertaining to the subject. In addition, package information and boxed warning alerts from regulatory agencies (European Medicines Agency (EMA) and US Food and Drug Administration (FDA)) were reviewed. Methodobiologic details are provided in the Introduction section of the present Supplement issue [1]. For each agent or class of agents, a common outline is offered: (a) summary of mechanism of action, approved indications and most common off-label uses; (b) theoretically expected impact on the host's susceptibility to infection; (c) available evidence emerging from the clinical use of that agent (i.e. randomized clinical trials (RCTs), postmarketing studies, case series and single case reports); and (d) suggested preventive and risk minimization strategies. This section is devoted to review the risk of infection entailed by the use of antineoplastic agents targeting tyrosine kinases and other key signaling proteins. It should be noted that the impact of antiangiogenic agents (such as monoclonal antibodies against vascular endothelial growth factor (VEGF) and its receptor, or VEGF tyrosine kinase inhibitors), antibodies against the epidermal growth factor receptor and inhibitors of the intracellular tyrosine kinase domain of cell-surface receptors of the ErbB family (including the so-called multikinase inhibitors) has been covered in another section of the issue [2].

Table 1 summarizes the development status, approved indications and theoretical impact on infectious susceptibility of the reviewed agents, whereas the suggested strategies to prevent such complications are depicted in Table 2. It should be emphasized, however, that in view of the limited data available so far for many of these agents, the provided recommendations are necessarily open for constant modifications on the basis of ongoing and future clinical observations. Increased awareness by clinicians is required to identify emerging infections occurring in patients treated with tyrosine kinase inhibitors, to report them promptly and to collect information systematically within multicentre collaborative groups in order not to miss uncommon but relevant events.

BCR-ABL tyrosine kinase inhibitors: imatinib, dasatinib, nilotinib, bosutinib and ponatinib

Mechanism of action, approved indications and off-label uses

Chronic myeloid leukaemia (CML) is characterized by the (9; 22) (q34; q11) translocation (cytogenetically visible as the Philadelphia chromosome (Ph)), which gives rise to the breakpoint cluster region gene—Abelson murine leukaemia viral oncogene homologue 1 (BCR-ABL) fusion protein, a constitutively active tyrosine kinase (TK) that induces cell survival and proliferation. Imatinib (Glivec or Gleevec, Novartis Pharmaceuticals) was approved in 2001 as the first TK inhibitor for the treatment of Ph^+ CML. Imatinib binds to the adenosine triphosphate (ATP)-binding pocket of the BCR-ABL protein, thus preventing the kinase to become active. This agent also blocks other TKs, such as the KIT (c-Kit) receptor, the stem-cell factor receptor, the discoidin domain receptors (DDR1 and DDR2) or the platelet-derived growth factor (PDGF) receptors (PDGFR-α and -β) [3,4]. Imatinib is currently approved as first-line therapy for newly diagnosed Ph^+ CML in adults and children whose disease is not suitable for haematopoietic stem-cell transplantation (HSCT), or for those with disease in blast, accelerated or chronic phases after failure of interferon (IFN)-α therapy. In addition, it is approved for relapsed or refractory Ph^+ acute lymphoblastic leukaemia (ALL), myelodysplastic or myeloproliferative diseases associated with *PDGFR* gene rearrangements, aggressive systemic mastocytosis without the D816V c-Kit mutation or with mutational status unknown, hypereosinophilic syndrome and/or chronic eosinophilic leukaemia, and unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans. Imatinib is the only first-line targeted therapy approved for patients with c-Kit–positive gastrointestinal stromal tumours, both as adjuvant therapy after resection and in the advanced/metastatic setting [3,4].

Dasatinib (Sprycel, Bristol-Myers Squibb) is a second-generation multitargeted TK inhibitor that binds to the active and inactive forms of the BCR-ABL kinase (as opposed to imatinib, which only binds to the inactive state). It has been shown *in vitro* to exert a 300-fold more potent inhibition than imatinib, being effective against most imatinib-resistant BCR-ABL mutations. Dasatinib also targets the SRC family kinases, c-Kit, PDGFR-α and -β, DDR1 and ephrin receptors. This TK inhibitor is currently approved for newly diagnosed Ph^+ CML in chronic phase, as well as for patients with Ph^+ CML in any phase or Ph^+ ALL and resistance or intolerance to prior therapy, including imatinib [3,4].

Nilotinib (Tasigna, Novartis Pharmaceuticals) was 20 to 30 times more potent than imatinib in preclinical studies. Nilotinib inhibits most imatinib-resistant BCR-ABL mutations, as well as c-Kit, PDGFR, DDR1, VEGF and ephrin receptors. It is recommended as first-line treatment of newly diagnosed Ph^+ CML in chronic phase and for patients with disease in chronic or accelerated phases resistant to or intolerant to prior therapy, including imatinib [3,4].

Bosutinib (Bosulif, Pfizer) is other dual-specific inhibitor of the SRC and ABL kinase families that remains active against most BCR-ABL resistance mutations, although it has minimal activity against PDGFR and c-Kit. More potent than imatinib, bosutinib has been approved for CML in patients who have developed resistance or intolerance to previous therapies [3].

Ponatinib (Iclusig, Incyte Corporation) is a third-generation multitargeted TK inhibitor that exhibits a unique carbon-carbon triple bond allowing BCR-ABL kinase inhibition even in presence of the T315I mutation, which alters the topology of the ATP-binding region [3]. It is approved for patients with Ph^+ ALL or CML (in all phases of disease) disease resistant or intolerant to prior TK inhibitor-based therapies.

Expected impact on infection risk

Myelotoxicity is one of the most important adverse effects associated with TK inhibitors, particularly among patients with

Table 1
Summary of reviewed inhibitors of intracellular signaling pathways, mode of action, approved indications and expected impact on immune response

Agent	Pathway affected	Approved indications (regulatory agency)	Type of regimen	Expected impact of immune function
Imatinib, dasatinib, nilotinib, bosutinib, ponatinib	BCR-ABL, c-Kyt, other off-target kinases	• Imatinib: Ph^+ CML and ALL, MDS/MPD, hypereosinophilic syndrome and/or chronic eosinophilic leukaemia, GIST (FDA and EMA), systemic mastocytosis, dermatofibrosarcoma protuberans (FDA only) • Remaining agents: Ph^+ CML	Monotherapy or sequential therapy	Neutropenia, reduced T-cell activation and proliferation, inhibition of $CD34^+$ DCs differentiation (imatinib)
Vemurafenib, dabrafenib, encorafenib, trametinib, cobimetinib, selumetinib,	Ras/Raf/*MEK*/ERK	• All agents: unresectable or metastatic melanoma (FDA and EMA) • Dabrafenib, trametinib: NSCLC (EMA only) • Selumetinib: thyroid carcinoma (FDA and EMA)	Monotherapy, combination of *BRAF* and *MEK* inhibitors	None
Ibrutinib, acalabrutinib	Bruton tyrosine kinase	• Ibrutinib: CLL, WM, mantle-cell lymphoma (FDA and EMA), marginal zone lymphoma (FDA only) • Acalabrutinib: mantle-cell lymphoma (FDA only)	Monotherapy or combined with rituximab and bendamustine (CLL)	Inhibition of BCR signaling and B-cell activation, HGG
Idelalisib, buparlisib, rigosertib, duvelisib	Ras/PI3K/Akt/mTOR	• Idelalisib: relapsed/refractory CLL, del(17p) CLL, follicular lymphoma	Monotherapy or combined with rituximab or ofatumumab (CLL)	Inhibition of BCR signaling, reduced chemokine production
Venetoclax	Bcl-2	• del(17p) CLL (FDA and EMA)	Monotherapy	Depletion of DCs, reduced IFN-α production (animal model only)
Ruxolitinib, tofacitinib, baricitinib	JAK/STAT	• Ruxolitinib: polycythaemia vera, myelofibrosis (FDA and EMA) • Tofacitinib: rheumatoid arthritis (FDA and EMA) • Baricitinib: rheumatoid arthritis (EMA only)	Monotherapy or combined with methotrexate or nonbiologic DMARDs (rheumatoid arthritis)	Inhibition of Th1 and Th17 cell differentiation, inhibition of cytokine secretion, reduction of Tregs, impaired DCs function and migration
Sirolimus, everolimus temsirolimus,	Ras/PI3K/Akt/mTOR	• Sirolimus: SOT (FDA and EMA) • Everolimus: RCC, breast carcinoma, neuroendocrine tumours (FDA and EMA, tuberous sclerosis-associated tumours (FDA only) • Temsirolimus: RCC (EMA and FDA), mantle-cell lymphoma (EMA only)	Monotherapy or combined with other immunosuppressive agents (SOT)	Impaired innate immunity, reduced neutrophil migration, reduced pro-inflammatory cytokine production

