DOSING OF A BRUTON'S TYROSINE KINASE INHIBITOR

The present invention relates to the use of (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide or a pharmaceutically acceptable salt thereof for the treatment of conditions such as cancer and autoimmune diseases.

Bruton's Tyrosine Kinase (BTK) is a member of the src-related Tec family of cytoplasmic tyrosine kinases. BTK plays a key role in the B-cell antigen receptor signaling pathway, which is required for the development, activation, and survival of normal white blood cells, known as B-cells. BTK also plays a critical role in the proliferation and survival of diverse B-cell malignancies. Therefore, BTK is a molecular target useful for treatment across numerous B-cell leukemias and lymphomas including, for example, indolent and aggressive mature B-cell non-Hodgkin lymphomas, chronic lymphocytic leukemia/small lymphocytic lymphoma, Waldenstrom's macroglobulinemia, mantle cell lymphoma, follicular lymphoma, diffuse large B-cell lymphoma, B-cell prolymphocytic leukemia, hairy cell leukemia, and marginal zone lymphoma.

It has also been reported that B-cells play a prominent role in the development of chronic graft versus host disease (cGVHD), a life-threatening complication of allogeneic stem cell transplantation, prompting studies of B-cell-targeted therapies for the prevention and treatment of cGVHD. Rituximab has shown mixed efficacy in steroid-refractory cGVHD and may help prevent its development. Additionally, the covalent BTK inhibitor, ibrutinib, was approved in 2017 by the US FDA in refractory cGVHD.

The compound, (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4- carboxamide (hereinafter referred to as "BTK-I"), and pharmaceutically acceptable salts thereof are disclosed in WO17/103611 and WO2020/028258 as selective inhibitors of BTK.

Many patients who are being treated with BTK inhibitors for cancer and specifically BTK-mediated cancers become refractory or resistant to further treatment or are intolerant to the treatment due to relapse or adverse events, which may be severe or even life threatening. For example, patients treated with the BTK inhibitor, ibrutinib, can become resistant and/or

diarrhea) toxicities in clinical trials (Byrd, Furman et al. N Engl J Med (July 4, 2013), 369:32-42; Byrd, Harrington et al. N Engl J Med (January 28, 2016); 374:323-332).

There remains a need to provide alternative treatment therapies for patients suffering from cancer and autoimmune diseases. In addition, there remains a need to provide alternative therapies for patients suffering from cGVHD. In particular, there remains a need to provide alternative treatment therapies for patients who develop resistance or become intolerant to current therapies, to provide alternative BTK inhibitors with activity against resistant mutants of BTK and that possess better tolerability profiles, or to provide alternative therapies that allow for maximum BTK inhibition with limited adverse events and fewer dose interruptions or discontinuations.

SUMMARY

In an aspect of the present disclosure, there is provided a use of a compound which is (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer wherein the compound or salt is to be administered at a daily dose of between about 125 mg and about 600 mg.

In another aspect of the present disclosure, there is provided a use of a compound which is (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting proliferation and/or survival of activated B-cells in a patient suffering from a BTK-mediated cancer,
wherein a therapeutically effective amount of the compound or salt thereof is to be orally administered to the patient suffering from the BTK-mediated cancer, on a continuous daily dose regimen until progression of the BTK-mediated cancer or unacceptable toxicity occurs,
wherein said administration of the therapeutically effective amount results in an $AUC_{(0-24)}$ of greater than or equal to about 52400 ng*h/mL; and
wherein said administration of the therapeutically effective amount results in an exposure of greater than or equal to about 806 ng/mL twenty-four hours following said administration.

DESCRIPTION

During human clinical trials, administration of BTK-I has not induced the severity of adverse effects that have been observed with other BTK inhibitors, such as ibrutinib and acalabrutinib, such as atrial fibrillation, hemorrhage, cytopenia, cardiac arrhythmias, along with severe leukopenia neutropenia, decreased platelet count, reticulocyte count, and red cell mass consistent with bone marrow suppression/toxicity. (Mato A., et al., "Toxicities and Outcomes of 616 Ibrutinib-Treated Patients in the United States: A Real-World Analysis", Haematologica, 2018, 103(5), 874-879.) Between March 21, 2019 and September 27, 2020, across 7 dose levels ranging from 25 mg once daily (QD) to 300 mg QD in 323 patients, the only treatment-emergent adverse events regardless of attribution or grade seen in ≥10% of patients (n=323) were fatigue (n=65, 20%), diarrhea (n=55, 17%), and contusion (n=42, 13%). In 121 efficacy-evaluable cBTKi-treated chronic lymphocytic leukemia (CLL) patients (median prior lines = 4), overall response rate (ORR) was 62% (95% CI: 53-71), rising to 84% in patients followed for ≥10 months. ORR was similar in (chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) patients with prior cBTKi resistance (67%, 53/79), cBTKi intolerance (52%, 22/42), *BTK* C481-mutant (71%, 17/24) and *BTK*-wildtype (66%, 43/65) disease. In 52 efficacy-evaluable cBTKi-treated mantle cell lymphoma (MCL) patients, the ORR was 52% (95% CI: 38-66). Of 117 responding CLL or MCL patients, all but 8 remain progression-free. Responses were also observed in Waldenstrom's macroglobulinemia (WM) (n=19, ORR 68%) and follicular lymphoma (FL)

wherein the therapeutically effective amount of the compound or salt is an amount that results in greater than 90 percent inhibition of BTK at steady state in the patient 24 hours following administration and wherein proliferation and survival of the activated B-cells are inhibited. Preferably, the compound is BTK-I.

