Bruton tyrosine kinase inhibitors as potential therapeutic agents for COVID-19: A review

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is first detected in December 2019 in Wuhan, China which is a new pandemic caused by SARS-COV-2 that has greatly affected the whole world. Bruton tyrosine kinase (BTK) inhibitors are drugs that are used for the management of cancer, and are being repurposed for COVID-19. BTK regulates macrophage and B cell activation, development, survival, and signaling. Inhibition of BTK has revealed an ameliorative effect on lung injury in patients with severe COVID-19. Thus, this review aimed to summarize evidence regarding the role of Bruton tyrosine kinase inhibitors against COVID-19. To include findings from diverse studies, publications related to BTK inhibitors and Covid-19 were searched from the databases such as SCOPUS, Web of Science, Medline, Google Scholar, PubMed, and Elsevier, using English key terms. Both experimental and clinical studies suggest that targeting excessive host inflammation with a BTK inhibitor is a potential therapeutic strategy in the treatment of patients with severe COVID-19. Currently, BTK inhibitors such as ibrutinib and acalabrutinib have shown a protective effect against pulmonary injury in a small series group of COVID-19 infected patients. Small molecule inhibitors like BTK inhibitors, targeting a wide range of pro-inflamatory singling pathways, may a key role in the management of COVID-19.

1. Introduction

Novel coronavirus disease 2019 (COVID-19), which originated from Wuhan, China, has created a dangerous and deadly public health disaster of international apprehension, with cases confirmed in several countries [1]. SARS-CoV-2 infects respiratory and nasal epithelial cells through binding to ACE2 [2,3], and enters into cell, replicates and induces recruitment of monocytes into the pulmonary system [4]. In patients with COVID-19, an inflammatory macrophage response is triggered resulting in lung injury, and respiratory failure. An extensive cellular infiltration dominated by macrophages was reported in patients that succumb to SARS-CoV-2 infection through the postmortem examination of the lungs [4].

Globally, as of July 8, 2021, more than 184,573,518 people have been infected with COVID-19, more than 3,993,602 have died, and more than 168,922,458 have recovered [5]. Among patients with COVID-19, about 25–50% of them are asymptomatic. Among symptomatic patients with COVID-19, symptoms range from mild symptoms of fever, malaise, and dry cough to severe symptoms like dyspnea due to acute respiratory distress syndrome and life-threatening pneumonia. Other sever complications of COVI-19 comprise neurologic dysfunction, thrombotic events, and cardiomypathy leading to cardiac arrest, multi-organ failure, disseminated intravascular coagulopathy, and eventually death [6].

Severe disease manifestations are more frequent in individuals who are elderly or have comorbidities [7,8]. The association of COVID-19 and cancer particularly hematologic cancers, remains uncertain [9–12], although evidence suggests that patients with cancer experience higher infection rate and a worse outcome [13]. A study conducted in China revealed that there is a higher occurrence of severe events such as intensive care unit admission and death among COVID-19 patients with cancer when compared to those without cancer [14].

Bruton’s tyrosine kinase (BTK) is a non-receptor tyrosine kinase that has its place in the TEC family [15,16]. BTK is expressed principally in myeloid cells and B cells, where it functions downstream of receptors such as the Fc receptors, B-cell receptor, and toll-like receptors [17–21]. B-cell receptor assignation cause BTK activation through phosphorylation on Y551 in the activation loop, which leads to direct activation and phosphorylation of phospholipase C gamma 2 (PLCγ2) activating regulation of gene transcription and calcium flux [17]. Furthermore, the clear role of the BTK catalytic domain in activating PLCγ2, the N-terminal regulatory domains of BTK, which include a proline-rich region, a
SRC homology 3 domain, SRC homology 2 domain, Pleckstrin homology, and Tec homology domain, mediates autoinhibitory and activating interactions that regulate BTK function [22,23].