ALL, acute lymphoblastic leukaemia; BCR, B-cell receptor; CCL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; DC, dendritic cell; del(17p), deletion of 17p; DMARD, disease-modifying antirheumatic drug; EMA, European Medicines Agency; FDA, US Food and Drug Administration; GIST, gastrointestinal stromal tumour; HGG, hypogammaglobulinaemia; MDS/MPD, myelodysplastic/myeloproliferative disease; NSCLC, non–small-cell lung carcinoma; Ph^+, positive Philadelphia chromosome; RCC, renal-cell carcinoma; SOT, solid organ transplantation; Treg, regulatory T-cell; WM, Waldenström macroglobulinaemia.

advanced disease (i.e. blastic-phase CML) [5]. Resulting neutropenia is expected to increase the risk of bacterial infection. It has been demonstrated that TK inhibitors also inhibit $CD4^+$ and $CD8^+$ T-cell proliferation in a dose-dependent manner through an off-target kinase inhibition. By inhibiting LCK, a member of the SRC family of TKs that phosphorylates the immunoreceptor tyrosine-based activation motifs on the T-cell receptor, imatinib interferes with T-cell activation and impairs cytomegalovirus (CMV)- and Epstein-Barr virus (EBV)-specific $CD8^+$ T-cell responses [6]. *In vitro* studies have shown that imatinib also inhibits the differentiation and function of $CD34^+$ dendritic cells (DCs) [7] and $CD4^+CD25^+$ regulatory T cells [8]. Both nilotinib and dasatinib have been associated with an inhibition of $CD8^+$ T-cell proliferation [9,10]. Similar to imatinib, dasatinib inhibits the proliferation of CMV-specific $CD8^+$ T cells, as well as influenza matrix protein–specific $CD8^+$ T-cell responses [10]. A recent study comparing the cellular and humoral responses to influenza and pneumococcal vaccines in CML patients on imatinib, dasatinib or nilotinib reported that TK inhibitors significantly impair B-cell responses. TK inhibitor-treated patients had significantly lower antipneumococcal IgM titers and lower frequencies of peripheral blood IgM memory B cells after vaccination compared to healthy controls [11].

Available clinical data

An initial trial that compared imatinib versus IFN-α plus low-dose cytarabine for CML showed only a moderate increase in the incidence of upper respiratory tract infection in the former group [12]. A subsequent RCT involving 250 imatinib-treated patients concluded that bacterial infection had a minor clinical impact and that the occurrence of opportunistic infection was unusual [13]. Phase 2 trials evaluating imatinib and conventional chemotherapy for Ph^+ ALL did not find significant differences in the risk of febrile episodes or documented infections compared to that observed with conventional chemotherapy alone [14,15]. Nevertheless, reactivation of hepatitis B virus (HBV) infection under imatinib treatment for CML has been repeatedly reported [16–19]. HBV reactivation was also described in two patients receiving imatinib for nonhaematobiologic conditions [20,21]. Some of these cases presented as fulminant hepatic failure, and at least two of them

Table 2
Summary of infection risks and suggested recommendations and management strategies

Agent	Increased risk of overall infection	Risk of OI	Risk of PCP	Risk of HBV reactivation	Observations and recommendations
Imatinib, dasatinib, nilotinib, bosutinib, ponatinib	Modest	IFI, HZ, tuberculosis, CMV (particularly with dasatinib)	No	Yes	• Higher risk of infection with dasatinib (particularly after HSCT) • Screening for chronic HBV infection before starting therapy •Antiviral prophylaxis while on therapy in HBsAg-positive patients • Monitoring for HBV virus load in anti-HBc positive, HBsAg-negative patients to assess eventual reactivation of occult HBV infection • No expected benefit from universal use of antibacterial, antiviral or anti-*Pneumocystis* prophylaxis
Vemurafenib, da*braf*enib, encorafenib, trametinib, cobimetinib selumetinib,	None	No	No	No	• No apparent increase in risk of infection • Some of most common drug-related adverse effects (pyrexia, fatigue, arthralgia and skin rash) may mimic ongoing infection
Ibrutinib, acalabrutinib	Modest	PCP, IFI, PML	Yes (particularly in presence of additional risk factors)	No	• Modest increase in risk of infection (contributing role of prior or concurrent therapies or inherent immune defects) • No expected benefit from universal use of antibacterial or antifungal prophylaxis • Anti-*Pneumocystis* prophylaxis for CLL patients with additional risk factors (e.g. purine analogues or high-dose corticosteroids) • PML occasionally associated with use of ibrutinib
Idelalisib, buparlisib, rigosertib, duvelisib	Major	IFI, PCP, CMV	Yes	No	• Increased risk of OIs and life-threatening adverse events (hepatotoxicity, colitis and pneumonitis) • Anti-*Pneumocystis* prophylaxis during course of therapy and for 2 to 6 months after discontinuation • Monitoring for CMV infection during course of therapy in CMV-seropositive patients or in presence of suspected CMV disease • Discontinuation of therapy in presence of suspected pneumonitis or grade 3/4 aminotransferase elevation or diarrhoea/colitis
Venetoclax	None	No	No	No	• No apparent increase in risk of infection
Ruxolitinib, tofacitinib, baricitinib	Major	PCP, HZ, tuberculosis, CMV, EBV, PML	Yes (particularly in presence of additional risk factors)	Yes	• Increased risk of overall infection and OIs • Screening for chronic HBV infection before starting therapy • Antiviral prophylaxis while on therapy in HBsAg-positive patients • Monitoring for HBV virus load in anti-HBc positive, HBsAg-negative patients to assess eventual reactivation of occult HBV infection • Screening for LTBI before starting treatment (followed by appropriate therapy if needed) • Anti-*Pneumocystis* prophylaxis in patients with additional risk factors (e.g. high-dose corticosteroids)
Sirolimus, everolimus temsirolimus,	Major	HZ, tuberculosis	No	Yes	• Increased risk of infection in cancer patients, especially in those with additional risk factors (i.e. RCC, prior or concomitant cancer therapies, delay in wound healing or aphthous stomatitis). • Screening for chronic HBV infection and LTBI before starting therapy (followed by appropriate therapy if needed) • No expected benefit from universal use of antibacterial, antiviral or anti-*Pneumocystis* prophylaxis

Anti-HBc, hepatitis B core antibody; CCL, chronic lymphocytic leukaemia; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HSCT, haematopoietic stem-cell transplantation; HZ, herpes zoster; IFI, invasive fungal infection; LTBI, latent tuberculous infection; OI, opportunistic infection; PCP, *Pneumocystis jirovecii* pneumonia; RCC, renal-cell carcinoma.

were successfully treated with liver transplantation and antiviral medication [18,20]. Although the mechanism underlying this complication is not completely understood, it appears to be associated with the inhibition of the T-cell response (which would allow intensive HBV replication) and the subsequent immune reconstitution (which would trigger the immune-mediated injury of infected hepatocytes) [18]. A retrospective analysis of 771 CML patients treated with imatinib found a rate of about 2.0% for varicella zoster virus *de novo* infection or reactivation (5.25 cases per 100 patient-years) [22]. Of note, varicella zoster virus infection was associated with a longer course of CML and a more intensive prior therapy, was not associated with disseminated forms and responded well to antiviral therapy. A case of herpes zoster (HZ) complicating imatinib therapy in a patient with gastrointestinal stromal tumours has been also reported [23], as have anecdotal examples of disseminated EBV infection [24], pulmonary [25,26] and peritoneal tuberculosis [27] and nocardiosis [28].

Data on nilotinib-related infection are scarce. Initial trials comparing nilotinib with imatinib did not describe in detail the occurrence of infectious complications [29,30]. A retrospective multicentre analysis on 88 CML patients treated with nilotinib found that seven of them (7.9%) developed infection (including one case of perianal mycosis) [31]. A nilotinib-related HBV reactivation has been recently reported [19].

A safety analysis of pooled data from dasatinib trials concluded that serious infections were rare, with only one case of grade 3/4 opportunistic infection [32]. However, a retrospective analysis of 69 dasatinib-treated patients reported an incidence of infection of 51% (with pneumonia and soft-tissue infections the most common forms), with two cases of infection-attributable death. Only one episode of proven invasive fungal infection (catheter-related *Candida krusei* bloodstream infection) was observed. Patients with infection were significantly more likely to have ALL and to have received high-dose corticosteroids. In multivariate analysis, treatment with three or more cycles of dasatinib increased the risk of infection [33]. A phase 3 study comparing two dosing regimens of dasatinib for Ph^+ ALL (140 mg once daily vs. 70 mg twice daily) reported an incidence of infection of 18% (8% for grade 3/4 events) in the once-daily arm [34]. A recent study found that the use of dasatinib in HSCT recipients to prevent or preemptively treat molecular relapse of Ph^+ haematobiologic malignancies significantly increased the risk of CMV reactivation during the first post-transplantation year (adjusted hazard ratio of 7.65 after controlling for acute graft-versus-host disease) [35]. Further cases of CMV disease (hepatitis and colitis) associated with the use of dasatinib have been reported [36–39]. Finally, there have been sporadic reports of PCP [40,41], HBV reaction [42], parvovirus B19 infection and human herpesvirus 6 reactivation [43].