Also provided herein is a compound which is BTK-I or a pharmaceutically acceptable salt thereof for use in inhibiting proliferation and/or survival of activated B-cells in a patient suffering from a BTK-mediated cancer wherein the patient received at least one prior anti-cancer therapy that includes at least one BTK inhibitor based therapy, comprising: orally administering to the patient suffering from the BTK-mediated cancer a therapeutically effective amount of the compound or salt, on a continuous daily dose regimen until progression of the BTK-mediated cancer or unacceptable toxicity occurs,

wherein the therapeutically effective amount of the compound or salt is an amount that results in greater than 90 percent inhibition of BTK at steady state in the patient 24 hours following administration and wherein proliferation and survival of the activated B-cells are inhibited; and

wherein the compound or salt is administered in simultaneous, separate, or sequential administration with a BCL-2 inhibitor and/or an anti-CD20 based therapy. Preferably, the anti-CD20 based therapy is administered on day 1 of a first 28-day cycle or as a split dose on day 1 and 2. Preferably, the anti-CD20 based therapy is administered on day 1 +/- 3 days of a first 28-day cycle at about 375 mg/m^2 or as a split dose on day 1 and 2. Preferably, the anti-CD20 based therapy is administered on day 1 of a first 28-day cycle or as a split dose on day 1 and 2 and then the anti-CD20 based therapy is either administered on day 1 or not at all during each of any subsequent cycles. Preferably, the BCL-2 inhibitor is administered during a fourth 28-day cycle. Preferably, the anti-CD20 based therapy is administered on day 1 of a first 28-day cycle or as a split dose on day 1 and 2 and the anti-CD20 based therapy is then either administered on day 1 or not at all during each of any subsequent cycles and the BCL-2 inhibitor is administered during a fourth 28-day cycle. Preferably, BTK-I is administered daily starting on day 1, the anti-CD20 based therapy is administered on day 1 of a first 28-day cycle or as a split dose on day 1 and 2 and the anti-CD20 based therapy is then either

least one prior anti-cancer therapy that includes at least one BTK inhibitor based therapy, comprising: orally administering to the patient suffering from the BTK-mediated cancer a therapeutically effective amount of the compound or salt, on a continuous daily dose regimen until progression of the BTK-mediated cancer or unacceptable toxicity occurs,

wherein the therapeutically effective amount of the compound or salt is an amount that results in greater than 90 percent inhibition of BTK at steady state in the patient 24 hours following administration; and

wherein the compound or salt is administered in simultaneous, separate, or sequential administration with a BCL-2 inhibitor and/or an anti-CD20 based therapy. Preferably, the anti-CD20 based therapy is administered on day 1 of a first 28-day cycle or as a split dose on day 1 and 2. Preferably, the anti-CD20 based therapy is administered on day 1 +/- 3 days of a first 28-day cycle at about 375 mg/m^2 or as a split dose on day 1 and 2. Preferably, the anti-CD20 based therapy is administered on day 1 of a first 28-day cycle or as a split dose on day 1 and 2 and then the anti-CD20 based therapy is either administered on day 1 or not at all during each of any subsequent cycles. Preferably, the BCL-2 inhibitor is administered during a fourth 28-day cycle. Preferably, the anti-CD20 based therapy is administered on day 1 of a first 28-day cycle or as a split dose on day 1 and 2 and the anti-CD20 based therapy is then either administered on day 1 or not at all during each of any subsequent cycles and the BCL-2 inhibitor is administered during a fourth 28-day cycle. Preferably, BTK-I is administered daily starting on day 1, the anti-CD20 based therapy is administered on day 1 of a first 28-day cycle or as a split dose on day 1 and 2 and the anti-CD20 based therapy is then either administered on day 1 or not at all during each of any subsequent cycles, and the BCL-2 inhibitor is administered during a fourth 28-day cycle. Preferably, the BCL-2 inhibitor is venetoclax. Preferably, the BCL-2 inhibitor is BCL2-I or a pharmaceutically acceptable salt thereof. Preferably, the BCL-2 inhibitor is BCL2-I. Preferably, the anti-CD20 based therapy is rituximab. Preferably, the anti-CD20 based therapy is obinutuzumab. Preferably, the anti-CD20 based therapy is R-CHOP. Preferably, rituximab is administered on day 1 of a first 28-day cycle at about 375 mg/m^2 or as a split dose on day 1 and 2. Preferably, rituximab is administered on day 1 +/- 3 days of a first 28-day cycle at about 375 mg/m^2 or as a split dose

cycle, and about 200 mg for days 22-28 of the cycle, and then is daily dosed at about 400 mg for any subsequent cycles. Preferably, rituximab is administered on day 1 of a first 28-day cycle at about 375 mg/m^2 or as a split dose on day 1 and 2 and rituximab is then either administered at about 500 mg/m^2 on day 1 or not at all during each of any subsequent cycles and venetoclax is administered during a fourth 28-day cycle at a dose of about 20 mg for days 1-7 of the cycle, about 50 mg for days 8-14 of the cycle, about 100 mg for days 15-21 of the cycle, and about 200 mg for days 22-28 of the cycle, and then is daily dosed at about 400 mg for any subsequent cycles. Preferably, BTK-I is administered at about 200 mg daily, rituximab is administered on day 1 of a first 28-day cycle at about 375 mg/m^2 or as a split dose on day 1 and 2 and rituximab is then either administered at about 500 mg/m^2 on day 1 or not at all during each of any subsequent cycles and venetoclax is administered during a fourth 28-day cycle at a dose of about 20 mg for days 1-7 of the cycle, about 50 mg for days 8-14 of the cycle, about 100 mg for days 15-21 of the cycle, and about 200 mg for days 22-28 of the cycle, and then is daily dosed at about 400 mg for any subsequent cycles.