BTK plays a significant role in triggering the receptor expressed on myeloid cells 1 such as CD354 and TREM1 signaling in monocytic cells that seems to be involved in the pathogenesis of infectious complications [24]. A previous in vivo study in a mouse model of X-linked agammaglobulinemia revealed that BTK is an important regulator of neutrophilic granulocyte function and maturation [25]. Moreover, ibrutinib (a BTK inhibitor) hinders platelet adhesion to lymphatic endothelial cells through the off-target binding of SRC kinases. Through this mechanism, platelet internalization of Aspergillus spp. is also repressed which could also contribute to amplified susceptibility for fungal infections [26].

2. The rationale for repurposing approved kinase inhibitors for COVID-19 treatment

SARS-CoV-2 has its place in the Baltimore Group IV classification of RNA viruses, which also includes dengue virus, hepatitis C virus, rhinoviruses, and West Nile virus, but then again it utmost closely resembles MERS-CoV and SARS-CoV [27]. SARS-CoV-2 shares 80% RNA sequence identity with SARS-CoV and 50% sequence identity with MERS-CoV, which is a member of the Beta coronavirus genus [28,29]. Although the rates of transmission and mortality differ between MERS-CoV, SARS-CoV, and SARS-CoV-2, there is a considerable intersection in the genetic makeup, pathogenesis, and clinical features of the infections caused by these viruses [30].

Several kinases have been proposed as being vital mediators of various viral infections, particularly MERS-CoV, SARS-CoV, and SARS-CoV-2. It is well known that protein kinases have become a remarkably investigated group of drug targets, accounting for 20–30% of the drug discovery programs of major drug companies and are therefore an appropriate drug target. Numerous kinase inhibitors exert important immunomodulatory actions that could help to alleviate symptoms of COVID-19, such as cytokine suppression, anti-inflammatory effect, and antifibrotic effect. Presently, kinase inhibitors with good pharmacokinetic profiles that have been repurposed for COVID-19, may be beneficial by suppressing disease symptoms and reduce infection through direct viral targeting [31,32]. On the other hand, kinase inhibitors have been verified in combination with antiviral agents or other targeted therapies that display potential activities in clinical trials for COVID-19 to attain superior efficacy than any one agent alone [32].

3. Signaling of BTK and SYK

BTK and SYK are cytoplasmic non-receptor tyrosine kinases, communicating signals from different cell surface receptors such as Fc receptors, BCR, integrins, and CD74 [33]. Receptor crosslinking subsequently cascade of enzymatic activation leads to the cooperation of conscripted BTK with SYK to trigger phospholipase C-gamma2, which eventually end up with Phosphoinositide 3-kinase and MAPK dependent downstream signaling cascades regulating miscellaneous cellular processes like proliferation, cytoskeletal remodeling, differentiation and cell growth [33]. The BTK family comprises 4 members and is expressed in all hematopoietic cells and lymphocytes except for mature plasma B cells and T cells [33]. Phosphorylated SYK was noticed in synovial tissue of RA patients and peripheral blood B cells [34,35]. Autoantibodies formed by most RA patients and B cells, mainly rheumatoid factor and anti-citrullinated peptide/protein antibody, play a significant role in the pathogenesis of different diseases. As BTK is essential for the regulation of the B cell activation and proliferation process, while SYK functions as a key molecule in B cell receptor signaling; therefore, both kinase proteins were suggested as a therapeutic target in the management of rheumatoid arthritis, glioastoma, carcinoma, lymphoma, leukemia, and lymphoproliferative disorders [36].

The SYK family contains 2 members: SYK kinase and zeta-chain-associated protein kinase 70 (ZAP70). ZAP70 expression is restricted to NK cells and T lymphocytes, whereas SYK is expressed in mast cells hematopoietic cells and synoviocytes [37]. SYK is activated in synoviocytes by pro-inflammatory cytokines like IL-1 and TNF, which stimulate IL-6 production and activate JNK, leads to stimulation of proliferation, survival, differentiation, degranulation, and phagocytosis, and IL-12 and IL-13 synthesis in synoviocytes [38].