Data on the risk of infection with bosutinib and ponatinib are still scarce. The BELA trial, which compared bosutinib and imatinib for CML, reported similar rates of upper respiratory tract infection (12% and 8%, respectively), with no cases of grade 3/4 infection [44,45]. A phase 2 trial including 449 CML and ALL patients treated with ponatinib reported six cases of infection-attributable death (1.3%). Nevertheless, only two of them were deemed by the investigators to be related to ponatinib [46].

Data on the cumulative impact on infection susceptibility resulting from the sequential use of different BCR-ABL tyrosine kinase inhibitors in patients with CML and resistance or intolerance to first- or second-line agents are currently limited [47]. Most studies, usually with small sample sizes, did not specifically report the occurrence of infectious complications [48–50]. Only one episode of infection (in the setting of grade 3/4 neutropenia) was observed in a phase 1/2 trial with bosutinib in 118 patients previously treated with imatinib followed by dasatinib and/or nilotinib [51]. However, evaluation of cross-intolerance found that 22% of patients with dasatinib intolerance experienced the same adverse event on bosutinib as a grade 3/4 event, suggesting that the development of deeper neutropenia might be expected with second or third lines of therapy.

Conclusions and suggested prevention strategies

- In view of available data, therapy with BCR-ABL TK inhibitors implies a modest increase in the risk of infection, most likely due to off-target inhibition of kinases involved in immune cells functionality rather than direct inhibition of the BCR-ABL signaling pathway.
- Dasatinib treatment appears to be associated with a higher rate of infectious complications, particularly CMV infection and HBV reactivation among HSCT recipients.
- Screening for chronic HBV infection should be performed before starting treatment with BCR-ABL TK inhibitors. Antiviral prophylaxis while on therapy should be offered to hepatitis B surface antigen (HBsAg)-positive patients for preventing HBV reactivation. In addition, monitoring for HBV virus load among hepatitis B core antibody (anti-HBc)-positive, HBsAg-negative patients could be indicated to assess the eventual reactivation of occult HBV infection. Alternatively, hepatitis specialist referral could be considered.
- No benefit is expected from the universal use of antibacterial or antiviral prophylaxis for patients receiving BCR-ABL TK inhibitors, although an individualized infection risk assessment seems advisable. Anti-*Pneumocystis* prophylaxis should be administered according to the general recommendations contained in the current guidelines for non–HIV-infected patients with haematobiologic conditions [52].

BRAF and MEK kinase inhibitors: vemurafenib, dabrafenib, trametinib, cobimetinib, selumetinib and encorafenib

Mechanism of action, approved indications and off-label uses

In the mitogen-activated protein kinase (MAPK) activating pathway, Ras oncoproteins activate Raf, MEK and ERK kinases to direct key cell proliferative and survival signals (Fig. 1). Activating mutations of the B-type Raf kinase (*BRAF*) oncogene are present in approximately 5% to 10% of all human malignancies and lead to constitutive activation of the MAPK pathway. Nearly half of the patients with advanced melanoma harbour the V600E mutation in the *BRAF* gene; other, less common mutations include V600K or V600R. Since the FDA approval of BRAF inhibitors for metastatic melanoma in 2011 and the subsequent introduction of combination therapy with MEK inhibitors, the outcome of patients with metastatic melanoma has dramatically changed. Survival has been increased from months to years, with long-term control in a minority of patients [53]. Four compounds have been approved by the FDA as monotherapy or combination therapy for metastatic *BRAF* V600E/K-mutant melanoma. Vemurafenib (Zelboraf, Roche) and dabrafenib (Tafinlar, GlaxoSmithKline) are BRAF inhibitors, whereas trametinib (Mekinist, Novartis Pharmaceuticals) and cobimetinib (Cotellic, Roche) are MEK1/2 inhibitors [53]. The ultimate mode of action of these agents is not entirely understood but appears to involve stimulation of T-cell proliferation and enhanced immune recognition of melanoma. In addition, the combination of dabrafenib and trametinib has been recently granted for non–small-cell lung carcinoma harbouring *BRAF* V600 mutations. Selumetinib and encorafenib are still in early phases of development.

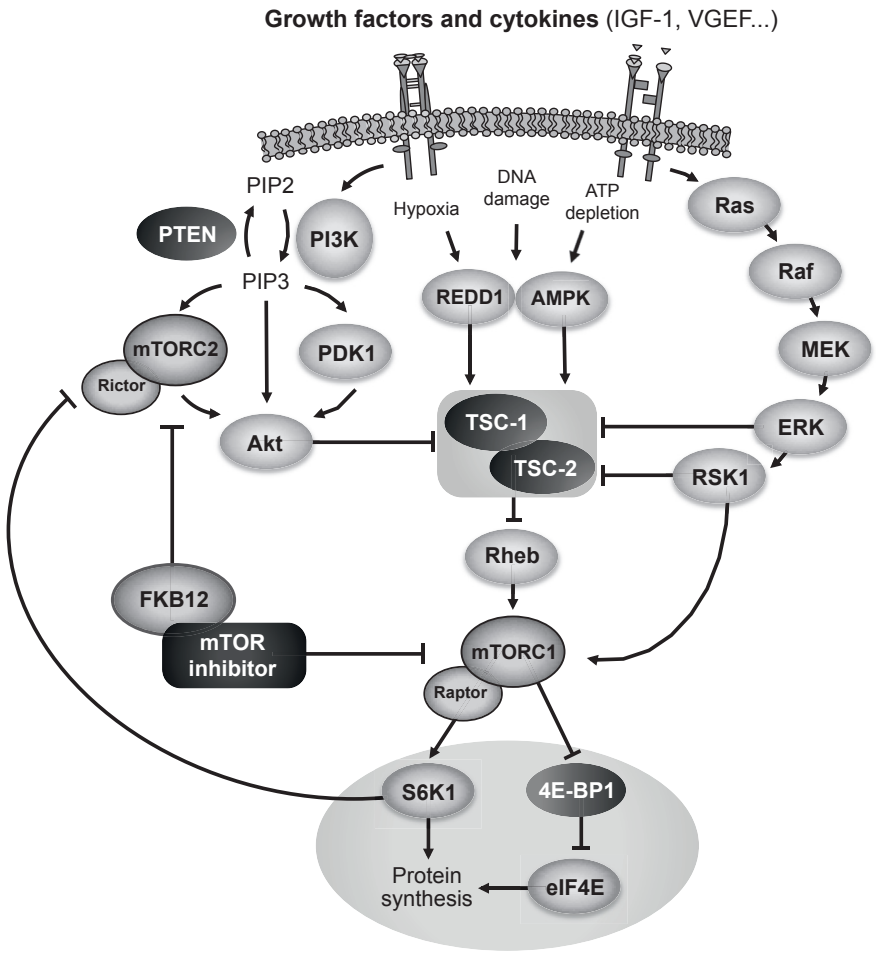

Fig. 1. Key components of Ras/PI3K/Akt/mTOR and Ras/Raf/MEK/ERK signaling pathways. mTORC1 and mTORC2 complexes modulate cell cycle via effects on p21, p27 and cyclin D1 and E. mTORC1 complex phosphorylates 4E-BP1 and S6K1 activate protein translation. Important feedback mechanisms include inactivation of mTORC2 complex and inhibition of Akt signaling by S6K1-mediated phosphorylation of Rictor and IRS1. Hypoxia, DNA damage and ATP deprivation activate TSC1/TSC2 to restrain mTORC1 and biosynthetic processes in normal tissue. Oncogenic PI3K/PDK1 and Ras/MAPK signaling cooperate to reduce TSC1/TSC2 activity. PTEN, which normally restrains PI3K activity, is also frequently deleted or inactivated in human cancer. mTOR inhibitors 3disrupt association between mTOR and Raptor. mTor, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homologue on chromosome 10.

Expected impact on susceptibility to infection

While some of the antitumour effect of BRAF and MEK kinases inhibition is believed to be mediated via the immune response (e.g. natural killer cells), targeting these pathways does not result in any apparent immunosuppression. Therefore, infection susceptibility is not expected to be directly increased.