The present invention also provides the use of a compound which is BTK-I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the inhibition of proliferation and/or survival of activated B-cells in a patient suffering from a BTK-mediated cancer, comprising: orally administering to the patient suffering from the BTK-mediated cancer a therapeutically effective amount of the compound or salt, on a continuous daily dose regimen until progression of the BTK-mediated cancer or unacceptable toxicity occurs,

wherein the therapeutically effective amount of the compound or salt is an amount that results in greater than 90 percent inhibition of BTK at steady state in the patient 24 hours following administration and wherein proliferation and survival of the activated B-cells are inhibited. Preferably, the compound is BTK-I.

Also provided herein is the use of a compound which is BTK-I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament ~~of~~for the inhibition of proliferation and/or survival of activated B-cells in a patient suffering from a BTK-mediated cancer, comprising: orally administering to the patient suffering from the BTK-mediated cancer a

on day 1 and 2. Preferably, rituximab is administered on day 1 of a first 28-day cycle at about 375 mg/m^2 or as a split dose on day 1 and 2 and rituximab is then either administered at about 500 mg/m^2 on day 1 or not at all during each of any subsequent cycles. Preferably, venetoclax is administered during a fourth 28-day cycle at a dose of about 20 mg for days 1-7 of the cycle, about 50 mg for days 8-14 of the cycle, about 100 mg for days 15-21 of the cycle, and about 200 mg for days 22-28 of the cycle, and then is daily dosed at about 400 mg for any subsequent cycles. Preferably, rituximab is administered on day 1 of a first 28-day cycle at about 375 mg/m^2 or as a split dose on day 1 and 2 and rituximab is then either administered at about 500 mg/m^2 on day 1 or not at all during each of any subsequent cycles and venetoclax is administered during a fourth 28-day cycle at a dose of about 20 mg for days 1-7 of the cycle, about 50 mg for days 8-14 of the cycle, about 100 mg for days 15-21 of the cycle, and about 200 mg for days 22-28 of the cycle, and then is daily dosed at about 400 mg for any subsequent cycles. Preferably, BTK-I is administered at about 200 mg daily, rituximab is administered on day 1 of a first 28-day cycle at about 375 mg/m^2 or as a split dose on day 1 and 2 and rituximab is then either administered at about 500 mg/m^2 on day 1 or not at all during each of any subsequent cycles and venetoclax is administered during a fourth 28-day cycle at a dose of about 20 mg for days 1-7 of the cycle, about 50 mg for days 8-14 of the cycle, about 100 mg for days 15-21 of the cycle, and about 200 mg for days 22-28 of the cycle, and then is daily dosed at about 400 mg for any subsequent cycles.

Also provided herein is the use of a compound which is BTK-I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the inhibition of proliferation and/or survival of activated B-cells in a patient suffering from a BTK-mediated cancer wherein the patient is treatment naive, comprising: orally administering to the patient suffering from the BTK-mediated cancer a therapeutically effective amount of the compound or salt,~~,~~ on a continuous daily dose regimen until progression of the BTK-mediated cancer or unacceptable toxicity occurs,

wherein said administration of the therapeutically effective amount results in an $AUC_{(0-24)}$ of greater than or equal to about 52400 ng*h/mL; and

wherein the therapeutically effective amount of the compound or salt is an amount that results in greater than 90 percent inhibition of BTK at steady state in the patient 24 hours following administration. Preferably, the compound is BTK-I.

Also provided herein is the use of a compound which is BTK-I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of a BTK-mediated cancer wherein the patient is relapsed or refractory, comprising: orally administering to the patient suffering from the BTK-mediated cancer a therapeutically effective amount of the compound or salt, on a continuous daily dose regimen until progression of the BTK-mediated cancer or unacceptable toxicity occurs,

wherein the therapeutically effective amount of the compound or salt is an amount that results in greater than 90 percent inhibition of BTK at steady state in the patient 24 hours following administration and

wherein the compound or salt is administered in simultaneous, separate, or sequential administration with a BCL-2 inhibitor and/or an anti-CD20 based therapy. Preferably, the anti-CD20 based therapy is administered on day 1 of a first 28-day cycle or as a split dose on day 1 and 2. Preferably, the anti-CD20 based therapy is administered on day 1 +/- 3 days of a first 28-day cycle at about 375 mg/m^2 or as a split dose on day 1 and 2. Preferably, the anti-CD20 based therapy is administered on day 1 of a first 28-day cycle or as a split dose on day 1 and 2 and then the anti-CD20 based therapy is either administered on day 1 or not at all during each of any subsequent cycles. Preferably, the BCL-2 inhibitor is administered during a fourth 28-day cycle. Preferably, the anti-CD20 based therapy is administered on day 1 of a first 28-day cycle or as a split dose on day 1 and 2 and the anti-CD20 based therapy is then either administered on day 1 or not at all during each of any subsequent cycles and the BCL-2 inhibitor is administered during a fourth 28-day cycle. Preferably, BTK-I is administered daily starting on day 1, the anti-CD20 based therapy is administered on day 1 of a first 28-day cycle or as a split dose on day 1 and 2 and the anti-CD20 based therapy is then either administered on day 1 or not at all during each of any subsequent cycles, and the BCL-2 inhibitor is administered during a fourth 28-day cycle. Preferably, the BCL-2 inhibitor is venetoclax. Preferably, the BCL-2 inhibitor is BCL2-I or a pharmaceutically acceptable salt