4. The role of BTK inhibitors in the treatment of COVID-19

4.1. BTK inhibition may attenuate the COVID-19-related acute respiratory distress syndrome

In the previous studies, the overexpression of BTK in the lungs is linked with the induction of an acute respiratory distress syndrome and lung injury has been conveyed [39–41]. Thus, BTK is anticipated to have a role in sepsis-induced acute lung injury [39]. Intratracheal injection of BTK siRNA (a silencing RNA, which knocks down BTK gene expression) confirms potent protection against sepsis-induced acute lung injury in a mice model of puncture-induced sepsis-induced acute lung injury and cecal ligation, as confirmed through a significant decrement in vascular permeability, epithelial cell apoptosis, pulmonary edema, pathological scores, and the expression of neutrophil infiltration and inflammatory cytokines in the lung tissues of septic mice [39]. Furthermore, constraining BTK by ibrutinib (a BTK inhibitor) saved mice from deadly influenza-driven acute lung injury. BTK inhibition produced significant morphological changes and decreased alveolar hemorrhage to the lungs [40]. A similar finding also revealed that BTK has a significant role in trauma hemorrhagic shock-induced lung injury in rats, and inhibiting BTK effect with the LFM-A13 inhibitor protects lungs from this damage [41]. Moreover, overexpression of BTK in the lung is linked with total basal membrane thickness, collagen deposition around airways, increasing airway resistance, and decreasing airway stiffness [42]. The role of BTK in collagen deposition is facilitated through matrix metalloproteinsase-9 [42]. All these findings suggest a solid role of BTK in various animal models of lung injury and that its blockage can improve some of the symptoms involved. Thus, it is postulated that BTK inhibitors may decrease the severity of COVID-19-associated lung injury through a direct effect on the general components of the exacerbated damage response to the COVID-19.

4.2. BTK inhibition reduces the hyperinflammatory response in the lung

In patients with COVID-19, virus-induced hyperinflammation is a key cause of death and disease severity [43–45]. Certainly, it has been lately anticipated that the actual reason for death by COVID-19 may be organ inflammation and injury as a result of the immune response itself, rather than the direct effects of the virus on body tissue [46]. Characteristic features of hyper inflammation comprise: augmented serum levels of several inflammatory chemokines and cytokines, such as IL-6, granulocyte-macrophage colony-stimulating factor, IL-10, IFN-γ, granulocyte colony-stimulating factor, IL-8, interferon-γ (IFN-γ), IFN-γ-inducible protein 10, IL-7, monocyte chemoattractant protein, IL-9, and macrophage inflammatory protein-1α and β [47–49]; increased macrophage activity [41]; and increased neutrophil-to-lymphocyte ratio [50–52].

An in vivo study demonstrated that inhibition of BTK improved immunity because of inhibition of macrophages [53]. BTK-mediated macrophage inhibition is mediated by hindering the activation of the NF-κB and the inflammasome [53]. Both NF-κB and inflammasome pathways are known to play a significant role in cytokine storm in patients with COVID-19 [54,55].

Studies have shown that BTK is implicated in the regulation of pro-inflammatory processes in the lung, which induce irreversible tissue damage [42,56,57]. Treatment with ibrutinib reduced lung inflammation by decreasing neutrophil influx, alveolar macrophage activation,
plasma leakage into the lung, and cytokine release in an animal model of pneumococcal pneumonia [58]. Furthermore, treatment of patients with chronic graft-versus-host disease (cGVHD) by ibrutinib prevents the IL-2 inducible T-cell kinase, which is involved in the selective activation of T-cells that drive immune reactivity toward healthy tissues [59]. This finding supports the suggested anti-inflammatory effect of BTK inhibitors in the lung. Similar studies have also revealed the role of BTK in neutrophil and macrophage/monocyte activity [60,61], which contribute to the inflammatory response to infections.