In fact, the contrary may be the case. The MEK signaling pathway is involved in influenza virus replication, and combination therapy with oseltamivir and MEK inhibitors showed *in vitro* synergistic activity [54]. The MEK pathway is also involved in the regulation of FoxP3, a crucial transcription factor that controls function and suppressive activity of regulatory T cells (Tregs). *Ex vivo* MEK inhibition with trametinib in blood samples obtained from HIV-infected patients with tuberculosis down-regulated resting and activated Tregs and reduced the production of proinflammatory cytokines in stimulated T cells, resulting in a net improvement of the host's immune response by decreasing the chronic proinflammatory state [55]. Trametinib suppresses lipopolysaccharide-induced tumour necrosis factor α production and endotoxin shock [56]. Further studies suggest that trametinib may block Merkel-cell human polyomavirus (HPyV) infection in fibroblasts [57] or exert some antischistosomal activity [58]. Taken together, these findings support a potential antimicrobial effect. Moreover, this research line opens interesting prospects for the eventual antiviral activity exerted by these agents and their added value in certain neoplasms in whose pathogenesis oncogene viruses play an active role.

All available data hitherto are in line with the assumption that BRAF and MEK kinases inhibition has no immunosuppressive effects.

Available clinical data

The most common adverse effects in the landmark study comparing vemurafenib with dacarbazine for metastatic melanoma with arthralgia, rash, fatigue, nausea, diarrhoea and cutaneous squamous-cell carcinoma or keratoacanthoma [59]. Some of these events may mimic an infectious aetiology but were attributed to a direct effect by the drug in almost all cases. The high incidence of squamous-cell carcinoma or keratoacanthoma, some of which are mediated by human papillomaviruses and/or HPyV, prompted additional research to clarify whether BRAF inhibition has a role in viral activation and subsequent development of skin tumours. The limited data available so far have been conflicting, with some studies showing an association [60] and others failing to

demonstrate any apparent connection [61]. An extended follow-up of the initial BRIM-3 trial [59] did not reveal any additional safety issues regarding infectious events [62]. A similar lack of association was reported in the comparator trial of cobimetinib with vemurafenib [63]. In a single-centre study, vemurafenib and dabrafenib were compared for the effect on lymphocyte counts. Vemurafenib therapy decreased lymphocyte counts and altered $CD4^+$ T-cell phenotype and function compared to dabrafenib [64]. In a further analysis, the concomitant use of systemic corticosteroids and vemurafenib was found to induce a more profound lymphopenia, which was believed to contribute to the occurrence of infection in some patients (with two of them dying from pneumonia). Unfortunately, no further details were given as to the nature of the pneumonia [65]. The occurrence of a sterile scrotal abscess was reported in one patient receiving vemurafenib therapy, which was believed to be related to the therapy [66].

Comparable to vemurafenib, dabrafenib therapy did not result in any measurable increase in the risk of infection in large trials. However, the more common adverse effects included skin-related toxic effects, pyrexia and fatigue, again suggestive of an infectious aetiology [67]. The most challenging issue may therefore be the distinction between drug-induced toxicities and ongoing infection. No association between the observed skin toxicity in dabrafenib-treated patients and human papillomavirus infection was demonstrated by immunohistochemical examination of skin samples [68]. However, the successful use of dabrafenib has been reported in a patient with refractory hairy-cell leukaemia diagnosed in the previous month with invasive pulmonary aspergillosis [69].

In phase 2 and 3 studies with trametinib in combination with dabrafenib, the occurrence of fever and chills was one of the most common adverse effects observed, although it was directly attributed to the drug combination. No specific infection risk was found [70–72].

Clinical data are still limited with selumetinib and cobimetinib, but the safety profile is expected to be in line with trametinib. Selumetinib has been tested for recurrent or persistent endometrial cancer but was not pursued further because of lack of efficacy [73]. Encorafenib is still at an early stage of development, and no clinical data exist so far.

Finally, the risk of infection was not increased with the use of *BRAF* and *MEK* inhibitors in a meta-analysis [74] and in two reviews on the management of most commonly observed toxicities [75,76].

Conclusions and suggested prevention strategies

- In view of available data, therapy with BRAF and MEK kinase inhibitors does not increase the risk of infection. However, a major clinical challenge is the mimicry of an ongoing infectious complication by some of the most common drug-related adverse effects observed with this therapy (i.e. pyrexia, fatigue, arthralgia and rash).
- No specific prevention strategies are recommended for patients receiving BRAF and MEK inhibitors, although continuous clinical surveillance is advisable because the underlying mechanisms of action are still poorly understood and rare infections may have been missed, given the limited drug exposure so far.

Bruton tyrosine kinase inhibitors: ibrutinib and acalabrutinib

Mechanism of action, approved indications and off-label uses

Ibrutinib (Imbruvica, Janssen) is an inhibitor of the Bruton TK (BTK), an important signaling molecule of the B-cell receptor (BCR) and cytokine receptor pathways. The BCR pathway is implicated in the pathogenesis of several B-cell malignancies, including chronic lymphocytic leukaemia (CLL), diffuse large B-cell lymphoma, mature (peripheral) B-cell neoplasm small lymphocytic lymphoma (SLL), follicular lymphoma, and mantle-cell lymphoma. Preclinical studies have shown that ibrutinib inhibits numerous processes, including ERK kinase signaling, nuclear factor kappa B DNA binding, cytosine–phosphate–guanine–mediated CLL-cell proliferation, and tumour-cell migration [77]. However, ibrutinib does not have toxic effects on normal T cells, which distinguishes it from most conventional therapy regimens used for CLL [77]. Ibrutinib as a single agent is indicated for the treatment of adult patients with previously untreated CLL or, in combination with bendamustine and rituximab, for those that have received at least one prior therapy. In addition, ibrutinib as a single agent has been approved for relapsed or refractory mantle-cell lymphoma and Waldenström macroglobulinaemia in patients who have received at least one prior therapy or as first-line treatment for those deemed to have disease unsuitable for chemoimmunotherapy. It was also recently granted an accelerated FDA approval for the treatment of marginal zone lymphoma.

Acalabrutinib (ACP-196, Acerta Pharma BV) is a second-generation, more selective, irreversible BTK inhibitor with improved pharmacologic features, including a more favourable plasma exposure, rapid oral absorption, short half-life and absence of irreversible targeting to alternative kinases. Compared to ibrutinib, which also targets ERK and other kinases, acalabrutinib exerts a more selective action on BTK [75]. Acalabrutinib has obtained a breakthrough therapy designation from the FDA for the treatment of patients with mantle-cell lymphoma who have received at least one prior therapy.

Expected impact on infection risk

Mutation of the *BTK* gene causes X-linked (or Bruton) agammaglobulinaemia. Patients with this primary immunodeficiency exhibit a block in early B-cell maturation that prevents development of antibody-producing cells, with the subsequent phenotype consisting of severe, life-threatening bacterial infections [78]. Therefore, an impairment of humoral immunity eventually leading to the development of hypogammaglobulinaemia could be *a priori* expected among patients treated with BTK inhibitors. However, some studies have reported an increase in peripheral blood B-cell counts during the course of treatment with ibrutinib, as well as a more rapid immune reconstitution and a significantly lower rate of infection compared to conventional chemotherapy. These findings would suggest in fact that ibrutinib allows for a clinically meaningful recovery of humoral immune function in patients with CLL and other B-cell malignancies [79].

Available clinical data

The benefit of ibrutinib for relapsed or refractory CLL have been demonstrated in several prospective clinical trials [80–82]. In a phase 1b-2 study to assess the safety and efficacy of ibrutinib in patients with relapsed or refractory CLL or SLL [81], long-term therapy with this agent was associated with modest toxicity because most adverse events were grade 1 or 2. Pneumonia (occurring in ten patients, 12%) was the most common adverse event of grade 3 or higher. The average rate of infection was 7.1 per 100 patient-months throughout the first 6 months and 2.6 per 100 patient-months thereafter. In addition, ibrutinib caused a transient increase in peripheral blood total lymphocyte counts [81]. In a phase 3 study comparing ibrutinib versus ofatumumab (a CD20-targeted monoclonal antibody) for relapsed or refractory CLL, the rate of adverse events of grade 3 or higher (including diarrhoea and new-onset atrial fibrillation) was increased in the ibrutinib group.

Infections of any grade were also more common with ibrutinib (70% vs. 54%), although the occurrence of episodes of grade 3 or higher was similar across both groups (24% vs. 22%). After upper respiratory tract infections, pneumonia and urinary tract infection (with rates of about 10% among ibrutinib-treated patients) were the most commonly observed syndromes [80]. In a phase 3 trial of ibrutinib (vs. placebo) in combination with bendamustine and rituximab for previously treated CLL or SLL, a safety profile similar to that previously reported for each treatment arm individually was noted (including the occurrence of neutropenia in more than 50% of patients) [82]. The overall proportion of patients with any adverse event or grade 3/4 adverse event did not significantly differ across groups. Infection of any grade (70% in both groups) and of grade 3 or higher (29% in the ibrutinib group and 25% in the placebo group) occurred similarly. A higher incidence of atrial fibrillation was reported, again in patients treated with ibrutinib [82]. Finally, the safety of ibrutinib in a phase 3 trial for previously untreated older patients with CLL or SLL (who often had clinically significant comorbidities) was consistent with that observed in previous reports. Serious pneumonia and upper respiratory tract infection occurred in 4% and 2% of patients, respectively [83].