first 28-day cycle or as a split dose on day 1 and 2 and the anti-CD20 based therapy is then either administered on day 1 or not at all during each of any subsequent cycles and the BCL-2 inhibitor is administered during a fourth 28-day cycle. Preferably, BTK-I is administered daily starting on day 1, the anti-CD20 based therapy is administered on day 1 of a first 28-day cycle or as a split dose on day 1 and 2 and the anti-CD20 based therapy is then either administered on day 1 or not at all during each of any subsequent cycles, and the BCL-2 inhibitor is administered during a fourth 28-day cycle. Preferably, the BCL-2 inhibitor is venetoclax. Preferably, the BCL-2 inhibitor is BCL2-I or a pharmaceutically acceptable salt thereof. Preferably, the BCL-2 inhibitor is BCL2-I. Preferably, the anti-CD20 based therapy is rituximab. Preferably, the anti-CD20 based therapy is obinutuzumab. Preferably, the anti-CD20 based therapy is R-CHOP. Preferably, rituximab is administered on day 1 of a first 28-day cycle at about 375 mg/m^2 or as a split dose on day 1 and 2. Preferably, rituximab is administered on day 1 +/- 3 days of a first 28-day cycle at about 375 mg/m^2 or as a split dose on day 1 and 2. Preferably, rituximab is administered on day 1 of a first 28-day cycle at about 375 mg/m^2 or as a split dose on day 1 and 2 and rituximab is then either administered at about 500 mg/m^2 on day 1 or not at all during each of any subsequent cycles. Preferably, venetoclax is administered during a fourth 28-day cycle at a dose of about 20 mg for days 1-7 of the cycle, about 50 mg for days 8-14 of the cycle, about 100 mg for days 15-21 of the cycle, and about 200 mg for days 22-28 of the cycle, and then is daily dosed at about 400 mg for any subsequent cycles. Preferably, rituximab is administered on day 1 of a first 28-day cycle at about 375 mg/m^2 or as a split dose on day 1 and 2 and rituximab is then either administered at about 500 mg/m^2 on day 1 or not at all during each of any subsequent cycles and venetoclax is administered during a fourth 28-day cycle at a dose of about 20 mg for days 1-7 of the cycle, about 50 mg for days 8-14 of the cycle, about 100 mg for days 15-21 of the cycle, and about 200 mg for days 22-28 of the cycle, and then is daily dosed at about 400 mg for any subsequent cycles. Preferably, BTK-I is administered at about 200 mg daily, rituximab is administered on day 1 of a first 28-day cycle at about 375 mg/m^2 or as a split dose on day 1 and 2 and rituximab is then either administered at about 500 mg/m^2 on day 1 or not at all during each of any subsequent cycles and venetoclax is administered during a

at about 500 mg/m^2 on day 1 or not at all during each of any subsequent cycles. Preferably, venetoclax is administered during a fourth 28-day cycle at a dose of about 20 mg for days 1-7 of the cycle, about 50 mg for days 8-14 of the cycle, about 100 mg for days 15-21 of the cycle, and about 200 mg for days 22-28 of the cycle, and then is daily dosed at about 400 mg for any subsequent cycles. Preferably, rituximab is administered on day 1 of a first 28-day cycle at about 375 mg/m^2 or as a split dose on day 1 and 2 and rituximab is then either administered at about 500 mg/m^2 on day 1 or not at all during each of any subsequent cycles and venetoclax is administered during a fourth 28-day cycle at a dose of about 20 mg for days 1-7 of the cycle, about 50 mg for days 8-14 of the cycle, about 100 mg for days 15-21 of the cycle, and about 200 mg for days 22-28 of the cycle, and then is daily dosed at about 400 mg for any subsequent cycles. Preferably, BTK-I is administered at about 200 mg daily, rituximab is administered on day 1 of a first 28-day cycle at about 375 mg/m^2 or as a split dose on day 1 and 2 and rituximab is then either administered at about 500 mg/m^2 on day 1 or not at all during each of any subsequent cycles and venetoclax is administered during a fourth 28-day cycle at a dose of about 20 mg for days 1-7 of the cycle, about 50 mg for days 8-14 of the cycle, about 100 mg for days 15-21 of the cycle, and about 200 mg for days 22-28 of the cycle, and then is daily dosed at about 400 mg for any subsequent cycles.

Also provided herein is the use of a compound which is BTK-I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of a BTK-mediated cancer wherein a patient is treatment naive, comprising: orally administering to the patient suffering from the BTK-mediated cancer a therapeutically effective amount of the compound or salt~~;~~, on a continuous daily dose regimen until progression of the BTK-mediated cancer or unacceptable toxicity occurs,

wherein said administration of the therapeutically effective amount results in an AUC$_{(0\text{-}24)}$ of greater than or equal to about 52400 ng*h/mL; and

wherein said administration of the therapeutically effective amount results in an exposure of greater than or equal to about 806 ng/mL twenty-four hours following said administration. Preferably, the compound is BTK-I.

to be between about 125 mg and about 400 mg. In another embodiment, the dose is selected to be between about 150 mg and about 400 mg. In another embodiment, the dose is selected to be between about 175 mg and about 400 mg. In another embodiment, the dose is selected to be between about 200 mg and about 400 mg. In another embodiment, the dose is selected to be between about 225 mg and about 400 mg. In another embodiment, the dose is selected to be between about 250 mg and about 400 mg. In another embodiment, the dose is selected to be between about 275 mg and about 400 mg. In another embodiment, the dose is selected to be between about 300 mg and about 400 mg. In another embodiment, the dose is selected to be between about 120 mg and about 300 mg. In another embodiment, the dose is selected to be between about 125 mg and about 300 mg. In another embodiment, the dose is selected to be between about 150 mg and about 300 mg. In another embodiment, the dose is selected to be between about 175 mg and about 300 mg. In another embodiment, the dose is selected to be between about 200 mg and about 300 mg. In another embodiment, the dose is selected to be between about 225 mg and about 300 mg. In another embodiment, the dose is selected to be between about 250 mg and about 300 mg. In another embodiment, the dose is selected to be between about 275 mg and about 300 mg. In another embodiment, the dose is selected to be about 300 mg. ~~In another embodiment, the dose is selected to be about 300 mg.~~ In another embodiment, the dose is selected to be between about 120 mg and about 200 mg. In another embodiment, the dose is selected to be between about 125 mg and about 200 mg. In another embodiment, the dose is selected to be between about 150 mg and about 200 mg. In another embodiment, the dose is selected to be between about 175 mg and about 200 mg. In another embodiment, the dose is selected to be about 200 mg. In another embodiment, the dose is selected to be about 200 mg and is administered in two 100 mg tablets. In another embodiment, the dose is selected to be between about 120 mg and about 150 mg. In another embodiment, the dose is selected to be between about 125 mg and about 150 mg. In another embodiment, the dose is elected to about 150 mg. In another embodiment, the dose is selected to be about 150 mg and is administered in a 100 mg tablet together with a 50 mg tablet.