The infiltrate of immune cells in alveoli of COVID-19 infected patients are mainly monocytes and macrophages, whereas modest multinucleated minimal lymphocytes, eosinophils, neutrophils, and giant cells are detected [62]. Furthermore, macrophages that express Toll-Like Receptors (TLR) play a significant role in identifying ssRNA cells are detected [62]. Furthermore, macrophages that express Toll-Like Receptors (TLR) play a significant role in identifying ssRNA virus. BTK has a significant role in the initiation of TLRs signaling by NF-κB, which activates the expression of numerous inflammatory chemokines, and cytokines (IL-1β, TNF-α, IL-6, IL-8, and IL-12, CCL2) [63,64]. In agreement with this, it was confirmed that treatment of COVID-19 infected patients with acalabrutinib (a BTK inhibitor) for about fourteen days showed improvement of lymphopenia and normalization of IL6 [65]. This finding may be linked with a reduction in inflammatory chemokines and cytokines [67].

Mice that are deficient to BTK have noticeably decreased recruitment of M1 macrophages since BTK is vital for M1 macrophage polarization [68]. It has been confirmed that BTK inhibition abrogates M1 polarization through the suppression of IL-10 and CSF1 in the mice model [69]. Several studies reported that there is a positive association between lymphopenia and COVID-19 severity. Presently, it is uncertain how lymphopenia augments SARS-CoV-2 infection. Though, it is confirmed that lymphopenia enhances the cytokine storm [70]. Prominently, treatment of CLL patients using ibrutinib showed an increment of the absolute lymphocyte count in the peripheral blood [71,72].

BTK inhibitors like ibrutinib, bind to other kinases (SRC family kinases) and suppress their actions [73]. Interestingly, some of the SRC family kinases play a significant role in the replication of viruses [32]. Specifically, Saracatinib showed a significant inhibitory action on MERS-CoV at the early stages of the viral life cycle through inhibition of SRC [74]. Therefore, BTK inhibitors may have a significant role in the treatment of patients infected with SARS-CoV-2 through SRC inhibition.

4.3. Association of absolute lymphocyte count, C-reactive protein, and oxygen uptake

A study showed that patients with COVID-19 receiving supplemental oxygen generally improved absolute lymphocyte count, their oxygen uptake efficiency, and reduced their C-reactive protein levels [75]. Furthermore, C-reactive protein levels were negatively related to absolute lymphocyte count values in the supplemental oxygen cohort. A similar finding was detected in the mechanical ventilation cohort, however, without statistical significance. C-reactive protein levels were negatively related to oxygen uptake in both the mechanical ventilation cohort and the supplemental oxygen cohort. Absolute lymphocyte count was positively correlated with oxygen uptake in the supplemental oxygen cohort, but not in the mechanical ventilation cohort. Thus, this finding showed that C-reactive protein and absolute lymphocyte count are associated with clinical improvement as measured by oxygen uptake [75].

4.4. BTK inhibitors may decrease thrombosis in patients with COVID-19

Patients with COVID-19 are in a high risk of thrombotic complications, and approximately 20% of them are critically ill patients presenting venous thromboembolism, which adversely affects the disease progression [76,77]. A previous study revealed that BTK inhibitors such as ibrutinib have resulted a reduction in arterial and venous thrombosis by unknown mechanism [78,79]. Therefore, this finding supports the use of BTK inhibitors in the treatment of COVID-19. Interestingly, BTK inhibitors would lack the bleeding side effects of regular anticoagulants [80].

4.5. The role of BTK in COVID-19 patients with cancer

Patients with cancer have been designated as one of the most vulnerable groups for COVID-19, having shown so far a high mortality rate [81–83]. Particularly, patients with lung cancer, myeloma, leukemia, lymphoma, and metastatic cancer had the highest incidence of severe complications of COVID-19, labeled as illness requiring admission to an ICU, the use of mechanical ventilation, or death [11]. Though, the possible risk factors that lead to high vulnerability in patients with cancer are poorly elucidated.