The experience with ibrutinib for malignancies other than CLL or SLL is also relevant [84–86]. Pneumonia of grade 3 or higher was the most common infection among patients with relapsed or refractory mantle-cell lymphoma and other types of non-Hodgkin lymphoma treated with ibrutinib (with a rate of approximately 6%) [84]. The safety profile was favourable for ibrutinib compared to temsirolimus in patients with relapsed or refractory mantle-cell lymphoma [85]. In a study of previously treated Waldenstrom macroglobulinaemia, one ibrutinib-treated patient with IgA and IgG hypogammaglobulinaemia developed streptococcal bacteraemia and infective endocarditis after a dental procedure [86]. However, the occurrence of infections deemed to be related to ibrutinib was uncommon because most patients who developed infection had preexisting hypogammaglobulinaemia [86].

Although the expected impact on T-cell function is low, opportunistic infections have been sporadically reported in patients treated with ibrutinib, including cryptococcosis [87–89], PCP [90,91], histoplasmosis [92], invasive aspergillosis [93,94] and disseminated fusariosis [95]. Of note, cases of fatal progressive multifocal leukoencephalopathy (PML) have been reported after the use of ibrutinib in the context of multiple prior treatment lines, including rituximab [96,97]. A recent literature review on the occurrence of invasive fungal infections, including PCP, cryptococcosis and invasive mould infection among patients treated with ibrutinib has drawn attention to the plausible notion that this agent could exert a deleterious off-target effect on the T cell–macrophage axis. Moreover, the authors emphasized the interplay between disease-related factors (i.e. status of underlying malignancy or comorbid conditions), environmental exposures to fungal conidia and synergy with other immunosuppressive therapies in conferring an increased susceptibility to fungal pathogens among patients treated with ibrutinib and other tyrosine kinase inhibitors [98]. Because relapsed CLL patients often harbour additional risk factors for PCP (such as multiple purine analog-based regimens or high-dose corticosteroids) [52], some experts advocate for the administration of anti-*Pneumocystis* prophylaxis throughout the entire course of ibrutinib therapy [99].

Safety data for acalabrutinib are still limited. In an uncontrolled phase 1/2 trial including 61 patients with relapsed CLL, most observed adverse events were of grade 1 or 2. Upper respiratory tract infection occurred in 23% of patients, and only one death (due to pneumonia) was observed during the course of the trial [100]. A phase 3 study (ClinicalTrials.gov NCT02477696) has commenced in which acalabrutinib is being compared to ibrutinib for high-risk patients with relapsed CLL.

Conclusions and suggested prevention strategies

- In view of available data, therapy with BTK inhibitors modestly increases the risk of infection. However, it is difficult to discern the attributable risk because these agents are usually used in combination with other immunosuppressive drugs in previously treated patients with B-cell malignancies that may be associated with inherent immune defects.
- The occurrence of infection (including pneumonia, PCP and invasive fungal infection) has been observed in ibrutinib-treated patients, especially in the presence of neutropenia.
- Although no benefit is expected from the universal use of antibacterial or antifungal prophylaxis, patients receiving ibrutinib should be closely monitored for fever or neutropenia, and appropriate anti-infective therapy should be instituted if appropriate.
- Anti-*Pneumocystis* prophylaxis should be administered according to current guidelines for non–HIV-infected patients with haematobiologic conditions [52], especially in those with relapsed or refractory CLL and additional risk factors for PCP (i.e. alemtuzumab, purine analogue-based chemotherapy or prolonged high-dose corticosteroids).
- PML is a life-threatening complication occasionally associated with the use of ibrutinib. The new onset of neurobiologic symptoms in ibrutinib-treated patients should prompt clinical suspicion and early treatment discontinuation, followed by appropriate diagnostic assessment.

Phosphatidylinositol-3-kinase inhibitors: idelalisib, Buparlisib, rigosertib and duvelisib

Mechanism of action, approved indications and off-label uses

The Ras/phosphatidylinositol-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway constitutes a critical signaling pathway frequently altered in human cancer. The PI3K is a lipid kinase that transmits signals from different surface receptors, such as BCR, thereby regulating cellular growth, survival and migration [101]. It comprises of a p85 regulatory and a p110 catalytic subunit with four different isoforms (α, β, γ and δ). The PI3Kδ signaling pathways are frequently overexpressed in B-cell malignancies, thus making its inhibition a promising therapeutic approach for CLL and SLL [102]. Idelalisib (Zydelig, Gilead) is a potent small-molecule PI3K inhibitor with highly selective activity against the δ isoform [103]. Idelalisib is currently indicated in combination with a CD20-targeted monoclonal antibody (rituximab or ofatumumab) for the treatment of adult patients with CLL after at least one prior therapy or as first-line treatment in the presence of 17p deletion (del(17p)) or *TP53* mutations in patients not eligible for alternative therapeutic approaches. It is also indicated as monotherapy in patients with refractory follicular lymphoma [104]. Buparlisib, rigosertib and duvelisib are other PI3K inhibitors (some of them with additional action on the pololike kinase 1 (PLK-1) signaling pathway) still in early phases of clinical development.

Expected impact on infection risk

In vitro, idelalisib significantly reduced chemotaxis towards CXCL12 and CXCL13, disrupted BCR signaling and interrupted paracrine chemokine production by LLC cell lines [105]. In addition to the role displayed by the PI3K/Akt/mTOR pathway in the survival of cancer cells, its importance in the homeostasis of normal

(nontumour) cells cannot be overstated. This signaling pathway contributes to regulation of cytokine production by immune cells [106], and therefore a risk of infection across all PI3K-targeted drugs has been communicated [107].

Available clinical data

Data on the safety profile of idelalisib mainly come from various phase 1/2 studies and two larger phase 3 trials [104]. The most frequently reported adverse drug reactions were rash, pyrexia, diarrhoea, neutropenia, pneumonitis, hepatotoxicity and infection. Serious infections described with idelalisib therapy include PCP and CMV disease [104]. No infectious agents have been documented in patients with idelalisib-related diarrhoea, and an autoreactive T-cell–mediated mechanism has been postulated [104]. The occurrence of fatal or serious pneumonitis not responding to conventional antimicrobial therapy has been reported in about 4% of idelalisib-treated patients (37/895) recruited across four RCTs, compared to 1% (6/548) in the comparator arm [104].

In a phase 3 trial that assessed the efficacy and safety of idelalisib plus with rituximab versus rituximab plus placebo in relapsed CLL, idelalisib significantly improved progression-free and overall survival [108]. The most frequent serious adverse events in the idelalisib and placebo groups were pneumonia (6% vs. 8%, respectively), pyrexia (6% vs. 3%) and febrile neutropenia (5% vs. 6%). The rates of PCP among idelalisib exposed and unexposed patients were 3% and 1% [108]. In a single-group phase 2 study for indolent non–Hodgkin lymphoma that had not responded to rituximab and an alkylating agent or had resulted in early relapse, the most commonly observed adverse events of grade 3 or higher were neutropenia (27%), elevation of aminotransferase levels (13%), diarrhoea/colitis (13%) and pneumonia (7%) [109]. Overall, this regimen exhibited a favourable toxicity profile, with low rates of drug discontinuation due to adverse effects.

It is more difficult to delineate the contributing role of idelalisib to the occurrence of infection among CLL patients with disease deemed unsuitable for standard chemotherapy; such patients are frequently excluded from clinical trials as a result of the presence of coexisting illnesses or relapsed markers. The most frequently observed infections are respiratory and septic events. In many instances, the causative agents were not documented, but both *P. jirovecii* and CMV seem to be frequently involved. Nearly all episodes of PCP, including fatal ones, occurred in the absence of specific prophylaxis. A retrospective analysis including data from eight clinical studies on CLL and SLL evaluated the clinical impact of PCP in these populations (Sehn LH et al., "A retrospective analysis of *Pneumocystis jirovecii* pneumonia infection in patients receiving idelalisib in clinical trials," paper presented at the American Society of Hematology meeting, December 2016, San Diego, CA). Overall, PCP occurred in 2.5% (35/1391) of idelalisib-treated patients and 0.25% (2/807) of control patients (mostly treated with CD20-targeted and alkylating agents). Of note, only 1.2% (7/598) of patients receiving anti-*Pneumocystis* prophylaxis developed this complication compared to 3.5% (28/793) of those without prophylaxis. *Post hoc* analysis of peripheral blood lymphocyte counts among idelalisib-treated patients with PCP or CMV infection suggested that quantitative monitoring may not be useful to properly assess the risk of these opportunistic infections; analysis also suggested that the functional dysregulation of immune cells function may predispose the patient to such events, even in the absence of significant lymphopenia [110]. Finally, an open-label trial comparing idelalisib with ofatumumab versus ofatumumab alone in 261 patients with relapsed CLL confirmed a higher incidence of severe infection in the idelalisib group: pneumonia (13% vs. 10%), sepsis (6% vs. 1%) and PCP (5% vs. 1%) [111]. Currently, the EMA recommends that anti-*Pneumocystis* prophylaxis should be administered to all patients throughout idelalisib therapy and for a period of 2 to 6 months after discontinuation, and that CMV infection should be regularly monitored among CMV-seropositive patients.