In another embodiment, the maximum daily dose is between about 120 mg and about 300 mg. In another embodiment, the maximum daily dose is between about 125 mg and about 300 mg. In another embodiment, the maximum daily dose is about 150 mg. In another embodiment, the maximum daily dose is about 200 mg. In another embodiment, the maximum daily dose is about 250 mg. In another embodiment, the maximum daily dose is about 300 mg.

Also provided herein is a method of dose reducing a compound which is BTK-I or a pharmaceutically acceptable salt thereof for a patient in need thereof wherein the starting dose of BTK-I may be reduced by 50 mg, then by 100 mg, and then by 150 mg (for example 200 mg starting dose, to 150 mg dose, to 100 mg dose, and then to 50 mg dose). Preferably, the dose reduction is due to toxicity. Preferably, the dose reduction is due to a clinically signification adverse event. Preferably, the dose reduction is due to intolerability. Preferably, the intolerability is related to a drug-drug interaction. Preferably, the intolerability is related to a food effect.

Also provided herein is a method of dose reducing a compound which is BTK-I or a pharmaceutically acceptable salt thereof for a patient in need thereof wherein the starting dose of BTK-I may be reduced by 100 mg and then by 150 mg (for example 200 mg starting dose, to 100 mg dose, and then to 50 mg dose). Preferably, the dose reduction is due to toxicity. Preferably, the dose reduction is due to a clinically signification adverse event. Preferably, the dose reduction is due to intolerability. Preferably, the intolerability is related to a drug-drug interaction. Preferably, the intolerability is related to a food effect.

In another embodiment of the methods and uses described herein, the cancer is selected from: B-cell malignancy, B-cell lymphoma, diffuse large B-cell lymphoma, mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL), non-Hodgkin lymphoma (NHL), small lymphocytic lymphoma (SLL), Waldenstrom's macroglobulinemia, marginal zone lymphoma (MZL), activated B-cell-like diffuse large B-cell lymphoma (ABC-DLBCL), follicular lymphoma, hairy cell leukemia, multiple myeloma, B-cell prolymphocytic leukemia, and B-cell non-Hodgkin lymphoma (B-cell NHL). In yet another embodiment, the cancer is selected from: diffuse large B-cell lymphoma (DLBCL), MCL, CLL, NHL, SLL,

between about 120 mg and about 200 mg. In another embodiment, the cancer is SLL and the dose is between about 125 mg and about 200 mg. In another embodiment, the cancer is SLL and the dose is between about 150 mg and about 200 mg. In another embodiment, the cancer is SLL and the dose is between about 175 mg and about 200 mg. In another embodiment, the cancer is SLL and the dose is between about 120 mg and about 150 mg. In another embodiment, the cancer is SLL and the dose is between about 125 mg and about 150 mg.

In another embodiment, the cancer is SLL and the patient has a PLCg2 mutation. In another embodiment, the cancer is SLL, the patient has a PLCg2 mutation, and the dose is between about 120 mg and about 300 mg. In another embodiment, the cancer is SLL, the patient has a PLCg2 mutation, and the dose is between about 125 mg and about 300 mg. In another embodiment, the cancer is SLL, the patient has a PLCg2 mutation, and the dose is between about 150 mg and about 300 mg. In another embodiment, the cancer is SLL, the patient has a PLCg2 mutation, and the dose is between about 175 mg and about 300 mg. In another embodiment, the cancer is SLL, the patient has a PLCg2 mutation, and the dose is between about 200 mg and about 300 mg. In another embodiment, the cancer is SLL, the patient has a PLCg2 mutation, and the dose is between about 225 mg and about 300 mg. In another embodiment, the cancer is SLL, the patient has a PLCg2 mutation, and the dose is between about 250 mg and about 300 mg. In another embodiment, the cancer is SLL, the patient has a PLCg2 mutation, and the dose is between about 275 mg and about 300 mg. In another embodiment, the cancer is SLL, the patient has a PLCg2 mutation, and the dose is between about 120 mg and about 200 mg. In another embodiment, the cancer is SLL, the patient has a PLCg2 mutation, and the dose is between about 125 mg and about 200 mg. In another embodiment, the cancer is SLL, the patient has a PLCg2 mutation and the dose is between about 150 mg and about 200 mg. In another embodiment, the cancer is SLL, the patient has a PLCg2 mutation, and the dose is between about 175 mg and about 200 mg. In another embodiment, the cancer is SLL, the patient has a PLCg2 mutation, and the dose is between about 120 mg and about 150 mg. In another embodiment, the cancer is SLL, the patient has a PLCg2 mutation, and the dose is between about 125 mg and about 150 mg.

the cancer is SLL, the patient has a 17p13 deletion and a TP53 mutation, and the dose is between about 120 mg and about 150 mg. In another embodiment, the cancer is SLL, the patient has a 17p13 deletion and a TP53 mutation, and the dose is between about 125 mg and about 150 mg.