4.5.1. Effect of BTK inhibitors in COVID-19 patients with blood malignancies

BTK inhibitors could serve as a supportive treatment in COVID-19 patients with blood cancer [66,84,85], given the beneficial activities of BTK inhibitors and the oncogenic activity of BTK [86–88]. The outcomes of the administration of ibrutinib to 8 COVID-19 patients with chronic lymphocytic leukemia (CLL) have been previously reported [85]. Six of them discontinued BTK inhibitor treatment and only two of them were permitted to continue BTK inhibitor treatment. According to this study, BTK inhibitor-treated group showed mild-to-moderate symptoms, minimal oxygen requirements, short hospital stays, and ultimately a full recovery [85].

A similar study revealed that administration of ibrutinib to COVID-19 infected patients with Waldenstrom’s Macroglobulinemia have shown a protective effect by shortening hospitalization, reducing requirement of mechanical ventilation, and improving symptoms [89]. However, additional investigation is required to understand and elucidate the exact mechanisms.

SARS-CoV-2 infection induces an immune response similar to the cytokine release syndrome, significant increase in serum levels of pro-inflammatory cytokines that are supposed to be the main causes of mortality and morbidity in patients with COVID-19 [47]. Numerous medications with anti-inflammatory activity such as Siltuximab, Tocilizumab, Anakinra, and Sarilumab have been proposed as adjuvant therapy in the treatment of COVID-19, and numerous clinical trials are ongoing [85].

The BTK inhibitors such as acalabrutinib, ibrutinib, and zanubrutinib are frequently used in the management of Waldenstrom’s Macroglobulinemia, cGVHD, chronic lymphocytic leukemia, and also displayed anti-inflammatory activities resulting in reduced levels of pro-inflammatory cytokines that are usually raised in patients with COVID-19 [90]. Moreover, BTK inhibitors may also attenuate some harmful pulmonary effects of SARS-CoV-2 and other analogous viruses, decreasing the degree of lung injury [40,91].

4.5.2. Role of BTK in cell death related to side effects of the BTK inhibitors in COVID-19

BTK has not been shown to have significant oncogenic properties seen in leukemias in the case of solid cancers. In contrast, BTK-dependent phosphorylation upregulates the activity and stability of a critical tumor suppressor in humans, and p53 in epithelial cells [92,93]. Numerous studies have established that p53 plays a key role in the host cell’s non-specific antiviral defense system [94]. For instance, viral infection causes the initiation of p53-mediated type I interferon signaling [95]. Hence, knockout of p53 promotes replication of SARS-CoV replicons, a novel coronavirus that emerged in 2003 and caused SARS at the beginning of the millennium, with a global lethality of ~10% [96,97]. Given the similarities between SARS-CoV-2 and SARS-CoV, it should be examined whether p53 has the identical activity on the former.

Viruses use diverse ways to weaken p53 action and induce death in
infected cells. For instance, SARS-CoV-2 produce papain-like protease 2 (PLP2), which directly interacts and deubiquitinates cellular oncoprotein and p53 inhibitor MDM2 and thus promotes proteasomal degradation of p53 [98]. This inhibits the p53-mediated production of type I interferon signaling and apoptosis and ensures viral growth [98]. Furthermore, proteo-transcriptomics examination of SARS-CoV-2 infected cells exhibited upregulation of numerous pro-survival pathways such as hypoxia-inducible factor-1 alpha, mammalian target of rapamycin, and phosphatidylinositol-3 kinase/Protein kinase B [99]. p53 is identified for suppressing all these pathways [99–102]. Thus, the detailed effect of BTK inhibitors on p53 activity in COVID-19 patients should be investigated.

4.6. BTK activation and IL-6 production in monocytes from COVID-19 patients

In order to examine whether the target of BTK inhibitor (Acalabrutinib) was activated in COVID-19 infected patients, BTK autophosphorylation at residue Y223 in whole blood samples from three patients with severe COVID-19 and five healthy volunteers was studied. The mean fluorescence intensity of phosphorylated BTK in CD14+ monocytes in COVID-19 infected patients, BTK autophosphorylation of p53 [98]. This inhibits the p53-mediated production of type I interferon signaling and apoptosis and ensures viral growth [98]. Furthermore, proteo-transcriptomics examination of SARS-CoV-2 infected cells exhibited upregulation of numerous pro-survival pathways such as hypoxia-inducible factor-1 alpha, mammalian target of rapamycin, and phosphatidylinositol-3 kinase/Protein kinase B [99]. p53 is identified for suppressing all these pathways [99–102]. Thus, the detailed effect of BTK inhibitors on p53 activity in COVID-19 patients should be investigated.

4.7. BTK inhibitors may protect against lung injury in COVID-19 patients

Ibrutinib is used to treat cGVHD and indolent B-cell malignancies [103]. A study conducted in an animal model revealed the potential protective effect of Ibrutinib on lung injury, pulmonary inflammatory cytokines, and death [40]. Ibrutinib administration in six patients with COVID-19 who suffered from Waldenstrom macroglobulinemia resulted in significant clinical improvement and recovery [89].

Ibrutinib, at a concentration of IC_{50}, 0.5 nM exhibited a significant inhibitory effect of BTK. In addition, Ibrutinib at a concentration of IC_{50}, 49 nM is also a strong reversible inhibitor of hematopoietic cell kinase (HCK). The IC_{50} values of orally administered Ibrutinib for HCK and BTK are within the pharmacologically reasonable dosimetry [104]. Consecutively collected blood samples from patients with Waldenstrom macroglobulinemia, cGVHD, and chronic lymphocytic leukemia on ibritinib treatment revealed significant decrements in chemokine and proinflammatory that significantly overlay with those reported to be raised in the plasma of ACE2 cells from lung tissue of SARS-CoV and SARS-CoV-2 infected patients [47,59,90,105–107]. In the previous study, patients with CLL treated with ibritinib instantly before administration of Obinutuzumab displayed a significant reduction of inflammatory cytokines [108].

5. Selected BTK inhibitors for COVID-19 treatment

BTK is a signaling molecule of the cytokine receptor and B-cell antigen receptor pathways. Acalabrutinib is a FDA approved 2nd generation orally effective BTK inhibitor, which is used for the treatment of B-cell malignancies such as mantle cell lymphoma and small lymphocytic lymphoma/chronic lymphocytic leukemia. Acalabrutinib showed a better safety profile than 1st generation BTK inhibitors like Ibrutinib due to minimal off-target effect for other kinases [109]. Acalabrutinib is suggested for the management of COVID-19 infected patients since it can modulate signaling that enhances inflammation. Data concerning acalabrutinib are limited to the findings from a previous study of 19 COVID-19 patients. Assessment of the data to determine any clinical benefit is incomplete by the lack of a control group and the study’s small sample size [66].

Administration of Acalabrutinib at a dose of 100 mg for 14 days (11 patients on mechanical ventilation) and 10 days (8 patients on supplemental oxygen) showed improvement among COVID-19 patients. A previous study suggested that Acalabrutinib should be withdrawn from COVID-19 patients who showed noticeable drug-related adverse effects [75]. Guidance was given to avoid the use of corticosteroids like inhaled steroids with BTK inhibitors since it slightly raises the risk of Aspergillus infections [60]. To reduce drug clearance by COVID-19 patients, CYP3A4 inhibitors should be switched to an alternative medication. Likewise, off-label use of hydroxychloroquine may raise the risk of cardiac-related toxicity. To improve drug absorption, the use of proton pump inhibitors should be avoided and substituted with H2 blockers [110] (Table 1).

Ibrutinib is a FDA approved 1st generation BTK inhibitor, which is used for the prevention of chronic graft-versus-host disease in stem cell transplant recipients, and for the management of various B-cell malignancies [111]. According to a previous study, Ibrutinib has shown activity through protecting against ensuing lung injury and reducing inflammation in patients with COVID-19 [89]. Data concerning Ibrutinib are inadequate to those from retrospective case series of 6 COVID-19 infected patients who were taking Ibrutinib for illness other than COVID-19 infection. Assessment of the data for any clinical benefit is inadequate by the lack of a control group and the series’ small sample size [89] (Table 1).

Zanubrutinib is FDA approved 2nd generation orally effective BTK inhibitor, which is used for the management of mantle cell lymphoma [112]. Zanubrutinib has been revealed to have fewer toxicities when compared with 1st generation BTK inhibitors like ibritinib. Zanubrutinib is suggested to benefit COVID-19 infected patients through modulating signaling that induces inflammation [113] (Table 1).

6. Conclusion

The urgent necessity of therapeutic agents for the treatment of COVID-19 has led to repurposing of various anti-inflammatory drugs. In this context, BTK inhibitors could be beneficial in COVID-19. This is in agreement with the hypothesis that the key factor for poor outcome of the disease is an exaggerated immune response, which BTK inhibitors would decrease through the mechanisms discussed. Small molecule inhibitors like BTK inhibitors, targeting a wide range of pro-inflammatory singling pathways, may have a role in the management of COVID-19. In spite of several recent findings supporting the effect of BTK inhibitors as a potential treatment modality for COVID-19; more clinical studies are required to elucidate the mechanisms involved in the positive effects and carefully consider any side effects. Overall, this review provides an update concerning small molecule inhibitors as a potential strategy for the management of COVID-19.

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Table 1
Summary of potential Bruton tyrosine kinase inhibitors for different disorders and clinical trials in COVID-19.

| Company               | BTK inhibitors | Indications as single drug or in combination                                      | Clinical trials on COVID-19 (identifier/status) |
|-----------------------|----------------|-----------------------------------------------------------------------------------|--------------------------------------------------|
| AstraZeneca/Acerta Pharma BV | Acalabrutinib | Non-hematological disorders: glioblastoma, and carcinoma                             | NCT04380688 (Phase 2, completed)                  |
|                       |                | Hematological disorders: Lymphoma, Leukemia, and Lymphoproliferative disorders,     | NCT04346199 (Phase 2, completed)                  |
| AbbVie/Pharmacyclics/ Johnson and Johnson | Ibrutinib | Non-hematological disorders: glioblastoma, urogenital carcinoma, prostate cancer, melanoma, breast neoplasm, and adenocarcinoma (gastrointestinal, lungs, kidney, and pancreas) | NCT04654766 (Phase 3, recruiting)                  |
|                       |                | Hematological disorders: Lymphoma, Leukemia, and Lymphoproliferative disorders      | NCT04735397 (Phase 2, completed)                  |
|                       |                | requested, cohort study.                                                           | NCT04439006 (Phase 2, recruiting)                  |
|                       |                |                                                                                  | NCT04665115 (Phase 2, not yet recruiting)          |
|                       |                |                                                                                  | NCT04382586 (Phase 2, completed)                  |
| BeGene                | Zanubrutinib | Autoimmune disorders: IgG4-RD                                                      |                                                 |
|                       |                | Non-hematological disorders: metastatic melanoma and carcinoma,                   |                                                 |
|                       |                | Autoimmune disorders: pemphigus Vulgaris and pemphigus, immune thrombocytopenia,  |                                                 |
|                       |                | immune thrombocytopenic purpura, IgG4-RD                                           |                                                 |
| Principia Biopharma   | Rilzabrutinib | Autoimmune disorders: relapsing-remitting or relapsing RA, MS, and SLE            |                                                 |
| Merck                 | Evobrutinib   | Autoimmune disorders: relapsing or primary progressive refractory CSU, RA, MS, and SLE |                                                 |
| Genentech             | Fenebrutinib  | Autoimmune disorders: relapsing-remitting or relapsing RA, MS, and SLE            |                                                 |
| InnoCare Pharma       | Orelabrutinib | Autoimmune disorder: SLE                                                           |                                                 |
|                       |                | Lymphoproliferative disorders: DLBCL and CLL                                       |                                                 |
| Sanofi/Principia      | Tolebrutinib  | Autoimmune disorder: MS, primary and secondary progressive MS, and relapsing MS,  |                                                 |

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CRediT authorship contribution statement

Zemene Demelash Kifle: Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest
The author declares that they have no competing interests.

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