In March 2016, the EMA jointly analysed the results obtained from three RCTs of idelalisib (with or without bendamustine and rituximab) for previously untreated CLL or SLL. An increased risk of death and higher incidence of serious adverse events (including serious and/or fatal hepatotoxicity, colitis and pneumonitis) was noted among subjects receiving idelalisib compared to the control groups. For the EMA, these results indicate that idelalisib-related toxicity is not outweighed by the expected benefits, in view of the favourable prognosis and low disease-related mortality of previously untreated CLL patients. On the basis of these results, this regulatory agency modified the prior terms of the marketing authorizations for idelalisib and considered that such agents should only be used in treatment-naive CLL patients with del(17p) if the patients are not considered eligible for other therapies. In addition, the FDA has required a specific warning about the risk of fatal and serious idelalisib-related toxicities.

Conclusions and suggested prevention strategies

- In view of available data, therapy with idelalisib is associated with an increased risk of opportunistic infections (including PCP and CMV infection), and serious and occasionally fatal adverse events (hepatotoxicity, colitis and pneumonitis).
- Anti-*Pneumocystis* prophylaxis is recommended for patients receiving idelalisib throughout the entire course of therapy and for 2 to 6 months after discontinuation.
- Regular monitoring for CMV infection during the course of idelalisib therapy is advisable among CMV-seropositive patients or in the presence of clinically suspected CMV disease.
- Idelalisib therapy must be discontinued upon occurrence of suspected pneumonitis, grade 3/4 aminotransferase elevation (>5 times the upper reference limit) or grade 3/4 diarrhoea/colitis.

Antiapoptotic protein Bcl-2 inhibitors: venetoclax

Mechanism of action, approved indications and off-label uses

The constitutively elevated expression of the antiapoptotic protein B-cell lymphoma 2 (Bcl-2), encoded by the *BCL2* gene, renders CLL cells resistant to apoptosis, resulting in the accumulation of long-lived clonal lymphocytes that characterize the disease. Venetoclax (Venclyxto, AbbVie) is a highly selective inhibitor of Bcl-2. *In vitro,* venetoclax induced apoptosis of primary CLL cells and tumour cells that overexpressed *BCL2,* with minimal effects on platelets [112]. Del(17p) is a cytogenetic abnormality leading to the loss of the *TP53* tumour suppressor gene that is found in 3% to 10% of treatment-naive CLL patients and in up to 50% of those with relapsed or refractory disease. Del(17p) is the most important poor prognosis marker in the context of standard chemo-immunotherapy; its presence is associated with lower treatment response rate and shorter progression-free and overall survival [113]. There are few effective therapeutic options for patients with del(17p) CLL. Allogeneic HSCT is potentially curative but is only suitable for selected patients. As previously mentioned, ibrutinib monotherapy and idelalisib with rituximab are effective treatments of greater duration than chemoimmunotherapy in these patients. Venetoclax has been recently approved by the EMA and FDA (under an accelerated procedure) for patients with del(17p) CLL who have received at least one prior therapy.

Expected impact on infection risk

In addition to its role as regulators of apoptosis, the Bcl-2 family of proteins also has other functions in nontumour cells, including autophagy, calcium handling, mitochondrial dynamics and energetics [114]. In a murine model of systemic erythematous lupus, Bcl-2 antagonists selectively killed plasmacytoid DCs (which act as antigen-presenting cells) and reduced IFN-α production [115].

Available clinical data

In a phase 1 study of oral venetoclax in a dose-escalation cohort (from 150 mg to 1200 mg daily) and an expansion cohort (400 mg daily) for relapsed or refractory CLL or SLL, the most important adverse event was tumour lysis syndrome (occurring in 5.4% of patients in the former group) [116]. A relevant feature in this study was the occurrence of neutropenia (considered as grade 3/4 in 41% of participants) and febrile neutropenia (in about 6%). Other serious adverse events included pneumonia (4%), upper respiratory tract infection (3%) and immune thrombocytopenia (3%) [116]. A phase 2 single-arm trial assessed the activity and safety of venetoclax monotherapy in 107 patients with relapsed or refractory del(17p) CLL [117]. Of note, the use of antimicrobial prophylaxis was not mandatory. The majority of venetoclax-treated patients experienced a reduction in absolute lymphocyte counts. The most common grade 3/4 adverse events were neutropenia (40.2%) and infection (1.6%). Serious infections occurring in two or more patients were pneumonia (5.6%) and lower or upper respiratory tract infection (1.9% each). One patient died from septic shock, and 12 (11.2%) developed infections requiring treatment interruption or dose reduction [117].

In an internal integrated safety analysis of phase 1 and 2 trials evaluating 330 patients with relapsed or refractory CLL who received at least one dose of venetoclax, infections of any grade occurred in approximately 70% of participants [118]. The most common events were upper respiratory tract infection (23%), pneumonia (11%) and nasopharyngitis (10%). Pneumonia was the predominant grade 3/4 infection, and there were five cases of infection-attributable death infection (due to septic shock and viral pneumonia). Opportunistic infections occurred in 3.6% of patients and included invasive aspergillosis, PCP, oral and esophageal candidiasis, ocular toxoplasmosis, nocardiosis, herpes pharyngitis and multidermatomal HZ [118]. Venetoclax is a CYP3A substrate, and plasma levels are accordingly modified if coadministered with CYP3A inducers or inhibitors [119].

Conclusions and suggested prevention strategies

- In view of (limited) available data, therapy with venetoclax seems not to be associated with a meaningful increase in the risk of infection, and no benefit is expected from the use of antibacterial, antiviral or anti-*Pneumocystis* prophylaxis.
- Continuous clinical surveillance in patients receiving venetoclax is advisable because the underlying mechanisms are still poorly understood, and rare infections may have been missed given the limited drug exposure so far.

Janus kinase inhibitors: ruxolitinib, tofacitinib and baricitinib

Mechanism of action, approved indications and off-label uses

The family of Janus kinases (JAKs), which comprises four different members (JAK1, JAK2, JAK3 and tyrosine kinase 2 (TyK2)), plays a significant role in haematopoiesis and immune-cell signaling and differentiation. JAKs phosphorylate sites on the cytoplasmic tail of a variety of haematopoietic and inflammatory cytokine receptors (i.e. erythropoietin or thrombopoietin receptors), thus effecting downstream targets via the signal transducer and activator of transcription (STAT) pathway. Different JAKs or TyK2 exert differential effects. *JAK1* and *JAK2* deletions in murine knockout models impair lymphoid and neural development and erythropoiesis, respectively. Lack of TyK2 is associated with a suboptimal interferon response [120]. Loss-of-function mutations in the *JAK3* gene lead to a clinical phenotype of severe combined immunodeficiency [121–124]. Because JAK3 is downstream of a variety of cytokine receptors involved in the inflammatory cascade, such as interleukin-2, -4 or -21, pharmacobiologic inhibition of these kinases was considered promising in treating autoimmune diseases or even organ transplantation. In haematobiologic diseases, the V617F activating mutation in the *JAK2* gene has been identified as one of the major hallmarks in the pathogenesis of myeloproliferative neoplasms and has been identified in up to 95% of patients with polycythaemia vera (PV) and in 50% to 60% of patients with myelofibrosis and essential thrombocythaemia [125,126]. Mutations in JAKs have also been identified in a variety of other haematobiologic malignancies, such as acute myeloid leukaemia and myelodysplastic syndromes [127].

Currently there are three EMA-approved JAK inhibitors. Ruxolitinib (Jakavi, Novartis Pharmaceuticals) targets JAK1 and JAK2 and is approved for the treatment of patients with myelofibrosis [128] or PV (with disease resistant to or intolerant of hydroxyurea) [129]. Tofacitinib (Xeljanz, Pfizer (formerly known as tasocitinib)) acts on JAK1, JAK2 and JAK3 (and to a lesser extent on TyK2) and is indicated, in combination with methotrexate, for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients whose disease has not responded or is intolerant to disease-modifying antirheumatic drugs (DMARDs) [130]. Baricitinib (Olumiant, Eli Lilly) is a selective and reversible inhibitor of JAK1 and JAK2 that recently has been demonstrated to be superior to placebo or adalimumab in refractory RA, thus receiving approval for this condition [131]. In addition, JAK inhibitors are being evaluated for a number of other indications, such as kidney transplantation [132,133], psoriasis [134], graft-versus-host disease [135], refractory leukaemia and solid malignancies [136].