In another embodiment, the cancer is SLL and the patient has a TP53 deletion. In another embodiment, the cancer is SLL, the patient has a TP53 deletion, and the dose is between about 120 mg and about 300 mg. In another embodiment, the cancer is ~~/~~SLL, the patient has a TP53 deletion, and the dose is between about 125 mg and about 300 mg. In another embodiment, the cancer is SLL, the patient has a TP53 deletion, and the dose is between about 150 mg and about 300 mg. In another embodiment, the cancer is SLL, the patient has a TP53 deletion, and the dose is between about 175 mg and about 300 mg. In another embodiment, the cancer is SLL, the patient has a TP53 deletion, and the dose is between about 200 mg and about 300 mg. In another embodiment, the cancer is SLL, the patient has a TP53 deletion, and the dose is between about 225 mg and about 300 mg. In another embodiment, the cancer is SLL, the patient has a TP53 deletion, and the dose is between about 250 mg and about 300 mg. In another embodiment, the cancer is SLL, the patient has a TP53 deletion, and the dose is between about 275 mg and about 300 mg. In another embodiment, the cancer is SLL, the patient has a TP53 deletion, and the dose is between about 120 mg and about 200 mg. In another embodiment, the cancer is SLL, the patient has a TP53 deletion, and the dose is between about 125 mg and about 200 mg. In another embodiment, the cancer is SLL, the patient has a TP53 deletion, and the dose is between about 150 mg and about 200 mg. In another embodiment, the cancer is SLL, the patient has a TP53 deletion, and the dose is between about 175 mg and about 200 mg. In another embodiment, the cancer is SLL, the patient has a TP53 deletion, and the dose is between about 120 mg and about 150 mg. In another embodiment, the cancer is SLL, the patient has a TP53 deletion, and the dose is between about 125 mg and about 150 mg.

In another embodiment, the cancer is SLL and the patient has a TP53 mutation. In another embodiment, the cancer is SLL, the patient has a TP53 mutation, and the dose is between about 120 mg and about 300 mg. In another embodiment, the cancer is ~~/~~SLL, the

the art. It is a cancer that starts in B-cells. Examples of B-cell NHL include, but are not limited to, DLBCL, ABC-DLBCL, MCL, MZL, CLL/SLL, Waldenstrom's macroglobulinemia, and follicular lymphoma.

As used herein the term "anti-cancer therapy" or "anti-cancer therapies" refers to chemotherapy, radiation therapy, surgery, immunotherapy such as anti-CD20 based therapy ~~based therapy~~, antibodies, antibody drug conjugates, small molecule inhibitors (for example BCL-2 inhibitors, mTOR inhibitors, proteasome inhibitors, PI3K inhibitors or lenalidomide), stem cell transplant (autologous or allogeneic), siRNAs, bispecific antibodies/T-cell engaging therapy, and CAR-T cell therapy. Unless otherwise stated, anti-cancer therapy may include a BTK inhibitor based therapy.

As used herein, the term "anti-CD20 based therapy" refers to a medical treatment that includes the use of an anti-CD20 antibody for example rituximab or obinutuzumab, or R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone) or a CD20 inhibitor.

As used herein, the term "BTK inhibitor" refers to an inhibitor of a tyrosine kinase that is encoded by the BTK gene in humans. Examples of BTK inhibitors include ibrutinib, acalabrutinib, zanabrutinib, and tirabrutinib.

As used herein, the term "BTK inhibitor based therapy" or "BTK inhibitor-based regimen" refers to a medical treatment that includes the use of a BTK inhibitor.

As used herein, the term "BTK inhibitor based therapy naïve" refers to the lack of a patient receiving a prior medical treatment that includes the use of a BTK inhibitor for a particular condition.

As used herein, the term "BCL-2 inhibitor" refers to inhibitors of B-cell lymphoma 2. Examples of BCL-2 inhibitors include venetoclax, BCL2-I, and compounds disclosed in WO2018/027097, WO2019/210828, WO2017/132474, WO2019/139899, WO2018/127130, and WO2018/192462, and any pharmaceutically acceptable salts thereof. Likewise, BCL-2 and BCL2 are used herein interchangeably.

The compound, N-[[(3S)-3-benzyl-5-nitro-3,4-dihydro-2H-1,4-benzoxazin-7-yl]sulfonyl]-4-[4-[[2-(4-chlorophenyl)-4,4-dimethyl-cyclohexen-1-yl]methyl]piperazin-1-yl]-

activation of parallel pathways more commonly implicated. Following progression on BTK inhibitors, survival of patients with MCL is very poor at only 4-10 months. While CD19-targeted CAR-T therapy has recently been approved in the US, this approach is resource intensive, limited in availability to large tertiary centers, and often associated with risk of severe toxicities that collectively limit usage. Moreover, CD19-targeted CAR-T therapy require an effective bridging therapy, which can be difficult in BTK inhibitor-resistant patients. Thus, the activity of BTK-I in relapsed, BTK-pretreated MCL is particularly promising and addresses an important unmet clinical need.

Waldenstrom's Macroglobulinemia, Follicular Lymphoma, Richter's Transformation, and other B-cell Malignancies

In 19 efficacy-evaluable WM patients, the ORR was 68% including 9 PR, 4 minor response (MR), 3 SD, and 3. Among 13 patients who had received a prior covalent BTK inhibitor, the ORR was 69% (5 PR, and 4 MR). Ten of 13 WM responders are ongoing at a median follow-up of 4.6 (range, 0.8-9.2+ months). Among 8 efficacy-evaluable patients with follicular lymphoma, responses were observed in 4 patients. Among 8 patients with Richter's transformation identified prior to enrollment, responses were observed in 6 (75%). Of the remaining 39 efficacy-evaluable patients, 8 responses were observed (6/25 patients with DLBCL, 2/9 patients with MZL).

