

**METHODS OF TREATING CANCER ASSOCIATED WITH REDUCED
INTERLEUKIN 1 BETA EXPRESSION**

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Patent Application No.: 63/546,016, filed on October 27, 2023, the contents of which are hereby incorporated by reference in their entirety.

BACKGROUND

Interleukin-1 (IL-1) Receptor-Associated Kinase 4 (IRAK4) is a serine/threonine kinase enzyme that plays an essential role in signal transduction by Toll/IL-1 receptors (TIRs). Diverse IRAK enzymes are key components in the signal transduction pathways mediated by interleukin-1 receptor (IL-1R) and Toll-like receptors (TLRs) (Janssens, S., et al. Mol. Cell. 11, 2003, 293–302). There are four members in the mammalian IRAK family: IRAK1, IRAK2, IRAK3 and IRAK4. These proteins are characterized by a typical N-terminal death domain that mediates interaction with MyD88-family adaptor proteins and a centrally located kinase domain. The IRAK proteins, as well as MyD88, have been shown to play a role in transducing signals other than those originating from IL-1R receptors, including signals triggered by activation of IL-18 receptors (Kanakaraj, et al. J. Exp. Med. 189(7):1999, 1129-38) and LPS receptors (Yang, et al., J. Immunol. 163, 1999, 639-643). Out of four members in the mammalian IRAK family, IRAK4 is considered to be the “master IRAK”. Under overexpression conditions, all IRAKs can mediate the activation of nuclear factor-kappa-B (NF-KB) and stress-induced mitogen activated protein kinase (MAPK)-signaling cascades. However, only IRAK-1 and IRAK4 have been shown to have active kinase activity. While IRAK-1 kinase activity could be dispensable for its function in IL-1-induced NF-KB activation (Kanakaraj et al, J. Exp. Med. 187(12), 1998, 2073–2079) and (Xiaoxia Li, et al. Mol. Cell. Biol. 19(7), 1999, 4643–4652), IRAK4 requires its kinase activity for signal transduction (Li S, et al. Proc. Natl. Acad. Sci. USA 99(8), 2002, 5567–5572) and (Lye, E et al, J. Biol. Chem. 279(39); 2004, 40653-8). Given the central role of IRAK4 in Toll-like/IL-1R signaling and immunological protection, IRAK4 inhibitors have been implicated as valuable therapeutics in inflammatory diseases, sepsis and autoimmune disorders (Wietek C, et al, Mol. Interv. 2: 2002, 212–215).

Mice lacking IRAK4 are viable and show complete abrogation of inflammatory cytokine production in response to IL-1, IL-18, or LPS (Suzuki et al. *Nature*, 416(6882), 2002, 750-756). Similarly, human patients lacking IRAK4 are severely immune-compromised and are not responsive to these cytokines (Medvedev et al. *J. Exp. Med.*, 198(4), 2003, 521-531 and Picard et al. *Science* 299(5615), 2003, 2076-2079). Knock-in mice containing inactive IRAK4 were completely resistant to lipopolysaccharide- and CpG-induced shock (Kim TW, et al. *J Exp Med* 204: 2007, 1025 -36) and (Kawagoe T, et al. *J Exp Med* 204(5): 2007, 1013-1024) and illustrated that IRAK4 kinase activity is essential for cytokine production, activation of MAPKs, and induction of NF-KB regulated genes in response to TLR ligands (Koziczak-Holbro M, et al. *J Biol Chem*; 282(18): 2007;13552-13560). Inactivation of IRAK4 kinase (IRAK4 KI) in mice leads to resistance to EAE due to reduction in infiltrating inflammatory cells into CNS and reduced antigen specific CD4+ T-cell mediated IL-17 production (Kirk A et al. *The Journal of Immunology*, 183(1), 2009, 568-577).

Non-Hodgkin lymphoma (NHL) is the most common hematologic malignancy in adults with approximately 80 thousand new cases and 20 thousand deaths estimated for 2023 in the United States. The molecular pathology driving NHL is varied, although a common theme is over activity of the NF-KB signaling pathway. Specific molecular changes have been identified that drive this pathway in subsets of NHL. For example, diffuse large B-cell lymphoma (hereafter also referred to as “DLBCL”) is an aggressive lymphoma that can arise in lymph nodes or outside of the lymphatic system, in the gastrointestinal tract, testes, thyroid, skin, breast, bone, or brain. DLBCL is a cancer of B cells, a type of white blood cell responsible for producing antibodies. It is the most common type of non-Hodgkin's lymphoma among adults, with an annual incidence of 7–8 cases per 100,000 people per year. This cancer occurs primarily in older individuals, with a median age of diagnosis at approximately 70 years of age, though it can also occur in children and young adults in rare cases. DLBCL is an aggressive tumor, and the first sign of this illness is typically the observation of a rapidly growing mass. The five-year survival rate is only 58%. DLBCL has subtypes that are named according to their cell of origin and include germinal center B-cell-like (GCB) and activated B-cell-like (ABC). They differ in having a worse prognosis and, in some cases, requiring particularized approaches to treatment.

Acute myeloid leukemia (AML), the one of the most common forms of leukemia in adults, with about 20,000 new cases diagnosed each year. AML remains a highly fatal disease with a five-

year survival rate of only 28.3%. Interleukin-1 receptor-associated kinase 4 (IRAK4) has been demonstrated as a potential therapeutic target in human AML. Although AML is a heterogeneous disease, common features of the leukemic blasts include a high proliferative potential, increased stem cell self-renewal and a block in differentiation at a relatively immature state, within the mitotic pool. It is also widely accepted that the specific genetic mutations present within the AML cells may guide therapy, as well as determine how long a patient is likely to survive.

Myelodysplastic syndromes are conditions that can occur when the blood-forming cells in the bone marrow become abnormal. The major clinical problems in these disorders are morbidities caused by cytopenias and the potential for MDS to evolve into AML. In general population, the incidence rate of MDS is approximately 4.9 per 100,000 people per year. High risk MDS (hrMDS) is defined as having a high risk with IPSS score of ≥ 2.5 and immature blast cells may make up more than 5% of the cells in the marrow. The low blood counts can lead to anemia, neutropenia, or thrombocytopenia. HrMDS carries a greater risk of progression to AML and a shorter survival period, with a median survival time of only 0.8 years when patients are untreated. The majority of MDS diagnoses are low risk MDS (LR-MDS). Although LR-MDS has a lower risk of death in the short term, it is associated with anemia and a high risk of treatment complications, leading to high mortality (Brunner, AM et al. Blood Cancer J. 12:166 (2022)).

Another example of an NHL is Waldenstrom's macroglobulinemia (WM). WM is a non-Hodgkin's lymphoma that affects two types of B cells, lymphoplasmacytoid cells and plasma cells. WM is characterized by having high levels of a circulating antibody, immunoglobulin M (IgM), which is made and secreted by the cells involved in the disease. WM is a rare disease, with only about 1,500 cases per year in the United States. There is no single accepted treatment for WM and a marked variation in clinical outcome due to gaps in knowledge of the disease's molecular basis. Objective response rates are high ($> 80\%$) but complete response rates are low (0–15%).

Other types of non-Hodgkin's lymphoma include mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), follicular lymphoma (FL), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), CNS lymphoma, and testicular lymphoma. Non-Hodgkin's lymphoma can be caused by a variety of factors such as infections agents (Epstein-Barr virus, hepatitis C virus and human T-Cell leukemia virus), radiation and chemotherapy treatments, and autoimmune diseases. As a group, non-Hodgkin's lymphoma affects 2.1% of the US population during their life. The percentage of people who survive beyond five years after diagnosis is 71%.

The targeting of intratumoral immune cells with immune checkpoint inhibitors has enabled new therapeutic regimens for many cancers. The leading clinically approved therapeutics focus on the programmed death 1 (PD-1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) pathways, though there are several other targets undergoing development. These therapeutics have proven effective in treating both Hodgkin's and non-Hodgkin lymphoma, although not all patients respond to these therapies.

In view of the foregoing, there is a clear and unmet need for additional therapies for the treatment of cancers and other diseases associated with IRAK4.

SUMMARY OF THE INVENTION

In certain aspects, the present disclosure provides methods of treating a cancer in a subject, comprising administering an IRAK4-modifying compound, wherein the subject has irregular expression of genes associated with NF-KB.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph showing the difference in *IL1B* expression in patients before and after receiving emavusertib for the treatment of hrMDS. *IL1B* expression, both before ("Baseline") and during treatment ("On_Tx"), was higher in patients who did not respond to emavusertib (Non-responder,) compared to hrMDS patients who responded to emavusertib (Responder) ($P \leq 0.01$).

FIG. 2 is a graph showing the difference in *IER3* expression in patients before and after receiving emavusertib for the treatment of hrMDS. *IER3* expression, both before ("Baseline") and during treatment ("On_Tx"), was higher in patients who did not respond to emavusertib ("Non-responder") compared to hrMDS patients who responded to emavusertib ("Responder") ($P \leq 0.01$).

FIG. 3 is a graph showing the difference in *IL1B* expression in patients before and after receiving emavusertib for the treatment of AML. *IL1B* expression, both before ("Baseline") and during treatment ("On_Tx"), was higher in patients who did not respond to emavusertib ("Non-responder") compared to AML patients who responded to emavusertib ("Responder") ($P \leq 0.01$).

FIG. 4 is a graph showing the difference in *IER3* expression in patients before and after receiving emavusertib for the treatment of AML. *IER3* expression, both before ("Baseline") and during treatment ("On_Tx"), was higher in patients who did not respond to emavusertib ("Non-responder") compared to AML patients who responded to emavusertib ("Responder") ($P = 0.57$).

FIG. 5 is a graph showing the difference in *CCL4* expression in patients with AML compared to those with high risk MDS. *CCL4* expression, both before (“Baseline”) and during treatment (“On_Tx”), was lower in AML patients compared to hrMDL patients ($P \leq 0.01$).

FIG. 6 shows differential expression of IRAK4/NF-KB pathway genes highlighting changes in gene expression by diagnosis, treatment status and response.

FIG. 7 shows Hallmark pathway analysis, for AML and MDS patients treated with emavusertib.

FIG. 8 shows gene enrichment plots for the Hallmark G2M Checkpoint pathway.

FIG. 9 shows gene enrichment plots for the Hallmark E2F Targets pathway.

FIG. 10 shows gene enrichment plots for the Hallmark Heme Metabolism pathway.

FIG. 11 shows gene enrichment plots for TNF-alpha/NF-KB signaling.

DETAILED DESCRIPTION OF THE INVENTION

The results of an ongoing Phase 1 study demonstrated clinical activity of IRAK4 inhibitor emavusertib in patients with AML and high-risk MDS. To support the development of effective treatment regimens with emavusertib, a study was conducted to monitor changes in gene expression in pre- and post-treatment samples obtained from AML and high risk MDS. Clinical response data showed that patients who were responders to treatment with emavusertib, had decreased expression levels of *IL1B* and *IER3* (targets of NF-KB) compared to non-responders. The present disclosure relates to methods of treating cancer with emavusertib and other IRAK4 inhibitors or degraders, wherein the subject has altered expression of genes associated with NF-KB.

In certain aspects, the present disclosure provides a method of treating a cancer in a subject comprising administering an IRAK4-modifying compound to the subject, wherein the subject has decreased expression of interleukin-1 beta or immediate early response gene 3.

In certain preferred embodiments, the subject has decreased expression of interleukin-1 beta.

In certain embodiments, the subject has decreased expression of interleukin-1 beta, as compared to a subject not having cancer.

In certain embodiments, the subject has decreased expression of interleukin-1 beta, as compared to a subject having cancer.

In certain embodiments, the subject has decreased expression of immediate early response gene 3.

In certain embodiments, the subject has decreased expression of immediate early response gene 3, as compared to a subject not having cancer.

In certain embodiments, the subject has decreased expression of immediate early response gene 3, as compared to a subject having cancer.

In another embodiment, the method comprises:
obtaining a biological sample(s) from the subject; determining a level(s) of expression of interleukin-1 beta or immediate early response gene 3 in the biological sample(s); comparing the level(s) of expression of the one or more genes to a reference expression level(s); and
administering the IRAK4-modifying compound.

In certain embodiments, the method comprises determining the level(s) of expression of interleukin-1 beta in the biological sample(s).

In certain embodiments, the method comprises determining the level(s) of expression of immediate early response gene 3 in the biological sample(s).

In certain embodiments, the biological sample(s) comprises tissue (e.g., bone marrow).

In certain embodiments, the biological sample(s) comprises blood (e.g. a peripheral blood sample).

In certain embodiments, the method comprises administering an interleukin-1 blocker to the subject.

In certain embodiments, the interleukin-1 blocker is an interleukin-1 receptor antagonist.

In certain embodiments, the interleukin-1 blocker is interleukin-1 receptor antagonist protein or a homologue thereof.

In certain preferred embodiments, the interleukin-1 blocker is anakinra.

In certain embodiments, the interleukin-1 blocker is a soluble decoy receptor.

In certain embodiments, the interleukin-1 blocker is a dimeric fusion protein comprising ligand-binding domains of the extracellular portions of the human interleukin-1 receptor component (IL-1R1) and IL-1 receptor accessory protein (IL-1RAcP) linked to the Fc region of human IgG1.

In certain preferred embodiments, the interleukin-1 blocker is rilonacept.

In certain embodiments, the interleukin-1 blocker is an IL-1 β neutralizing antibody.

In certain preferred embodiments, the interleukin-1 blocker is canakinumab.

In certain embodiments, the interleukin-1 blocker is gevokizumab.

In certain embodiments, the interleukin-1 blocker is LY2189102.

In certain embodiments, the interleukin-1 blocker is an IL-1 α neutralizing antibody.

In certain embodiments, the interleukin-1 blocker is MABp1.

In certain embodiments, the interleukin-1 blocker is an interleukin-1 receptor 1 blocking antibody.

In certain embodiments, the interleukin-1 blocker is MEDI-8968.

In certain embodiments, the interleukin-1 blocker is a caspase 1 inhibitor.

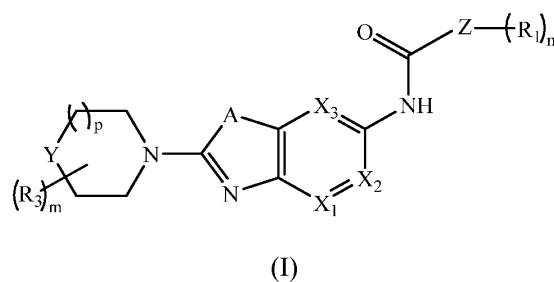
In certain embodiments, the method further comprises administering an agent that inhibits the activity of NF-KB.

In certain embodiments, the IRAK4-modifying compound is an IRAK4 inhibitor. In other embodiments, the IRAK4-modifying compound is an IRAK4 degrader.

IRAK4 Inhibitors

Broadly speaking, the methods disclosed herein may be performed with any IRAK4 inhibitor. For example, the methods may be performed using IRAK4 inhibitors disclosed in PCT/IB2015/050119, PCT/IB2015/050217, PCT/IB2015/0054620, PCT/IB2016/054203, and/or PCT/IB2016/054229. The contents of each of the aforementioned international applications is fully incorporated by reference herein, and in particular for the IRAK4 inhibitors disclosed therein.

In certain embodiments, the IRAK4 inhibitor is represented by formula I:



or a pharmaceutically acceptable salt thereof;

wherein

X₁ and X₃ independently are CH or N; X₂ is CR₂ or N; provided one and not more than one of X₁,

X₂ or X₃ is N;

A is O or S;

Y is -CH₂- or O;

Z is aryl or heterocyclyl;

R₁, at each occurrence, is independently halo or optionally substituted heterocyclyl; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl, hydroxyalkyl or -NR_aR_b;

R₂ is hydrogen, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl or -NR_aR_b; wherein the substituent is alkyl, amino, halo or hydroxyl;

R₃, at each occurrence, is alkyl or hydroxyl;

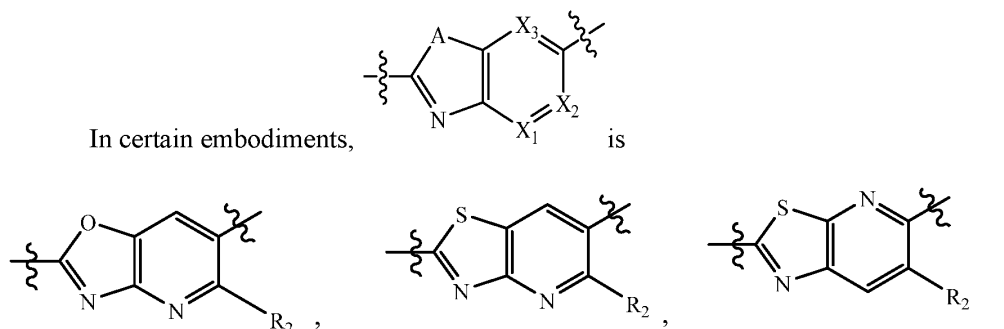
R_a and R_b are independently hydrogen, alkyl, acyl or heterocyclyl;

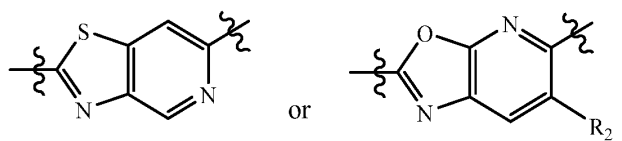
'm' and 'n' are independently 0, 1 or 2;

'p' is 0 or 1.

In certain embodiments, A is O or S; Y is -CH₂- or O; Z is aryl or heterocyclyl; R₁, at each occurrence, is independently halo or optionally substituted heterocyclyl, wherein the substituent is alkyl, aminoalkyl, halo, or -NR_aR_b; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl; R₂ is hydrogen, cycloalkyl, heterocyclyl or -NR_aR_b; 'm' is 0; and 'n' is 1.

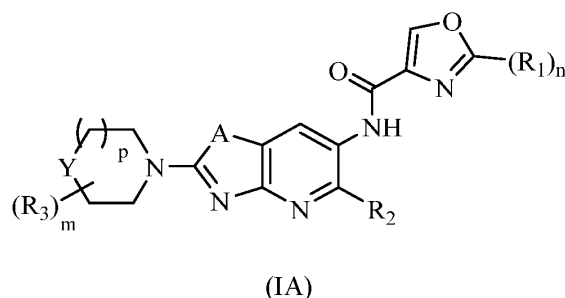
In other embodiments, A is O or S; Y is -CH₂- or O; Z is aryl or heterocyclyl; R₁, at each occurrence, is independently halo or optionally substituted heterocyclyl; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl or -NR_aR_b; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl; R₂ is hydrogen, cycloalkyl, optionally substituted heterocyclyl or -NR_aR_b, where the substituent is selected from amino, halo or hydroxyl; 'm' and 'n' are independently 0, 1 or 2; and 'p' is 0 or 1.





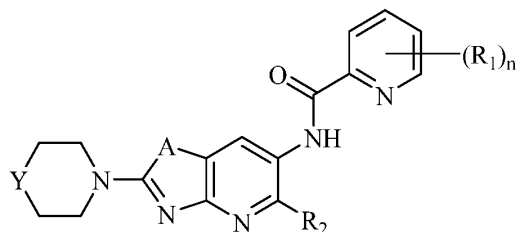
In certain embodiments, Z is aryl or 5- or 6-membered heterocyclyl. In certain embodiments, Z is an optionally substituted heterocyclyl selected from phenyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1H-tetrazolyl, oxadiazolyl, triazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, azetidyl, oxetanyl, imidazolidinyl, pyrrolidinyl, oxazolidinyl, thiazolidinyl, pyrazolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, 1,4-dioxanyl, dioxidothiomorpholinyl, oxapiperazinyl, oxapiperidinyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiophenyl, dihydropyranyl and azabicyclo[3.2.1]octanyl; each of which is optionally substituted with alkyl, alkoxy, halo, hydroxyl, hydroxyalkyl or $-NR_aR_b$; and R_a and R_b are independently hydrogen, alkyl or acyl.