Expected impact on infection risk

Preclinical data show a distinct influence of JAK inhibitors on several components of adaptive immunity. JAK inhibitors impair T-cell function by decreasing the potential of producing proinflammatory cytokines, and therefore Th1 and Th17 responses result decreased both *in vivo* and *in vitro* [137]. Patients with myeloproliferative neoplasms treated with ruxolitinib showed a profound reduction in Tregs and a silencing of T-cell helper cytokine secretion [138]. Additionally, function and migration of DCs are impeded by ruxolitinib, thus further aggravating immune system dysfunction [139]. Lastly, ruxolitinib exposure led to a severe decrease in natural killer cell counts, a phenomenon that was linked to an increase in risk of infection [140]. Tofacitinib suppresses cytokine production, proliferation and expansion of $CD4^+$ T cells in RA patients [141], and it has been shown to modulate innate and adaptive immune responses by preventing the generation and differentiation of Th1 and Th17 cells [142].

Taken together, immunosuppressive properties of JAK inhibitors are probably mediated by a combination of immune defects. However, other factors (such as previous treatments, concurrent immunosuppressive therapy, preexisting cytopenias, patient age and comorbidities) most certainly contribute to modulate infection susceptibility.

Available clinical data

For ruxolitinib, which is the agent with the longest time period since approval, an increased risk of infection has been repeatedly observed in clinical trials. In a pivotal trial that compared ruxolitinib with best available therapy for myelofibrosis patients, infections were more frequently observed in the experimental arm [143], including urinary tract infection (24.6%), pneumonia (13.1%), HZ (11.5%), sepsis and septic shock (7.9%) and tuberculosis (1.0%) [144]. However, it should be stated that grade 3/4 neutropenia was recognized in 7.1% and 2% of patients in the ruxolitinib and placebo arms, respectively, thus confounding the immunosuppressive potential of ruxolitinib. In addition, long-term follow-up did not show an increase but rather a decrease in the incidence of infection, most likely due to stabilization of the underlying disease [143]. Outside the trial setting, recent real-life data from myelofibrosis patients treated with ruxolitinib identified several episodes of lethal infection [145], although the long-time evaluation of patients treated within an expanded access program overall reported low incidence and severity of infection [146]. For PV patients, data from a phase 3 trial indicate that ruxolitinib compared to standard therapy was associated with an increased rate of overall (42% vs. 37%) and grade 3/4 infections (3.6% vs. 2.7%). In particular, HZ was more commonly observed in ruxolitinib-treated patients (6% vs. 0) [129]. In patients with relapsed acute myeloid leukaemia treated with ruxolitinib, the most common grade 3/4 nonhaematologic events consisted of infection, especially pneumonia (57.7%, 15/26, of patients) [147]. Pneumonia was also much more frequent among patients with metastatic pancreatic carcinoma receiving ruxolitinib compared to placebo (plus capecitabine in both arms) [136]. Safety evaluation of allogeneic HSCT recipients who had been treated with JAK inhibitors before transplantation also found atypical and opportunistic infections to occur frequently, including CMV and EBV reactivation (leading to posttransplantation lymphoproliferative disorder in one case), BK HPyV-associated hemorrhagic cystitis and invasive fungal infection [148]. In addition, case reports of severe opportunistic infections in patients receiving ruxolitinib have been repeatedly published, such as HBV reactivation (including occult HBV infection reactivation in anti-HBc–positive, HBsAg-negative patients) [149,150], *Cryptococcus neoformans* pneumonia [151], PCP [152], bilateral *Toxoplasma* chorioretinitis [153], disseminated tuberculosis [154] and PML [155].

Regarding the use of JAK inhibitors in rheumatologic conditions, most data derive from tofacitinib. In a pivotal RCT, an increased rate of serious infections was observed compared to placebo [156]. A safety analysis of pooled data from RA trials (covering approximately 4800 patients) found a significant incidence of infection and infection-related mortality with tocilizumab that, however, was similar to that observed with other biologic agents. Age, diabetes, prior corticosteroid therapy, low lymphocyte counts and tofacitinib dose were independently linked to risk of serious infection [157]. A recent meta-analysis evaluating 66 RCTs and 22 long-term extension studies also illustrated a higher incidence of infection with tofacitinib compared to placebo, although such risk was comparable to that observed with other biologic DMARDs [158]. Another recent analysis evaluating the efficacy and safety of tofacitinib in patients whose disease had inadequate response to conventional synthetic or biologic DMARDs confirmed that patients receiving concurrent corticosteroid therapy had more serious infections, especially HZ [159].

A recent trial compared tofacitinib (5 or 10 mg daily) with etanercept for the treatment of psoriasis. Rates of infection were similar across study arms, with nasopharyngitis and upper respiratory tract infections as the most common events [134]. Two recently published trials in patients with psoriatic arthritis and inadequate response to prior therapy with tumour necrosis factor α–targeted agents or conventional DMARDs, serious infections (pneumonia and pyelonephritis) and HZ (including cases with multidermatomal involvement) were more common with tofacitinib than placebo [160] or adalimumab [161].

With regard to classic opportunistic infections, Winthrop et al. [162] analysed phase 1/2 RCTs and long-term extension studies in RA and identified 60 episodes among 5671 subjects. Tuberculosis was the most common event and was associated with a higher tofacitinib dose (tofacitinib 10 mg twice daily). Importantly, prior treatment of latent tuberculosis infection with isoniazid seemed to be protective. Other opportunistic infections included esophageal candidiasis (nine cases), disseminated or multidermatomal HZ (eight cases), CMV infection (six cases) and PCP (four cases) [162]. On the basis of the immunosuppressive properties of DMARDs including tofacitinib, screening for viral hepatitis has been proposed for patients receiving tofacitinib treatment, with prophylaxis for those at medium or high risk of HBV reactivation [163].

Tofacitinib has been also compared to cyclosporine A in a phase 2b trial for kidney transplant recipients [132]. Serious infections (including CMV disease and EBV-associated posttransplantation lymphoproliferative disorder) were significantly more common among tofacitinib-treated patients. Pharmacokinetic analysis suggested an exposure-dependent mechanism in infection susceptibility [164].

For the newest EMA-approved JAK inhibitor baricitinib, clinical data on the risk of infectious complications can be only extracted from phase 2 and 3 trials. In the initial study comparing different doses with placebo, infection was more frequent among baricitinib-treated patients, although the rate of serious infections was comparable across groups (about 3%). Although HZ occurred in all three arms, the largest numbers were seen with baricitinib at the highest analysed dose (4 mg) [165].

Conclusions and suggested prevention strategies

- In view of available data, therapy with JAK inhibitors is associated with a markedly increased risk of infection due to the direct suppression of critical components of the immune system.
- Screening for chronic HBV infection should be performed before initiating treatment with JAK inhibitors. Antiviral prophylaxis while receiving therapy should be offered to HBsAg-positive patients for preventing HBV reactivation. In addition, monitoring for HBV virus load among anti-HBc positive, HBsAg-negative patients may be indicated to assess the eventual reactivation of occult HBV infection. Alternatively, specialist referral could be considered.
- Screening for latent tuberculosis infection may also be considered before starting treatment with JAK inhibitors (followed by appropriate therapy if needed), as tuberculosis constitutes the most common opportunistic infection observed.
- Clinicians caring for patients receiving JAK inhibitors should be aware of the increased risk of overall and opportunistic infection (including tuberculosis, PCP, HZ and invasive fungal infection), especially in those with additional risk factors (i.e. prior or concomitant corticosteroid therapy, low lymphocyte counts or high-dose therapy with JAK inhibitors).
- In view of (limited) available data, the administration of antiviral and anti-*Pneumocystis* prophylaxis should be individualized considered, especially in patients with additional risk factors.

mTOR inhibitors: sirolimus, temsirolimus and everolimus

Mechanism of action, approved indications and off-label uses

As previously mentioned, the Ras/PI3K/Akt/mTOR pathway (Fig. 1) plays a crucial role in cell survival, growth and proliferation

[166]. mTOR is a serine/threonine kinase and a member of the PI3K-related kinase superfamily [167]. Two distinct mTOR complexes have been identified, mTORC1 and mTORC2. The effects of mTOR on growth, division and metabolism are largely attributable to mTORC1, which is regulated by signals generated from growth factors and cytokine receptors (such as human epidermal growth factor receptor 2 (HER2), c-Kit, VEGF and PDGF) and by changes in intracellular ATP content [168]. In addition, it is increasingly clear that many cancer-promoting lesions activate the mTORC1 pathway [169]. The key factor upstream of mTOR is PI3K, which, upon activation, is able to recruit Akt to the cell membrane that regulates cell metabolism and mTOR activity. Phosphatase and tensin homologue on chromosome 10 (PTEN) is a phosphatidylinositol-3-phosphatase that negatively regulates this pathway and reverses the action of PI3K [170]. The second mTOR-containing complex (mTORC2) is less understood than mTORC1, but it seems to constitute a critical part of a feedback loop in the PI3K/Akt pathway [171].