In this initial Phase 1/2 experience of BTK-I, the data demonstrate favorable safety and promising efficacy in multiple B-cell neoplasms, including heavily pretreated CLL, MCL, WM, and FL. Importantly, activity was seen in patients with multiple B-cell neoplasms previously treated with covalent BTK inhibitors, including those with resistance mediated by BTK C481 mutations, those with uncharacterized resistance mechanisms, and those who discontinued their prior BTK inhibitor due to intolerance. Consistent with its highly selective profile, BTK-I appeared to be well tolerated, with a wide therapeutic index, as demonstrated by the observed efficacy at all dose levels tested and the lack of an MTD. To date, low rates of important BTK-mediated toxicities including atrial arrhythmias and major

bleeding have been observed, despite permitting patients with history of these events and patients on concurrent anticoagulation. Collectively, these data suggest that the reversible BTK binding mode and PK properties of BTK-I result in a clinically distinct profile with important implications for future clinical development and the treatment paradigm of these diseases. Pharmacokinetic analyses during the dose escalation phase demonstrated dose-~~5~~ dependent and linear increases in BTK-I exposure with increasing dose. Starting at the 50 mg QD dose, BTK-I delivered >IC90 target coverage for wild-type and C481S-mutated BTK, based on estimates from cell-based potencies. Despite the high plasma concentration levels DLTS have not been observed in the treated patients.

BTK-I exhibited linear dose-proportional exposures (Cmax and AUC) and low interpatient variability throughout the entire dosing range of 25 mg to 300 mg daily. Observed half-life was approximately 20 hours. Efficacy was observed at all dose levels and safety data supported selection of a 200 mg dose.

The pharmacokinetic profiles and adverse events for BTK-I doses are summarized in the below tables.

Embodiment 62. The compound or salt for use according to any one of embodiments 56 to 61 wherein the dose is administered daily for a 28-day cycle.

Embodiment 63. The compound or salt for use according to any one of embodiments 56 to 57 and embodiments 59 to 62 wherein a maximum dose administered per day is between about 120 mg and about 300 mg.

Embodiment 64. The compound or salt for use according to any one of embodiments 56 to 63 wherein the dose is between about 125 mg and about 300 mg.

Embodiment 65. The compound or salt for use according to any one of embodiments 56 to 64 wherein the dose is between about 150 mg and about 300 mg.

Embodiment 66. The compound or salt for use according to any one of embodiments 56 to 65 wherein the dose is between about 175 mg and about 300 mg.

Embodiment 67. The compound or salt for use according to any one of embodiments 56 to 66 wherein the dose is between about 200 mg and about 300 mg.

Embodiment 68. The ~~e~~ compound or salt for use according to any one of embodiments 56 to 65 wherein the dose is about 150 mg.

Embodiment 69. The compound or salt for use according to any one of embodiments 56 to 67 wherein the dose is about 200 mg.

Embodiment 70. The compound or salt for use according to any one of embodiments 56 to 67 wherein the dose is about 300 mg.

We claim:

1. A method of treating cancer or an autoimmune disease in a patient in need thereof comprising administering to the patient a daily dose of between about 120 mg and about 600 mg of a compound which is (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide or a pharmaceutically acceptable salt thereof.

2. The method according to claim 1 wherein the method is treating cancer.

3. The method according to either claim 1 or 2 wherein the compound is (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide.

4. The method according to any one of claims 1 to 3 wherein the dose is between about 125 mg and about 300 mg.

5. The method according to any one of claims 1 to 4 wherein the dose is between about 175 mg and about 300 mg.

6. The method according to any one of claims 1 to 5 wherein the dose is about 200 mg.

7. The method according to any one of claims 1 to 6 wherein the cancer is B-cell non-Hodgkin lymphoma.

8. The method according to any one of claims 1 to 6 wherein the cancer is mantle cell lymphoma.

9. The method according to any one of claims 1 to 6 wherein the cancer is chronic lymphocytic leukemia/small lymphocytic lymphoma.

10. The method according to any one of claims 1 to 9 wherein the patient is relapsed or refractory.

11. The method according to any one of claims 1 to 9 wherein the patient is treatment naive.

12. The method according to any one of claims 1 to 10 wherein the patient received at least one prior anti-cancer therapy.

13. The method according to any one of claims 1 to 10 or 12 wherein the patient received no prior anti-cancer therapy containing a BTK inhibitor.

~~14.~~1. Use of a~~A~~ compound which is (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for ~~use in~~ the treatment of cancer ~~or an autoimmune disease~~ wherein the compound or salt is to be administered at a daily dose of between about 125~~0~~ mg and about 600 mg.

~~15. The compound or salt for use according to claim 14 wherein the use is in the treatment is cancer.~~

~~16. The compound or salt for use according to either claim 14 or 15 which is (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide.~~

~~17.~~2. The ~~compound or salt for~~ use according to claim 1,~~any one of claims 14 to 16~~ wherein the dose is between about ~~125~~ 150 mg and about 300 mg.

~~18. The compound or salt for use according to any one of claims 14 to 17 wherein the dose is between about 175 mg and about 300 mg.~~

~~19.~~3. The ~~compound or salt for~~ use according to claim 1,~~any one of claims 14 to 18~~ wherein the dose is about 200 mg.

4. The use according to any one of claims 1 to 3, wherein the dose is to be administered once daily.

5. The use according to any one of claims 1 to 3 wherein the dose is to be administered daily for a 28-day cycle.

~~20. The compound or salt for use according to any one of claims 14 to 19 wherein the cancer is B-cell non-Hodgkin lymphoma.~~

6. The use according to any one of claims 1 to 5, wherein (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide or a pharmaceutically acceptable salt thereof is to be administered to patients in an oral form.

7. The use according to claim 6, wherein (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide or a pharmaceutically acceptable salt thereof is to be administered to patients in tablets or capsules.

8. The use according to claim 7, wherein each of the tablets or capsules are formulated to contain about 25 mg, or about 50 mg, or about 100 mg of (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide or a pharmaceutically acceptable salt thereof.