In certain embodiments, the IRAK4 inhibitor is represented by formula (IA):



or a pharmaceutically acceptable salt thereof. In certain embodiments, A is O or S; Y is $-CH_2-$ or O; R_1 , at each occurrence, is independently halo or optionally substituted heterocyclyl, wherein the substituent is alkyl, aminoalkyl, halo, or $-NR_aR_b$; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl; R_2 is hydrogen, cycloalkyl, heterocyclyl or $-NR_aR_b$; 'm' is 0; and 'n' is 1. In other embodiments, A is O or S; Y is $-CH_2-$ or O; R_1 , at each occurrence, is independently halo or optionally substituted heterocyclyl; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl or $-NR_aR_b$; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl; R_2 is hydrogen, cycloalkyl, optionally substituted heterocyclyl or $-NR_aR_b$, where the substituent is selected from amino, halo or hydroxyl; and 'm' and 'n' are independently 0, 1 or 2.

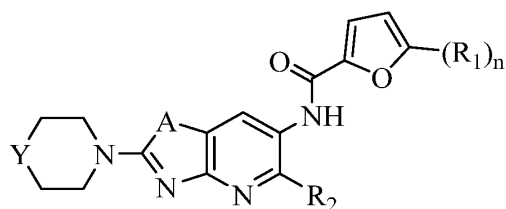
In certain embodiments, the IRAK4 inhibitor is represented by formula (IB):



(IB)

or a pharmaceutically acceptable salt thereof. In certain embodiments, A is O or S; Y is -CH₂- or O; R₁, at each occurrence, is independently halo or optionally substituted heterocyclyl, wherein the substituent is alkyl, aminoalkyl, halo, or -NR_aR_b; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl; R₂ is hydrogen, cycloalkyl, heterocyclyl or -NR_aR_b; and 'n' is 1. In other embodiments, A is O or S; Y is -CH₂- or O; R₁, at each occurrence, is independently halo or optionally substituted heterocyclyl; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl or -NR_aR_b; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl; R₂ is hydrogen, cycloalkyl, optionally substituted heterocyclyl or -NR_aR_b, where the substituent is selected from amino, halo or hydroxyl; and 'm' and 'n' are independently 0, 1 or 2.

In certain embodiments, the IRAK4 inhibitor is represented by formula (IC):



(IC)

or a pharmaceutically acceptable salt thereof.

In certain embodiments, R₁ is optionally substituted heterocyclyl; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl, hydroxyalkyl or -NR_aR_b; and R_a and R_b are independently hydrogen or acyl. In other embodiments, R₁ is optionally substituted heterocyclyl; wherein the substituent is alkyl, aminoalkyl, halo, or -NR_aR_b; and R_a and R_b are independently hydrogen or acyl. In yet other embodiments, R₁ is optionally substituted heterocyclyl; and the

substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl or $-NR_aR_b$; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl. In certain embodiments, R_1 is pyridyl, pyrazolyl, pyrrolidinyl or piperidinyl. In certain embodiments, R_1 is optionally substituted pyrazolyl, wherein the substituent is alkyl, hydroxyl or $-NR_aR_b$. In other embodiments, R_1 is halo.

In certain embodiments, R_2 is hydrogen, cycloalkyl, optionally substituted heterocyclyl or $-NR_aR_b$, where the substituent is selected from amino, halo or hydroxyl. In certain embodiments, R_2 is hydrogen, cycloalkyl, optionally substituted heterocyclyl or $-NR_aR_b$, where the substituent is selected from amino, halo or hydroxyl. In certain embodiments, R_2 is optionally substituted heterocyclyl selected from piperidinyl, pyrrolidinyl, morpholinyl, piperazinyl, azetidiny, pyrazolyl, furanyl or azabicyclo[3.2.1]octanyl; wherein the substituent is hydroxyl, halo, alkyl or amino. In certain embodiments, R_2 is piperidinyl, pyrrolidinyl, morpholinyl, or piperazinyl. In other embodiments, R_2 is hydrogen. In yet other embodiments, is cycloalkyl. In certain embodiments, R_2 is cyclopropyl.

In certain embodiments, R_3 is alkyl.

In certain embodiments, m is 0 and p is 1. In other embodiments, m is 0 or 2, and p is 0 or 1.

In certain embodiments, the IRAK4 inhibitor is selected from:

6'-amino-N-(2-morpholinooxazolo[4,5-b]pyridin-6-yl)-[2,3'-bipyridine]-6-carboxamide;

6'-amino-N-(5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-[2,3'-bipyridine]-6-carboxamide hydrochloride;

N-(5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride;

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide hydrochloride;

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide;

2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

6-chloro-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)picolinamide;
N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-6-(1-methyl-1H-pyrazol-4-yl)picolinamide;
2-(2-chloropyridin-4-yl)-N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
(S)-2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(pyrrolidin-3-ylamino)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
6'-amino-N-(2-morpholinooxazolo[5,4-b]pyridin-5-yl)-[2,3'-bipyridine]-6-carboxamide;
6'-amino-N-(2-morpholinothiazolo[4,5-c]pyridin-6-yl)-[2,3'-bipyridine]-6-carboxamide;
6'-amino-N-(2-morpholinothiazolo[5,4-b]pyridin-5-yl)-[2,3'-bipyridine]-6-carboxamide;
2-(2-methylpyridin-4-yl)-N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
6'-amino-N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)-[2,3'-bipyridine]-6-carboxamide;
N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide;
3-(4-(aminomethyl)piperidin-1-yl)-5-fluoro-N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)benzamide;
2-(4-(aminomethyl)piperidin-1-yl)-5-fluoro-N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)benzamide;
2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide;
N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide;
N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(2,5-dimorpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(4-methylpiperazin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-3-yl)oxazole-4-carboxamide;

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-hydroxypyridin-3-yl)oxazole-4-carboxamide;

2-(2-hydroxypyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(6-hydroxypyridin-3-yl)oxazole-4-carboxamide;

2-(2-methoxypyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

2-(2-methylpyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

2-(3-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(3-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(6-methylpyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

6-(1-methyl-1H-pyrazol-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)picolinamide;

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(6-methylpyridin-3-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-aminopyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(R)-N-(5-(3-aminopyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(R)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(S)-2-(3-aminopyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

(S)-6-(3-hydroxypyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)picolinamide;

(S)-6-(3-aminopyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)picolinamide;

(S)-2-(3-hydroxypyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

(S)-N-(5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(3-hydroxypyrrolidin-1-yl)oxazole-4-carboxamide;

(S)-2-(3-aminopyrrolidin-1-yl)-N-(5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

2-(2-methylpyridin-4-yl)-N-(5-(piperidin-1-yl)-2-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride;

N-(2-(2,6-dimethylmorpholino)-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride;

N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-6-(1-methyl-1H-pyrazol-4-yl)picolinamide hydrochloride;

6-(1-methyl-1H-pyrazol-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide;

N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-3-yl)oxazole-4-carboxamide hydrochloride;

N-(2-((2S,6R)-2,6-dimethylmorpholino)-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(2-methylpyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

2-(2-hydroxypyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methoxypyridin-4-yl)oxazole-4-carboxamide;

2-(6-methoxypyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

2-(2-methoxypyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(6-methylpyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

2-(3-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

(S)-6-(3-aminopyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide;

(S)-6-(3-hydroxypyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide;

(S)-6-(3-aminopyrrolidin-1-yl)-N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide;

(S)-N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-6-(3-hydroxypyrrolidin-1-yl)picolinamide;

(S)-2-(3-aminopyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-aminopyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(S)-2-(3-aminopyrrolidin-1-yl)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(S)-2-(3-hydroxypyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(S)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-(3-hydroxypyrrolidin-1-yl)picolinamide;

(S)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(3-hydroxypyrrolidin-1-yl)oxazole-4-carboxamide;

(S)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-(1-(2-hydroxypropyl)-1H-pyrazol-4-yl)picolinamide;

(S)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(1-(2-hydroxypropyl)-1H-pyrazol-4-yl)oxazole-4-carboxamide;

N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;

(R)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;

(S)-N-(5-(azetidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-(3-hydroxypyrrolidin-1-yl)picolinamide;

N-(5-(3-hydroxyazetidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)thiophene-2-carboxamide;

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;

(S)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide
(R)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;
N-(5-(azetidin-1-yl)-2-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
2-(2-methylpyridin-4-yl)-N-(2-(piperidin-1-yl)-5-(pyrrolidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(pyrrolidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
5-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)furan-2-carboxamide;
N-(5-(azepan-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
2-(2-aminopyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride;
N-(5-(azetidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
(R)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
(R)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;
(S)-6-(1-(2-hydroxypropyl)-1H-pyrazol-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide
N-(5-(4-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide
N-(5-(4-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride

N-(5-(1-methyl-1H-pyrazol-4-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(3-fluorophenyl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;

N-(5-(3-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;

N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(R)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;

N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;

(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)thiophene-2-carboxamide;

N-(5-(azetidin-1-yl)-2-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(2-methylpyridin-4-yl)-N-(2-(piperidin-1-yl)-5-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

5-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)furan-2-carboxamide;

N-(5-(azetidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinoxazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;

(R)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinoxazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;

N-(5-(furan-3-yl)-2-morpholinoxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(3-fluoropiperidin-1-yl)-2-morpholinoxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinoxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(4-fluoropiperidin-1-yl)-2-morpholinoxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

(S)-N-(5-(3-aminopiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(1H-pyrazol-4-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

N-(5-(6-fluoropyridin-3-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(5-(3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

N-(2-(3-hydroxypiperidin-1-yl)-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(2-acetamidopyridin-4-yl)-N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

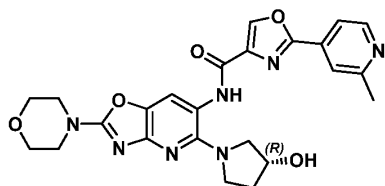
N-(2-(3-hydroxypiperidin-1-yl)-5-(4-hydroxypiperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

2-(2-acetamidopyridin-4-yl)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

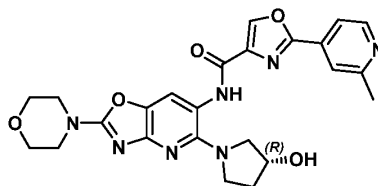
2-(2-aminopyridin-4-yl)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride;

5-(2-aminopyridin-4-yl)-N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)furan-3-carboxamide hydrochloride;
 2-(2-aminopyridin-4-yl)-N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride;
 2-(2-aminopyridin-4-yl)-N-(5-(4-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride;
 N-(5-(2-fluoropyridin-4-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
 N-(5-(4-fluoropiperidin-1-yl)-2-(3-hydroxypiperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
 N-(5-(4-aminopiperidin-1-yl)-2-(3-hydroxypiperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride; and
 N-(5-(2-hydroxypyridin-4-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride;
 or a pharmaceutically acceptable salt or a stereoisomer thereof.

In certain preferred embodiments, the IRAK4 inhibitor is

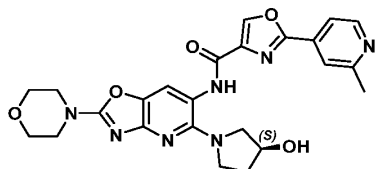


. In other preferred embodiments, the IRAK4 inhibitor is a

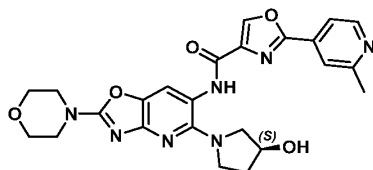


pharmaceutically acceptable salt of

In certain preferred embodiments, the IRAK4 inhibitor is

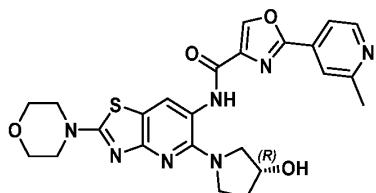


. In other preferred embodiments, the IRAK4 inhibitor is a

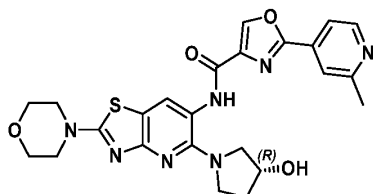


pharmaceutically acceptable salt of

In certain preferred embodiments, the IRAK4 inhibitor is

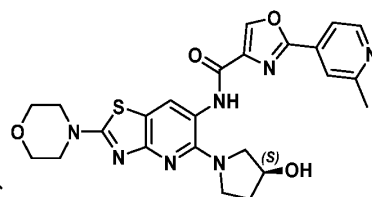


. In other preferred embodiments, the IRAK4 inhibitor is a



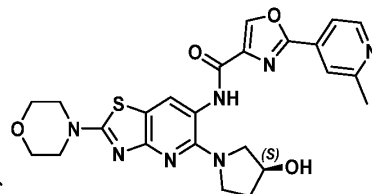
pharmaceutically acceptable salt of

In certain preferred embodiments, the IRAK4 inhibitor is . In other preferred embodiments,



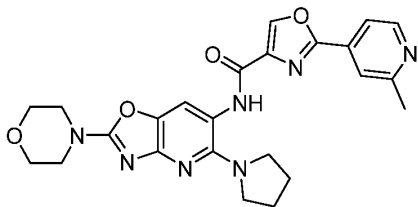
the IRAK4 inhibitor is a pharmaceutically acceptable salt of

In certain preferred embodiments, the IRAK4 inhibitor is . In other preferred embodiments,

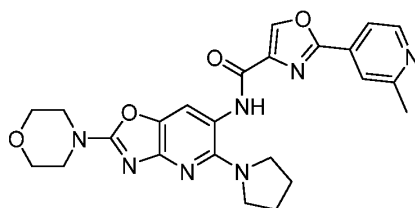


the IRAK4 inhibitor is a pharmaceutically acceptable salt of

In certain preferred embodiments, the IRAK4 inhibitor is

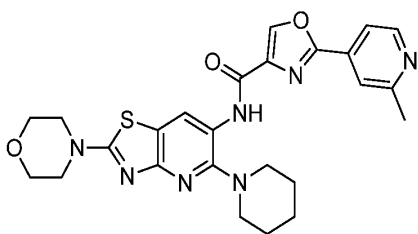


. In other preferred embodiments, the IRAK4 inhibitor is a

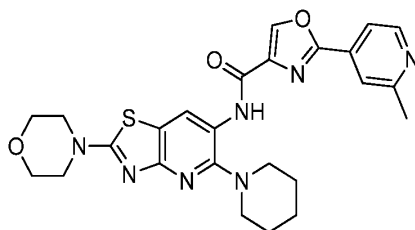


pharmaceutically acceptable salt of

In certain preferred embodiments, the IRAK4 inhibitor is

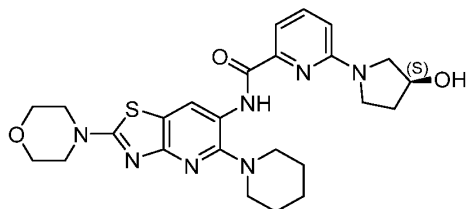


. In other preferred embodiments, the IRAK4 inhibitor is a

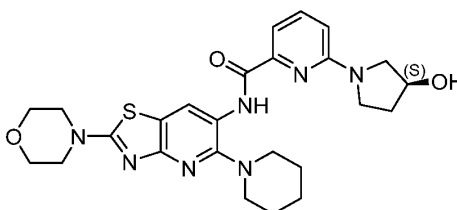


pharmaceutically acceptable salt of

In certain preferred embodiments, the IRAK4 inhibitor is

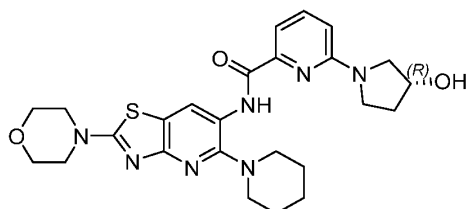


. In other preferred embodiments, the IRAK4 inhibitor

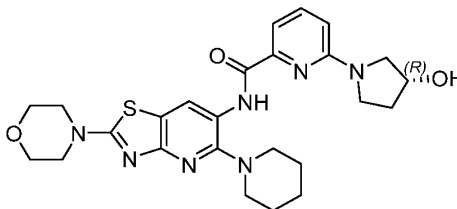


is a pharmaceutically acceptable salt of

In certain preferred embodiments, the IRAK4 inhibitor is



. In other preferred embodiments, the IRAK4 inhibitor



is a pharmaceutically acceptable salt of

Generally, the compounds recited herein may be administered in any amount or manner that elicits the desired response in the subject. For example, 100 – 400 mg of an IRAK4 inhibitor chosen from the compounds recited herein can be administered to the subject twice per day or 200 – 1000 mg of the IRAK4 inhibitor can be administered to the subject once per day. In certain embodiments, 100 – 400 mg of the IRAK4 inhibitor is administered to the subject twice per day. In certain embodiments, 200 – 400 mg of the IRAK4 inhibitor is administered to the subject twice per day. In certain preferred embodiments, 250 – 350 mg of the IRAK4 inhibitor is administered to the subject twice per day. In certain embodiments, about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about

275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, or about 500 mg of the IRAK4 inhibitor is administered to the subject twice per day. In certain embodiments, about 50 mg, about 75 mg, about 100 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, or about 400 mg of the IRAK4 inhibitor is administered to the subject twice per day. In certain embodiments, about 50 mg, about 100 mg, about 200 mg, or about 300 mg of the IRAK4 inhibitor is administered to the subject twice per day. In certain embodiments, about 50 mg of the IRAK4 inhibitor is administered to the subject twice per day. In other embodiments, about 200 mg of the IRAK4 inhibitor is administered to the subject twice per day. In other embodiments, about 225 mg of the IRAK4 inhibitor is administered to the subject twice per day. In other embodiments, about 250 mg of the IRAK4 inhibitor is administered to the subject twice per day. In other embodiments, about 275 mg of the IRAK4 inhibitor is administered to the subject twice per day. In particularly preferred embodiments, about 300 mg of the IRAK4 inhibitor is administered to the subject twice per day. In other embodiments, about 325 mg of the IRAK4 inhibitor is administered to the subject twice per day. In other embodiments, about 350 mg of the IRAK4 inhibitor is administered to the subject twice per day. In other embodiments, about 375 mg of the IRAK4 inhibitor is administered to the subject twice per day. In other embodiments, about 400 mg of the IRAK4 inhibitor is administered to the subject twice per day.

In certain embodiments, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, or about 500 mg of the IRAK4 inhibitor is administered to the subject once per day. In certain embodiments, about 50 mg of the IRAK4 inhibitor is administered to the subject once per day. In certain embodiments, about 75 mg of the IRAK4 inhibitor is administered to the subject once per day. In certain embodiments, about 100 mg of the IRAK4 inhibitor is administered to the subject once per day. In certain embodiments, about 125 mg of the IRAK4 inhibitor is administered to the subject once per day. In certain embodiments, about 150 mg of the IRAK4 inhibitor is administered to the subject once per day.

In certain preferred embodiments, the IRAK4 inhibitor or degrader is orally administered to the subject. In certain embodiments, about 50 mg of the IRAK4 inhibitor or degrader is orally administered to the subject twice per day. In other embodiments, about 200 mg of the IRAK4

inhibitor or degrader is orally administered to the subject twice per day. In other embodiments, about 250 mg of the IRAK4 inhibitor or degrader is orally administered to the subject twice per day. In particularly preferred embodiments, about 300 mg of the IRAK4 inhibitor or degrader is orally administered to the subject twice per day. In other embodiments, about 325 mg of the IRAK4 inhibitor or degrader is orally administered to the subject twice per day. In other embodiments, about 350 mg of the IRAK4 inhibitor or degrader is orally administered to the subject twice per day. In other embodiments, about 375 mg of the IRAK4 inhibitor or degrader is orally administered to the subject twice per day. In other embodiments, about 400 mg of the IRAK4 inhibitor or degrader is orally administered to the subject twice per day. In other embodiments, about 50 mg of the IRAK4 inhibitor or degrader is orally administered to the subject once per day. In yet other embodiments, about 75 mg of the IRAK4 inhibitor or degrader is orally administered to the subject once per day. In yet other embodiments, about 100 mg of the IRAK4 inhibitor or degrader is orally administered to the subject once per day. In yet other embodiments, about 125 mg of the IRAK4 inhibitor or degrader is orally administered to the subject once per day. In yet other embodiments, about 150 mg of the IRAK4 inhibitor or degrader is orally administered to the subject once per day.

In other embodiments, the IRAK4 inhibitor is PF-06650833 or BAY 1830839.

IRAK4 Degraders

In certain embodiments, the method comprises administering an IRAK4 degrader. In certain embodiments, the IRAK4 degrader is KT-474.

Combination Therapies

In certain embodiments of the methods disclosed herein, the method further comprises administering an IL-1 β inhibitor or antagonist to the subject. In certain embodiments, the IL-1 β inhibitor is an antibody that targets IL-1 β . In certain preferred embodiments, the IL-1 β inhibitor is canakinumab. In certain embodiments, the IL-1 β inhibitor is a protein with at least 90% sequence identity to the interleukin-1 receptor antagonist protein (IL-1RN). In certain preferred embodiments, the IL-1 β inhibitor is anakinra. In certain embodiments, the IL-1 β inhibitor is a dimeric fusion protein comprising ligand-binding domains of the extracellular portions of the human interleukin-1 receptor component (IL-1R1) and IL-1 receptor accessory protein (IL-

1RAcP) linked to the Fc region of human IgG1. In certain preferred embodiments, the IL-1 β inhibitor is rilonacept.

In certain embodiments of the methods disclosed herein, the method further comprises conjointly administering a BCL-2 inhibitor to the subject. In certain preferred embodiments, the BCL-2 inhibitor is venetoclax. In certain embodiments, the method further comprises administering 400 mg of venetoclax daily. In certain embodiments, the venetoclax is administered orally. In certain preferred embodiments, the method further comprises orally administering 400 mg of venetoclax daily.

In other embodiments, the method further comprises conjointly administering a BTK inhibitor to the subject. In certain embodiments, the BTK inhibitor is ibrutinib, acalabrutinib, zanubrutinib, evobrutinib, ONO-4059, spebrutinib, or HM7 1224. In certain embodiments, the BTK inhibitor is ibrutinib, acalabrutinib, zanubrutinib, evobrutinib, ONO-4059, spebrutinib, or HM7 1224. In certain embodiments, the BTK inhibitor is acalabrutinib. In certain embodiments, the method comprises administering 200 mg of acalabrutinib daily. In certain embodiments, the acalabrutinib is administered orally. In certain embodiments, the method comprises orally administering 200 mg of acalabrutinib daily. In certain preferred embodiments, the BTK inhibitor is ibrutinib. In certain embodiments, the method comprises administering 420 mg of ibrutinib daily. In other embodiments, the method comprises administering 420 mg of ibrutinib daily. In certain embodiments, the ibrutinib is administered orally. In certain preferred embodiments, orally administering 420 mg of ibrutinib daily. In other preferred embodiments, the method comprises administering 560 mg of ibrutinib daily. In certain embodiments, the BTK inhibitor is zanubrutinib. In certain embodiments, the method administering 160 mg of zanubrutinib twice daily. In other embodiments, the method comprises administering 320 mg of zanubrutinib once daily. In certain embodiments, the zanubrutinib is administered orally. In certain embodiments, the method comprises orally administering 160 mg of zanubrutinib twice daily. In other embodiments, the method comprises orally administering 320 mg of zanubrutinib once daily. In certain embodiments, the method further comprises conjointly administering one or more of ABT-737, BAY-1143572, 5-fluorouracil, abiraterone acetate, acetylcholine, adotrastuzumab emtansine, afatinib, aldesleukin, alectinib, alemtuzumab, alitretinoin, aminolevulinic acid, anastrozole, anastrozole, aprepitant, arsenic trioxide, asparaginase erwinia chrysanthemi, atezolizumab, axitinib, azacitidine, belinostat, bendamustine, benzyl isothiocyanate, bevacizumab,

bexarotene, bicalutamide, bleomycin, blinatumomab, bortezomib, bosutinib, brentuximab vedotin, busulfan, cabazitaxel, cabozantinib, capecitabine, carboplatin, carfilzomib, carmustine, ceritinib, cetuximab, chlorambucil, cisplatin, clofarabine, cobimetinib, copanlisib, crizotinib, cyclophosphamide, cytarabine, dabrafenib, dacarbazine, dacarbazine, dactinomycin, daratumumab, dasatinib, daunorubicin, decitabine, defibrotide sodium, degarelix, denileukin diftitox, denosumab, dexamethasone, dexrazoxane, dihydrotestosterone (DHT), dinutuximab, docetaxel, doxorubicin, elotuzumab, eltrombopag, enzalutamide, epirubicin, eribulin mesylate, erlotinib, etoposide, everolimus, exemestane, exemestane, filgrastim, fludarabine phosphate, flutamide, fulvestrant, fulvestrant, gefitinib, gemcitabine, gemtuzumab, gemtuzumab ozogamicin, glucarpidase, goserelin acetate, hydroxyurea, ibritumomab tiuxetan, ibrutinib, idarubicin, idelalisib, ifosfamide, imatinib, imiquimod, interferon alfa-2b, ipilimumab, irinotecan, ixabepilone, ixazomib, lanreotide, lapatinib, lenalidomide, lenvatinib, letrozole, leucovorin, leuprolide, lomustine, mechlorethamine, megestrol acetate, melphalan, mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, navitoclax, necitumumab, nelarabine, netupitant, nilotinib, nilutamide, nivolumab, obinutuzumab, ofatumumab, olaparib, omacetaxine mepesuccinate, osimertinib, oxaliplatin, ozogamicin, paclitaxel, palbociclib, palifermin, pamidronate, panitumumab, panobinostat, pazopanib, pegaspargase, peginterferon alfa-2b, pembrolizumab, pemetrexed, pertuzumab, plerixafor, pomalidomide, ponatinib, pralatrexate, prednisone, procarbazine, propranolol, radium 223 dichloride, raloxifene, ramucirumab, rasburicase, regorafenib, rituximab, rolapitant, romidepsin, romiplostim, ruxolitinib, siltuximab, sipuleucel-t, sonidegib, sorafenib, sunitinib, talimogene laherparepvec, tamoxifen, temozolomide, temsirolimus, thalidomide, thioguanine, thiotepa, tipiracil, topotecan, toremifene, toremifene, tositumomab, trabectedin, trametinib, trastuzumab, tretinoin, trifluridine, uridine triacetate, vandetanib, vemurafenib, venetoclax, vinblastine, vincristine, vinorelbine, vismodegib, vorinostat, ziv-aflibercept, zoledronic acid, and pharmaceutically acceptable salts thereof. In some embodiments, the second therapeutic agent is one or more of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

Diseases and Disorders

The methods disclosed herein relate to the treatment of cancer. In certain embodiments, the cancer is a hematological malignancy, such as a leukemia or lymphoma, for example a non-Hodgkin's lymphoma. In certain embodiments, the hematological malignancy is myelogenous

leukemia, myeloid leukemia (*e.g.*, acute myeloid leukemia), myelodysplastic syndrome, lymphoblastic leukemia (*e.g.*, acute lymphoblastic leukemia), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, follicular lymphoma, diffuse large B-cell lymphoma (DLBCL) (*e.g.*, DLBCL or ABC-DLBCL), mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia (WM), multiple myeloma, marginal zone lymphoma (MZL), Burkitt's lymphoma, non-Burkitt high grade B cell lymphoma, extranodal marginal zone B cell lymphoma, transformed high grade B-cell lymphoma (HGBL), lymphoplasmacytic lymphoma (LPL), central nervous system lymphoma (CNSL), or MALT lymphoma. In certain embodiments, the hematological malignancy is myelogenous leukemia. In other embodiments, the hematological malignancy is myeloid leukemia (*e.g.*, acute myeloid leukemia). In certain embodiments, the hematological malignancy is acute myeloid leukemia (*e.g.*, AML). In certain embodiments, the AML is primary AML. In other embodiments, the AML is secondary AML. In yet other embodiments, the hematological malignancy is myelodysplastic syndrome. In certain embodiments, the myelodysplastic syndrome is high grade. In other embodiments, the myelodysplastic syndrome is low grade. In certain embodiments, the myelodysplastic syndrome is high risk. In other embodiments, the myelodysplastic syndrome is low risk. In yet other embodiments, the hematological malignancy is lymphoblastic leukemia (*e.g.*, acute lymphoblastic leukemia). In yet other embodiments, the hematological malignancy is chronic lymphocytic leukemia (CLL). In certain embodiments, the CLL is high risk CLL. In yet other embodiments, the hematological malignancy is small lymphocytic lymphoma (SLL). In yet other embodiments, the hematological malignancy is follicular lymphoma. In yet other embodiments, the hematological malignancy is diffuse large B-cell lymphoma (DLBCL). In yet other embodiments, the hematological malignancy is activated B cell-like (ABC) DLBCL. In yet other embodiments, the hematological malignancy is germinal center B cell-like (GCB) DLBCL. In certain embodiments, the DLBCL is extranodal. In certain embodiments, the DLBCL is extranodal leg lymphoma, extranodal testicle lymphoma, or extra nodal not otherwise specified (NOS) type lymphoma. In yet other embodiments, the hematological malignancy is mantle cell lymphoma. In further embodiments, the hematological malignancy is Waldenstrom's macroglobulinemia. In yet other embodiments, the hematological malignancy is multiple myeloma. In still other embodiments, the hematological malignancy is marginal zone lymphoma. In yet other embodiments, the hematological malignancy is Burkitt's lymphoma. In yet other embodiments,

the hematological malignancy is non-Burkitt high grade B cell lymphoma. In still other embodiments, the hematological malignancy is extranodal marginal zone B cell lymphoma. In yet other embodiments, the hematological malignancy is transformed high grade B-cell lymphoma (HGBL). In yet other embodiments, the hematological malignancy is lymphoplasmacytic lymphoma (LPL). In yet other embodiments, the hematological malignancy is CNS lymphoma. In yet other embodiments, the CNS lymphoma is primary CNS lymphoma (PCNSL). In yet other embodiments, the hematological malignancy is MALT lymphoma. In certain embodiments, the hematological malignancies described above may be relapsed or refractory.

In certain embodiments, the subject has previously received a BTK inhibitor for the treatment of cancer. In certain embodiments, the hematological malignancies described above are resistant to treatment with a BTK inhibitor. In certain embodiments, the hematological malignancies described above are resistant to treatment with a BTK inhibitor as a monotherapy. In certain embodiments, the hematological malignancies is resistant to treatment with ibrutinib, acalabrutinib, zanubrutinib, evobrutinib, ONO-4059, spebrutinib, or HM7 1224. In certain preferred embodiments, the hematological malignancy is resistant to treatment with ibrutinib. In certain embodiments, the cancer is selected from brain cancer, kidney cancer, liver cancer, stomach cancer, penile cancer, vaginal cancer, ovarian cancer, gastric cancer, breast cancer, bladder cancer, colon cancer, prostate cancer, pancreatic cancer, lung cancer, cervical cancer, epidermal cancer, melanoma, prostate cancer, head or neck cancer. In certain preferred embodiments, the cancer is pancreatic cancer. In other embodiments, the cancer is colon cancer. In certain embodiments, the cancer is a solid tumor. In various such embodiments, the cancer may be relapsed or refractory. In certain embodiments, the cancers described above are resistant to treatment with a BTK inhibitor. In certain embodiments, the cancers described above are resistant to treatment with a BTK inhibitor as a monotherapy. In certain embodiments, the cancers are resistant to treatment with ibrutinib, acalabrutinib, zanubrutinib, evobrutinib, ONO-4059, spebrutinib, or HM7 1224. In certain preferred embodiments, the cancer is resistant to treatment with ibrutinib.

In certain embodiments, the subject is an adult human.

In certain embodiments, the IRAK4 inhibitor or degrader is administered at a dosage of about 50 mg orally once per day; and the cancer is DLBCL. In certain embodiments, the DLBCL is relapsed or refractory.

In certain embodiments, the IRAK4 inhibitor or degrader is administered at a dosage of about 50 mg orally once per day; and the cancer is FL. In certain embodiments, the FL is relapsed or refractory.

In certain embodiments, the IRAK4 inhibitor or degrader is administered at a dosage of about 300 mg orally once per day; and the cancer is WM. In certain embodiments, the WM is relapsed or refractory.

In certain embodiments, the IRAK4 inhibitor or degrader is administered at a dosage of about 50 mg orally twice per day; and the cancer is DLBCL. In certain embodiments, the DLBCL is relapsed or refractory.

In certain embodiments, the IRAK4 inhibitor or degrader is administered at a dosage of about 300 mg orally twice per day; and the cancer is LPL. In certain embodiments, the LPL is relapsed or refractory.

In certain embodiments, the IRAK4 inhibitor or degrader is administered at a dosage of about 300 mg orally twice per day; and the cancer is GCB DLBCL. In certain embodiments, the GCB DLBCL is relapsed or refractory.

In certain embodiments, the IRAK4 inhibitor or degrader is administered at a dosage of about 400 mg orally twice per day; and the cancer is ABC DLBCL. In certain embodiments, the ABC DLBCL is relapsed or refractory.

In certain embodiments, the IRAK4 inhibitor or degrader is administered at a dosage of about 400 mg orally twice per day; and the cancer is MZL. In certain embodiments, the MZL is relapsed or refractory.

In certain embodiments, the IRAK4 inhibitor or degrader is administered at a dosage of about 300 mg orally twice per day; and the cancer is MZL. In certain embodiments, the MZL is relapsed or refractory.

In certain embodiments, the IRAK4 inhibitor or degrader is administered at a dosage of about 300 mg orally twice per day; and the cancer is MALT. In certain embodiments, the MALT is relapsed or refractory.

In certain embodiments, the IRAK4 inhibitor or degrader is administered continuously (*e.g.*, emavusertib is administered without a drug holiday). In other embodiments, the IRAK4 inhibitor or degrader is administered intermittently (*e.g.*, emavusertib is administered continuously interrupted by one or more drug holidays). In certain embodiments, each drug holiday lasts for a

period of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 days. In certain preferred embodiments, a drug holiday lasts for 7 days. In further preferred embodiments, the IRAK4 inhibitor or degrader is administered daily for three weeks followed by a one-week drug holiday, optionally followed by three weeks of daily administration and a one-week drug holiday, which cycle may be further repeated. In certain embodiments, the aforementioned dosing regimen continues, alternating periods of administration with holidays, until a change of disease state is observed (e.g., until a complete response, a partial response, or unacceptable toxicity is observed). Methods of treating certain diseases and disorders with emavusertib are disclosed in PCT/US2021/030192 and PCT/US23/21812, the contents of which are fully incorporated by reference herein.

Prior Therapies

The methods disclosed herein may be used as a first line therapy or they may be applied to patients who have failed to achieve a response, either partial or full, using one or more previous anti-cancer therapies or anti-inflammatory therapies. In certain embodiments, the subject has previously received at least one anti-cancer therapy. In certain embodiments, the patient has previously received one anti-cancer therapy. In other embodiments, the patient has previously received two anti-cancer therapies. In yet other embodiments, the patient has previously received three anti-cancer therapies. In yet other embodiments, the patient has previously received four anti-cancer therapies. In yet other embodiments, the patient has previously received five anti-cancer therapies. In certain embodiments, the at least one anti-cancer therapy comprises an anti-CD20 antibody, a nitrogen mustard, a steroid, a purine analog, a DNA topoisomerase inhibitor, a DNA intercalator, a tubulin inhibitor, a BCL-2 inhibitor, a proteasome inhibitor, a toll-like receptor inhibitor, a kinase inhibitor, an SRC kinase inhibitor, a PI3K kinase inhibitor, BTK inhibitor, a glutaminase inhibitor, or a methylating agent; or a combination thereof. In certain embodiments, the anti-cancer therapy comprises ibrutinib, rituximab, bendamustine, bortezomib, dexamethasone, chlorambucil, cladribine, cyclophosphamide, doxorubicin, vincristine, venetoclax, ifosfamide, prednisone, oprozomib, ixazomib, acalabrutinib, zanubrutinib, IMO-08400, idelalisib, umbrelasib, CB-839, fludarabine, or thalidomide; or a combination thereof. In certain embodiments, the anti-cancer therapy comprises ibrutinib. In certain embodiments, the anti-cancer therapy comprises ibrutinib and rituximab. In certain embodiments, the anti-cancer therapy comprises bendamustine. In certain embodiments, the anti-cancer therapy comprises bendamustine and rituximab. In certain embodiments, the anti-cancer therapy comprises

bortezomib. In certain embodiments, the anti-cancer therapy comprises bortezomib and dexamethasone. In certain embodiments, the anti-cancer therapy comprises bortezomib and rituximab. In certain embodiments, the anti-cancer therapy comprises bortezomib, rituximab, and dexamethasone. In certain embodiments, chlorambucil. In certain embodiments, the anti-cancer therapy comprises cladribine. In certain embodiments, the anti-cancer therapy comprises cladribine and rituximab. In certain embodiments, the anti-cancer therapy comprises cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab (*i.e.*, CHOP-R). In certain embodiments, the anti-cancer therapy comprises cyclophosphamide, prednisone, and rituximab (*i.e.*, CPR). In certain embodiments, the anti-cancer therapy comprises fludarabine. In certain embodiments, the anti-cancer therapy comprises fludarabine and rituximab. In certain embodiments, the anti-cancer therapy comprises fludarabine, cyclophosphamide, and rituximab. In certain preferred embodiments, the anti-cancer therapy comprises rituximab. In certain preferred embodiments, the anti-cancer therapy comprises rituximab. In certain embodiments, the anti-cancer therapy comprises rituximab, cyclophosphamide, and dexamethasone (*i.e.*, RCD). In certain embodiments, the anti-cancer therapy comprises thalidomide. In certain embodiments, the anti-cancer therapy comprises thalidomide and rituximab. In certain embodiments, the anti-cancer therapy comprises venetoclax. In certain embodiments, the anti-cancer therapy comprises cyclophosphamide, bortezomib, and dexamethasone (*i.e.*, R-CyBorD). In certain embodiments, the anti-cancer therapy comprises a hypomethylating agent. In certain embodiments, the subject has previously received at least 6 cycles of a hypomethylating agent. In certain embodiments, the anti-cancer therapy comprises a combination of any of the foregoing, for example the subject may first receive rituximab and then at a later date receive a combination of rituximab, cyclophosphamide, and dexamethasone (*i.e.*, RCD).

The subject may also have received or been prepared for other, non-chemotherapeutic treatments, such as surgery, radiation, or a bone marrow transplant. In certain embodiments, the subject has previously received etoposide chemo-mobilization therapy. In certain embodiments, the subject has previously received a bone marrow transplant. In certain embodiments, the subject has previously received a stem cell transplant. In certain embodiments, the subject has previously received an autologous cell transplant. In certain embodiments, the subject has previously received an allogenic stem cell transplant. In certain embodiments, the subject has previously received a hematopoietic cell transplantation. In certain embodiments, the subject has previously received

carmustine, etoposide, cytarabine, and melphalan (*i.e.*, BEAM conditioning). In certain embodiments, the subject has previously received re-induction therapy.

The subject may have also previously exhibited a favorable outcome to prior therapy only to require additional treatment at a later date. In certain embodiments, the subject has previously achieved a partial response. In certain embodiments, the subject has previously achieved a good partial response. In certain embodiments, the subject has previously achieved a complete response. In certain embodiments, the cancer is relapsed. In certain embodiments, the cancer is refractory.

In certain embodiments, the subject has not previously received a BTK inhibitor for the treatment of cancer.

In certain embodiments, the subject has previously received one or more immune checkpoint inhibitors for the treatment of cancer.

The subject may also have preexisting or developed one or more genetic mutations that render the subject's cancer more or less resistant to therapy. In certain embodiments, the subject has a mutation in RICTOR. In certain embodiments, the subject has a N1065S mutation in RICTOR. In certain preferred embodiments, the subject has a mutation in MYD88. In certain even further preferred embodiments, the subject has a L265P mutation in MYD88. In certain embodiments, the subject has a mutation in TET2. In certain embodiments, the subject does not have a mutation in CXCR4. In other embodiments, the subject has a mutation in CXCR4. In certain preferred embodiments, the subject has a mutation in SF3B1 (*e.g.*, an insertion, deletion, loss, or spliceosome mutation). In certain preferred embodiments, the subject has a mutation in U2AF1 (*e.g.*, an insertion, deletion, loss, or spliceosome mutation). In certain preferred embodiments, the subject has a mutation (*e.g.*, an insertion, deletion, loss, or internal tandem duplication) in FLT3 kinase. In certain preferred embodiments, the mutation of FLT3 kinase is selected from one or more of an internal tandem duplication (ITD), a mutation in a mutation in D835, a mutation in F691, a mutation in K663, and/or a mutation in N841. In certain embodiments, the mutation in FLT3 kinase comprises a D835H mutation. In certain embodiments, the mutation in FLT3 kinase comprises a D835V mutation. In certain embodiments, the mutation in FLT3 kinase comprises a D835Y mutation. In certain embodiments, the mutation in FLT3 kinase comprises a K663Q mutation. In certain embodiments, the mutation in FLT3 kinase comprises an N841I mutation. In certain embodiments, the mutation in FLT3 kinase comprises an ITD and a D835V mutation. In certain embodiments, the mutation in FLT3 kinase comprises an ITD and an F691L mutation. In

certain embodiments, the mutation in FLT3 kinase comprises an ITD and a D835Y mutation. In certain embodiments, the subject has a mutation (*e.g.*, an insertion, deletion, or loss) in STAG2. In certain embodiments, the subject has a mutation (*e.g.*, an insertion, deletion, or loss) in DNMT3A. In certain embodiments, the subject has a mutation (*e.g.*, an insertion, deletion, or loss) in BCOR. In certain embodiments, the subject has a mutation (*e.g.*, an insertion, deletion, or loss) in WT1. In certain embodiments, the subject has a mutation in NRAS. In certain embodiments, the subject shows early progression.

In certain embodiments, following administration of the compound, the subject achieves a partial response. In certain embodiments, following administration of the compound, the subject achieves a good partial response. In other embodiments, following administration of the compound, the subject achieves a complete response. In certain embodiments, the subject achieves a partial response within 7 days of receiving the compound. In certain embodiments, the subject achieves a good partial response within 7 days of receiving the compound. In certain embodiments, the subject achieves a complete response within 7 days of receiving the compound. In certain embodiments, the subject's tumor volume is reduced by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, or about 95%. In certain embodiments, the subject's tumor volume is reduced by 5%. In certain embodiments, the subject's tumor volume is reduced by 10%. In certain embodiments, the subject's tumor volume is reduced by 15%. In certain embodiments, the subject's tumor volume is reduced by 20%. In certain embodiments, the subject's tumor volume is reduced by 25%. In certain embodiments, the subject's tumor volume is reduced by 30%. In certain embodiments, the subject's tumor volume is reduced by 35%. In certain embodiments, the subject's tumor volume is reduced by 40%. In certain embodiments, the subject's tumor volume is reduced by 45%. In certain embodiments, the subject's tumor volume is reduced by 50%. In certain embodiments, the subject's tumor volume is reduced by 55%. In certain embodiments, the subject's tumor volume is reduced by 60%. In certain embodiments, the subject's tumor volume is reduced by 65%. In certain embodiments, the subject's tumor volume is reduced by 70%. In certain embodiments, the subject's tumor volume is reduced by 80%. In certain embodiments, the subject's tumor volume is reduced by 85%. In certain embodiments, the subject's tumor volume is reduced by 90%. In certain embodiments, the subject's tumor volume is reduced by 95%.

Pharmaceutical Compositions

The compositions and methods of the present invention may be utilized to treat an individual in need thereof. In certain embodiments, the individual is a mammal such as a human, or a non-human mammal. When administered to an animal, such as a human, the composition or the compound is preferably administered as a pharmaceutical composition comprising, for example, a compound of the invention and a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers are well known in the art and include, for example, aqueous solutions such as water or physiologically buffered saline or other solvents or vehicles such as glycols, glycerol, oils such as olive oil, or injectable organic esters. In preferred embodiments, when such pharmaceutical compositions are for human administration, particularly for invasive routes of administration (*i.e.*, routes, such as injection or implantation, that circumvent transport or diffusion through an epithelial barrier), the aqueous solution is pyrogen-free, or substantially pyrogen-free. The excipients can be chosen, for example, to effect delayed release of an agent or to selectively target one or more cells, tissues or organs. The pharmaceutical composition can be in dosage unit form such as tablet, capsule (including sprinkle capsule and gelatin capsule), granule, lyophile for reconstitution, powder, solution, syrup, suppository, injection or the like. The composition can also be present in a transdermal delivery system, *e.g.*, a skin patch. The composition can also be present in a solution suitable for topical administration, such as a lotion, cream, or ointment.

A pharmaceutically acceptable carrier can contain physiologically acceptable agents that act, for example, to stabilize, increase solubility or to increase the absorption of a compound such as a compound of the invention. Such physiologically acceptable agents include, for example, carbohydrates, such as glucose, sucrose or dextrans, antioxidants, such as ascorbic acid or glutathione, chelating agents, low molecular weight proteins or other stabilizers or excipients. The choice of a pharmaceutically acceptable carrier, including a physiologically acceptable agent, depends, for example, on the route of administration of the composition. The preparation or pharmaceutical composition can be a self-emulsifying drug delivery system or a self-microemulsifying drug delivery system. The pharmaceutical composition (preparation) also can be a liposome or other polymer matrix, which can have incorporated therein, for example, a compound of the invention. Liposomes, for example, which comprise phospholipids or other lipids, are nontoxic, physiologically acceptable and metabolizable carriers that are relatively simple to make and administer.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The phrase "pharmaceutically acceptable carrier" as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

A pharmaceutical composition (preparation) can be administered to a subject by any of a number of routes of administration including, for example, orally (for example, drenches as in aqueous or non-aqueous solutions or suspensions, tablets, capsules (including sprinkle capsules and gelatin capsules), boluses, powders, granules, pastes for application to the tongue); absorption through the oral mucosa (*e.g.*, sublingually); subcutaneously; transdermally (for example as a patch applied to the skin); and topically (for example, as a cream, ointment or spray applied to the skin). The compound may also be formulated for inhalation. In certain embodiments, a compound may be simply dissolved or suspended in sterile water. Details of appropriate routes of administration and compositions suitable for same can be found in, for example, U.S. Pat. Nos. 6,110,973, 5,763,493, 5,731,000, 5,541,231, 5,427,798, 5,358,970 and 4,172,896, as well as in patents cited therein.

The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated and the particular mode of administration. The amount of active ingredient that can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of one hundred percent, this amount will range from about 1 percent to about ninety-nine percent of active ingredient, preferably from about 5 percent to about 70 percent, most preferably from about 10 percent to about 30 percent.

Methods of preparing these formulations or compositions include the step of bringing into association an active compound, such as a compound of the invention, with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Formulations of the invention suitable for oral administration may be in the form of capsules (including sprinkle capsules and gelatin capsules), cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), lyophile, powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. Compositions or compounds may also be administered as a bolus, electuary or paste.

To prepare solid dosage forms for oral administration (capsules (including sprinkle capsules and gelatin capsules), tablets, pills, dragees, powders, granules and the like), the active ingredient is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds;

(7) wetting agents, such as, for example, cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; (10) complexing agents, such as, modified and unmodified cyclodextrins; and (11) coloring agents. In the case of capsules (including sprinkle capsules and gelatin capsules), tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The tablets, and other solid dosage forms of the pharmaceutical compositions, such as dragees, capsules (including sprinkle capsules and gelatin capsules), pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Liquid dosage forms useful for oral administration include pharmaceutically acceptable emulsions, lyophiles for reconstitution, microemulsions, solutions, suspensions, syrups and elixirs.

In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, cyclodextrins and derivatives thereof, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Dosage forms for the topical or transdermal administration include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that may be required.

The ointments, pastes, creams and gels may contain, in addition to an active compound, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to an active compound, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by dissolving or dispersing the active compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion. Pharmaceutical compositions suitable for parenteral administration comprise one or more active compounds in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and nonaqueous carriers that may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents that delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsulated matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions that are compatible with body tissue.

For use in the methods of this invention, active compounds can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99.5% (more preferably, 0.5 to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

Methods of introduction may also be provided by rechargeable or biodegradable devices. Various slow release polymeric devices have been developed and tested *in vivo* in recent years for the controlled delivery of drugs, including proteinaceous biopharmaceuticals. A variety of biocompatible polymers (including hydrogels), including both biodegradable and non-degradable polymers, can be used to form an implant for the sustained release of a compound at a particular target site.

Actual dosage levels of the active ingredients in the pharmaceutical compositions may be varied so as to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

The selected dosage level will depend upon a variety of factors including the activity of the particular compound or combination of compounds employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound(s) being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound(s) employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe therapeutically effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the pharmaceutical composition or compound at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved. By “therapeutically effective

amount” it is meant the concentration of a compound that is sufficient to elicit the desired therapeutic effect. It is generally understood that the effective amount of the compound will vary according to the weight, sex, age, and medical history of the subject. Other factors which influence the effective amount may include, but are not limited to, the severity of the patient's condition, the disorder being treated, the stability of the compound, and, if desired, another type of therapeutic agent being administered with the compound of the invention. A larger total dose can be delivered by multiple administrations of the agent. Methods to determine efficacy and dosage are known to those skilled in the art (Isselbacher et al. (1996) Harrison's Principles of Internal Medicine 13 ed., 1814-1882, herein incorporated by reference).

In general, a suitable daily dose of an active compound used in the compositions and methods of the invention will be that amount of the compound that is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above.

If desired, the effective daily dose of the active compound may be administered as one, two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. In certain embodiments of the present invention, the active compound may be administered two or three times daily. In preferred embodiments, the active compound will be administered once daily.

The patient receiving this treatment is any animal in need, including primates, in particular humans; and other mammals such as equines, cattle, swine, sheep, cats, and dogs; poultry; and pets in general.

In certain embodiments, compounds of the invention may be used alone or conjointly administered with another type of therapeutic agent.

The present disclosure includes the use of pharmaceutically acceptable salts of compounds of the invention in the compositions and methods of the present invention. In certain embodiments, contemplated salts of the invention include, but are not limited to, alkyl, dialkyl, trialkyl or tetra-alkyl ammonium salts. In certain embodiments, contemplated salts of the invention include, but are not limited to, L-arginine, benethamine, benzathine, betaine, calcium hydroxide, choline, deanol, diethanolamine, diethylamine, 2-(diethylamino)ethanol, ethanolamine, ethylenediamine, N-methylglucamine, hydrabamine, 1H-imidazole, lithium, L-lysine, magnesium, 4-(2-hydroxyethyl)morpholine, piperazine, potassium, 1-(2-hydroxyethyl)pyrrolidine, sodium,

triethanolamine, tromethamine, and zinc salts. In certain embodiments, contemplated salts of the invention include, but are not limited to, Na, Ca, K, Mg, Zn or other metal salts. In certain embodiments, contemplated salts of the invention include, but are not limited to, 1-hydroxy-2-naphthoic acid, 2,2-dichloroacetic acid, 2-hydroxyethanesulfonic acid, 2-oxoglutaric acid, 4-acetamidobenzoic acid, 4-aminosalicylic acid, acetic acid, adipic acid, l-ascorbic acid, l-aspartic acid, benzenesulfonic acid, benzoic acid, (+)-camphoric acid, (+)-camphor-10-sulfonic acid, capric acid (decanoic acid), caproic acid (hexanoic acid), caprylic acid (octanoic acid), carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, d-glucoheptonic acid, d-gluconic acid, d-glucuronic acid, glutamic acid, glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, l-malic acid, malonic acid, mandelic acid, methanesulfonic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, nicotinic acid, nitric acid, oleic acid, oxalic acid, palmitic acid, pamoic acid, phosphoric acid, propionic acid, l-pyroglutamic acid, salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, l-tartaric acid, thiocyanic acid, p-toluenesulfonic acid, trifluoroacetic acid, and undecylenic acid salts.

The pharmaceutically acceptable acid addition salts can also exist as various solvates, such as with water, methanol, ethanol, dimethylformamide, and the like. Mixtures of such solvates can also be prepared. The source of such solvate can be from the solvent of crystallization, inherent in the solvent of preparation or crystallization, or adventitious to such solvent.

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

Examples of pharmaceutically acceptable antioxidants include: (1) water-soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal-chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

Definitions

Unless otherwise defined herein, scientific and technical terms used in this application shall have the meanings that are commonly understood by those of ordinary skill in the art. Generally, nomenclature used in connection with, and techniques of, chemistry, cell and tissue culture, molecular biology, cell and cancer biology, neurobiology, neurochemistry, virology, immunology, microbiology, pharmacology, genetics and protein and nucleic acid chemistry, described herein, are those well-known and commonly used in the art.

The methods and techniques of the present disclosure are generally performed, unless otherwise indicated, according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout this specification. See, e.g. “Principles of Neural Science”, McGraw-Hill Medical, New York, N.Y. (2000); Motulsky, “Intuitive Biostatistics”, Oxford University Press, Inc. (1995); Lodish et al., “Molecular Cell Biology, 4th ed.”, W. H. Freeman & Co., New York (2000); Griffiths et al., “Introduction to Genetic Analysis, 7th ed.”, W. H. Freeman & Co., N.Y. (1999); and Gilbert et al., “Developmental Biology, 6th ed.”, Sinauer Associates, Inc., Sunderland, MA (2000).

Chemistry terms used herein, unless otherwise defined herein, are used according to conventional usage in the art, as exemplified by “The McGraw-Hill Dictionary of Chemical Terms”, Parker S., Ed., McGraw-Hill, San Francisco, C.A. (1985).

All of the above, and any other publications, patents and published patent applications referred to in this application are specifically incorporated by reference herein. In case of conflict, the present specification, including its specific definitions, will control.

The term “agent” is used herein to denote a chemical compound (such as an organic or inorganic compound, a mixture of chemical compounds), a biological macromolecule (such as a nucleic acid, an antibody, including parts thereof as well as humanized, chimeric and human antibodies and monoclonal antibodies, a protein or portion thereof, *e.g.*, a peptide, a lipid, a carbohydrate), or an extract made from biological materials such as bacteria, plants, fungi, or animal (particularly mammalian) cells or tissues. Agents include, for example, agents whose structure is known, and those whose structure is not known. The ability of such agents to inhibit AR or promote AR degradation may render them suitable as “therapeutic agents” in the methods and compositions of this disclosure.

A “patient,” “subject,” or “individual” are used interchangeably and refer to either a human or a non-human animal. These terms include mammals, such as humans, primates, livestock animals (including bovines, porcines, etc.), companion animals (*e.g.*, canines, felines, etc.) and rodents (*e.g.*, mice and rats).

“Treating” a condition or patient refers to taking steps to obtain beneficial or desired results, including clinical results. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of extent of disease, stabilized (*i.e.*, not worsening) state of disease, preventing spread of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. “Treatment” can also mean prolonging survival as compared to expected survival if not receiving treatment.

The term “preventing” is art-recognized, and when used in relation to a condition, such as a local recurrence (*e.g.*, pain), a disease such as cancer, a syndrome complex such as heart failure or any other medical condition, is well understood in the art, and includes administration of a composition which reduces the frequency of, or delays the onset of, symptoms of a medical condition in a subject relative to a subject which does not receive the composition. Thus, prevention of cancer includes, for example, reducing the number of detectable cancerous growths in a population of patients receiving a prophylactic treatment relative to an untreated control population, and/or delaying the appearance of detectable cancerous growths in a treated population versus an untreated control population, *e.g.*, by a statistically and/or clinically significant amount.

“Administering” or “administration of” a substance, a compound or an agent to a subject can be carried out using one of a variety of methods known to those skilled in the art. For example, a compound or an agent can be administered, intravenously, arterially, intradermally, intramuscularly, intraperitoneally, subcutaneously, ocularly, sublingually, orally (by ingestion), intranasally (by inhalation), intraspinally, intracerebrally, and transdermally (by absorption, *e.g.*, through a skin duct). A compound or agent can also appropriately be introduced by rechargeable or biodegradable polymeric devices or other devices, *e.g.*, patches and pumps, or formulations, which provide for the extended, slow or controlled release of the compound or agent. Administering can also be performed, for example, once, a plurality of times, and/or over one or more extended periods.

Appropriate methods of administering a substance, a compound or an agent to a subject will also depend, for example, on the age and/or the physical condition of the subject and the chemical and biological properties of the compound or agent (*e.g.*, solubility, digestibility, bioavailability, stability and toxicity). In certain embodiments, a compound or an agent is administered orally, *e.g.*, to a subject by ingestion. In certain embodiments, the orally administered compound or agent is in an extended release or slow release formulation, or administered using a device for such slow or extended release.

As used herein, the phrase “conjoint administration” refers to any form of administration of two or more different therapeutic agents such that the second agent is administered while the previously administered therapeutic agent is still effective in the body (*e.g.*, the two agents are simultaneously effective in the patient, which may include synergistic effects of the two agents). For example, the different therapeutic compounds can be administered either in the same formulation or in separate formulations, either concomitantly or sequentially. Thus, an individual who receives such treatment can benefit from a combined effect of different therapeutic agents.

A “therapeutically effective amount” or a “therapeutically effective dose” of a drug or agent is an amount of a drug or an agent that, when administered to a subject will have the intended therapeutic effect. The full therapeutic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a therapeutically effective amount may be administered in one or more administrations. The precise effective amount needed for a subject will depend upon, for example, the subject’s size, health and age, and the nature and extent of the condition being treated, such as cancer or MDS. The skilled worker can readily determine the effective amount for a given situation by routine experimentation.

As used herein, the terms “optional” or “optionally” mean that the subsequently described event or circumstance may occur or may not occur, and that the description includes instances where the event or circumstance occurs as well as instances in which it does not. For example, “optionally substituted alkyl” refers to the alkyl may be substituted as well as where the alkyl is not substituted.

It is understood that substituents and substitution patterns on the compounds of the present invention can be selected by one of ordinary skilled person in the art to result chemically stable compounds which can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself

substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure results.

As used herein, the term “optionally substituted” refers to the replacement of one to six hydrogen radicals in a given structure with the radical of a specified substituent including, but not limited to: hydroxyl, hydroxyalkyl, alkoxy, halogen, alkyl, nitro, silyl, acyl, acyloxy, aryl, cycloalkyl, heterocyclyl, amino, aminoalkyl, cyano, haloalkyl, haloalkoxy, -OCO-CH₂-O-alkyl, -OP(O)(O-alkyl)₂ or -CH₂-OP(O)(O-alkyl)₂. Preferably, “optionally substituted” refers to the replacement of one to four hydrogen radicals in a given structure with the substituents mentioned above. More preferably, one to three hydrogen radicals are replaced by the substituents as mentioned above. It is understood that the substituent can be further substituted.

As used herein, the term “alkyl” refers to saturated aliphatic groups, including but not limited to C₁-C₁₀ straight-chain alkyl groups or C₁-C₁₀ branched-chain alkyl groups. Preferably, the “alkyl” group refers to C₁-C₆ straight-chain alkyl groups or C₁-C₆ branched-chain alkyl groups. Most preferably, the “alkyl” group refers to C₁-C₄ straight-chain alkyl groups or C₁-C₄ branched-chain alkyl groups. Examples of “alkyl” include, but are not limited to, methyl, ethyl, 1-propyl, 2-propyl, n-butyl, sec-butyl, tert-butyl, 1-pentyl, 2-pentyl, 3-pentyl, neo-pentyl, 1-hexyl, 2-hexyl, 3-hexyl, 1-heptyl, 2-heptyl, 3-heptyl, 4-heptyl, 1-octyl, 2-octyl, 3-octyl or 4-octyl and the like. The “alkyl” group may be optionally substituted.

The term “acyl” is art-recognized and refers to a group represented by the general formula hydrocarbylC(O)-, preferably alkylC(O)-.

The term “acylamino” is art-recognized and refers to an amino group substituted with an acyl group and may be represented, for example, by the formula hydrocarbylC(O)NH-.

The term “acyloxy” is art-recognized and refers to a group represented by the general formula hydrocarbylC(O)O-, preferably alkylC(O)O-.

The term “alkoxy” refers to an alkyl group having an oxygen attached thereto. Representative alkoxy groups include methoxy, ethoxy, propoxy, tert-butoxy and the like.

The term “alkoxyalkyl” refers to an alkyl group substituted with an alkoxy group and may be represented by the general formula alkyl-O-alkyl.

The term “alkyl” refers to saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl-substituted cycloalkyl groups, and cycloalkyl-substituted alkyl groups. In preferred embodiments, a straight chain or branched

chain alkyl has 30 or fewer carbon atoms in its backbone (*e.g.*, C₁₋₃₀ for straight chains, C₃₋₃₀ for branched chains), and more preferably 20 or fewer.

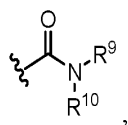
Moreover, the term “alkyl” as used throughout the specification, examples, and claims is intended to include both unsubstituted and substituted alkyl groups, the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone, including haloalkyl groups such as trifluoromethyl and 2,2,2-trifluoroethyl, etc.

The term “C_{x-y}” or “C_x-C_y”, when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups that contain from x to y carbons in the chain. C₀alkyl indicates a hydrogen where the group is in a terminal position, a bond if internal. A C₁₋₆alkyl group, for example, contains from one to six carbon atoms in the chain.

The term “alkylamino”, as used herein, refers to an amino group substituted with at least one alkyl group.

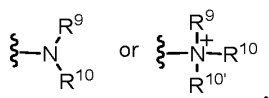
The term “alkylthio”, as used herein, refers to a thiol group substituted with an alkyl group and may be represented by the general formula alkylS-.

The term “amide”, as used herein, refers to a group



wherein R⁹ and R¹⁰ each independently represent a hydrogen or hydrocarbyl group, or R⁹ and R¹⁰ taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure.

The terms “amine” and “amino” are art-recognized and refer to both unsubstituted and substituted amines and salts thereof, *e.g.*, a moiety that can be represented by



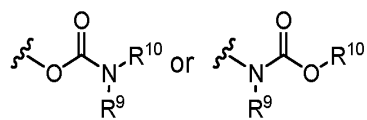
wherein R⁹, R¹⁰, and R¹⁰⁺ each independently represent a hydrogen or a hydrocarbyl group, or R⁹ and R¹⁰ taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure.

The term “aminoalkyl”, as used herein, refers to an alkyl group substituted with an amino group.

The term “aralkyl”, as used herein, refers to an alkyl group substituted with an aryl group.

The term “aryl” as used herein includes substituted or unsubstituted single-ring aromatic groups in which each atom of the ring is carbon. Preferably the ring is a 5- to 7-membered ring, more preferably a 6-membered ring. The term “aryl” also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is aromatic, *e.g.*, the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Aryl groups include benzene, naphthalene, phenanthrene, phenol, aniline, and the like.

The term “carbamate” is art-recognized and refers to a group



wherein R^9 and R^{10} independently represent hydrogen or a hydrocarbonyl group.

The term “carbocyclalkyl”, as used herein, refers to an alkyl group substituted with a carbocycle group.

The term “carbocycle” includes 5-7 membered monocyclic and 8-12 membered bicyclic rings. Each ring of a bicyclic carbocycle may be selected from saturated, unsaturated and aromatic rings. Carbocycle includes bicyclic molecules in which one, two or three or more atoms are shared between the two rings. The term “fused carbocycle” refers to a bicyclic carbocycle in which each of the rings shares two adjacent atoms with the other ring. Each ring of a fused carbocycle may be selected from saturated, unsaturated and aromatic rings. In an exemplary embodiment, an aromatic ring, *e.g.*, phenyl, may be fused to a saturated or unsaturated ring, *e.g.*, cyclohexane, cyclopentane, or cyclohexene. Any combination of saturated, unsaturated and aromatic bicyclic rings, as valence permits, is included in the definition of carbocyclic. Exemplary “carbocycles” include cyclopentane, cyclohexane, bicyclo[2.2.1]heptane, 1,5-cyclooctadiene, 1,2,3,4-tetrahydronaphthalene, bicyclo[4.2.0]oct-3-ene, naphthalene and adamantane. Exemplary fused carbocycles include decalin, naphthalene, 1,2,3,4-tetrahydronaphthalene, bicyclo[4.2.0]octane, 4,5,6,7-tetrahydro-1H-indene and bicyclo[4.1.0]hept-3-ene. “Carbocycles” may be substituted at any one or more positions capable of bearing a hydrogen atom.

The term “carbocyclalkyl”, as used herein, refers to an alkyl group substituted with a carbocycle group.

The term “carbonate” is art-recognized and refers to a group $-\text{OCO}_2-$.

The term “carboxy”, as used herein, refers to a group represented by the formula $-\text{CO}_2\text{H}$.

The term “cycloalkyl” includes substituted or unsubstituted non-aromatic single ring structures, preferably 4- to 8-membered rings, more preferably 4- to 6-membered rings. The term “cycloalkyl” also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is cycloalkyl and the substituent (*e.g.*, R^{100}) is attached to the cycloalkyl ring, *e.g.*, the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryl, and/or heterocyclyls. Heteroaryl groups include, for example, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrazine, pyridazine, pyrimidine, denzodioxane, tetrahydroquinoline, and the like.

The term “ester”, as used herein, refers to a group $-\text{C}(\text{O})\text{OR}^9$ wherein R^9 represents a hydrocarbyl group.

The term “ether”, as used herein, refers to a hydrocarbyl group linked through an oxygen to another hydrocarbyl group. Accordingly, an ether substituent of a hydrocarbyl group may be hydrocarbyl-O-. Ethers may be either symmetrical or unsymmetrical. Examples of ethers include, but are not limited to, heterocycle-O-heterocycle and aryl-O-heterocycle. Ethers include “alkoxyalkyl” groups, which may be represented by the general formula alkyl-O-alkyl.

The terms “halo” and “halogen” as used herein means halogen and includes chloro, fluoro, bromo, and iodo.

The terms “hetaralkyl” and “heteroaralkyl”, as used herein, refers to an alkyl group substituted with a hetaryl group.

The terms “heteroaryl” and “hetaryl” include substituted or unsubstituted aromatic single ring structures, preferably 5- to 7-membered rings, more preferably 5- to 6-membered rings, whose ring structures include at least one heteroatom, preferably one to four heteroatoms, more preferably one or two heteroatoms. The terms “heteroaryl” and “hetaryl” also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is heteroaromatic, *e.g.*, the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryl, and/or heterocyclyls. Heteroaryl groups include, for example, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrazine, pyridazine, and pyrimidine, and the like.

The term “heteroatom” as used herein means an atom of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, and sulfur.

The term “heterocyclalkyl”, as used herein, refers to an alkyl group substituted with a heterocycle group.

The terms “heterocycl”, “heterocycle”, and “heterocyclic” refer to substituted or unsubstituted non-aromatic ring structures, preferably 3- to 10-membered rings, more preferably 3- to 7-membered rings, whose ring structures include at least one heteroatom, preferably one to four heteroatoms, more preferably one or two heteroatoms. The terms “heterocycl” and “heterocyclic” also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is heterocyclic, *e.g.*, the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryl, and/or heterocycls. Heterocycl groups include, for example, piperidine, piperazine, pyrrolidine, morpholine, lactones, lactams, and the like.

The term “hydrocarb”, as used herein, refers to a group that is bonded through a carbon atom that does not have a =O or =S substituent, and typically has at least one carbon-hydrogen bond and a primarily carbon backbone, but may optionally include heteroatoms. Thus, groups like methyl, ethoxyethyl, 2-pyridyl, and even trifluoromethyl are considered to be hydrocarb for the purposes of this application, but substituents such as acetyl (which has a =O substituent on the linking carbon) and ethoxy (which is linked through oxygen, not carbon) are not. Hydrocarb groups include, but are not limited to aryl, heteroaryl, carbocycle, heterocycle, alkyl, alkenyl, alkynyl, and combinations thereof.

The term “hydroxyalkyl”, as used herein, refers to an alkyl group substituted with a hydroxy group.

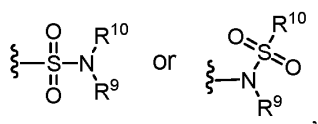
The term “lower” when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups where there are ten or fewer atoms in the substituent, preferably six or fewer. A “lower alkyl”, for example, refers to an alkyl group that contains ten or fewer carbon atoms, preferably six or fewer. In certain embodiments, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy substituents defined herein are respectively lower acyl, lower acyloxy, lower alkyl, lower alkenyl, lower alkynyl, or lower alkoxy, whether they appear alone or in combination with other substituents, such as in the recitations hydroxyalkyl and aralkyl (in

which case, for example, the atoms within the aryl group are not counted when counting the carbon atoms in the alkyl substituent).

The terms “polycyclyl”, “polycycle”, and “polycyclic” refer to two or more rings (*e.g.*, cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls) in which two or more atoms are common to two adjoining rings, *e.g.*, the rings are “fused rings”. Each of the rings of the polycycle can be substituted or unsubstituted. In certain embodiments, each ring of the polycycle contains from 3 to 10 atoms in the ring, preferably from 5 to 7.

The term “sulfate” is art-recognized and refers to the group $-\text{OSO}_3\text{H}$, or a pharmaceutically acceptable salt thereof.

The term “sulfonamide” is art-recognized and refers to the group represented by the general formulae



wherein R^9 and R^{10} independently represents hydrogen or hydrocarbyl.

The term “sulfoxide” is art-recognized and refers to the group $-\text{S}(\text{O})-$.

The term “sulfonate” is art-recognized and refers to the group SO_3H , or a pharmaceutically acceptable salt thereof.

The term “sulfone” is art-recognized and refers to the group $-\text{S}(\text{O})_2-$.

The term “substituted” refers to moieties having substituents replacing a hydrogen on one or more carbons of the backbone. It will be understood that “substitution” or “substituted with” includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, *e.g.*, which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. As used herein, the term “substituted” is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. Substituents can

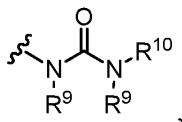
include any substituents described herein, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxy carbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxy, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate.

The term “thioalkyl”, as used herein, refers to an alkyl group substituted with a thiol group.

The term “thioester”, as used herein, refers to a group $-C(O)SR^9$ or $-SC(O)R^9$ wherein R^9 represents a hydrocarbyl.

The term “thioether”, as used herein, is equivalent to an ether, wherein the oxygen is replaced with a sulfur.

The term “urea” is art-recognized and may be represented by the general formula



wherein R^9 and R^{10} independently represent hydrogen or a hydrocarbyl.

The term “modulate” as used herein includes the inhibition or suppression of a function or activity (such as cell proliferation) as well as the enhancement of a function or activity.

The phrase “pharmaceutically acceptable” is art-recognized. In certain embodiments, the term includes compositions, excipients, adjuvants, polymers and other materials and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

“Pharmaceutically acceptable salt” or “salt” is used herein to refer to an acid addition salt or a basic addition salt which is suitable for or compatible with the treatment of patients.

The term “pharmaceutically acceptable acid addition salt” as used herein means any non-toxic organic or inorganic salt of any base compounds represented by Formula I. Illustrative inorganic acids which form suitable salts include hydrochloric, hydrobromic, sulfuric and phosphoric acids, as well as metal salts such as sodium monohydrogen orthophosphate and potassium hydrogen sulfate. Illustrative organic acids that form suitable salts include mono-, di-,

and tricarboxylic acids such as glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, benzoic, phenylacetic, cinnamic and salicylic acids, as well as sulfonic acids such as p-toluene sulfonic and methanesulfonic acids. Either the mono or di-acid salts can be formed, and such salts may exist in either a hydrated, solvated or substantially anhydrous form. In general, the acid addition salts of compounds of Formula I are more soluble in water and various hydrophilic organic solvents, and generally demonstrate higher melting points in comparison to their free base forms. The selection of the appropriate salt will be known to one skilled in the art. Other non-pharmaceutically acceptable salts, *e.g.*, oxalates, may be used, for example, in the isolation of compounds of Formula I for laboratory use, or for subsequent conversion to a pharmaceutically acceptable acid addition salt.

The term “pharmaceutically acceptable basic addition salt” as used herein means any non-toxic organic or inorganic base addition salt of any acid compounds represented by Formula I or any of their intermediates. Illustrative inorganic bases which form suitable salts include lithium, sodium, potassium, calcium, magnesium, or barium hydroxide. Illustrative organic bases which form suitable salts include aliphatic, alicyclic, or aromatic organic amines such as methylamine, trimethylamine and picoline or ammonia. The selection of the appropriate salt will be known to a person skilled in the art.

Many of the compounds useful in the methods and compositions of this disclosure have at least one stereogenic center in their structure. This stereogenic center may be present in an R or a S configuration, said R and S notation is used in correspondence with the rules described in Pure Appl. Chem. (1976), 45, 11-30. The disclosure contemplates all stereoisomeric forms such as enantiomeric and diastereoisomeric forms of the compounds, salts, prodrugs or mixtures thereof (including all possible mixtures of stereoisomers). See, *e.g.*, WO 01/062726.

Furthermore, certain compounds which contain alkenyl groups may exist as Z (zusammen) or E (entgegen) isomers. In each instance, the disclosure includes both mixture and separate individual isomers.

Some of the compounds may also exist in tautomeric forms. Such forms, although not explicitly indicated in the formulae described herein, are intended to be included within the scope of the present disclosure.

“Prodrug” or “pharmaceutically acceptable prodrug” refers to a compound that is metabolized, for example hydrolyzed or oxidized, in the host after administration to form the

compound of the present disclosure (*e.g.*, compounds of formula I). Typical examples of prodrugs include compounds that have biologically labile or cleavable (protecting) groups on a functional moiety of the active compound. Prodrugs include compounds that can be oxidized, reduced, aminated, deaminated, hydroxylated, dehydroxylated, hydrolyzed, dehydrolyzed, alkylated, dealkylated, acylated, deacylated, phosphorylated, or dephosphorylated to produce the active compound. Examples of prodrugs using ester or phosphoramidate as biologically labile or cleavable (protecting) groups are disclosed in U.S. Patents 6,875,751, 7,585,851, and 7,964,580, the disclosures of which are incorporated herein by reference. The prodrugs of this disclosure are metabolized to produce a compound of Formula I. The present disclosure includes within its scope prodrugs of the compounds described herein. Conventional procedures for the selection and preparation of suitable prodrugs are described, for example, in “Design of Prodrugs” Ed. H. Bundgaard, Elsevier, 1985.

The phrase “pharmaceutically acceptable carrier” as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filter, diluent, excipient, solvent or encapsulating material useful for formulating a drug for medicinal or therapeutic use.

The term “Log of solubility”, “LogS” or “logS” as used herein is used in the art to quantify the aqueous solubility of a compound. The aqueous solubility of a compound significantly affects its absorption and distribution characteristics. A low solubility often goes along with a poor absorption. LogS value is a unit stripped logarithm (base 10) of the solubility measured in mol/liter.

As used herein, “expression” refers individually and/or cumulatively to one or more biological process that result in production from a nucleic acid sequence of an encoded agent. Expression specifically includes either or both of transcription and translation. For example, expression of a DNA sequence can result in the production of RNA and/or a protein. In another example, expression of an RNA sequence results in the production of a polypeptide (*e.g.*, a protein). A cell, tissue, biological sample, or subject that produces the encoded agent can be said to express the encoded agent.

As used herein, the phrase “expression product” refers to a product of expression. Expression products specifically include products of transcription (*i.e.*, RNA) and translation (*i.e.*, polypeptides).

As used herein, the phrases “expression level” and “level of expression” refer to the level and or prevalence of expression of an expression product. For example, the expression level refers to the level and or prevalence of an expression product and/or its precursors within a cell, tissue, biological sample, or subject. For example, the expression level of a gene can be measured by measuring the prevalence (*i.e.*, occurrence) and/or level of its transcription product(s) (*e.g.*, RNA) and/or measuring the prevalence and/or level of its translation product(s) (*e.g.*, polypeptides). For example, the expression level of a protein can be measured by measuring the prevalence (*i.e.*, occurrence) and/or level of its transcription precursors (*e.g.*, mRNA) and/or measuring the prevalence and/or level of the protein and/or its components (*e.g.*, peptide fragments).

The term “AZA”, as used herein, indicates azacitidine.

The term “VEN”, as used herein, indicates venetoclax.

The term “BID”, as used herein, indicates twice daily administration of a drug.

The term “QD”, as used herein, indicates daily administration of a drug.

The term “CR”, as used herein, indicates complete response.

The term “CRi”, as used herein, indicates CR with incomplete hematologic recovery.

The term “CRh”, as used herein, indicates CR with partial hematologic recovery.

The term “mCR”, as used herein, indicates marrow complete response.

The term “OS”, as used herein, indicates overall survival rate.

The term “PR”, as used herein, indicates partial response.

The term “MTD”, as used herein, indicates maximum tolerated dose.

The term “RP2D”, as used herein, indicates recommended phase 2 dose.

The term “ANC”, as used herein, indicates absolute neutrophil count.

The term “WBC” indicates white blood cell count.

EXAMPLES

The invention now being generally described, it will be more readily understood by reference to the following examples which are included merely for purposes of illustration of certain aspects and embodiments of the present invention and are not intended to limit the invention.

Exemplary methods and compounds related to the contents of this disclosure may be found, in U.S. Patent Nos. 10/160,753, 10/758,518, and 11/419,875; US Application No. 17/680,995; and

Pending PCT Patent Application Nos. US21/59668, US2021/030192, WO22/031330, and US23/21812; the contents of which are fully incorporated by reference herein.

Example 1: Exemplary performance of emavusertib in subjects having AML or MDS with or without prior BCL-2 therapy

Objectives and Endpoints

Phase 1 (Monotherapy) /Phase 1b (Combination Therapy) Primary Objectives

- Phase 1: To determine the MTD and RP2D for emavusertib in patients with AML, or intermediate, high, or very high risk MDS (hrMDS) based on the safety and tolerability, dose-limiting toxicities, and pharmacokinetic and pharmacodynamic findings
- Phase 1b: To determine MTD and RP2D for emavusertib in combination with AZA in treatment-naïve patients with AML or hrMDS or in combination with VEN in relapsed/refractory patients, after first line treatment based on the safety and tolerability, dose-limiting toxicities and pharmacokinetic and pharmacodynamic findings

Phase 1 (Monotherapy)/Phase 1b (Combination Therapy) Primary Endpoints

- MTD (defined as the highest dose at which there is < 33% dose-limiting toxicity rate in the first cycle of treatment in a minimum of 6 patients [time frame: 28 days])
- RP2D (determined by the Sponsor in consultation with the CSC, considering all aspects of safety, tolerability, biologic activity, pharmacokinetic and preliminary efficacy in the trial population [time frame: 24 months])
- Safety measured by adverse events, ECGs, chemistry and hematology laboratory values, vital signs, and physical examinations

Phase 1 (Monotherapy)/Phase 1b (Combination Therapy) Secondary Objectives

- To characterize the pharmacokinetic parameters of emavusertib using non-compartmental analysis and appropriate pharmacokinetic model
- To assess anti-cancer activity

Phase 1 (Monotherapy) /Phase 1b (Combination Therapy) Secondary Endpoints

- Pharmacokinetic parameters of emavusertib measured by C_{max} , C_{min} , T_{max} , AUC_{0-24} , AUC_{0-inf} , and $T_{1/2}$ (time frame 24 months)
- Clinical response in AML or hrMDS assessed as follows:

- AML:
 - Proportion of patients who reach CR + CRh
 - Proportion of patients who reach CRi, or CR or CRh
- hrMDS: overall response rate of CR + PR + mCR
- Transfusion independence

Phase 1 (Monotherapy) /Phase 1b (Combination Therapy) Exploratory Objectives

- To assess the potential association between target-related biomarkers, selected genetic mutations, gene expression signatures, cell of origin, or other molecular classification subtypes and anti-leukemic activity
- To assess the pharmacodynamic effects of emavusertib on selected biomarkers in peripheral blood and bone marrow
- To further assess anti-cancer activity at RP2D

Phase 1 (Monotherapy) /Phase 1b (Combination Therapy) Exploratory Endpoint

- RNA expression profiling, DNA/RNA sequencing, protein profiling, IRAK4/ NF-KB pathway status, differentiation markers/apoptosis, etc., may be conducted on peripheral blood and/or tumor samples to analyze changes induced by study treatment, and to identify potential predictive biomarkers.
- Clinical response in AML or hrMDS assessed as follows:
 - Duration of response (DOR)
 - Time to response
 - Overall survival (OS)

Study Design

This is a Phase 1, open-label dose escalation and cohort expansion study of emavusertib as a monotherapy in patients with AML or MDS and in combination with AZA in treatment-naïve, adult patients with AML or hrMDS or in combination with VEN in patients with relapsed/refractory AML or hrMDS, after first line therapy.

The Phase 1 Dose Escalation (Monotherapy) portion is in patients with AML and hrMDS.

The Phase 1b portion of the study (Combination Therapy), in which patients with AML or hrMDS receive emavusertib in combination with azacitidine (AZA) or venetoclax (VEN). Patients

currently receiving combination therapy who are benefiting from treatment should continue study per protocol at doses of 300 mg BID or lower.

This study utilizes a Clinical Safety Committee (CSC), which is tasked with reviewing all available safety information. The CSC is responsible for determining if a dose level is expanded or if a new dose level will be opened. The CSC also defines if a waiting period for any or all patients enrolled into a new cohort will be required.

Phase 1 Dose Escalation (Monotherapy)

The starting dose level was 200 mg BID which was determined to be safe, capable of achieving relevant levels of drug exposure as well as demonstrating signs of biologic activity and clinical efficacy in Study emavusertib-101. Three patients with AML or MDS will be enrolled at the designated dose. If none of the first 3 patients experience a dose-limiting toxicity during the first cycle, patients may be enrolled into the next higher dose level. If 1 patient out of the first 3 experiences a dose-limiting toxicity, the dose level may be expanded with an additional 3 patients.

If 2 or 3 patients out of the first 6 experience a dose-limiting toxicity, this dose level will be considered to be above the MTD, and additional enrollment will proceed at a lower dose level. Any adverse event that leads to dose reduction or discontinuation is considered a dose-limiting toxicity unless the adverse event is clearly and solely related to disease. Provisional dose levels are outlined in Table 1.

Table 1: Emavusertib Provisional Dose Levels for AML and MDS

Dose Level*	Dose of emavusertib (BID) (mg)	Total Daily Dose (mg)
2	400	800
1	300	600
0	200	400
-1	150	300
-2	100	200

* If the MTD is not reached at dose level 2, higher dose levels may be tested. These levels will be determined by the CSC after review of all available data.

Phase 1b (Combination Therapy)*Emavusertib + AZA*

The starting dose level for emavusertib will be 200 mg BID for 21 days (Day 1-21) of a 28-day Cycle. Dose escalation details are provided below. AZA 75mg/m² intravenously (IV) or subcutaneously (SC) will be administered as 7 doses on a 28-day Cycle (*e.g.*, 7 consecutive doses or split doses with weekend break 5-2, starting at Day 1), and in accordance with local prescribing information (Table 2).

Notes:

- AZA dose reductions in case of toxicity 50mg/m² or lower per label.
- Anticipated emavusertib doses will 200, 300, 400 mg BID; de-escalation DL-1 and DL-2; 150 mg, 100 mg, with 21-day dosing of 28-day Cycle.

Table 2: Emavusertib + Azacitidine Dose Levels

Dose Level	Dose of Emavusertib (BID) (mg)	Total Daily Dose (mg)
2	400	800
1	300	600
0	200	400
-1	150	300
-2	100	200
Azacitidine Dosing	First Cycle and Subsequent Cycles	
Baseline laboratory values: WBC ≥ 3.0 ×10 ⁹ /L, ANC ≥ 1.5 ×10 ⁹ /L, and platelets ≥75.0 ×10 ⁹ /L	75/mg/m ²	
Dose adjustments are based on nadir lab values.		

Emavusertib + VEN

The starting dose level for emavusertib will be 200 mg BID for 21 days (Day 1-21) of a 28-day Cycle. Dose escalation details are provided below. VEN will be administered at 100 mg orally (Day 1) per the product label at the same time each day with a ramp up over 3 days to 400

mg for 21 days of a 28-day Cycle. Second and subsequent cycles start with target dose level (Table 3).

Notes:

- Anticipated emavusertib doses will be 200, 300, 400 mg BID; de-escalation DL-1 DL-2: 150 mg, 100 mg, with 21-day dosing of 28-day Cycle
- VEN with labeled dosing regimen, second and subsequent cycles start with target dose level.
 - Bone marrow assessment after 2 weeks of dosing and continuous safety assessments may shorten cycle length to 14 days
 - Lower starting dose and target dose level as per label to adjust for drug-drug interactions, dose reduction as label.

Table 3: Emavusertib + Venetoclax Dose Levels

Dose Level	Dose of Emavusertib (BID) (mg)	Total Daily Dose (mg)
2*	400	800
1	300	600
0	200	400
-1	150	300
-2	100	200
Venetoclax Ramp-up Phase	Day	Daily Dose
	1	100 mg
	2	200 mg
	3	400 mg
	4-21	400 mg
Subsequent Cycles	1-21	400 mg
Dose Adjustments are based on toxicities, CYP3A and P-gp inhibitor use.		

Example 2: Exemplary results of RNA sequencing applied to clinical samples from the Phase 1/2a trial

Myelodysplastic syndrome (MDS) and Acute myeloid leukemia (AML) are myeloid malignancies that exhibit a dynamic and diverse mutational landscape as the disease progresses.

Mutations in the spliceosome (*e.g.*, mutations in the splicing factors SF3B1 and U2AF1) drive overexpression of a highly active long isoform of interleukin-1 receptor-associated kinase 4 (IRAK4), upstream signaling of NFκB activation, triggering inflammation, oncogenesis and survival of cancer cells. NFκB target genes *CCL4*, *IL1B*, and *IER3* are highly expressed in patients with MDS and AML and are associated with a poor prognosis. Emavusertib is a potent oral inhibitor of IRAK4 and FLT3 kinase with proven efficacy in pre-clinical models of leukemia.

In Phase 1/2 of the Example 1 trial, patients with relapsed/refractory (R/R) AML or Higher-Risk MDS were treated with emavusertib. Bulk RNA-sequencing was performed on mononuclear cells from bone marrow or peripheral blood, from 26 AML and 16 MDS patients (including 24 paired samples) using the Illumina NGS platform (San Diego, CA) at Tempus laboratory (Chicago, IL). RNA-seq quality control was performed with FASTQC V0.11.8 and low-quality reads were removed using Trimgalore V0.6.3. Raw counts were normalized to total number of reads by calculating log2CPM (Counts Per Million). Patients were classified as responders or non-responders based on actual response data, including changes in bone marrow blast counts.

NF-KB target genes (*CCL4*, *IL1B* and *IER3*), that have been previously associated with AML/MDS pathophysiology and prognosis showed important differences between samples.

As shown in **FIG. 1 and FIG. 2**, high-risk MDS patients that responded to emavusertib had decreased levels of *IL1B* and *IER3* expression ($P \leq 0.01$ and $P \leq 0.01$, respectively). As shown in **FIG. 3 and FIG. 4**, AML patients that responded to emavusertib had decreased levels of *IL1B* and *IER3* expression ($P \leq 0.01$ and $P = 0.57$, respectively). On average, responders had lower *IL1B* and *IER3* expression than non-responders both before and during treatment for both AML and hrMDS, indicating that low *IL1B* and/or low *IER3* expression could be predictive of response to emavusertib treatment. This indicates that inhibition of IRAK4 could influence genes relevant to the development and pathophysiology of AML/MDS. Previous clinical research supports the findings describing *IL1B* and *IE3* as important markers in the prognosis of AML/MDS.

Thus, if *IL1B* expression levels become a companion diagnostic for AML or MDS, patients with low levels of *IL1B* expression would be candidates for primary treatment with emavusertib, and patients with high levels of *IL1B* expression would be candidates for treatment with a combination of emavusertib and an IL-1β inhibitor or degrader.

Additionally, as shown in **FIG. 5**, *CCL4*, a known chemokine associated with the pathophysiology of heme malignancies, is expressed at higher levels in patients with MDS

compared to those with AML. Patients with MDS demonstrate higher expression of *CCL4* ($P \leq 0.05$) when compared to AML at baseline and on-treatment patient samples. Other chemokines downstream of IRAK4 and associated with AML/MDS (e.g. *CCL3*), present a similar differential expression pattern, as shown in **FIG. 6**.

As shown in **FIG. 7**, pathway analysis also revealed significant downregulation of the Hallmark G2M Checkpoint (**FIG. 8**), Hallmark E2F Targets (**FIG. 9**), and Hallmark Heme Metabolism (**FIG. 10**) pathways in on-treatment samples in AML/MDS patients (FDR p-value < 0.005 for all, normalized enrichment score = -3.39, -1.97 & -2.17, respectively), indicating a decrease in cell cycle proliferation and metabolic markers. Notably *E2F2* was decreased in on-treatment samples compared to baseline samples with a log2FC of ~ 1.3 . These results indicate that emavusertib potentially downregulates pathways associated with heme metabolism, proliferation and cell cycle regulation (such as the *E2F* associated genes). Additionally, pathway analysis revealed significant upregulation of TNF-alpha signaling via NF-KB, indicating an increase in apoptosis (**FIG. 11**). In conclusion, MDS shows specific predictive biomarkers associated with clinical responses to emavusertib, with non-responders presenting higher expression of *IL1B* and *IER3* when compared to responders. Next, Chemokine *CCL4* demonstrates a higher expression in hrMDS when compared to AML, reflecting an associated increase in inflammatory status. Also, G2M checkpoint, E2F targets, and heme metabolism Hallmark pathways are negatively enriched in AML/MDS patients treated with emavusertib compared to baseline, suggesting that these pathways are downregulated by emavusertib, while TNF-alpha/NF-KB signaling is upregulated, suggesting an increase in apoptosis. The data presented here demonstrates that Emavusertib increases apoptosis/cell death, and decreases cell proliferation and cell cycle. Overall, this data supports targeting the IRAK4/NF-KB pathway with emavusertib in hematological malignancies.

INCORPORATION BY REFERENCE

All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

EQUIVALENTS

While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification and the claims below. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

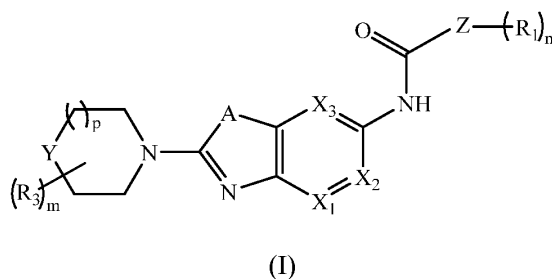
We claim:

1. A method of treating a cancer in a subject comprising administering an IRAK4-modifying compound to the subject, wherein the subject has decreased expression of interleukin-1 beta or immediate early response gene 3.
2. The method of claim 1, wherein the subject has decreased expression of interleukin-1 beta.
3. The method of claim 2, wherein the subject has decreased expression of interleukin-1 beta, as compared to a subject not having cancer.
4. The method of claim 2, wherein the subject has decreased expression of interleukin-1 beta, as compared to a subject having cancer.
5. The method of claim 1, wherein the subject has decreased expression of immediate early response gene 3.
6. The method of claim 5, wherein the subject has decreased expression of immediate early response gene 3, as compared to a subject not having cancer.
7. The method of claim 5, wherein the subject has decreased expression of immediate early response gene 3, as compared to a subject having cancer.
8. The method of any one of claims 1-7, comprising:
obtaining a biological sample(s) from the subject;
determining a level(s) of expression of interleukin-1 beta or immediate early response gene 3 in the biological sample(s);
comparing the level(s) of expression of the one or more genes to a reference expression level(s);
and
administering the IRAK4-modifying compound if the level(s) of expression of the one or more genes is lower than a reference expression level(s).

9. The method of claim 8, comprising determining the level(s) of expression of interleukin-1 beta in the biological sample(s).
10. The method of claim 8 or 9, comprising determining the level(s) of expression of immediate early response gene 3 in the biological sample(s).
11. The method of any one of claims 8-10, wherein the biological sample(s) comprises tissue (e.g., bone marrow).
12. The method of any one of claims 8-11, wherein the biological sample(s) comprises blood (e.g. a peripheral blood sample).
13. The method of any one of claims 1-12, wherein the method further comprises administering an interleukin-1 blocker to the subject.
14. The method of claim 13, wherein the interleukin-1 blocker is an interleukin-1 receptor antagonist.
15. The method of claim 13 or 14, wherein the interleukin-1 blocker is interleukin-1 receptor antagonist protein or a homologue thereof.
16. The method of any one of claims 13-15, wherein the interleukin-1 blocker is anakinra.
17. The method of claim 13, wherein the interleukin-1 blocker is a soluble decoy receptor.
18. The method of claim 13 or 17, wherein the interleukin-1 blocker is a dimeric fusion protein comprising ligand-binding domains of the extracellular portions of the human interleukin-1 receptor component (IL-1R1) and IL-1 receptor accessory protein (IL-1RAcP) linked to the Fc region of human IgG1.
19. The method of any one of claims 13, 17, or 18, wherein the interleukin-1 blocker is rilonacept.

20. The method of claim 13, wherein the interleukin-1 blocker is an IL-1 β neutralizing antibody.
21. The method of claim 13 or 20, wherein the interleukin-1 blocker is canakinumab.
22. The method of claim 13 or 20, wherein the interleukin-1 blocker is gevokizumab.
23. The method of claim 13 or 20, wherein the interleukin-1 blocker is LY2189102.
24. The method of claim 13, wherein the interleukin-1 blocker is an IL-1 α neutralizing antibody.
25. The method of claim 13 or 24, wherein the interleukin-1 blocker is MABp1.
26. The method of claim 13, wherein the interleukin-1 blocker is an interleukin-1 receptor 1 blocking antibody.
27. The method of claim 13 or 26, wherein the interleukin-1 blocker is MEDI-8968.
28. The method of claim 13, wherein the interleukin-1 blocker is a caspase 1 inhibitor.
29. The method of any one of claims 1-28, wherein the method further comprises administering an agent that inhibits the activity of NF-KB.
30. The method of any one of claims 1-29, wherein the IRAK4-modifying compound is an IRAK4 inhibitor.
31. The method of any one of claims 1-29, wherein the IRAK4-modifying compound is an IRAK4 degrader.
32. The method of claim 31, wherein the IRAK4 degrader is KT-474.

33. The method of claim 30, wherein the IRAK4 inhibitor has a structure represented by formula I:



or a pharmaceutically acceptable salt thereof;

wherein

X₁ and X₃ independently are CH or N; X₂ is CR₂ or N; provided one and not more than one of X₁, X₂ or X₃ is N;

A is O or S;

Y is -CH₂- or O;

Z is aryl or heterocyclyl;

R₁, at each occurrence, is independently halo or optionally substituted heterocyclyl; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl, hydroxyalkyl or -NR_aR_b;

R₂ is hydrogen, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl or -NR_aR_b; wherein the substituent is alkyl, amino, halo or hydroxyl;

R₃, at each occurrence, is alkyl or hydroxyl;

R_a and R_b are independently hydrogen, alkyl, acyl or heterocyclyl;

'm' and 'n' are independently 0, 1 or 2; and

'p' is 0 or 1.

34. The method of claim 33, wherein

A is O or S;

Y is -CH₂- or O;

Z is aryl or heterocyclyl;

R₁, at each occurrence, is independently halo or optionally substituted heterocyclyl, wherein the substituent is alkyl, aminoalkyl, halo, or -NR_aR_b; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl;

R₂ is hydrogen, cycloalkyl, heterocyclyl or -NR_aR_b;

'm' is 0; and

'n' is 1.

35. The method of claim 33, wherein

A is O or S;

Y is -CH₂- or O;

Z is aryl or heterocyclyl;

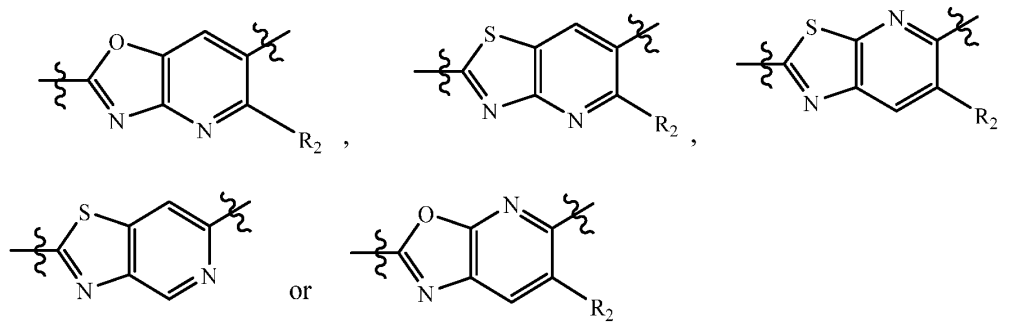
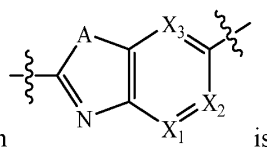
R₁, at each occurrence, is independently halo or optionally substituted heterocyclyl; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl or -NR_aR_b; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl;

R₂ is hydrogen, cycloalkyl, optionally substituted heterocyclyl or -NR_aR_b, where the substituent is selected from amino, halo or hydroxyl;

'm' and 'n' are independently 0, 1 or 2; and

'p' is 0 or 1.

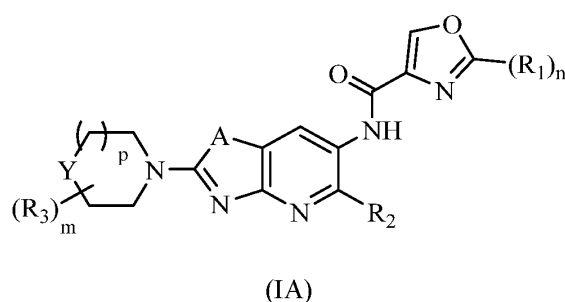
36. The method of any one of claims 33-35, wherein



37. The method of any one of claims 33-36, wherein Z is aryl or 5- or 6-membered heterocyclyl.

38. The method of any one of claims 33-37, wherein Z is an optionally substituted heterocyclcyl selected from phenyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1H-tetrazolyl, oxadiazolyl, triazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, azetidinsyl, oxetanyl, imidazolidinyl, pyrrolidinyl, oxazolidinyl, thiazolidinyl, pyrazolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, 1,4-dioxanyl, dioxidothiomorpholinyl, oxapiperazinyl, oxapiperidinyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiophenyl, dihydropyranyl and azabicyclo[3.2.1]octanyl; each of which is optionally substituted with alkyl, alkoxy, halo, hydroxyl, hydroxyalkyl or $-NR_aR_b$; and R_a and R_b are independently hydrogen, alkyl or acyl.

39. The method of claim 33, wherein the IRAK4 inhibitor has a structure represented by formula (IA):



or a pharmaceutically acceptable salt thereof.

40. The method of claim 39, wherein

A is O or S;

Y is $-CH_2-$ or O;

R_1 , at each occurrence, is independently halo or optionally substituted heterocyclcyl, wherein the substituent is alkyl, aminoalkyl, halo, or $-NR_aR_b$; where R_a and R_b are independently hydrogen, alkyl, or heterocyclcyl;

R_2 is hydrogen, cycloalkyl, heterocyclcyl or $-NR_aR_b$;

'm' is 0; and

'n' is 1.

41. The method of claim 39, wherein

A is O or S;

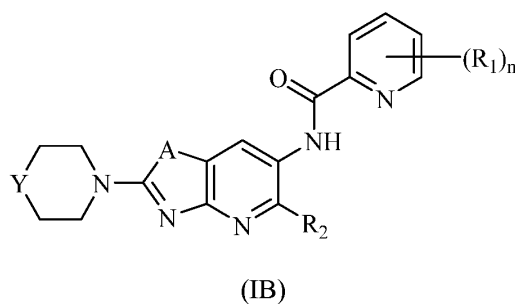
Y is -CH₂- or O;

R₁, at each occurrence, is independently halo or optionally substituted heterocyclyl; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl or -NR_aR_b; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl;

R₂ is hydrogen, cycloalkyl, optionally substituted heterocyclyl or -NR_aR_b, where the substituent is selected from amino, halo or hydroxyl; and

'm' and 'n' are independently 0, 1 or 2.

42. The method of claim 33, wherein the IRAK4 inhibitor has a structure represented by formula (IB):



or a pharmaceutically acceptable salt thereof.

43. The method of claim 42, wherein

A is O or S;

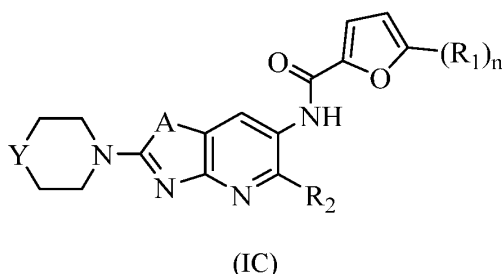
Y is -CH₂- or O;

R₁, at each occurrence, is independently halo or optionally substituted heterocyclyl; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl or -NR_aR_b; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl;

R₂ is hydrogen, cycloalkyl, optionally substituted heterocyclyl or -NR_aR_b, where the substituent is selected from amino, halo or hydroxyl; and

'm' and 'n' are independently 0, 1 or 2.

44. The method according to claim 33, wherein the IRAK4 inhibitor has a structure represented by formula (IC)



or a pharmaceutically acceptable salt thereof.

45. The method of any one of claims 33-44, wherein R₁ is optionally substituted heterocyclyl; wherein the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl, hydroxyalkyl or -NR_aR_b; and R_a and R_b are independently hydrogen or acyl.

46. The method of any one of claims 33-44, wherein R₁ is optionally substituted heterocyclyl; wherein the substituent is alkyl, aminoalkyl, halo, or -NR_aR_b; and R_a and R_b are independently hydrogen or acyl.

47. The method of any one of claims 33-44, wherein R₁ is optionally substituted heterocyclyl; and the substituent is alkyl, aminoalkyl, halo, or -NR_aR_b; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl.

48. The method of any one of claims 33-44, wherein R₁ is optionally substituted heterocyclyl; and the substituent is alkyl, alkoxy, aminoalkyl, halo, hydroxyl or -NR_aR_b; where R_a and R_b are independently hydrogen, alkyl, or heterocyclyl.

49. The method of any one of claims 33-44, wherein R₁ is pyridyl, pyrazolyl, pyrrolidinyl or piperidinyl.

50. The method of any one of claims 33-44, wherein R₁ is optionally substituted pyrazolyl, wherein the substituent is alkyl, hydroxyl or -NR_aR_b.

51. The method of any one of claims 33-44, wherein R₁ is halo.
52. The method of any one of claims 33-51, wherein R₂ is hydrogen, cycloalkyl, heterocyclyl or -NR_aR_b.
53. The method of any one of claims 33-51, wherein R₂ is hydrogen, cycloalkyl, optionally substituted heterocyclyl or -NR_aR_b, where the substituent is selected from amino, halo or hydroxyl.
54. The method of any one of claims 33-51, wherein R₂ is optionally substituted heterocyclyl selected from piperidinyl, pyrrolidinyl, morpholinyl, piperazinyl, azetidiny, pyrazolyl, furanyl or azabicyclo[3.2.1]octanyl; wherein the substituent is hydroxyl, halo, alkyl or amino.
55. The method of any one of claims 33-51, wherein R₂ is piperidinyl, pyrrolidinyl, morpholinyl, or piperazinyl.
56. The method of any one of claims 33-51, wherein R₂ is hydrogen.
57. The method of any one of claims 33-51, wherein R₂ is cycloalkyl.
58. The method of claim 57, wherein R₂ is cyclopropyl.
59. The method of any one of claims 33-58, wherein R₃ is alkyl.
60. The method of any one of claims 33-59, wherein m is 0 and p is 1.
61. The method of any one of claims 33-59, wherein m is 0 or 2, and p is 0 or 1.
62. The method of claim 30, wherein the IRAK4 inhibitor is selected from:

6'-amino-N-(2-morpholinooxazolo[4,5-b]pyridin-6-yl)-[2,3'-bipyridine]-6-carboxamide;
--

6'-amino-N-(5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-[2,3'-bipyridine]-6-carboxamide hydrochloride;
--

N-(5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride;
N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide hydrochloride;
N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide;
2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
6-chloro-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)picolinamide;
N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-6-(1-methyl-1H-pyrazol-4-yl)picolinamide;
2-(2-chloropyridin-4-yl)-N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
(S)-2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(pyrrolidin-3-ylamino)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
6'-amino-N-(2-morpholinooxazolo[5,4-b]pyridin-5-yl)-[2,3'-bipyridine]-6-carboxamide;
6'-amino-N-(2-morpholinothiazolo[4,5-c]pyridin-6-yl)-[2,3'-bipyridine]-6-carboxamide;
6'-amino-N-(2-morpholinothiazolo[5,4-b]pyridin-5-yl)-[2,3'-bipyridine]-6-carboxamide;
2-(2-methylpyridin-4-yl)-N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
6'-amino-N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)-[2,3'-bipyridine]-6-carboxamide;
N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide;
3-(4-(aminomethyl)piperidin-1-yl)-5-fluoro-N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)benzamide;

2-(4-(aminomethyl)piperidin-1-yl)-5-fluoro-N-(2-morpholinothiazolo[4,5-b]pyridin-6-yl)benzamide;
2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide;
N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-6-(1H-pyrazol-4-yl)picolinamide;
N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
N-(2,5-dimorpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
N-(5-(4-methylpiperazin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;
N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-3-yl)oxazole-4-carboxamide;
N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-hydroxypyridin-3-yl)oxazole-4-carboxamide;
2-(2-hydroxypyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(6-hydroxypyridin-3-yl)oxazole-4-carboxamide;
2-(2-methoxypyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
2-(2-methylpyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
2-(3-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;

N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(3-methylpyridin-4-yl)oxazole-4-carboxamide;
2-(6-methylpyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
6-(1-methyl-1H-pyrazol-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)picolinamide;
N-(2,5-di(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(6-methylpyridin-3-yl)oxazole-4-carboxamide;
(S)-N-(5-(3-aminopyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
(R)-N-(5-(3-aminopyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
(R)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
(S)-2-(3-aminopyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
(S)-6-(3-hydroxypyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)picolinamide;
(S)-6-(3-aminopyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)picolinamide;
(S)-2-(3-hydroxypyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
(S)-N-(5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(3-hydroxypyrrolidin-1-yl)oxazole-4-carboxamide;
(S)-2-(3-aminopyrrolidin-1-yl)-N-(5-cyclopropyl-2-morpholinooxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
2-(2-methylpyridin-4-yl)-N-(5-(piperidin-1-yl)-2-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride;

N-(2-(2,6-dimethylmorpholino)-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride;
N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-6-(1-methyl-1H-pyrazol-4-yl)picolinamide hydrochloride;
6-(1-methyl-1H-pyrazol-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide;
N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-3-yl)oxazole-4-carboxamide hydrochloride;
N-(2-((2S,6R)-2,6-dimethylmorpholino)-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
2-(2-methylpyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
2-(2-hydroxypyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methoxypyridin-4-yl)oxazole-4-carboxamide;
2-(6-methoxypyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
2-(2-methoxypyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
(S)-N-(5-(3-fluoropiperidin-1-yl)-2-morpholinethiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
2-(6-methylpyridin-3-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
2-(3-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
(S)-6-(3-aminopyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide;
(S)-6-(3-hydroxypyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide;

(S)-6-(3-aminopyrrolidin-1-yl)-N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide;
(S)-N-(2,5-di(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-6-(3-hydroxypyrrolidin-1-yl)picolinamide;
(S)-2-(3-aminopyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
(S)-N-(5-(3-aminopyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
(S)-2-(3-aminopyrrolidin-1-yl)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
(S)-2-(3-hydroxypyrrolidin-1-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
(S)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-(3-hydroxypyrrolidin-1-yl)picolinamide;
(S)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(3-hydroxypyrrolidin-1-yl)oxazole-4-carboxamide;
(S)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-(1-(2-hydroxypropyl)-1H-pyrazol-4-yl)picolinamide;
(S)-N-(5-cyclopropyl-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(1-(2-hydroxypropyl)-1H-pyrazol-4-yl)oxazole-4-carboxamide;
N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;
(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;
(R)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;

(S)-N-(5-(azetidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-6-(3-hydroxypyrrolidin-1-yl)picolinamide;
N-(5-(3-hydroxyazetidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)thiophene-2-carboxamide;
(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;
(S)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide
(R)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;
N-(5-(azetidin-1-yl)-2-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
2-(2-methylpyridin-4-yl)-N-(2-(piperidin-1-yl)-5-(pyrrolidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(pyrrolidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
5-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)furan-2-carboxamide;
N-(5-(azepan-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
2-(2-aminopyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride;
N-(5-(azetidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

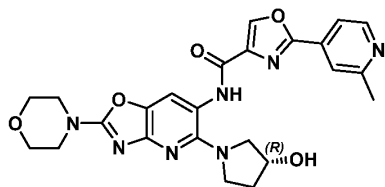
(R)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
(R)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;
(S)-6-(1-(2-hydroxypropyl)-1H-pyrazol-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)picolinamide
N-(5-(4-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide
N-(5-(4-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride
N-(5-(1-methyl-1H-pyrazol-4-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
N-(5-(3-fluorophenyl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;
N-(5-(3-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;
(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinoxazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;
N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinoxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
(R)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinoxazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;
N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinoxazolo[4,5-b]pyridin-6-yl)-2-(6-methoxypyridin-3-yl)oxazole-4-carboxamide;
(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinoxazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;
(S)-N-(5-(3-hydroxypyrrolidin-1-yl)-2-morpholinoxazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)thiophene-2-carboxamide;

N-(5-(azetidin-1-yl)-2-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
2-(2-methylpyridin-4-yl)-N-(2-(piperidin-1-yl)-5-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
5-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(piperidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)furan-2-carboxamide;
N-(5-(azetidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(pyrrolidin-1-yl)oxazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;
(R)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-5-(2-methylpyridin-4-yl)furan-2-carboxamide;
N-(5-(furan-3-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
N-(5-(3-fluoropiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
N-(5-(4-fluoropiperidin-1-yl)-2-morpholinooxazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
(S)-N-(5-(3-aminopiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
2-(2-methylpyridin-4-yl)-N-(2-morpholino-5-(1H-pyrazol-4-yl)thiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
N-(5-(6-fluoropyridin-3-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
N-(5-(3-hydroxy-8-azabicyclo[3.2.1]octan-8-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;

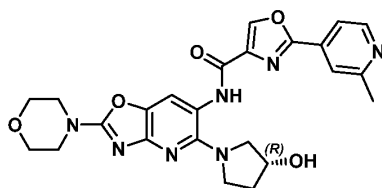
N-(2-(3-hydroxypiperidin-1-yl)-5-(piperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
2-(2-acetamidopyridin-4-yl)-N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
N-(2-(3-hydroxypiperidin-1-yl)-5-(4-hydroxypiperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
2-(2-acetamidopyridin-4-yl)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide;
2-(2-aminopyridin-4-yl)-N-(5-(3-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride;
5-(2-aminopyridin-4-yl)-N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)furan-3-carboxamide hydrochloride;
2-(2-aminopyridin-4-yl)-N-(5-(4-hydroxypiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride;
2-(2-aminopyridin-4-yl)-N-(5-(4-fluoropiperidin-1-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)oxazole-4-carboxamide hydrochloride;
N-(5-(2-fluoropyridin-4-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
N-(5-(4-fluoropiperidin-1-yl)-2-(3-hydroxypiperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide;
N-(5-(4-aminopiperidin-1-yl)-2-(3-hydroxypiperidin-1-yl)thiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride; and
N-(5-(2-hydroxypyridin-4-yl)-2-morpholinothiazolo[4,5-b]pyridin-6-yl)-2-(2-methylpyridin-4-yl)oxazole-4-carboxamide hydrochloride;

or a pharmaceutically acceptable salt or a stereoisomer thereof.

63. The method of claim 30, wherein the IRAK4 inhibitor is

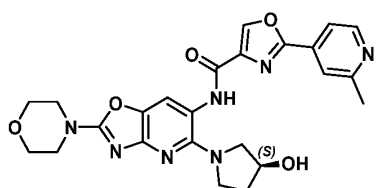


64. The method of claim 30, wherein the IRAK4 inhibitor is a pharmaceutically

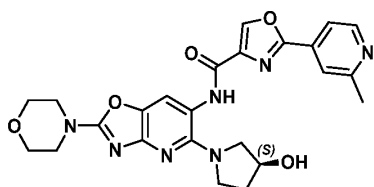


acceptable salt of

65. The method of claim 30, wherein the IRAK4 inhibitor is

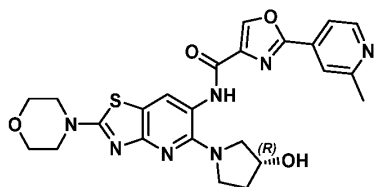


66. The method of claim 30, wherein the IRAK4 inhibitor is a pharmaceutically acceptable

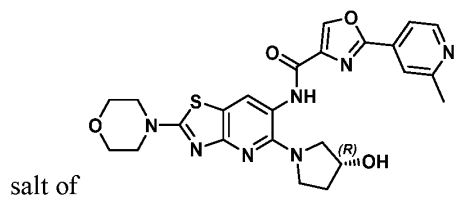


salt of

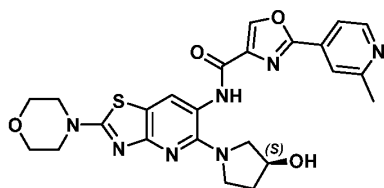
67. The method of claim 30, wherein the IRAK4 inhibitor is



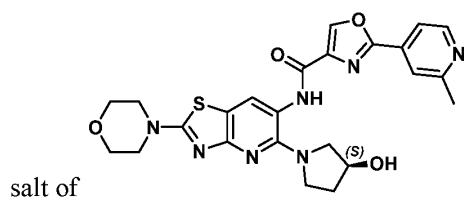
68. The method of claim 30, wherein the IRAK4 inhibitor is a pharmaceutically acceptable



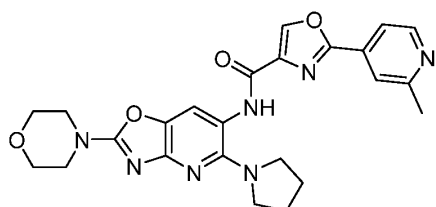
69. The method of claim 30, wherein the IRAK4 inhibitor is



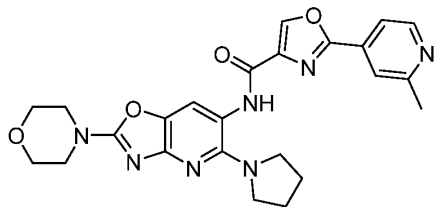
70. The method of claim 30, wherein the IRAK4 inhibitor is a pharmaceutically acceptable



71. The method of claim 30, wherein the IRAK4 inhibitor is

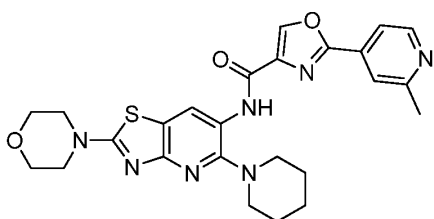


72. The method of claim 30, wherein the IRAK4 inhibitor is a pharmaceutically acceptable

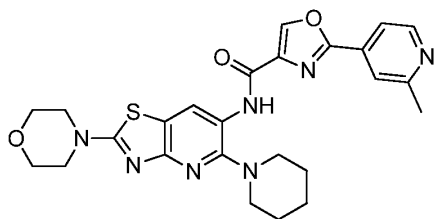


salt of

73. The method of claim 30, wherein the IRAK4 inhibitor is

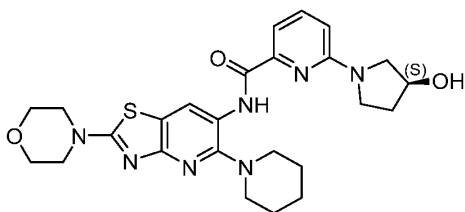


74. The method of claim 30, wherein the IRAK4 inhibitor is a pharmaceutically acceptable

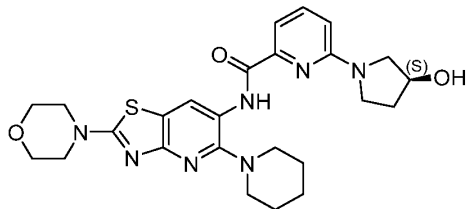


salt of

75. The method of claim 30, wherein the IRAK4 inhibitor is

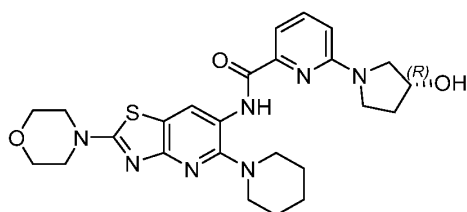


76. The method of claim 30, wherein the IRAK4 inhibitor is a pharmaceutically acceptable

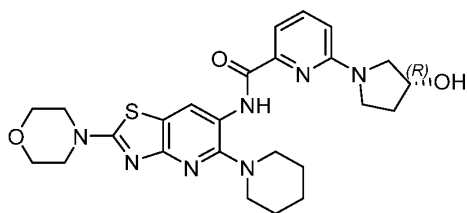


salt of

77. The method of claim 30, wherein the IRAK4 inhibitor is



78. The method of claim 30, wherein the IRAK4 inhibitor is a pharmaceutically acceptable



salt of

79. The method of any one of claims 33-78, comprising administering 100 – 400 mg of the IRAK4 inhibitor to the subject twice per day.

80. The method of any one of claims 33-78, comprising administering 200 – 400 mg of the IRAK4 inhibitor to the subject twice per day.

81. The method of any one of claims 33-78, comprising administering 250 – 350 mg of the IRAK4 inhibitor to the subject twice per day.

82. The method of any one of claims 33-78, comprising administering about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg,

about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, or about 500 mg of the IRAK4 inhibitor to the subject twice per day.

83. The method of any one of claims 33-78, comprising administering about 50 mg, about 75 mg, about 100 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, or about 400 mg of the IRAK4 inhibitor to the subject twice per day.

84. The method of any one of claims 33-78, comprising administering about 100 mg, about 150 mg, about 200 mg, about 300 mg, or about 400 mg of the IRAK4 inhibitor to the subject twice per day.

85. The method of any one of claims 33-78, comprising administering about 100 mg of the IRAK4 inhibitor to the subject twice per day.

86. The method of any one of claims 33-78, comprising administering about 150 mg of the IRAK4 inhibitor to the subject twice per day.

87. The method of any one of claims 33-78, comprising administering about 200 mg of the IRAK4 inhibitor to the subject twice per day.

88. The method of any one of claims 33-78, comprising administering about 225 mg of the IRAK4 inhibitor to the subject twice per day.

89. The method of any one of claims 33-78, comprising administering about 250 mg of the IRAK4 inhibitor to the subject twice per day.

90. The method of any one of claims 33-78, comprising administering about 275 mg of the IRAK4 inhibitor to the subject twice per day.

91. The method of any one of claims 33-78, comprising administering about 300 mg of the IRAK4 inhibitor to the subject twice per day.
92. The method of any one of claims 33-78, comprising administering about 325 mg of the IRAK4 inhibitor to the subject twice per day.
93. The method of any one of claims 33-78, comprising administering about 350 mg of the IRAK4 inhibitor to the subject twice per day.
94. The method of any one of claims 33-78, comprising administering about 375 mg of the IRAK4 inhibitor to the subject twice per day.
95. The method of any one of claims 33-78, comprising administering about 400 mg of the IRAK4 inhibitor to the subject twice per day.
96. The method of any one of claims 33-78, comprising administering about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, or about 500 mg of the IRAK4 inhibitor to the subject once per day.
97. The method of any one of claims 33-78, comprising administering about 25 mg of the IRAK4 inhibitor to the subject once per day.
98. The method of any one of claims 33-78, comprising administering about 50 mg of the IRAK4 inhibitor to the subject once per day.
99. The method of any one of claims 33-78, comprising administering about 75 mg of the IRAK4 inhibitor to the subject once per day.
100. The method of any one of claims 33-78, comprising administering about 100 mg of the IRAK4 inhibitor to the subject once per day.

101. The method of any one of claims 33-78, comprising administering about 125 mg of the IRAK4 inhibitor to the subject once per day.
102. The method of any one of claims 33-78, comprising administering about 150 mg of the IRAK4 inhibitor to the subject once per day.
103. The method of any one of claims 33-78, comprising administering about 175 mg of the IRAK4 inhibitor to the subject once per day.
104. The method of any one of claims 33-78, comprising administering about 200 mg of the IRAK4 inhibitor to the subject once per day.
105. The method of any one of claims 33-78, comprising administering about 225 mg of the IRAK4 inhibitor to the subject once per day.
106. The method of any one of claims 33-78, comprising administering about 250 mg of the IRAK4 inhibitor to the subject once per day.
107. The method of any one of claims 33-78, comprising administering about 275 mg of the IRAK4 inhibitor to the subject once per day.
108. The method of any one of claims 33-78, comprising administering about 300 mg of the IRAK4 inhibitor to the subject once per day.
109. The method of any one of claims 33-78, comprising administering about 325 mg of the IRAK4 inhibitor to the subject once per day.
110. The method of any one of claims 33-78, comprising administering about 350 mg of the IRAK4 inhibitor to the subject once per day.
111. The method of any one of claims 33-78, comprising administering about 375 mg of the IRAK4 inhibitor to the subject once per day.

112. The method of any one of claims 33-78, comprising administering about 400 mg of the IRAK4 inhibitor to the subject once per day.
113. The method of any one of claims 33-78, comprising administering about 425 mg of the IRAK4 inhibitor to the subject once per day.
114. The method of any one of claims 33-78, comprising administering about 450 mg of the IRAK4 inhibitor to the subject once per day.
115. The method of any one of claims 33-78, comprising administering about 475 mg of the IRAK4 inhibitor to the subject once per day.
116. The method of any one of claims 33-78, comprising administering about 500 mg of the IRAK4 inhibitor to the subject once per day.
117. The method of any one of claims 1-116, wherein the IRAK4-modifying compound is orally administered to the subject.
118. The method of any one of claims 33-78, comprising administering about 50 mg of the IRAK4 inhibitor to the subject once per day.
119. The method of any one of claims 33-78, comprising administering about 75 mg of the IRAK4 inhibitor to the subject once per day.
120. The method of any one of claims 33-78, comprising orally administering about 100 mg of the IRAK4 inhibitor to the subject twice per day.
121. The method of any one of claims 33-78, comprising orally administering about 125 mg of the IRAK4 inhibitor to the subject twice per day.
122. The method of any one of claims 33-78, comprising orally administering about 150 mg of the IRAK4 inhibitor to the subject twice per day.

123. The method of any one of claims 33-78, comprising orally administering about 175 mg of the IRAK4 inhibitor to the subject twice per day.
124. The method of any one of claims 33-78, comprising orally administering about 200 mg of the IRAK4 inhibitor to the subject twice per day.
125. The method of any one of claims 33-78, comprising orally administering about 225 mg of the IRAK4 inhibitor to the subject twice per day.
126. The method of any one of claims 33-78, comprising orally administering about 250 mg of the IRAK4 inhibitor to the subject twice per day.
127. The method of any one of claims 33-78, comprising orally administering about 275 mg of the IRAK4 inhibitor to the subject twice per day.
128. The method of any one of claims 33-78, comprising orally administering about 300 mg of the IRAK4 inhibitor to the subject twice per day.
129. The method of any one of claims 33-78, comprising orally administering about 325 mg of the IRAK4 inhibitor to the subject twice per day.
130. The method of any one of claims 33-78, comprising orally administering about 350 mg of the IRAK4 inhibitor to the subject twice per day.
131. The method of any one of claims 33-78, comprising orally administering about 375 mg of the IRAK4 inhibitor to the subject twice per day.
132. The method of any one of claims 33-78, comprising orally administering about 400 mg of the IRAK4 inhibitor to the subject twice per day.
133. The method of any one of claims 1-132, comprising additionally administering 75 mg/m² of azacitidine to the subject once per day.

134. The method of any one of claims 1-29, wherein the IRAK4-modifying compound is PF-06650833.
135. The method of any one of claims 1-29, wherein the IRAK4-modifying compound is BAY 1830839.
136. The method of any one of claims 1-135, wherein the method further comprises conjointly administering a BCL-2 inhibitor to the subject.
137. The method of claim 136, wherein the BCL-2 inhibitor is venetoclax.
138. The method of claim 137, comprising administering 400 mg of venetoclax daily.
139. The method of claim 137, wherein the venetoclax is administered orally.
140. The method of claim 137, comprising orally administering 400 mg of venetoclax daily.
141. The method of any one of claims 1-140, wherein the method further comprises conjointly administering a BTK inhibitor to the subject.
142. The method of claim 141, wherein the BTK inhibitor is ibrutinib, acalabrutinib, zanubrutinib, evobrutinib, ONO-4059, spebrutinib, or HM7 1224.
143. The method of claim 142, wherein the BTK inhibitor is acalabrutinib.
144. The method of claim 143, comprising administering 200 mg of acalabrutinib daily.
145. The method of claim 143, wherein the acalabrutinib is administered orally.
146. The method of claim 143, comprising orally administering 200 mg of acalabrutinib daily.
147. The method of claim 142, wherein the BTK inhibitor is ibrutinib.

148. The method of claim 147, comprising administering 420 mg of ibrutinib daily.
149. The method of claim 147, comprising administering 560 mg of ibrutinib daily.
150. The method of claim 147, wherein the ibrutinib is administered orally.
151. The method of claim 147, comprising orally administering 420 mg of ibrutinib daily.
152. The method of claim 147, comprising orally administering 560 mg of ibrutinib daily.
153. The method of claims 142, wherein the BTK inhibitor is zanubrutinib.
154. The method of claim 153, comprising administering 160 mg of zanubrutinib twice daily.
155. The method of claim 153, comprising administering 320 mg of zanubrutinib once daily.
156. The method of claim 153, wherein the zanubrutinib is administered orally.
157. The method of claim 153, comprising orally administering 160 mg of zanubrutinib twice daily.
158. The method of claim 153, comprising orally administering 320 mg of zanubrutinib once daily.
159. The method of any one of claims 1-158, wherein the cancer is a hematological malignancy.
160. The method of claim 159, wherein the hematological malignancy is a non-Hodgkin's lymphoma.
161. The method of claim 159, wherein the hematological malignancy is a leukemia.
162. The method of claim 159, wherein the hematological malignancy is a lymphoma.

163. The method of any one of claims 159-162, wherein the hematological malignancy is myelogenous leukemia, myeloid leukemia (*e.g.*, acute myeloid leukemia), myelodysplastic syndrome, lymphoblastic leukemia (*e.g.*, acute lymphoblastic leukemia), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, follicular lymphoma, diffuse large B-cell lymphoma (DLBCL) (*e.g.*, DLBCL or ABC-DLBCL), mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia (WM), multiple myeloma, marginal zone lymphoma (MZL), Burkitt's lymphoma, non-Burkitt high grade B cell lymphoma, extranodal marginal zone B cell lymphoma, transformed high grade B-cell lymphoma (HGBL), lymphoplasmacytic lymphoma (LPL), central nervous system lymphoma (CNSL), or MALT lymphoma.

164. The method of claim 159, wherein the hematological malignancy is myelogenous leukemia.

165. The method of claim 159, wherein the hematological malignancy is myeloid leukemia (*e.g.*, acute myeloid leukemia).

166. The method of claim 159, wherein the hematological malignancy is acute myeloid leukemia (*e.g.*, AML).

167. The method of claim 166, wherein the AML is primary AML.

168. The method of claim 166, wherein the AML is secondary AML.

169. The method of any one of claims 166-168, wherein the AML is treatment related AML.

170. The method of claim 159, wherein the hematological malignancy is myelodysplastic syndrome.

171. The method of claim 170, wherein the myelodysplastic syndrome is high grade.

172. The method of claim 170, wherein the myelodysplastic syndrome is low grade.

173. The method of any one of claims 170-172, wherein the myelodysplastic syndrome is high risk.
174. The method of claim 159, wherein the hematological malignancy is lymphoblastic leukemia (*e.g.*, acute lymphoblastic leukemia).
175. The method of claim 159, wherein the hematological malignancy is chronic lymphocytic leukemia (CLL).
176. The method of claim 175, wherein the CLL is high risk CLL.
177. The method of claim 159, wherein the hematological malignancy is small lymphocytic lymphoma (SLL).
178. The method of claim 159, wherein the hematological malignancy is follicular lymphoma.
179. The method of claim 159, wherein the hematological malignancy is diffuse large B-cell lymphoma (DLBCL).
180. The method of claim 159, wherein the hematological malignancy is activated B cell-like (ABC) DLBCL.
181. The method of claim 159, wherein the hematological malignancy is germinal center B cell-like (GCB) DLBCL.
182. The method of any one of claims 179-181, wherein the DLBCL is extranodal.
183. The method of any one of claims 179-181, wherein the DLBCL is extranodal leg lymphoma, extranodal testicle lymphoma, or extra nodal not otherwise specified (NOS) type lymphoma.
184. The method of claim 159, wherein the hematological malignancy is mantle cell lymphoma.

185. The method of claim 159, wherein the hematological malignancy is Waldenstrom's macroglobulinemia.
186. The method of claim 159, wherein the hematological malignancy is multiple myeloma.
187. The method of claim 159, wherein the hematological malignancy is marginal zone lymphoma.
188. The method of claim 159, wherein the hematological malignancy is Burkitt's lymphoma.
189. The method of claim 159, wherein the hematological malignancy is non-Burkitt high grade B cell lymphoma.
190. The method of claim 159, wherein the hematological malignancy is extranodal marginal zone B cell lymphoma.
191. The method of claim 159, wherein the hematological malignancy is transformed high grade B-cell lymphoma (HGBL).
192. The method of claim 159, wherein the hematological malignancy is lymphoplasmacytic lymphoma (LPL).
193. The method of claim 159, wherein the hematological malignancy is CNS lymphoma.
194. The method of claim 193, wherein the CNS lymphoma is primary CNS lymphoma (PCNSL).
195. The method of claim 159, wherein the hematological malignancy is MALT lymphoma.
196. The method of any one of claims 159-195, wherein the hematological malignancy is relapsed.

197. The method of any one of claims 159-196, wherein the hematological malignancy is refractory.
198. The method of any one of claims 1-158, wherein the cancer is selected from brain cancer, kidney cancer, liver cancer, stomach cancer, penile cancer, vaginal cancer, ovarian cancer, gastric cancer, breast cancer, bladder cancer, colon cancer, prostate cancer, pancreatic cancer, lung cancer, cervical cancer, melanoma, epidermal cancer, prostate cancer, head or neck cancer.
199. The method of any one of claims 1-158, wherein the cancer is pancreatic cancer.
200. The method of any one of claims 1-158, wherein the cancer is colon cancer.
201. The method of any one of claims 198-200, wherein the cancer is a solid tumor.
202. The method of any one of claims 198-201, wherein the cancer is relapsed.
203. The method of any one of claims 198-202, wherein the cancer is refractory.
204. The method of any one of claims 1-203, wherein the cancer is resistant to treatment with a BTK inhibitor.
205. The method of claim 204, wherein the cancer is resistant to treatment with ibrutinib, acalabrutinib, zanubrutinib, evobrutinib, ONO-4059, spebrutinib, or HM7 1224.
206. The method of claim 205, wherein the cancer is resistant to treatment with ibrutinib.
207. The method of claim 205, wherein the cancer is resistant to treatment with acalabrutinib.
208. The method of any one of claims 1-207, wherein the subject is an adult human.
209. The method of any one of claims 1-208, wherein the subject has previously received at least one anti-cancer therapy (*e.g.*, an anti-cancer therapy or an anti-inflammatory therapy).

210. The method of claim 209, wherein the subject has previously received one anti-cancer therapy.
211. The method of claim 209, wherein the subject has previously received two anti-cancer therapies.
212. The method of claim 209, wherein the subject has previously received three anti-cancer therapies.
213. The method of claim 209, wherein the subject has previously received four anti-cancer therapies.
214. The method of claim 209, wherein the subject has previously received five anti-cancer therapies.
215. The method of any one of claims 209-214, wherein the at least one anti-cancer therapy comprises an anti-CD20 antibody, a nitrogen mustard, a steroid, a purine analog, a DNA a topoisomerase inhibitor, a DNA intercalator, a tubulin inhibitor, a BCL-2 inhibitor, a proteasome inhibitor, a toll-like receptor inhibitor, a kinase inhibitor, an SRC kinase inhibitor, a PI3K kinase inhibitor, BTK inhibitor, a glutaminase inhibitor, a steroid, or a methylating agent; or a combination thereof.
216. The method of any one of claims 209-215, wherein the anti-cancer therapy comprises ibrutinib, rituximab, bendamustine, bortezomib, dexamethasone, chlorambucil, cladribine, cyclophosphamide, doxorubicin, vincristine, venetoclax, ifosfamide, prednisone, oprozomib, ixazomib, acalabrutinib, zanubrutinib, IMO-08400, idelalisib, umbrelasib, CB-839, fludarabine, or thalidomide; or a combination thereof.
217. The method of any one of claims 209-216, wherein the anti-cancer therapy comprises dexamethasone.

218. The method of any one of claims 209-216, wherein the anti-cancer therapy comprises ibrutinib.
219. The method of any one of claims 209-216, wherein the anti-cancer therapy comprises ibrutinib and rituximab.
220. The method of any one of claims 209-216, wherein the anti-cancer therapy comprises bendamustine.
221. The method of any one of claims 209-216, wherein the anti-cancer therapy comprises bendamustine and rituximab.
222. The method of any one of claims 209-216, wherein the anti-cancer therapy comprises bortezomib.
223. The method of any one of claims 209-216, wherein the anti-cancer therapy comprises bortezomib and dexamethasone.
224. The method of any one of claims 209-216, wherein the anti-cancer therapy comprises bortezomib and rituximab.
225. The method of any one of claims 209-216, wherein the anti-cancer therapy comprises bortezomib, rituximab, and dexamethasone.
226. The method of any one of claims 209-216, wherein the anti-cancer therapy comprises chlorambucil.
227. The method of any one of claims 209-216, wherein the anti-cancer therapy comprises cladribine.
228. The method of any one of claims 209-216, wherein the anti-cancer therapy comprises cladribine and rituximab.

229. The method of any one of claims 209-216, wherein the anti-cancer therapy comprises cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab (*i.e.*, CHOP-R).
230. The method of any one of claims 209-216, wherein the anti-cancer therapy comprises cyclophosphamide, prednisone, and rituximab (*i.e.*, CPR).
231. The method of any one of claims 209-216, wherein the anti-cancer therapy comprises fludarabine.
232. The method of any one of claims 209-216, wherein the anti-cancer therapy comprises fludarabine and rituximab.
233. The method of any one of claims 209-216, wherein the anti-cancer therapy comprises fludarabine, cyclophosphamide, and rituximab.
234. The method of any one of claims 209-216, wherein the anti-cancer therapy comprises rituximab.
235. The method of any one of claims 209-216, wherein the anti-cancer therapy comprises rituximab, cyclophosphamide, and dexamethasone (*i.e.*, RCD).
236. The method of any one of claims 209-216, wherein the anti-cancer therapy comprises thalidomide.
237. The method of any one of claims 209-216, wherein the anti-cancer therapy comprises thalidomide and rituximab.
238. The method of any one of claims 209-216, wherein the anti-cancer therapy comprises venetoclax.
239. The method of any one of claims 209-216, wherein the anti-cancer therapy comprises cyclophosphamide, bortezomib, and dexamethasone (*i.e.*, R-CyBorD).

240. The method of any one of claims 209-216, wherein the anti-cancer therapy comprises a hypomethylating agent.
241. The method of any one of claims 1-240, wherein the subject has previously received at least 6 cycles of a hypomethylating agent.
242. The method of any one of claims 1-241, wherein the subject has previously received etoposide chemo-mobilization therapy.
243. The method of any one of claims 1-242, wherein the subject has previously received a bone marrow transplant.
244. The method of any one of claims 1-243, wherein the subject has previously received a hematopoietic cell transplantation.
245. The method of any one of claims 1-244, wherein the subject has previously received a stem cell transplant.
246. The method of any one of claims 1-245, wherein the subject has previously received an autologous stem cell transplant.
247. The method of any one of claims 1-246, wherein the subject has previously received an allogenic stem cell transplant.
248. The method of any one of claims 1-247, wherein the subject has previously received carmustine, etoposide, cytarabine, and melphalan (*i.e.*, BEAM conditioning).
249. The method of any one of claims 1-248, wherein the subject has previously received re-induction therapy.
250. The method of any one of claims 1-249, wherein the subject has previously achieved a partial response.

251. The method of any one of claims 1-250, wherein the subject has previously achieved a good partial response.
252. The method of any one of claims 1-251, wherein the subject has previously achieved a complete response.
253. The method of any one of claims 1-252, wherein the subject has a mutation in RICTOR.
254. The method of claim 253, wherein the subject has a N1065S mutation in RICTOR.
255. The method of any one of claims 1-254, wherein the subject has a mutation in MYD88.
256. The method of claim 255, wherein the subject has an L265P mutation in MYD88.
257. The method of any one of claims 1-256, wherein the subject has a mutation in TET2.
258. The method of any one of claims 1-257, wherein the subject does not have a mutation in CXCR4.
259. The method of any one of claims 1-257, wherein the subject has a mutation in CXCR4.
260. The method of any one of claims 1-259, wherein the subject has a mutation (*e.g.*, an insertion, deletion, loss, or spliceosome mutation) of SF3B1.
261. The method of any one of claims 1-260, wherein the subject has a mutation (*e.g.*, an insertion, deletion, loss, or spliceosome mutation) of U2AF1.
262. The method of any one of claims 1-261, wherein the subject has a mutation (*e.g.*, an insertion, deletion, loss, or internal tandem duplication) of FLT3 kinase.
263. The method of claim 262, wherein the mutation of FLT3 kinase is selected from an internal tandem duplication (ITD); a mutation in D835, F691, K663, or N841; and an ITD in combination with a mutation in D835, F691, K663, or N841.

264. The method of claim 263, wherein the mutation in FLT3 kinase is D835H.
265. The method of claim 263, wherein the mutation in FLT3 kinase is D835V.
266. The method of claim 263, wherein the mutation in FLT3 kinase is D835Y.
267. The method of claim 263, wherein the mutation in FLT3 kinase is K663Q.
268. The method of claim 263, wherein the mutation in FLT3 kinase is N841I.
269. The method of claim 263, wherein the mutation in FLT3 kinase is ITD and D835V.
270. The method of claim 263, wherein the mutation in FLT3 kinase is ITD and F691L.
271. The method of claim 263, wherein the mutation in FLT3 kinase is ITD and D835Y.
272. The method of any one of claims 1-271, wherein the subject has a mutation (*e.g.*, an insertion, deletion, or loss) of STAG2.
273. The method of any one of claims 1-272, wherein the subject has a mutation (*e.g.*, an insertion, deletion, or loss) of DNMT3A.
274. The method of any one of claims 1-273, wherein the subject has a mutation (*e.g.*, an insertion, deletion, or loss) of BCOR.
275. The method of any one of claims 1-274, wherein the subject has a mutation (*e.g.*, an insertion, deletion, or loss) of WT1.
276. The method of any one of claims 1-275, wherein the subject has a mutation (*e.g.*, an insertion, deletion, or loss) of NRAS.
277. The method of any one of claims 1-276, wherein the subject shows early progression.

278. The method of any one of claims 1-277, wherein the subject has not previously received a BTK inhibitor.
279. The method of any one of claims 1-278, wherein following administration of the IRAK4-modifying compound, the subject achieves a partial response.
280. The method of any one of claims 1-279, wherein following administration of the IRAK4-modifying compound, the subject achieves a good partial response.
281. The method of any one of claims 1-279, wherein following administration of the IRAK4-modifying compound, the subject achieves a complete response.
282. The method of any one of claims 1-281, wherein following administration of the IRAK4-modifying compound, the subjects IL-1 induced signaling decreases.
283. The method of any one of claims 1-282, wherein following administration of the IRAK4-modifying compound, the subject's cytokine production decreases.
284. The method of any one of claims 1-283, wherein the IRAK4-modifying compound is administered until disease progression or unacceptable toxicity.
285. The method of any one of claims 209-284, wherein the subject has previously received a BTK inhibitor for the treatment of cancer.