The mTORC1 complex regulates protein synthesis through two downstream pathways, namely inactivation of the repressor of mRNA translation 4E-BP1 (eukaryotic translation initiation factor 4E-binding protein) and activation of S6K1 (ribosomal S6 kinase 1) that enhances mRNA translation. By phosphorylating the 4E-BP family of proteins, mTORC1 represses their capacity to inhibit eIF4E (eukaryotic translation initiation factor 4E), thus promoting protein synthesis [172]. Akt is a positive regulator of mTORC1 that phosphorylates and thereby inhibits the heterodimeric tumour suppressor complex (TSC)-1 (harmartin) and TSC2 (tuberin) by removing its inhibitory effect on mTORC1 [168,173]. TSC1/TSC2 inhibits Rheb (Ras homologue enriched in brain), a positive regulator of mTOR that acts downstream of TSC1/TSC2, PI3K and Akt. Aberrant PI3K/mTOR activation is frequently observed in human cancers [174]. The most common underlying mechanism is the loss of *PTEN* gene expression due to deletion or inactivating mutations. Up-regulation can also result from the activation of receptor TKs or alterations of the different isoforms of PI3K [175].

The mTOR inhibitors comprise a unique drug class in possessing both immunosuppressive and anticancer activity. Rapamycin (Rapamune, Pfizer; also known as sirolimus) and its analogues, the macrolides everolimus (Certican or Afinitor, Novartis Pharmaceuticals) and temsirolimus (Torisel, Pfizer), act by forming an allosteric inhibitory complex with their intracellular receptor, the immunophilin FK506-binding protein (FKBP12), which binds a region in mTORC1 termed FRB (FKB12-rapamycin binding). Thus, these agents inhibit mTORC1 kinase activity [176] (Fig. 1). In addition to direct effects on tumour cells, rapamycin also potently inhibits angiogenesis and endothelial cell proliferation [177,178].

The investigation of mTOR inhibitors as anticancer therapies was aided by the fact that rapamycin (sirolimus) had been already approved in 1998 to prevent acute rejection in solid organ transplant (SOT) recipients. Several clinical trials have tested the efficacy of rapamycin and its analogues as anticancer therapy [179]. Analyses of neuroendocrine pancreatic tumours have shown alterations in the mTOR pathway, with down-regulation of PTEN and TSC2 observed in most cases [180]. The antineoplastic properties of mTOR inhibitors were first demonstrated for renal angiomyolipoma or pulmonary lymphangioleiomyomatosis in the setting of tuberous sclerosis complex [181,182] and for Kaposi sarcoma [183,184]. Experimental and clinical evidence also indicated a role for the PI3K/mTOR pathway in the development of resistance in patients with hormone receptor–positive breast cancer [185].

Everolimus has been approved by the FDA and EMA for the treatment of advanced renal-cell carcinoma (RCC) after failure of VEGF receptor–targeted therapies (sunitinib or sorafenib) [186–189], advanced neuroendocrine pancreatic tumours [190], advanced hormone receptor–positive HER2-negative breast cancer (in combination with exemestane) [191] and progressive nonfunctional neuroendocrine gastrointestinal and lung tumours. In addition, everolimus is FDA approved for subependymal giant-cell astrocytoma and angiomyolipoma associated with tuberous sclerosis [192]. Temsirolimus has been approved for advanced RCC. In addition, there are promising results from a phase 3 trial for refractory mantle-cell lymphoma [193]. However, even though PTEN loss is frequently observed in sporadic glioma and melanoma, mTOR inhibitors have had only little efficacy in these malignancies [194–196]. In fact, the efficacy of such agents has also been disappointing in patients with metastatic breast cancer [197,198] despite frequent PI3K activation [174].

Expected impact on infection susceptibility

In addition to the well-demonstrated direct inhibition on virus replication exerted by mTOR inhibitors (particularly investigated for CMV in the setting of SOT [199–201]), it should be highlighted that mTORC1-mediated functions include both immunosuppressive and immune-activating properties. The mTORC1 complex promotes T-cell anergy, induces Treg expansion and inhibits maturation of DC [202]. However, the use of mTOR inhibitors results in the enhancement of central and effector memory $CD8^+$ T-cell responses after vaccination in nonhuman primates [203]. The role of mTOR in B-cell development and function has recently been reviewed [204]. Relevant to the present review is the notion that patients receiving mTOR inhibitors may have a hampered innate immune response [205]. The migration of neutrophils to sites of inflammation requires mTOR [206–208], as well as the production of proinflammatory cytokines [206,209,210]. The defects in innate immunity may be further compromised by the effect of mTOR inhibition on stromal cells, leading to impaired wound healing [211]. A relevant proportion of mTOR inhibitor-treated patients develop stomatitis and pneumonitis, which may constitute an entry port for pathogenic microorganisms [212]. The mTOR pathway has been also implicated in neutrophil function, including formation of extracellular traps that capture and kill microbes, in a process involving the hypoxia-inducible factor 1α (HIF1α) pathway [213]. About 50% to 60% of cases or RCC exhibit loss of the von Hippel-Lindau tumour suppressor, which encodes a negative regulator of HIF1α [186]. Accordingly, an increased risk of respiratory and genitourinary tract infections with everolimus or temsirolimus has been observed in patients with RCC compared to those with other carcinomas [214].

Available clinical data

Despite long-term experience with mTOR inhibitors in SOT recipients, the widespread use of these agents has been limited by the relatively high discontinuation rates, reaching up to 20% to 30% of participants in most transplantation trials [215–219]. These observations have posed a significant challenge to the perception of the efficacy of mTOR inhibitors as immunosuppressive and/or antineoplastic agents in relation to their tolerability. The most common adverse effects attributed to mTOR inhibitors include anaemia, thrombocytopenia and increased triglyceride and/or cholesterol levels. Theoretically, therapeutic drug monitoring could be helpful in preventing adverse events [220]. For everolimus, however, a dose-dependent association has only been shown for thrombocytopenia, not for leucopenia or hyperlipidaemia [221]. Aphthous stomatitis and diarrhoea are more frequently reported than in patients treated with a calcineurin inhibitors and mycophenolic acid [222–224]. An infrequent but potentially life-threatening adverse effect is noninfectious pneumonitis. This entity is characterized by (nonspecific) inflammatory infiltrates in

combination with negative results for infectious causes in blood and bronchoalveolar lavage tests [225]. The incidence of pneumonitis associated with sirolimus or everolimus has been reported to be between 1% and 12% [226]. No definite risk factors have been identified, and in case of pneumonitis related to a mTOR inhibitor therapy, the drug class should be discontinued.

A systematic review of 12 RCTs reported an increased risk of infectious complications associated with the use of high-dose everolimus or temsirolimus in cancer patients [227]. Dosing strategies of mTOR inhibitors in cancer patients often differ from those used in SOT recipients [228–232]. Of note, a higher risk of mortality associated with the use of sirolimus has been found in a systemic review based on individual patient data from 21 transplant trials (involving about 6000 patients). This increased mortality rate was not related to graft loss with return to dialysis but to cardiovascular- and infection-related deaths [233]. A recent meta-analysis utilizing data from 12 phase 2 and 3 trials comparing everolimus or temsirolimus versus placebo in cancer patients also reported a significantly higher risk of infection with mTOR inhibitors, with incidences for all-grade and severe mTOR inhibitor-attributable infection of 9.3% and 2.3%, respectively. The risk substantially varied across different tumour types, being higher for RCC, lymphoma and neuroendocrine tumours. There was no significant difference between everolimus and temsirolimus. Upper respiratory tract infection, urinary tract infection and pneumonia were the predominant forms, with some examples of opportunistic infection (i.e. tuberculosis and HZ) and HBV reactivation. Unfortunately, specific information on the type of infection was not provided in most of included trials [234]. Further case reports have highlighted the risk of HBV reactivation in cancer patients receiving mTOR inhibitors [235,236].

Conclusions and suggested prevention strategies

- In view of available data, therapy with mTOR inhibitors in cancer patients is associated with an increased risk of infection, an association that may be partially explained by the different dosing strategies used in this population compared to SOT recipients.
- Clinicians caring for patients receiving mTOR inhibitors should be aware of the increased risk of overall infection, especially in those with additional risk factors (i.e. certain specific malignancies, prior or concomitant use of potent cancer therapies or presence of drug-related delay in wound healing or aphthous stomatitis).
- Screening for chronic (latent) infections, including HBV and latent tuberculosis infection, may be advisable before initiating treatment with mTOR inhibitors (followed by appropriate prophylaxis or therapy if needed).
- No benefit is expected from the universal use of antibacterial, antiviral or anti-*Pneumocystis* prophylaxis for patients receiving mTOR inhibitors, although it seems advisable to individualize infection risk assessment.

Transparency declaration

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