9. The use according to any one of claims 1 to 8, wherein the cancer is selected from B-cell malignancy, B-cell lymphoma, diffuse large B-cell lymphoma, mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL), non-Hodgkin lymphoma (NHL), small lymphocytic lymphoma (SLL), Waldenstrom's macroglobulinemia, marginal zone lymphoma (MZL), activated B-cell-like diffuse large B-cell lymphoma (ABC-DLBCL), follicular lymphoma, hairy cell leukemia, multiple myeloma, B-cell prolymphocytic leukemia, and B-cell non-Hodgkin lymphoma (B-cell NHL).

~~21.~~10. The ~~compound or salt for~~ use according to any one of claims 1~~14~~ to 8~~19~~ wherein the cancer is mantle cell lymphoma.

~~22.~~11. The ~~compound or salt for~~ use according to any one of claims 1~~14~~ to 8~~19~~ wherein the cancer is chronic lymphocytic leukemia/small lymphocytic lymphoma.

~~23.~~12. The ~~compound or salt for~~ use according to any one of claims 9~~14~~ to 11,~~22~~ wherein the ~~compound or salt is administered to a~~ patient has a C481S BTK mutation~~who is relapsed or refractory~~.

13. The use according to claim 3 wherein the dose is reduced to 100 mg.

14. The use according to claim 3 or 13 wherein the dose is reduced to 50 mg.

15. The use according to claim 1 wherein the starting dose of 200 mg of (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide or salt is reduced to 100 mg dose and then to 50 mg dose.

16. The use according to claim 15 wherein the dose is reduced due to toxicity.

17. The use according to claim 15 wherein the dose is reduced due to a clinically significant adverse event.

18. The use according to claim 15 wherein the dose is reduced due to intolerability.

19. The use according to any one of claims 1 to 18 wherein the compound or salt is to be administered to a patient who is relapsed or refractory.

20. The use according to claim 19 wherein for the relapsed patient there is evidence of disease progression according to disease-defined criteria in a patient who has previously achieved a complete response or partial response for ≥ 6 months.

21. The use according to claim 19 wherein for the refractory patient there is treatment failure as defined by less than complete response or partial response or progression within 6 months from the last dose of therapy.

~~24.~~22. The ~~compound or salt for~~ use according to any one of claims 1~~14~~ to 18~~22~~ wherein the compound or salt is to be administered to a patient who is treatment naive.

~~25.~~23. The ~~compound or salt for~~ use according to any one of claims 1~~14~~ to 21~~23~~ wherein the compound or salt is to be administered to a patient who received at least one prior anti-cancer therapy.

24. The use according to any one of claims 1 to 21 or 23 wherein the compound or salt is to be administered to a patient who received at least one prior anti-cancer therapy that includes at least one BTK inhibitor based therapy.

25. The use according claim 24 wherein the BTK inhibitor based therapy is selected from ibrutinib, acalabrutinib, zanubrutinib, and tirabrutinib.

26. The ~~compound or salt for~~ use according to any one of claims 1~~14~~ to 21~~23~~ or 23~~25~~ wherein the compound or salt is to be administered to a patient who received no prior anti-cancer therapy containing a BTK inhibitor~~.~~

27. The use according to any one of claims 1 to 26 wherein the compound or salt is to be administered in simultaneous, separate, or sequential administration with a BCL-2 inhibitor and/or an anti-CD20 based therapy.

28. The use according to claim 27 wherein the BCL-2 inhibitor is venetoclax.

29. The use according to claim 27 wherein the BCL-2 inhibitor is N-[[(3S)-3-benzyl-5-nitro-3,4-dihydro-2H-1,4-benzoxazin-7-yl]sulfonyl]-4-[4-[[2-(4-chlorophenyl)-4,4-dimethyl-cyclohexen-1-yl]methyl]piperazin-1-yl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

30. The use according to any one of claims 27 to 29 wherein the anti-CD20 based therapy is rituximab.

31. The use according to any one of claims 1 to 30 wherein the administration of (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-

2-yl)-1H-pyrazole-4-carboxamide or salt does not induce the severity of adverse effects observed with ibrutinib and acalabrutinib, wherein the adverse effect is selected from atrial fibrillation, hemorrhage, cytopenia, cardiac arrhythmias, along with severe leukopenia neutropenia, decreased platelet count, reticulocyte count, and red cell mass consistent with bone marrow suppression/toxicity.

32. Use of a compound which is (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting proliferation and/or survival of activated B-cells in a patient suffering from a BTK-mediated cancer,

wherein a therapeutically effective amount of the compound or salt thereof is to be orally administered to the patient suffering from the BTK-mediated cancer, on a continuous daily dose regimen until progression of the BTK-mediated cancer or unacceptable toxicity occurs,

wherein said administration of the therapeutically effective amount results in an $AUC_{(0-24)}$ of greater than or equal to about 52400 ng*h/mL; and

wherein said administration of the therapeutically effective amount results in an exposure of greater than or equal to about 806 ng/mL twenty-four hours following said administration.

33. The use according to any one of claims 1 to 4 wherein the administration of (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide or salt results in a mean trough plasma level exceeding 2200 ng/mL.

34. The use according to any one of claims 1 to 4 wherein the administration of (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide or salt in patients at steady state results in an $AUC_{(0-24)}$ of 91000 ng*h/mL.

35. The use according to any one of claims 1 to 4 wherein the administration of (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide or salt in patients at steady state results in a maximum drug concentration of 3910 ng/mL.

36. The use according to any one of claims 1 to 4 wherein the administration of (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide or salt in patients at steady state results in a maximum drug concentration of 5770 ng/mL.

37. The use according to any one of claims 1-36, wherein the compound is (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide.