

METHODS OF TREATING KIT POSITIVE CANCERS WITH A MENIN INHIBITOR

FIELD

[0001] This application claims the benefit of U.S. Provisional Application No. 63/600,575, filed November 17, 2023 and U.S. Provisional Application No. 63/710,310, filed October 22, 2024, each of which is incorporated herein by reference.

FIELD

[0002] Provided herein are methods of treating KIT positive cancers with a menin inhibitor, such as ziftomenib, optionally in combination with a KIT inhibitor. Pharmaceutical compositions, kits, and related products are also embodied within this disclosure.

BACKGROUND

[0003] Cancers that are dependent on the receptor tyrosine kinase (RTK), KIT, represent a cross-section of cancer types for which there are limited treatment options coupled with high relapse rates and poor clinical outcomes. KIT is a member of the class III transmembrane RTK class. Dysregulation of KIT can affect cell proliferation, tumor growth, and metastasis in a wide range of cancer types.

[0004] Approximately 2-3% of all cancers include an activating *KIT* (or c-Kit) mutation (such as a point mutation, substitution, or deletion), with gastrointestinal stromal tumor (GIST), lung adenocarcinoma, colon adenocarcinoma, endometrial endometrioid adenocarcinoma, and melanoma showing the highest prevalence. (The AACR Project GENIE Consortium, AACR Project GENIE: Powering precision medicine through an international consortium, Cancer Discovery 2017, 7(8), 818-831.) Activating mutations in *KIT* occur at a rate of about 70-80% of GIST, 35% in systemic mastocytosis, 16% in sarcoma (including 30% in soft tissue sarcoma), 9% in malignant germ cell tumors, 7% in melanoma (including 18% in mucosal melanoma, 12% in acral lentiginous melanoma), 6% in thymic carcinoma, and 6% in glioblastoma. (*Id.*; My Cancer Genome, Biomarkers, KIT Mutation, at <https://www.mycancergenome.org/content/alteration/kit-mutation/>).

[0005] Tyrosine kinase inhibitors (TKIs) that target KIT are currently the only FDA-approved treatment options for KIT positive GIST. Although some promising clinical activity has been observed with imatinib in certain forms of melanoma, KIT inhibitors have not been approved for

treatment of melanoma or other KIT-activated cancers. In KIT positive melanoma, conventional cytotoxic agents alone or in combination with immunologic drugs have shown little benefit.

[0006] Imatinib (imatinib mesylate) is a KIT inhibitor that is FDA-approved for first-line (1L) treatment of adult patients with aggressive systemic mastocytosis (ASM) or with KIT positive unresectable and/or metastatic malignant GIST, or as adjuvant treatment of adult patients following resection of KIT positive GIST. The 1L patients who received imatinib have activating mutations in KIT exon 9 or 11. Although about 80% of GIST patients treated with 1L imatinib show clinical benefit, including an objective response rate (ORR) of about 50% in KIT-mutant unresectable and/or metastatic GIST, up to 90% of patients eventually progress due to the emergence of cellular subpopulations harboring heterogeneous secondary alterations in KIT. In addition, while imatinib can achieve durable responses, with overall survival (OS) of about 50 months, those responses are largely incomplete, with most responding patients achieving at most a partial response (PR) or stable disease (SD) rather than a complete response (CR), and a progression-free survival (PFS) of only about 20 months.

[0007] Sunitinib (sunitinib malate; SUTENT®) and regorafenib (regorafenib monohydrate; STIVARGA®) are multi-kinase inhibitors that target a broader spectrum of altered forms of KIT, including those with secondary alterations, and these agents are approved as second- and third-line (2L and 3L) therapies, respectively. Specifically, sunitinib is approved for treatment of adult patients with GIST after disease progression on or intolerance to imatinib mesylate. Sunitinib targets KIT with mutations in exon 9/11 and exon 13/14. Regorafenib is approved for treatment of locally advanced, unresectable or metastatic GIST in adult patients who have been previously treated with imatinib mesylate and sunitinib malate. Regorafenib targets KIT mutated at exon 9 or 11. The response rates to these agents are generally poor (about 6.8% objective response rate (ORR) for sunitinib and 4.5% for regorafenib) and the clinical benefit is limited (PFS of about 8 months for sunitinib and about 5 months for regorafenib). In addition, sunitinib (sunitinib malate) and regorafenib are associated with more toxicities than imatinib in most GIST patients. Ripretinib (QINLOCK®) is approved for the fourth-line (4L) treatment of adult patients with advanced GIST who have received prior treatment with three or more TKIs, including imatinib, but its efficacy and associated clinical benefit are similarly limited (9.3% ORR and 6.3 months PFS). (Serrano et al., Br. J. Cancer 2019, 120(6), 612–620; Schaefer, E.-M. et al., Am. Soc. Clin. Oncol. Educ. Book 2022, 42, 1-15.) However, physicians employ ripretinib in the 2L setting for sunitinib-intolerant patients, particularly for exon 11 and exon

17/18 mutated disease. Treatment with these agents can induce alterations in several domains of the KIT protein that drive resistance to the TKIs to TKIs that are used in later settings.

SUMMARY

[0008] Due to these limitations in the use of TKIs in KIT positive cancers such as GIST and melanoma, including high rates of relapse and limited durability of response, new therapeutic options are needed to treat these cancers of high unmet need. In particular, there is a significant need for therapeutic options for patients with KIT positive cancers, such as GIST, who are not responding sufficiently to, who are progressing on, or who have failed on imatinib or on one or more lines of treatment with KIT inhibitors.

[0009] In some embodiments, provided herein is a method of treating a KIT positive cancer in an individual comprising administering a menin inhibitor to the individual. In some embodiments, provided herein is a method of treating KIT positive GIST or treating a KIT positive melanoma in an individual comprising administering to the individual a menin inhibitor. In some embodiments, provided herein is a method of enhancing the antitumor activity of a KIT inhibitor in a KIT positive cancer in an individual comprising administering a menin inhibitor and a concomitant KIT inhibitor to the individual. In some embodiments, provided herein is a method of reducing the effective dose of a KIT inhibitor for treating a KIT positive cancer in an individual comprising administering to the individual a menin inhibitor and a concomitant KIT inhibitor, wherein the effective dose of the concomitant KIT inhibitor is lower than the effective dose for the KIT inhibitor without the menin inhibitor. In some embodiments, provided herein is a method of reducing the safety risk of treating an individual with a KIT positive cancer with a KIT inhibitor comprising administering to the individual a menin inhibitor and a concomitant KIT inhibitor, wherein the safety risk of the KIT inhibitor is lower when administered with the menin inhibitor than the safety risk of the KIT inhibitor without the menin inhibitor. In some embodiments, provided herein is a method of reducing the level of KIT in a KIT positive cancer cell comprising contacting the KIT positive cancer cell with a menin inhibitor and a concomitant KIT inhibitor. In some embodiments, provided herein is a method of reducing the level of phosphorylated KIT in a KIT positive cancer cell comprising contacting the KIT positive cancer cell with a menin inhibitor and a concomitant KIT inhibitor. In some embodiments, provided herein is a method of reducing KIT activity in a KIT positive cancer cell comprising contacting the KIT positive cancer cell with a menin inhibitor and a concomitant KIT inhibitor. In some embodiments, provided herein is a method of reducing *KIT* transcription in a KIT positive

cancer cell comprising contacting the KIT positive cancer cell with a menin inhibitor, optionally in combination with a KIT inhibitor. In some embodiments, provided herein is a method of increasing or inducing apoptosis, reducing AKT levels, reducing S6 levels, inhibiting AKT signaling, reducing mTOR, increasing levels of cleaved PARP, reducing ERK1/2, reducing cell proliferation, or decreasing Rb levels, or a combination thereof, in a KIT positive cancer comprising contacting the KIT positive cancer cell with a menin inhibitor, optionally in combination with a KIT inhibitor. In some embodiments, provided herein is a method of increasing or inducing apoptosis, reducing p-AKT levels, reducing p-S6 levels, inhibiting AKT signaling, reducing p-mTOR, increasing levels of cleaved PARP, reducing p-ERK1/2, reducing cell proliferation, or decreasing p-Rb levels, or a combination thereof, in a KIT positive cancer comprising contacting the KIT positive cancer cell with a menin inhibitor, optionally in combination with a KIT inhibitor.

[0010] In some embodiments, the menin inhibitor is a compound of Formula (II-A) or (III-A), or a pharmaceutically acceptable form thereof. In some embodiments, the menin inhibitor is ziftomenib or a pharmaceutically acceptable form thereof.

INCORPORATION BY REFERENCE

[0011] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] FIG. 1: Schematic of the roles of imatinib and the menin-MLL complex in KIT degradation and *KIT* gene transcription. IM: imatinib; P: phosphate; MLL: mixed-lineage leukemia protein (KMT2A); stars: mutation on exon number indicated.

[0013] FIG. 2: Plot of mean tumor volume (TV) over time for GS11331 GIST patient-derived xenograft (PDX) model study of ziftomenib, imatinib, sunitinib, ziftomenib plus imatinib, and ziftomenib plus sunitinib. Dosing stopped on Day 28 as indicated. Error bars represent standard error of the mean (SEM). CR = complete response.

[0014] FIG. 3: Plot of mean TV over time for GS11331 GIST PDX model study of ziftomenib, revumenib, imatinib, regorafenib, ziftomenib (at 0.5X, 1X, or 2X mg/kg doses) plus imatinib, ziftomenib plus regorafenib, and revumenib plus imatinib. Dosing was stopped on Day 28 as indicated. Error bars represent SEM. CR = complete response.

[0015] **FIG. 4:** Plot of extracted data from **FIG. 3** showing mean TV over time for GS11331 GIST PDX model study of ziftomenib (at 2X mg/kg), imatinib, and ziftomenib (at 0.5X, 1X, or 2X mg/kg doses) plus imatinib. Dosing was stopped on Day 28 as indicated. Error bars represent SEM. CR = complete response.

[0016] **FIG. 5:** Plot of extracted data from **FIG. 3** showing mean TV over time for GS11331 GIST PDX model study of ziftomenib, ziftomenib plus imatinib, regorafenib, and ziftomenib plus regorafenib. Dosing was stopped on Day 28 as indicated. Error bars represent SEM. CR = complete response.

[0017] **FIG. 6:** Plot of mean TV over time for GS11331 GIST PDX model study of ziftomenib, imatinib, and ziftomenib plus imatinib. Error bars represent SEM.

[0018] **FIG. 7:** Immunoblot analysis of GS11311 GIST PDX model tumor samples collected on Day 5 of treatment with ziftomenib, imatinib, or ziftomenib plus imatinib.

[0019] **FIG. 8:** Immunoblot analysis of GS11311 GIST PDX model tumor samples collected on Day 8 of treatment with ziftomenib, imatinib, or ziftomenib plus imatinib.

[0020] **FIG. 9:** Plot of mean TV over time for GS5106 GIST PDX model study of ziftomenib, imatinib, and ziftomenib plus imatinib. Error bars represent SEM.

[0021] **FIG. 10:** Plot of mean TV over time for GS5108 GIST PDX model study of ziftomenib, imatinib, and ziftomenib plus imatinib. Error bars represent SEM.

[0022] **FIGS. 11A-B:** Plots of mean TV over time for GS11341 (**FIG. 11A**) and GS11338 (**FIG. 11B**) GIST PDX model studies of ziftomenib, imatinib, and ziftomenib plus imatinib. Error bars represent SEM.

[0023] **FIG. 12:** Plot of mean TV over time for GS11360 GIST PDX model study of ziftomenib, imatinib and ziftomenib plus imatinib. Dosing was stopped on Day 33 and dosing of ziftomenib and imatinib was resumed on Day 43 as indicated. Error bars represent SEM.

[0024] **FIG. 13:** Plot of mean TV over time for GIST-T1 cell line-derived xenograft (CDX) model study of ziftomenib, imatinib, and ziftomenib plus imatinib. Error bars represent SEM. **, $p < 0.01$, t-test between imatinib and the combination.

[0025] **FIGS. 14A-C:** For a GIST-T1 CDX model study of ziftomenib, imatinib, and ziftomenib plus imatinib, plot of mean TV over time (**FIG. 14A**; error bars represent SEM), immunoblot analysis (**FIG. 14B**) and qPCR results for KIT and POLR2A (control) (**FIG. 14C**; error bars represent standard deviation; *, $p < 0.05$; **, $p < 0.01$) of tumor samples collected on Day 7 of dosing.

[0026] **FIGS. 15A-D:** For a GS5108 GIST PCX model pharmacodynamics study of ziftomenib, imatinib, and ziftomenib plus imatinib, plot of mean TV over time (**FIG. 15A**; error bars represent SEM); immunoblot (**FIG. 15B**) and qPCR (**FIG. 15C**; KIT, ETV1, and POLR2A (control); error bars represent standard deviation; no significant difference was observed) analyses of tumor samples collected on Day 8 of dosing, and immunoblot analysis (**FIG. 15D**) of samples collected on Day 5 of dosing.

[0027] **FIGS. 16A and 16B:** Plots of mean TV over time (**FIG. 16A**) and % TV change (Day 0 to Day 28) (**FIG. 16B**) for ME12098 melanoma PDX model study of ziftomenib, imatinib, and ziftomenib plus imatinib. Error bars represent SEM (**FIG. 16A**) or standard deviation (**FIG. 16B**). **** represents $p < 0.0001$.

[0028] **FIGS. 17A-17C:** Plots of mean TV over time (**FIG. 17A**) and % TV change (Day 0 to Day 28) (**FIG. 17B**) for ME3332 melanoma PDX model study of ziftomenib, imatinib, and ziftomenib plus imatinib, and of %TV during tumor regrowth observation period (**FIG. 17C**). Dosing was stopped at Day 27 as indicated. Error bars represent SEM (**FIG. 17A**) or standard deviation (**FIG. 17B**). -100% on the y-axis in **FIG. 17B** indicates complete response as shown. ns = not significant.

[0029] **FIG. 18:** Plot of mean TV over time for ME6928 model study of ziftomenib, imatinib, and ziftomenib plus imatinib. Error bars represent SEM.

[0030] **FIG. 19:** Plot of mean TV over time for ME12172 model study of ziftomenib, imatinib, and ziftomenib plus imatinib. Error bars represent SEM. ns, not significant; *, $p < 0.05$; **, $p < 0.01$.

[0031] **FIG. 20:** Bar chart showing differentially expressed genes in GS5108 GIST and ME12098 melanoma PDX models after five days of treatment with vehicle, ziftomenib, imatinib, and ziftomenib plus imatinib. The x-axis shows the comparison between the groups.

[0032] **FIG. 21:** Gene Set Enrichment Analysis plot showing statistically significantly enriched KEGG pathways (in blue) that change with ziftomenib plus imatinib compared to vehicle in GS5108 GIST model. NES = normalized enrichment score; $-\log(\text{adjp})$ = negative log of adjusted p-value.

DETAILED DESCRIPTION

[0033] KIT positive cancers such as GIST rely on epigenetic regulation of the *KIT* gene and other related genes to promote tumor growth and metastasis. TKIs that inhibit KIT target KIT positive cancer cells by blocking the MEK/MAPK pathway that typically leads to expression of

the transcription factor, ETV1, which is required for growth and survival of KIT positive cancer cells. ETV1 co-localizes with the GIST “pioneer factor” FOXF1 at the *KIT* gene enhancer region to enhance transcription. However, while exposure of KIT positive tumors to a KIT inhibitor, such as imatinib, leads to rapid depletion of ETV1 in a MAPK-dependent manner, overall levels of KIT protein are not depleted.

[0034] Shown in **FIG. 1** is a proposed mechanism by which the combination treatment of ziftomenib and imatinib creates synthetic lethality by targeting the imatinib-resistant KIT oncoprotein (imatinib-resistant mutants such as tumors that have progressed on or are progressing on imatinib treatment, or 2+L KIT mutants) both at the protein level and at the gene expression level.

[0035] The receptor tyrosine kinase KIT (blue parallel rectangle pairs) is continuously internalized and recycled by lysosomal degradation. When KIT is activated and auto-phosphorylated (“P” circles), this lysosomal-mediated recycling process is mediated by the E3 ubiquitin ligase Cbl (not shown), which recognizes the auto-phosphorylation sites. This auto-regulation mechanism forces the constitutively active KIT to be internalized and degraded (recycled) more rapidly, making oncogenic KIT activity more dependent on the replenishment of KIT protein levels in GIST cells through other mechanisms. It has been reported that the upregulation of *KIT* gene transcription mediated by epigenetic machineries such as the menin/MLL complex may play an important role in GIST cells, in part due to the transcriptional demand required to resupply rapidly recycled KIT proteins (Masson et al., Biochem J. 2006, 399, 59-67; Hemming et al., Cancer Discov. 2022, 12(7), 1804-1823). In this context, menin (green ovals) acts as a scaffold protein and, in a complex with MLL1 (orange ovals), plays an important role in regulating *KIT* gene transcription.

[0036] Upon treatment with imatinib, KIT positive cells, which typically have exon 9 and/or 11 *KIT* mutations, acquire secondary mutations in exons 13 and 17 that encode for secondary alterations in KIT; these perturbations render the cells resistant to imatinib (green stars). Although imatinib does not inhibit the enzymatic activity of these imatinib-resistant KIT proteins, it still can bind to KIT proteins bearing secondary mutations (in some instances, with the exception of the T670 mutation in exon 14). It was reported that imatinib-binding accelerates KIT degradation by displacing the juxtamembrane loop and reducing KIT protein stability (D'allard et al., PLOS One 2013, 8(4), e60961). In the presence of imatinib in imatinib-resistant cells, KIT recycling/degradation is accelerated further, which forces the cells to become critically dependent on the efficient replenishment of KIT proteins through the robust

transcriptional upregulation of *KIT*. As noted above, the menin/MLL complex is found at the promoter of the *KIT* gene, and this complex likely becomes a crucial contributor in sustaining the expression of secondary KIT mutant proteins in the presence of imatinib. Thus, the accelerated degradation of KIT protein in imatinib-resistant cells in the presence of imatinib leads to a critical depletion of total KIT and drives increased dependence on the menin-mediated transcription pathway.

[0037] As explained above, imatinib monotherapy may create a vulnerability in KIT positive cancer cells by forcing tumors into a state of critical dependence on the epigenetic upregulation of *KIT* gene transcription. Upon exposure of KIT positive tumor cells bearing secondary mutations with a menin inhibitor (such as ziftomenib) and imatinib, the menin inhibitor targets the epigenetic machinery at the *KIT* gene promoter and causes the collapse of *KIT* gene expression. As the KIT protein in these imatinib-resistant cells is already subject to rapid degradation, downregulation of *KIT* transcription induced by menin inhibition causes an acute crisis of KIT expression in KIT positive tumor cells. This overall depletion of KIT, the key oncogenic driver in these tumors, leads to robust tumor regressions. As reported in the Examples, such robust tumor regressions were observed in multiple models of imatinib-resistant GIST upon exposure to ziftomenib and imatinib.

[0038] In some embodiments, provided herein is a method of treating a KIT positive cancer in an individual comprising administering a menin inhibitor to the individual. In some embodiments, the method comprises administering a concomitant KIT inhibitor to the individual. In some embodiments, the method comprises administering an effective amount of the menin inhibitor. In some embodiments, the method comprises administering an effective amount of the concomitant KIT inhibitor. In some embodiments, the concomitant KIT inhibitor is imatinib, sunitinib, regorafenib, ripretinib, dasatinib, avapritinib, masitinib, or nilotinib, or a pharmaceutically acceptable form thereof. In some embodiments, the concomitant KIT inhibitor is imatinib or a pharmaceutically acceptable form thereof, optionally imatinib mesylate. In some embodiments, the concomitant KIT inhibitor is sunitinib or a pharmaceutically acceptable form thereof, optionally sunitinib malate. In some embodiments, the concomitant KIT inhibitor is regorafenib or ripretinib, or a pharmaceutically acceptable form thereof.

[0039] In some embodiments, the KIT positive cancer is unresectable, recurrent, progressive, and/or metastatic, or has been resected, e.g., by surgery, prior to administering the menin inhibitor and the concomitant KIT inhibitor (e.g., adjuvant setting). In some embodiments, the KIT positive cancer is resectable or becomes resectable from the methods described herein

(neoadjuvant setting). In some embodiments, the KIT positive cancer is unresectable or metastatic. In some embodiments, the KIT positive cancer has relapsed after treatment with a prior KIT inhibitor. In some embodiments, the KIT positive cancer has relapsed after one line of treatment with the prior KIT inhibitor. In some embodiments, the KIT positive cancer is locally advanced. In some embodiments, the KIT positive cancer is intermediate risk or is high risk per NCCN Guidelines (Version 2.2024; Predictors of GIST Biologic Risk), and College of American Pathologists (Protocol for the Examination of Resection Specimens from Patients with Gastrointestinal Stromal Tumor, v. 4.2.0.0, June 2021, page 10), e.g., for GIST or gastric GIST or non-gastric GIST, based on tumor size (e.g., greater than 2, 5, or 10 cm), mitotic rate (e.g., greater than 5 mitoses/50 high-power fields), metastasis rate (e.g., at least 10% or at least 20% or at least 50%), tumor location (gastric, duodenum, jejunum/ileum, rectum), or KIT mutation profile (mutations in exons 9, 11, 13, 14, 17, 18). In some embodiments, the prior KIT inhibitor is imatinib, sunitinib, regorafenib, ripretinib, dasatinib, avapritinib, masitinib, or nilotinib, or a pharmaceutically acceptable form thereof. In some embodiments, the prior KIT inhibitor and the concomitant KIT inhibitor are the same. In some embodiments, the prior KIT inhibitor is imatinib or a pharmaceutically acceptable form thereof, optionally imatinib mesylate. In some embodiments, the KIT positive cancer has relapsed after, or failed, or progressed on, or responded insufficiently to treatment with a prior KIT inhibitor, optionally wherein:

- (a) treatment with the prior KIT inhibitor comprises one line of treatment with imatinib or a pharmaceutically acceptable form thereof;
- (b) treatment with the prior KIT inhibitor comprises two or three lines of treatment with imatinib, sunitinib, regorafenib, ripretinib, dasatinib, avapritinib, masitinib, nilotinib, or cabozantinib, or a pharmaceutically acceptable form thereof; or
- (c) the KIT positive cancer is newly diagnosed or untreated.

[0040] In some embodiments, the KIT positive cancer is progressing or is in stable disease on the prior KIT inhibitor, e.g., imatinib. In some embodiments, the KIT positive cancer achieved a response of stable disease, partial response, or complete response on the prior KIT inhibitor. In some embodiments, the KIT positive cancer achieved a response of stable disease or partial response on the prior KIT inhibitor. In some embodiments, the KIT positive cancer achieved clinical benefit (at least stable disease) on the prior KIT inhibitor. In some embodiments, the KIT positive cancer has achieved clinical benefit (at least stable disease, for example, stable disease, partial response, or complete response, or any combination thereof) lasting for at least 4 weeks, at least 8 weeks, at least 12 weeks, at least 16 weeks, at least 20 weeks, at least 24 weeks,

or at least 6 months, or at least 9 months, or at least 12 months, prior to administering the menin inhibitor and the concomitant KIT inhibitor. In such situations, treatment with the combination increases the time to progression or progression-free survival. In some embodiments, the prior KIT inhibitor and concomitant KIT inhibitor are the same, and there is no break in dosing (i.e., the menin inhibitor is added to the KIT inhibitor regimen without a wash-out period, which would increase risk of progression).

[0041] In some embodiments, the KIT positive cancer is progressing on or progressed on a prior KIT inhibitor. In some embodiments, the KIT positive cancer achieved clinical benefit (stable disease, partial response, or complete response) on the prior KIT inhibitor and subsequently progressed on the prior KIT inhibitor. In some embodiments, the prior KIT inhibitor and concomitant KIT inhibitor are the same, and there is no break in dosing (i.e., the menin inhibitor is added to the KIT inhibitor regimen without a wash-out period, which could increase rate of progression).

[0042] In some embodiments, the menin inhibitor and the concomitant KIT inhibitor are administered as adjuvant therapy. In some embodiments, the menin inhibitor and the concomitant KIT inhibitor are administered as neoadjuvant therapy. In some embodiments, the menin inhibitor and the concomitant KIT inhibitor are administered in combination with radiation therapy (e.g., before, during the same period, or after).

[0043] In some embodiments, the KIT positive cancer has progressed/relapsed after at least two lines of treatment with prior KIT inhibitors, or after at least three lines of treatment with prior KIT inhibitors, or after two lines of treatment with prior KIT inhibitors, or after three lines of treatment with prior KIT inhibitors. In some embodiments, the prior KIT inhibitors are independently selected from imatinib, sunitinib, regorafenib, ripretinib, dasatinib, avapritinib, masitinib, and nilotinib, and pharmaceutically acceptable forms thereof. In some embodiments, one of the prior KIT inhibitors is imatinib or a pharmaceutically acceptable form thereof, optionally imatinib mesylate. In some embodiments, one of the prior KIT inhibitors is sunitinib, or pharmaceutically acceptable forms thereof, optionally sunitinib malate.

[0044] In some embodiments, the KIT positive cancer is refractory to treatment with a prior KIT inhibitor. In some embodiments, the prior KIT inhibitor is imatinib and/or sunitinib, or a pharmaceutically acceptable form thereof, optionally imatinib mesylate and/or sunitinib malate.

[0045] In some embodiments, provided herein is a method of treating KIT positive GIST or melanoma in an individual comprising administering to the individual a menin inhibitor. In some embodiments, the KIT positive GIST or melanoma comprises KIT with an activating KIT

alteration, wherein the activating KIT alteration is encoded by a *KIT* mutation in exon 9 or exon 11. In some embodiments, the method comprises administering a concomitant KIT inhibitor to the individual. In some embodiments, the concomitant KIT inhibitor is selected from imatinib, sunitinib, ripretinib, regorafenib, dasatinib, avapritinib, masitinib, and nilotinib, and pharmaceutically acceptable forms thereof. In some embodiments, the concomitant KIT inhibitor is imatinib or sunitinib, or a pharmaceutically acceptable form thereof, optionally imatinib mesylate or sunitinib malate. In some embodiments, the GIST or melanoma has relapsed after treatment with or is refractory to a prior KIT inhibitor. In some embodiments, wherein the prior KIT inhibitor is imatinib or a pharmaceutically acceptable form thereof, optionally imatinib mesylate. In some embodiments, the GIST or melanoma comprises KIT with a secondary KIT inhibitor-resistant alteration, optionally wherein the secondary KIT inhibitor-resistant alteration is an imatinib-resistant alteration. In some embodiments, the concomitant KIT inhibitor is ripretinib. In some embodiments, the GIST was previously treated with a prior KIT inhibitor, for example, imatinib, and the concomitant KIT inhibitor is ripretinib. In some embodiments, the GIST or melanoma has relapsed after, or failed, or progressed on, or responded insufficiently to treatment with a prior KIT inhibitor, optionally wherein:

- (a) treatment with the prior KIT inhibitor comprises one line of treatment with imatinib or a pharmaceutically acceptable form thereof;
- (b) treatment with the prior KIT inhibitor comprises two or three lines of treatment with imatinib, sunitinib, regorafenib, ripretinib, dasatinib, avapritinib, masitinib, nilotinib, or cabozantinib, or a pharmaceutically acceptable form thereof; or
- (c) the GIST or melanoma is newly diagnosed or untreated.

[0046] In some embodiments, the administering reduces the level of KIT in the KIT positive cancer, GIST, or melanoma. In some embodiments, the level of KIT is reduced by at least 50%, or at least 60%, or at least 70%, or at least 75%, or at least 80%, or at least 85%, or at least 90%, or at least 95%. In some embodiments, the administering reduces *KIT* transcription in the KIT positive cancer, GIST, or melanoma. In some embodiments, the *KIT* transcription is reduced by at least 50%, or at least 60%, or at least 70%, or at least 75%, or at least 80%, or at least 85%, or at least 90%, or at least 95%. In some embodiments, KIT levels and *KIT* transcription are measured using methods known in the art, for example, the methods shown in the Examples.

[0047] In some embodiments, provided herein is a method of reducing the effective amount of a KIT inhibitor for treating a KIT positive cancer in an individual comprising administering to the individual a menin inhibitor and a concomitant KIT inhibitor, wherein the effective amount

of the concomitant KIT inhibitor is lower than the effective amount for the KIT inhibitor without the menin inhibitor. In some embodiments, the effective amount is reduced by at least 10%, or at least 20%, or at least 30%, or at least 40%, or at least 50% by mass.

[0048] In some embodiments, provided herein is a method of reducing the safety risk of treating an individual with a KIT positive cancer with a KIT inhibitor comprising administering to the individual a menin inhibitor and a concomitant KIT inhibitor, wherein the safety risk of the KIT inhibitor is lower when administered with the menin inhibitor than the safety risk of the KIT inhibitor administered without the menin inhibitor. In some embodiment, the reducing comprises reducing the incidence of or rate of at least one adverse event. In some embodiments, the adverse event is selected from edema, fluid retention, cytopenias (e.g., anemia, neutropenia, thrombocytopenia), congestive heart failure, left ventricular dysfunction, hepatotoxicity, hemorrhage, gastrointestinal perforation, nausea, vomiting, muscle cramps, musculoskeletal pain, diarrhea, rash, fatigue, abdominal pain, decreased appetite, hypertension, infection, dysphonia, hyperbilirubinemia, fever, and mucositis.

[0049] In some embodiments, provided herein is a method of reducing the level of KIT in a KIT positive cancer cell comprising contacting the KIT positive cancer cell with a menin inhibitor and a concomitant KIT inhibitor. In some embodiments, the contacting reduces the level of KIT by at least 50%, or at least 60%, or at least 70%, or at least 75%, or at least 80%, or at least 85%, or at least 90%, or at least 95%.

[0050] In some embodiments, provided herein is a method of reducing the level of phosphorylated KIT in a KIT positive cancer cell comprising contacting the KIT positive cancer cell with a menin inhibitor and a concomitant KIT inhibitor. In some embodiments, the contacting reduces the level of phosphorylated KIT by at least 50%, or at least 60%, or at least 70%, or at least 75%, or at least 80%, or at least 85%, or at least 90%, or at least 95%.

[0051] In some embodiments, provided herein is a method of reducing KIT activity in a KIT positive cancer cell comprising contacting the KIT positive cancer cell with a menin inhibitor and a concomitant KIT inhibitor. In some embodiments, the contacting reduces the level of KIT activity by at least 50%, or at least 60%, or at least 70%, or at least 75%, or at least 80%, or at least 85%, or at least 90%, or at least 95%.

[0052] In some embodiments, provided herein is a method of reducing *KIT* transcription in a KIT positive cancer cell comprising contacting the KIT positive cancer cell with a menin inhibitor, optionally in combination with a KIT inhibitor. In some embodiments, the contacting

reduces *KIT* transcription by at least 50%, or at least 60%, or at least 70%, or at least 75%, or at least 80%, or at least 85%, or at least 90%, or at least 95%.

[0053] In some embodiments, provided herein is a method of increasing or inducing apoptosis, reducing AKT levels, reducing S6 levels, inhibiting AKT signaling, reducing mTOR, increasing levels of cleaved PARP, reducing ERK1/2, reducing cell proliferation, or decreasing Rb levels, or a combination thereof, in a KIT positive cancer comprising contacting the KIT positive cancer cell with a menin inhibitor, optionally in combination with a KIT inhibitor. In some embodiments, provided herein is a method of increasing or inducing apoptosis, reducing p-AKT levels, reducing p-S6 levels, inhibiting AKT signaling, reducing p-mTOR, increasing levels of cleaved PARP, reducing p-ERK1/2, reducing cell proliferation, or decreasing p-Rb levels, or a combination thereof, in a KIT positive cancer comprising contacting the KIT positive cancer cell with a menin inhibitor, optionally in combination with a KIT inhibitor. In some embodiments, these changes are measured using methods known in the art, such as immunoblot (e.g., Western blot) of signaling markers or markers of cell death.

[0054] In some embodiments, the individual has had a resection of the KIT positive cancer and the concomitant KIT inhibitor is an adjuvant treatment. In some embodiments, the tumor is unresectable and the individual is treated with the menin inhibitor and the concomitant KIT inhibitor until the tumor becomes resectable, and the individual is then treated with surgery (neoadjuvant setting).

[0055] In some embodiments, the menin inhibitor and the concomitant KIT inhibitor exhibit a synergistic effect. In some embodiments, the synergistic effect is in an efficacy or safety parameter, such as rate of response (e.g., clinical benefit rate (CBR), CR rate, PR rate, SD rate, duration of response, time to progression, ORR, PFS, OS) or rate of one or more adverse events. In some embodiments, the combination of the menin inhibitor and the concomitant KIT inhibitor provides an improved rate of response or a reduced rate of one or more adverse events relative to standard of care therapy or relative to either agent alone. In some embodiments, where the prior KIT inhibitor and the concomitant KIT inhibitor are the same (e.g., imatinib), the addition of the menin inhibitor increases the duration of response of the KIT positive cancer to the prior KIT inhibitor. In some embodiments, the prior KIT inhibitor is imatinib and the concomitant KIT inhibitor is sunitinib, ripretinib, or regorafenib, the combination treatment provides an improvement (e.g., in activity and/or safety) compared to the concomitant KIT inhibitor alone in the same setting. For example, in some embodiments, the combination of ziftomenib and sunitinib in the second-line setting after first-line imatinib provides improved results compared

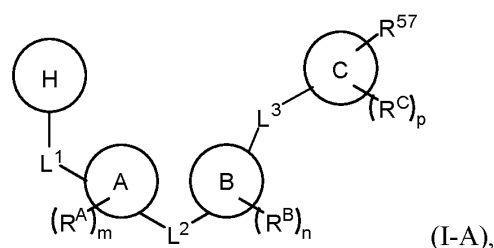
to sunitinib alone in the same setting. In some embodiments, the combination of ziftomenib and ripretinib in the second-line setting after first-line imatinib provides improved results compared to ripretinib alone in the second-line setting. In some embodiments, the individual has not been treated previously with a KIT inhibitor, and the combination of the menin inhibitor and the concomitant KIT inhibitor provides an improved rate of response (e.g., one or more of CBR, ORR, CR rate, PR rate, SD rate, DOR, PFS, and OS) than the KIT inhibitor produces as monotherapy in the same setting (e.g., 1L). For example, in some embodiments, the individual is treated in the 1L setting with the menin inhibitor and the concomitant KIT inhibitor, with an improved response rate relative to the same KIT inhibitor as monotherapy in the 1L setting (e.g., imatinib).

[0056] In some embodiments, the menin inhibitor is a compound of Formula (I-A), (I-B), (II-A), (III-A), or (IV-B), or a pharmaceutically acceptable form thereof. In some embodiments, wherein the menin inhibitor is ziftomenib or a pharmaceutically acceptable form thereof.

Menin Inhibitors

[0057] In some embodiments, the menin inhibitor is a menin inhibitor described in any of U.S. Patent Nos. 8,993,552, 9,216,993, 9,505,781, 9,505,782, 10,077,271, 10,160,769, 10,174,041, 10,246,464, 10,588,907, 10,752,639, 10,781,218, 11,542,248, 11,555,041, 11,649,251, 11,673,898, or RE49,687, each of which disclosure is incorporated by reference herein

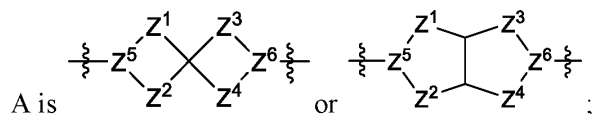
[0058] In some embodiments of the method described herein, the menin inhibitor is a compound of Formula (I-A):



or a pharmaceutically acceptable form thereof, wherein:

- (a) H is selected from C₅₋₁₂ carbocycle and 5- to 12-membered heterocycle, each of which is optionally substituted with one or more R⁵⁰;
- A is selected from bond, C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle;
- B is selected from C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle; and
- C is 3- to 12-membered heterocycle; or

(b) H is selected from C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle;



each of Z¹, Z², Z³, and Z⁴ is independently selected from -C(R^{A1})(R^{A2})-, -C(R^{A1})(R^{A2})-C(R^{A1})(R^{A2})-, -C(O)-, and -C(R^{A1})(R^{A2})-C(O)-, wherein no more than one of Z¹, Z², Z³, and Z⁴ is -C(O)- or -C(R^{A1})(R^{A2})-C(O)-;

R^{A1} is, at each occurrence, independently selected from hydrogen and R⁵⁰;

R^{A2} is, at each occurrence, independently selected from hydrogen and R⁵⁰;

each of Z⁵ and Z⁶ is independently selected from -C(H)- and -N-;

B is selected from C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle; and

C is selected from bond, C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle;

L¹, L², and L³ are each independently selected from bond, -O-, -S-, -N(R⁵¹)-, -N(R⁵¹)CH₂-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)O-, -C(O)N(R⁵¹)-, -C(O)N(R⁵¹)C(O)-, -C(O)N(R⁵¹)C(O)N(R⁵¹)-, -N(R⁵¹)C(O)-, -N(R⁵¹)C(O)N(R⁵¹)-, -N(R⁵¹)C(O)O-, -OC(O)N(R⁵¹)-, -C(NR⁵¹)-, -N(R⁵¹)C(NR⁵¹)-, -C(NR⁵¹)N(R⁵¹)-, -N(R⁵¹)C(NR⁵¹)N(R⁵¹)-, -S(O)₂-, -OS(O)-, -S(O)O-, -S(O)-, -OS(O)₂-, -S(O)₂O-, -N(R⁵¹)S(O)₂-, -S(O)₂N(R⁵¹)-, -N(R⁵¹)S(O)-, -S(O)N(R⁵¹)-, -N(R⁵¹)S(O)₂N(R⁵¹)-, and -N(R⁵¹)S(O)N(R⁵¹)-; and alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, wherein each of the alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene is optionally substituted with one or more R⁵⁰, wherein two R⁵⁰ groups attached to the same atom or different atoms of any one of L¹, L², or L³ can together optionally form a bridge or ring;

R^A, R^B, and R^C are each independently selected at each occurrence from R⁵⁰, or two R^A groups, two R^B groups, or two R^C groups attached to the same atom or different atoms can together optionally form a bridge or ring;

m, n, and p are each independently an integer from 0 to 6;

R⁵⁰ is independently selected at each occurrence from:

halogen, -NO₂, -CN, -OR⁵², -SR⁵², -N(R⁵²)₂, -NR⁵³R⁵⁴, -S(=O)R⁵², -S(=O)₂R⁵², -S(=O)₂N(R⁵²)₂, -S(=O)₂NR⁵³R⁵⁴, -NR⁵²S(=O)₂R⁵², -NR⁵²S(=O)₂N(R⁵²)₂, -NR⁵²S(=O)₂NR⁵³R⁵⁴, -C(O)R⁵², -C(O)OR⁵², -OC(O)R⁵², -OC(O)OR⁵², -OC(O)N(R⁵²)₂, -OC(O)NR⁵³R⁵⁴, -NR⁵²C(O)R⁵², -NR⁵²C(O)OR⁵², -NR⁵²C(O)N(R⁵²)₂, -NR⁵²C(O)NR⁵³R⁵⁴, -C(O)N(R⁵²)₂, -C(O)NR⁵³R⁵⁴, -P(O)(OR⁵²)₂, -

$P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$,
 $-P(O)(NR^{52})(OR^{52})$, and $-P(O)(NR^{52})_2$; or two R^{50} groups attached to the same atom
 taken together form $=O$, $=S$, or $=N(R^{52})$;

C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl, each of which is independently optionally
 substituted at each occurrence with one or more substituents selected from halogen,
 $-NO_2$, $-CN$, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$,
 $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$,
 $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$,
 $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$,
 $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-$
 $P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$,
 $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, $=O$, $=S$, $=N(R^{52})$, C_{3-12} carbocycle, and 3- to 12-
 membered heterocycle; and

C_{3-12} carbocycle and 3- to 12-membered heterocycle, wherein each C_{3-12} carbocycle and 3- to
 12-membered heterocycle in R^{50} is independently optionally substituted with one or
 more substituents selected from halogen, $-NO_2$, $-CN$, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$,
 $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$, $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$,
 $-NR^{52}S(=O)_2N(R^{52})_2$, $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$,
 $-OC(O)OR^{52}$, $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$,
 $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$,
 $-P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$,
 $-P(O)(NR^{52})(OR^{52})$, $-P(O)(NR^{52})_2$, $=O$, $=S$, $=N(R^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6}
 alkenyl, and C_{2-6} alkynyl;

R^{51} is independently selected at each occurrence from:

hydrogen, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$;

C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, each of which is independently optionally
 substituted at each occurrence with one or more substituents selected from halogen,
 $-NO_2$, $-CN$, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$,
 $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$,
 $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$,
 $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$,
 $-NR^{52}C(O)N(R^{52})_2$, $-NR^{52}C(O)NR^{53}R^{54}$, $-C(O)N(R^{52})_2$, $-C(O)NR^{53}R^{54}$, $-P(O)(OR^{52})_2$, $-$
 $P(O)(R^{52})_2$, $-P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$,

-P(O)(NR⁵²)(OR⁵²), -P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle; and

C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle,

wherein each C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle in R⁵¹ is independently

optionally substituted with one or more substituents selected from halogen,

-NO₂, -CN, -OR⁵², -SR⁵², -N(R⁵²)₂, -NR⁵³R⁵⁴, -S(=O)R⁵², -S(=O)₂R⁵²,

-S(=O)₂N(R⁵²)₂, -S(=O)₂NR⁵³R⁵⁴, -NR⁵²S(=O)₂R⁵², -NR⁵²S(=O)₂N(R⁵²)₂,

-NR⁵²S(=O)₂NR⁵³R⁵⁴, -C(O)R⁵², -C(O)OR⁵², -OC(O)R⁵², -OC(O)OR⁵²,

-OC(O)N(R⁵²)₂, -OC(O)NR⁵³R⁵⁴, -NR⁵²C(O)R⁵², -NR⁵²C(O)OR⁵²,

-NR⁵²C(O)N(R⁵²)₂, -NR⁵²C(O)NR⁵³R⁵⁴, -C(O)N(R⁵²)₂, -C(O)NR⁵³R⁵⁴, -P(O)(OR⁵²)₂, -

P(O)(R⁵²)₂, -P(O)(OR⁵²)(R⁵²), -P(O)(NR⁵²)(R⁵²), -NR⁵²P(O)(R⁵²),

-P(O)(NR⁵²)(OR⁵²), -P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆

alkenyl, and C₂₋₆ alkynyl;

R⁵² is independently selected at each occurrence from hydrogen; and C₁₋₂₀ alkyl, C₂₋₂₀ alkenyl,

C₂₋₂₀ alkynyl, 1- to 6-membered heteroalkyl, C₃₋₁₂ carbocycle, and 3- to 12-membered

heterocycle, each of which is optionally substituted by halogen, -CN, -NO₂,

-NH₂, -NHCH₃, -NHCH₂CH₃, =O, -OH, -OCH₃, -OCH₂CH₃, C₃₋₁₂ carbocycle, or 3- to 6-membered heterocycle;

R⁵³ and R⁵⁴ are taken together with the nitrogen atom to which they are attached to form a heterocycle; and

R⁵⁷ is selected from:

halogen, -NO₂, -CN, -SR⁵², -NR⁵³R⁵⁴, -S(=O)R⁵², -S(=O)₂R⁵², -S(=O)₂N(R⁵²)₂,

-S(=O)₂NR⁵³R⁵⁴, -NR⁵²S(=O)₂R⁵², -NR⁵²S(=O)₂N(R⁵²)₂, -NR⁵²S(=O)₂NR⁵³R⁵⁴,

-C(O)OR⁵², -OC(O)R⁵², -OC(O)OR⁵², -OC(O)N(R⁵²)₂, -OC(O)NR⁵³R⁵⁴,

-NR⁵²C(O)OR⁵², -NR⁵²C(O)N(R⁵²)₂, -NR⁵²C(O)NR⁵³R⁵⁴, -C(O)NH(C₁₋₆ alkyl),

-C(O)NR⁵³R⁵⁴, -P(O)(OR⁵²)₂, -P(O)(R⁵²)₂, -P(O)(OR⁵²)(R⁵²), -P(O)(NR⁵²)(R⁵²),

-NR⁵²P(O)(R⁵²), -P(O)(NR⁵²)(OR⁵²), -P(O)(NR⁵²)₂, =S, =N(R⁵²); and

C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, and C₂₋₁₀ alkynyl, each of which is independently substituted at

each occurrence with one or more substituents selected from -NO₂, -CN,

-SR⁵², -N(R⁵²)₂, -NR⁵³R⁵⁴, -S(=O)R⁵², -S(=O)₂R⁵², -S(=O)₂N(R⁵²)₂, -S(=O)₂NR⁵³R⁵⁴, -

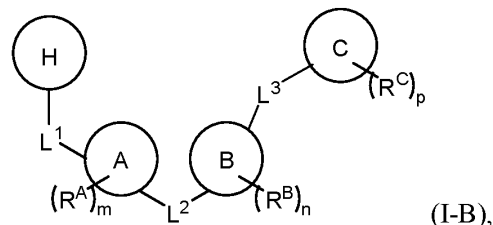
NR⁵²S(=O)₂R⁵², -NR⁵²S(=O)₂N(R⁵²)₂, -NR⁵²S(=O)₂NR⁵³R⁵⁴, -C(O)R⁵², -C(O)OR⁵²,

-OC(O)R⁵², -OC(O)OR⁵², -OC(O)N(R⁵²)₂, -OC(O)NR⁵³R⁵⁴, -NR⁵²C(O)R⁵²,

-NR⁵²C(O)OR⁵², -NR⁵²C(O)N(R⁵²)₂, -NR⁵²C(O)NR⁵³R⁵⁴, -P(O)(OR⁵²)₂, -P(O)(R⁵²)₂, -

$P(O)(OR^{52})(R^{52})$, $-P(O)(NR^{52})(R^{52})$, $-NR^{52}P(O)(R^{52})$, $-P(O)(NR^{52})(OR^{52})$,
 $-P(O)(NR^{52})_2$, $=S$, and $=N(R^{52})$.

[0059] In some embodiments, the menin inhibitor is a compound of Formula (I-B):



or a pharmaceutically acceptable form thereof, wherein:

H is selected from C_{5-12} carbocycle and 5- to 12-membered heterocycle, each of which is optionally substituted with one or more R^{50} ;

A, B, and C are each independently selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle;

L^1 and L^2 are each independently selected from bond, $-O-$, $-S-$, $-N(R^{51})-$, $-N(R^{51})CH_2-$, $-C(O)-$, $-C(O)O-$, $-OC(O)-$, $-OC(O)O-$, $-C(O)N(R^{51})-$, $-C(O)N(R^{51})C(O)-$, $-C(O)N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)-$, $-N(R^{51})C(O)N(R^{51})-$, $-N(R^{51})C(O)O-$, $-OC(O)N(R^{51})-$, $-C(NR^{51})-$, $-N(R^{51})C(NR^{51})-$, $-C(NR^{51})N(R^{51})-$, $-N(R^{51})C(NR^{51})N(R^{51})-$, $-S(O)_2-$, $-OS(O)-$, $-S(O)O-$, $-S(O)-$, $-OS(O)_2-$, $-S(O)_2O-$, $-N(R^{51})S(O)_2-$, $-S(O)_2N(R^{51})-$, $-N(R^{51})S(O)-$, $-S(O)N(R^{51})-$, $-N(R^{51})S(O)_2N(R^{51})-$, and $-N(R^{51})S(O)N(R^{51})-$; and alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, wherein each of the alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene is optionally substituted with one or more R^{50} ;

L^3 is selected from alkylene, alkenylene, and alkynylene, each of which is substituted with one or more R^{56} and optionally further substituted with one or more R^{50} ;

R^A , R^B , and R^C are each independently selected at each occurrence from R^{50} ; or two R^A groups, two R^B groups, or two R^C groups attached to the same atom or different atoms can together optionally form a bridge or ring;

m, n, and p are each independently an integer from 0 to 6;

R^{50} is independently selected at each occurrence from:

halogen, $-NO_2$, $-CN$, $-OR^{52}$, $-SR^{52}$, $-N(R^{52})_2$, $-NR^{53}R^{54}$, $-S(=O)R^{52}$, $-S(=O)_2R^{52}$,
 $-S(=O)_2N(R^{52})_2$, $-S(=O)_2NR^{53}R^{54}$, $-NR^{52}S(=O)_2R^{52}$, $-NR^{52}S(=O)_2N(R^{52})_2$,
 $-NR^{52}S(=O)_2NR^{53}R^{54}$, $-C(O)R^{52}$, $-C(O)OR^{52}$, $-OC(O)R^{52}$, $-OC(O)OR^{52}$,
 $-OC(O)N(R^{52})_2$, $-OC(O)NR^{53}R^{54}$, $-NR^{52}C(O)R^{52}$, $-NR^{52}C(O)OR^{52}$,

-NR⁵²C(O)N(R⁵²)₂, -NR⁵²C(O)NR⁵³R⁵⁴, -C(O)N(R⁵²)₂, -C(O)NR⁵³R⁵⁴, -P(O)(OR⁵²)₂, -P(O)(R⁵²)₂, -P(O)(OR⁵²)(R⁵²), -P(O)(NR⁵²)(R⁵²), -NR⁵²P(O)(R⁵²), -P(O)(NR⁵²)(OR⁵²), and -P(O)(NR⁵²)₂, or two R⁵⁰ groups attached to the same atom taken together form =O, =S, or =N(R⁵²);

C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, and C₂₋₁₀ alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, -NO₂, -CN, -OR⁵², -SR⁵², -N(R⁵²)₂, -NR⁵³R⁵⁴, -S(=O)R⁵², -S(=O)₂R⁵², -S(=O)₂N(R⁵²)₂, -S(=O)₂NR⁵³R⁵⁴, -NR⁵²S(=O)₂R⁵², -NR⁵²S(=O)₂N(R⁵²)₂, -NR⁵²S(=O)₂NR⁵³R⁵⁴, -C(O)R⁵², -C(O)OR⁵², -OC(O)R⁵², -OC(O)OR⁵², -OC(O)N(R⁵²)₂, -OC(O)NR⁵³R⁵⁴, -NR⁵²C(O)R⁵², -NR⁵²C(O)OR⁵², -NR⁵²C(O)N(R⁵²)₂, -NR⁵²C(O)NR⁵³R⁵⁴, -C(O)N(R⁵²)₂, -C(O)NR⁵³R⁵⁴, -P(O)(OR⁵²)₂, -P(O)(R⁵²)₂, -P(O)(OR⁵²)(R⁵²), -P(O)(NR⁵²)(R⁵²), -NR⁵²P(O)(R⁵²), -P(O)(NR⁵²)(OR⁵²), -P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle; and

C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle,

wherein each C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle in R⁵⁰ is independently optionally substituted with one or more substituents selected from halogen, -NO₂, -CN, -OR⁵², -SR⁵², -N(R⁵²)₂, -NR⁵³R⁵⁴, -S(=O)R⁵², -S(=O)₂R⁵², -S(=O)₂N(R⁵²)₂, -S(=O)₂NR⁵³R⁵⁴, -NR⁵²S(=O)₂R⁵², -NR⁵²S(=O)₂N(R⁵²)₂, -NR⁵²S(=O)₂NR⁵³R⁵⁴, -C(O)R⁵², -C(O)OR⁵², -OC(O)R⁵², -OC(O)OR⁵², -OC(O)N(R⁵²)₂, -OC(O)NR⁵³R⁵⁴, -NR⁵²C(O)R⁵², -NR⁵²C(O)OR⁵², -NR⁵²C(O)N(R⁵²)₂, -NR⁵²C(O)NR⁵³R⁵⁴, -C(O)N(R⁵²)₂, -C(O)NR⁵³R⁵⁴, -P(O)(OR⁵²)₂, -P(O)(R⁵²)₂, -P(O)(OR⁵²)(R⁵²), -P(O)(NR⁵²)(R⁵²), -NR⁵²P(O)(R⁵²), -P(O)(NR⁵²)(OR⁵²), -P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl;

R⁵¹ is independently selected at each occurrence from:

hydrogen, -C(O)R⁵², -C(O)OR⁵², -C(O)N(R⁵²)₂, -C(O)NR⁵³R⁵⁴,

C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, -NO₂, -CN, -OR⁵², -SR⁵², -N(R⁵²)₂, -NR⁵³R⁵⁴, -S(=O)R⁵², -S(=O)₂R⁵², -S(=O)₂N(R⁵²)₂, -S(=O)₂NR⁵³R⁵⁴, -NR⁵²S(=O)₂R⁵², -NR⁵²S(=O)₂N(R⁵²)₂, -NR⁵²S(=O)₂NR⁵³R⁵⁴, -C(O)R⁵², -C(O)OR⁵², -OC(O)R⁵², -OC(O)OR⁵², -OC(O)N(R⁵²)₂, -OC(O)NR⁵³R⁵⁴, -NR⁵²C(O)R⁵², -NR⁵²C(O)OR⁵²,

-NR⁵²C(O)N(R⁵²)₂, -NR⁵²C(O)NR⁵³R⁵⁴, -C(O)N(R⁵²)₂, -C(O)NR⁵³R⁵⁴, -P(O)(OR⁵²)₂, -P(O)(R⁵²)₂, -P(O)(OR⁵²)(R⁵²), -P(O)(NR⁵²)(R⁵²), -NR⁵²P(O)(R⁵²), -P(O)(NR⁵²)(OR⁵²), -P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle; and

C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle,

wherein each C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle in R⁵¹ is independently

optionally substituted with one or more substituents selected from halogen,

-NO₂, -CN, -OR⁵², -SR⁵², -N(R⁵²)₂, -NR⁵³R⁵⁴, -S(=O)R⁵², -S(=O)₂R⁵², -S(=O)₂N(R⁵²)₂, -S(=O)₂NR⁵³R⁵⁴, -NR⁵²S(=O)₂R⁵², -NR⁵²S(=O)₂N(R⁵²)₂, -NR⁵²S(=O)₂NR⁵³R⁵⁴, -C(O)R⁵², -C(O)OR⁵², -OC(O)R⁵², -OC(O)OR⁵², -OC(O)N(R⁵²)₂, -OC(O)NR⁵³R⁵⁴, -NR⁵²C(O)R⁵², -NR⁵²C(O)OR⁵², -NR⁵²C(O)N(R⁵²)₂, -NR⁵²C(O)NR⁵³R⁵⁴, -C(O)N(R⁵²)₂, -C(O)NR⁵³R⁵⁴, -P(O)(OR⁵²)₂, -P(O)(R⁵²)₂, -P(O)(OR⁵²)(R⁵²), -P(O)(NR⁵²)(R⁵²), -NR⁵²P(O)(R⁵²), -P(O)(NR⁵²)(OR⁵²), -P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl;

R⁵² is independently selected at each occurrence from hydrogen; and C₁₋₂₀ alkyl, C₂₋₂₀ alkenyl,

C₂₋₂₀ alkynyl, 1- to 6-membered heteroalkyl, C₃₋₁₂ carbocycle, and 3- to 12-membered

heterocycle, each of which is optionally substituted by halogen, -CN, -NO₂,

-NH₂, -NHCH₃, -NHCH₂CH₃, =O, -OH, -OCH₃, -OCH₂CH₃, C₃₋₁₂ carbocycle, or 3- to 6-membered heterocycle;

R⁵³ and R⁵⁴ are taken together with the nitrogen atom to which they are attached to form a heterocycle;

R⁵⁶ is independently selected at each occurrence from:

-NO₂, -OR⁵⁹, -SR⁵², -NR⁵³R⁵⁴, -S(=O)R⁵², -S(=O)₂R⁵², -S(=O)₂N(R⁵²)₂, -S(=O)₂NR⁵³R⁵⁴, -NR⁵²S(=O)₂R⁵², -NR⁵²S(=O)₂N(R⁵²)₂, -NR⁵²S(=O)₂NR⁵³R⁵⁴, -C(O)R⁵², -C(O)OR⁵², -OC(O)R⁵², -OC(O)OR⁵², -OC(O)N(R⁵²)₂, -OC(O)NR⁵³R⁵⁴, -NR⁵²C(O)R⁵², -NR⁵²C(O)OR⁵², -NR⁵²C(O)N(R⁵²)₂, -NR⁵²C(O)NR⁵³R⁵⁴, -C(O)N(R⁵²)₂, -C(O)NR⁵³R⁵⁴, -P(O)(OR⁵²)₂, -P(O)(R⁵²)₂, -P(O)(OR⁵²)(R⁵²), -P(O)(NR⁵²)(R⁵²), -NR⁵²P(O)(R⁵²), -P(O)(NR⁵²)(OR⁵²), -P(O)(NR⁵²)₂, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle, or two R⁵⁶ groups attached to the same atom taken together form =O, =S, or =N(R⁵²);

wherein each C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, and C₂₋₁₀ alkynyl in R⁵⁶ is independently optionally substituted at each occurrence with one or more substituents selected from halogen, -

NO₂, -CN, -OR⁵⁹, -SR⁵², -N(R⁵²)₂, -NR⁵³R⁵⁴, -S(=O)R⁵², -S(=O)₂R⁵²,
 -S(=O)₂N(R⁵²)₂, -S(=O)₂NR⁵³R⁵⁴, -NR⁵²S(=O)₂R⁵², -NR⁵²S(=O)₂N(R⁵²)₂,
 -NR⁵²S(=O)₂NR⁵³R⁵⁴, -C(O)R⁵², -C(O)OR⁵², -OC(O)R⁵², -OC(O)OR⁵²,
 -OC(O)N(R⁵²)₂, -OC(O)NR⁵³R⁵⁴, -NR⁵²C(O)R⁵², -NR⁵²C(O)OR⁵²,
 -NR⁵²C(O)N(R⁵²)₂, -NR⁵²C(O)NR⁵³R⁵⁴, -C(O)N(R⁵²)₂, -C(O)NR⁵³R⁵⁴, -P(O)(OR⁵²)₂, -
 P(O)(R⁵²)₂, -P(O)(OR⁵²)(R⁵²), -P(O)(NR⁵²)(R⁵²), -NR⁵²P(O)(R⁵²),
 -P(O)(NR⁵²)(OR⁵²), -P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), C₃₋₁₂ carbocycle, and 3- to 12-
 membered heterocycle;

wherein each C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle in R⁵⁶ is independently
 optionally substituted with one or more substituents selected from halogen,

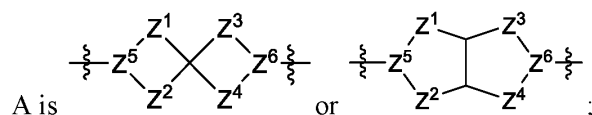
-NO₂, -CN, -OR⁵², -SR⁵², -N(R⁵²)₂, -NR⁵³R⁵⁴, -S(=O)R⁵², -S(=O)₂R⁵²,
 -S(=O)₂N(R⁵²)₂, -S(=O)₂NR⁵³R⁵⁴, -NR⁵²S(=O)₂R⁵², -NR⁵²S(=O)₂N(R⁵²)₂,
 -NR⁵²S(=O)₂NR⁵³R⁵⁴, -C(O)R⁵², -C(O)OR⁵², -OC(O)R⁵², -OC(O)OR⁵²,
 -OC(O)N(R⁵²)₂, -OC(O)NR⁵³R⁵⁴, -NR⁵²C(O)R⁵², -NR⁵²C(O)OR⁵²,
 -NR⁵²C(O)N(R⁵²)₂, -NR⁵²C(O)NR⁵³R⁵⁴, -C(O)N(R⁵²)₂, -C(O)NR⁵³R⁵⁴, -P(O)(OR⁵²)₂, -
 P(O)(R⁵²)₂, -P(O)(OR⁵²)(R⁵²), -P(O)(NR⁵²)(R⁵²), -NR⁵²P(O)(R⁵²),
 -P(O)(NR⁵²)(OR⁵²), -P(O)(NR⁵²)₂, =O, =S, =N(R⁵²), C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆
 alkenyl, and C₂₋₆ alkynyl; and

further wherein R⁵⁶ optionally forms a bond to ring C; and

R⁵⁹ is independently selected at each occurrence from C₁₋₂₀ alkyl, C₂₋₂₀ alkenyl, C₂₋₂₀ alkynyl, 1-
 to 6-membered heteroalkyl, C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle, each of
 which is optionally substituted by halogen, -CN, -NO₂, -NH₂, -NHCH₃, -NHCH₂CH₃, =O, -
 OH, -OCH₃, -OCH₂CH₃, C₃₋₁₂ carbocycle, or 3- to 6-membered heterocycle.

[0060] In some embodiments, for a compound of Formula (I-A) or (I-B), R^C is selected from -
 C(O)R⁵², -S(=O)R⁵², -S(=O)₂R⁵², -S(=O)₂N(R⁵²)₂, -S(=O)₂NR⁵³R⁵⁴, -NR⁵²S(=O)₂R⁵², =O, C₁₋₃
 alkyl, and C₁₋₃ haloalkyl, or two R^C groups attached to different atoms can together form a C₁₋₃
 bridge.

[0061] In some embodiments of Formula (I-B):



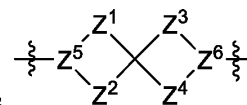
each of Z¹, Z², Z³, and Z⁴ is independently selected from -C(R^{A1})(R^{A2})-, -C(R^{A1})(R^{A2})-
 C(R^{A1})(R^{A2})-, -C(O)-, and -C(R^{A1})(R^{A2})-C(O)-, wherein no more than one of Z¹, Z², Z³,

and Z^4 is $-C(O)-$ or $-C(R^{A1})(R^{A2})-C(O)-$;

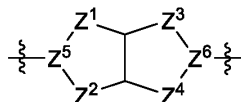
R^{A1} is, at each occurrence, independently selected from hydrogen and R^{50} ;

R^{A2} is, at each occurrence, independently selected from hydrogen and R^{50} ; and

each of Z^5 and Z^6 is independently selected from $-C(H)-$ and $-N-$;

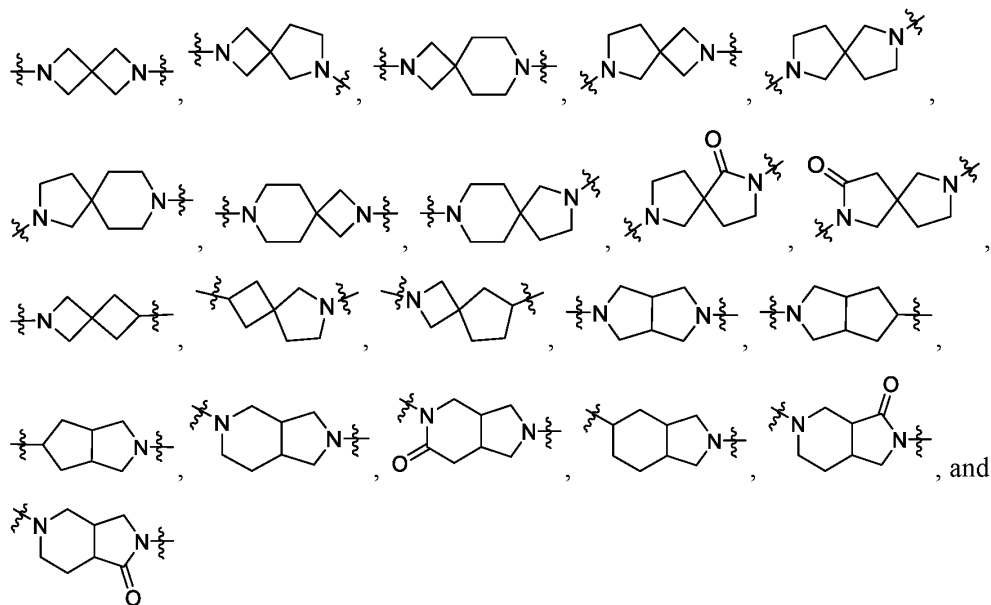


[0062] In some embodiments of Formula (I-A) or Formula (I-B), A is

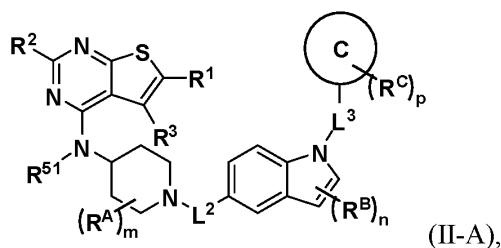


In some embodiments, A is

In some embodiments, A is selected from:



[0063] In some embodiments, the menin inhibitor is a compound of Formula (II-A):



or a pharmaceutically acceptable form thereof, wherein:

C is selected from C_{3-12} carbocycle and 3- to 12-membered heterocycle;

L^2 is selected from bond, $-C(O)-$, $-C(O)O-$, $-C(O)N(R^{51})-$, $-C(O)N(R^{51})C(O)-$,

$-C(O)N(R^{51})C(O)N(R^{51})-$, $-C(NR^{51})-$, $-S(O)_2-$, $-S(O)O-$, $-S(O)-$, $-S(O)_2O-$, $S(O)_2N(R^{51})-$, and

-S(O)N(R⁵¹)-; and alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene, wherein each of the alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, and heteroalkynylene is optionally substituted with one or more R⁵⁰;

L³ is selected from alkylene, alkenylene, and alkynylene, each of which is substituted with one or more R⁵⁶ and optionally further substituted with one or more R⁵⁰;

R¹ and R³ are each independently selected from hydrogen and R⁵⁰;

R² is R⁵⁰;

R^A, R^B, and R^C are each independently selected at each occurrence from R⁵⁰, or two R^A groups, two R^B groups, or two R^C groups attached to the same atom or different atoms can together optionally form a bridge or ring;

m, n, and p are each independently an integer from 0 to 6;

R⁵⁰ is independently selected at each occurrence from:

halogen, -NO₂, -CN, -OR⁵², -SR⁵², -N(R⁵²)₂, -NR⁵³R⁵⁴, -S(=O)R⁵², -S(=O)₂R⁵², -S(=O)₂N(R⁵²)₂, -S(=O)₂NR⁵³R⁵⁴, -NR⁵²S(=O)₂R⁵², -NR⁵²S(=O)₂N(R⁵²)₂, -NR⁵²S(=O)₂NR⁵³R⁵⁴, -C(O)R⁵², -C(O)OR⁵², -OC(O)R⁵², -OC(O)OR⁵², -OC(O)N(R⁵²)₂, -OC(O)NR⁵³R⁵⁴, -NR⁵²C(O)R⁵², -NR⁵²C(O)OR⁵², -NR⁵²C(O)N(R⁵²)₂, -NR⁵²C(O)NR⁵³R⁵⁴, -C(O)N(R⁵²)₂, -C(O)NR⁵³R⁵⁴, -P(O)(OR⁵²)₂, and -P(O)(R⁵²)₂, or two R⁵⁰ groups attached to the same atom taken together form =O, =S, or =N(R⁵²);

C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, and C₂₋₁₀ alkynyl, each of which is independently optionally substituted at each occurrence with one or more substituents selected from halogen, -NO₂, -CN, -OR⁵², -SR⁵², -N(R⁵²)₂, -NR⁵³R⁵⁴, -S(=O)R⁵², -S(=O)₂R⁵², -S(=O)₂N(R⁵²)₂, -S(=O)₂NR⁵³R⁵⁴, -NR⁵²S(=O)₂R⁵², -NR⁵²S(=O)₂N(R⁵²)₂, -NR⁵²S(=O)₂NR⁵³R⁵⁴, -C(O)R⁵², -C(O)OR⁵², -OC(O)R⁵², -OC(O)OR⁵², -OC(O)N(R⁵²)₂, -OC(O)NR⁵³R⁵⁴, -NR⁵²C(O)R⁵², -NR⁵²C(O)OR⁵², -NR⁵²C(O)N(R⁵²)₂, -NR⁵²C(O)NR⁵³R⁵⁴, -C(O)N(R⁵²)₂, -C(O)NR⁵³R⁵⁴, -P(O)(OR⁵²)₂, -P(O)(R⁵²)₂, =O, =S, =N(R⁵²), C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle; and C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle,

wherein each C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle in R⁵⁰ is independently optionally substituted with one or more substituents selected from halogen, -NO₂, -CN, -OR⁵², -SR⁵², -N(R⁵²)₂, -NR⁵³R⁵⁴, -S(=O)R⁵², -S(=O)₂R⁵², -S(=O)₂N(R⁵²)₂, -S(=O)₂NR⁵³R⁵⁴, -NR⁵²S(=O)₂R⁵², -NR⁵²S(=O)₂N(R⁵²)₂, -NR⁵²S(=O)₂NR⁵³R⁵⁴, -C(O)R⁵², -C(O)OR⁵², -OC(O)R⁵², -OC(O)OR⁵²,

-OC(O)N(R⁵²)₂, -OC(O)NR⁵³R⁵⁴, -NR⁵²C(O)R⁵², -NR⁵²C(O)OR⁵²,
 -NR⁵²C(O)N(R⁵²)₂, -NR⁵²C(O)NR⁵³R⁵⁴, -C(O)N(R⁵²)₂, -C(O)NR⁵³R⁵⁴, -P(O)(OR⁵²)₂, -
 P(O)(R⁵²)₂, =O, =S, =N(R⁵²), C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl;

R⁵¹ is independently selected at each occurrence from:

hydrogen, -C(O)R⁵², -C(O)OR⁵², -C(O)N(R⁵²)₂, and -C(O)NR⁵³R⁵⁴; and

C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl, each of which is independently optionally

substituted at each occurrence with one or more substituents selected from halogen,

-NO₂, -CN, -OR⁵², -SR⁵², -N(R⁵²)₂, -NR⁵³R⁵⁴, -S(=O)R⁵², -S(=O)₂R⁵²,

-S(=O)₂N(R⁵²)₂, -S(=O)₂NR⁵³R⁵⁴, -NR⁵²S(=O)₂R⁵², -NR⁵²S(=O)₂N(R⁵²)₂,

-NR⁵²S(=O)₂NR⁵³R⁵⁴, -C(O)R⁵², -C(O)OR⁵², -OC(O)R⁵², -OC(O)OR⁵²,

-OC(O)N(R⁵²)₂, -OC(O)NR⁵³R⁵⁴, -NR⁵²C(O)R⁵², -NR⁵²C(O)OR⁵²,

-NR⁵²C(O)N(R⁵²)₂, -NR⁵²C(O)NR⁵³R⁵⁴, -C(O)N(R⁵²)₂, -C(O)NR⁵³R⁵⁴, -P(O)(OR⁵²)₂, -

P(O)(R⁵²)₂, =O, =S, =N(R⁵²), C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle; and

C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle,

wherein each C₃₋₁₂ carbocycle and 3- to 12-membered heterocycle in R⁵¹ is independently

optionally substituted with one or more substituents selected from halogen,

-NO₂, -CN, -OR⁵², -SR⁵², -N(R⁵²)₂, -NR⁵³R⁵⁴, -S(=O)R⁵², -S(=O)₂R⁵²,

-S(=O)₂N(R⁵²)₂, -S(=O)₂NR⁵³R⁵⁴, -NR⁵²S(=O)₂R⁵², -NR⁵²S(=O)₂N(R⁵²)₂,

-NR⁵²S(=O)₂NR⁵³R⁵⁴, -C(O)R⁵², -C(O)OR⁵², -OC(O)R⁵², -OC(O)OR⁵²,

-OC(O)N(R⁵²)₂, -OC(O)NR⁵³R⁵⁴, -NR⁵²C(O)R⁵², -NR⁵²C(O)OR⁵²,

-NR⁵²C(O)N(R⁵²)₂, -NR⁵²C(O)NR⁵³R⁵⁴, -C(O)N(R⁵²)₂, -C(O)NR⁵³R⁵⁴, -P(O)(OR⁵²)₂, -

P(O)(R⁵²)₂, =O, =S, =N(R⁵²), C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl;

R⁵² is independently selected at each occurrence from hydrogen; and C₁₋₂₀ alkyl, C₂₋₂₀ alkenyl,

C₂₋₂₀ alkynyl, C₁₋₆ heteroalkyl, C₃₋₁₂ carbocycle, and 3- to 12-membered heterocycle, each of

which is optionally substituted by halogen, -CN, -NO₂, -NH₂,

-NHCH₃, -NHCH₂CH₃, =O, -OH, -OCH₃, -OCH₂CH₃, C₃₋₁₂ carbocycle, or 3- to 6-membered heterocycle;

R⁵³ and R⁵⁴ are taken together with the nitrogen atom to which they are attached to form a heterocycle, optionally substituted with one or more R⁵⁰;

R⁵⁶ is independently selected at each occurrence from: -NO₂, -OR⁵⁹, -SR⁵², -NR⁵³R⁵⁴,

-S(=O)R⁵², -S(=O)₂R⁵², -S(=O)₂N(R⁵²)₂, -S(=O)₂NR⁵³R⁵⁴, -NR⁵²S(=O)₂R⁵²,

-NR⁵²S(=O)₂N(R⁵²)₂, -NR⁵²S(=O)₂NR⁵³R⁵⁴, -C(O)R⁵², -C(O)OR⁵², -OC(O)R⁵²,

-OC(O)OR⁵², -OC(O)N(R⁵²)₂, -OC(O)NR⁵³R⁵⁴, -NR⁵²C(O)R⁵², -NR⁵²C(O)OR⁵²,

$-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{R}^{52})_2$, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, or two R^{56} groups attached to the same atom taken together form $=\text{O}$, $=\text{S}$, or $=\text{N}(\text{R}^{52})$;

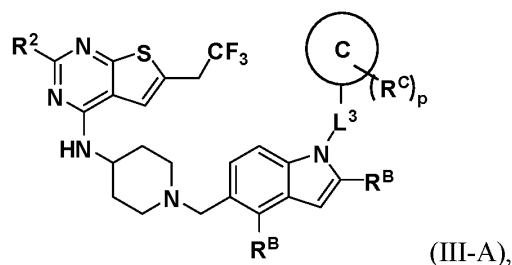
wherein each C_{1-10} alkyl, C_{2-10} alkenyl, and C_{2-10} alkynyl in R^{56} is independently optionally substituted at each occurrence with one or more substituents selected from halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{59}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(=\text{O})\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{OR}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{R}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{3-12} carbocycle, and 3- to 12-membered heterocycle;

wherein each C_{3-12} carbocycle and 3- to 12-membered heterocycle in R^{56} is independently optionally substituted with one or more substituents selected from halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}^{52}$, $-\text{SR}^{52}$, $-\text{N}(\text{R}^{52})_2$, $-\text{NR}^{53}\text{R}^{54}$, $-\text{S}(=\text{O})\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{R}^{52}$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{S}(=\text{O})_2\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{R}^{52}$, $-\text{C}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{R}^{52}$, $-\text{OC}(\text{O})\text{OR}^{52}$, $-\text{OC}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{OC}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{NR}^{52}\text{C}(\text{O})\text{R}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{OR}^{52}$, $-\text{NR}^{52}\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{NR}^{52}\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{C}(\text{O})\text{N}(\text{R}^{52})_2$, $-\text{C}(\text{O})\text{NR}^{53}\text{R}^{54}$, $-\text{P}(\text{O})(\text{OR}^{52})_2$, $-\text{P}(\text{O})(\text{R}^{52})_2$, $=\text{O}$, $=\text{S}$, $=\text{N}(\text{R}^{52})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl; and

further wherein R^{56} optionally forms a bond to ring C; and

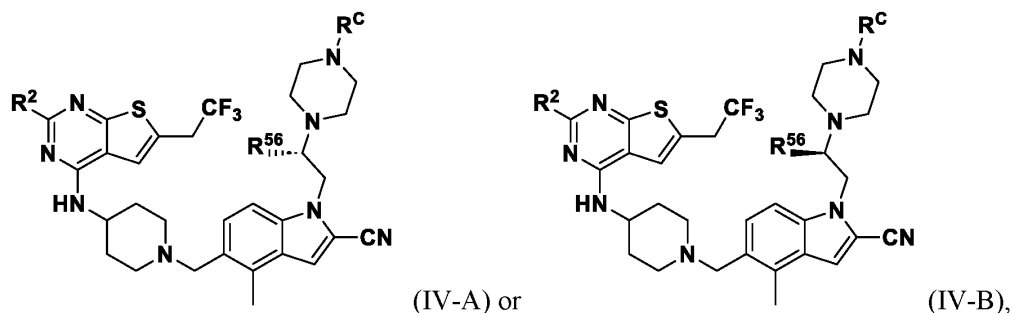
R^{59} is independently selected at each occurrence from C_{1-20} alkyl, C_{2-20} alkenyl, C_{2-20} alkynyl, C_{1-6} heteroalkyl, C_{3-12} carbocycle, and 3- to 12-membered heterocycle, each of which is optionally substituted by halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $=\text{O}$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, C_{3-12} carbocycle, or 3- to 6-membered heterocycle.

[0064] In some embodiments, the menin inhibitor is a compound of Formula (III-A):



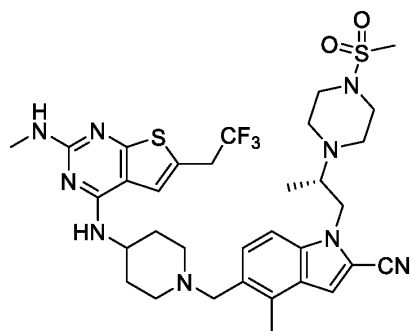
or a pharmaceutically acceptable form thereof, wherein R^2 , each R^B , each R^C , L^3 , C , and p are each defined as described for Formula (II-A).

[0065] In some embodiments, the menin inhibitor is a compound of Formula (IV-A) or Formula (IV-B):



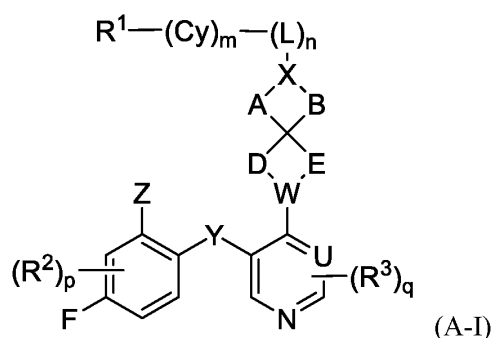
or a pharmaceutically acceptable form thereof, wherein R^2 , R^{56} , and R^C are each defined as described for Formula (II-A).

[0066] In some embodiments, the menin inhibitor is ziftomenib:



or a pharmaceutically acceptable form thereof, such as a pharmaceutically acceptable salt or solvate thereof.

[0067] In some embodiments, the menin inhibitor is a menin inhibitor described in U.S. Patent No. 10,683,302, which disclosure is incorporated by reference herein. In some embodiments, the menin inhibitor is a compound of Formula (A-I):



or a pharmaceutically acceptable form thereof, wherein:

A, B, D, and E are each independently selected from $\text{---C(R}^{A1}\text{)(R}^{A2}\text{)---}$, $\text{---C(R}^{A1}\text{)(R}^{A2}\text{)---}$, $\text{C(R}^{A1}\text{)(R}^{A2}\text{)---}$, $\text{---C(R}^{A1}\text{)(R}^{A2}\text{)---O---}$, $\text{---C(R}^{A1}\text{)(R}^{A2}\text{)---NR}^{A3}\text{---}$, ---C(=O)--- , $\text{C(R}^{A1}\text{)(R}^{A2}\text{)---C(=O)---}$, and $\text{---N=C(NH}_2\text{)---}$ wherein no more than one of A, B, D, and E is $\text{---C(R}^{A1}\text{)(R}^{A2}\text{)---O---}$, $\text{---C(R}^{A1}\text{)(R}^{A2}\text{)---NR}^{A3}\text{---}$, $\text{---C(R}^{A1}\text{)(R}^{A2}\text{)---C(=O)---}$, ---C(=O)--- , or $\text{---N=C(NH}_2\text{)---}$;

U is N or CR^U , wherein R^U is H, halo, CN, OH, C_{1-4} alkyl, C_{1-4} alkoxy, amino, C_{1-4} alkyl amino, or C_{2-8} dialkylamino;

W is N or CR^W , wherein R^W is H, halo, CN, OH, C_{1-4} alkyl, C_{1-4} alkoxy, amino, C_{1-4} alkyl amino, or C_{2-8} dialkylamino;

X is N or CR^X , wherein R^X is H, halo, CN, OH, C_{1-4} alkyl, C_{1-4} alkoxy, amino, C_{1-4} alkyl amino, or C_{2-8} dialkylamino, wherein when X is N, the atom of L that is directly bonded with X is other than N, O, or S;

L is selected from ---C_{1-6} alkylene- and $\text{---(C}_{1-4}\text{ alkylene)}_a\text{---Q---(C}_{1-4}\text{ alkylene)}_b\text{---}$, wherein the C_{1-6} alkylene group and any C_{1-4} alkylene group of the $\text{---(C}_{1-4}\text{ alkylene)}_a\text{---Q---(C}_{1-4}\text{ alkylene)}_b\text{---}$ group is optionally substituted with 1, 2, or 3 substituents independently selected from halo, CN, OH, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} haloalkyl, C_{1-3} haloalkoxy, amino, C_{1-3} alkylamino, and $\text{di(C}_{1-3}\text{ alkyl)amino}$;

Q is ---O--- , ---S--- , ---S(=O)--- , $\text{---S(=O)}_2\text{---}$, ---C(=O)--- , $\text{---C(=O)NR}^{q1}\text{---}$, ---C(=O)O--- , $\text{---OC(=O)NR}^{q1}\text{---}$, $\text{---NR}^{q1}\text{---}$, $\text{---NR}^{q1}\text{C(=O)O---}$, $\text{---NR}^{q1}\text{C(=O)NR}^{q1}\text{---}$, $\text{---S(=O)}_2\text{NR}^{q1}\text{---}$, $\text{---C(=NR}^{q2}\text{)---}$, or $\text{---C(=NR}^{q2}\text{)---NR}^{q1}\text{---}$, wherein each R^{q1} is independently selected from H or C_{1-6} alkyl, and wherein each R^{q2} is independently selected from H, C_{1-6} alkyl, and CN;

Cy is a linking C_{6-14} aryl, C_{3-18} cycloalkyl, 5-16 membered heteroaryl, or 4-18 membered heterocycle group, each of which is optionally substituted with 1, 2, 3, or 4 substituents

independently selected from R^{Cy} , wherein the heteroaryl or heterocycle has 1-3 rings and 1-4 heteroatoms independently selected from nitrogen, sulfur, and oxygen;

each R^{Cy} is independently selected from halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycle, CN, NO_2 , OR^{a1} , SR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^{c1})NR^{c1}R^{d1}$, $NR^{c1}C(=NR^{c1})NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycle are each optionally substituted by 1, 2, 3, or 4 substituents independently selected from CN, NO_2 , OR^{a1} , SR^{a1} , $C(O)R^{b1}$, $C(O)NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $OC(O)R^{b1}$, $OC(O)NR^{c1}R^{d1}$, $C(=NR^{c1})NR^{c1}R^{d1}$, $NR^{c1}C(=NR^{c1})NR^{c1}R^{d1}$, $NR^{c1}R^{d1}$, $NR^{c1}C(O)R^{b1}$, $NR^{c1}C(O)OR^{a1}$, $NR^{c1}C(O)NR^{c1}R^{d1}$, $NR^{c1}S(O)R^{b1}$, $NR^{c1}S(O)_2R^{b1}$, $NR^{c1}S(O)_2NR^{c1}R^{d1}$, $S(O)R^{b1}$, $S(O)NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, and $S(O)_2NR^{c1}R^{d1}$, wherein the heteroaryl or heterocycle has 1-3 rings and 1-4 heteroatoms independently selected from nitrogen, sulfur, and oxygen;

R^1 is H, Cy^1 , halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-CN$, $-NO_2$, $-OR^{a2}$, $-SR^{a2}$, $-C(O)R^{b2}$, $-C(O)NR^{c2}R^{d2}$, $-C(O)OR^{a2}$, $-OC(O)R^{b2}$, $-OC(O)NR^{c2}R^{d2}$, $-C(=NR^{c2})NR^{c2}R^{d2}$, $-NR^{c2}C(=NR^{c2})NR^{c2}R^{d2}$, $-NR^{c2}R^{d2}$, $-NR^{c2}C(O)R^{b2}$, $-NR^{c2}C(O)OR^{a2}$, $-NR^{c2}C(O)NR^{c2}R^{d2}$, $-NR^{c2}S(O)R^{b2}$, $-NR^{c2}S(O)_2R^{b2}$, $-NR^{c2}S(O)_2NR^{c2}R^{d2}$, $-S(O)R^{b2}$, $-S(O)NR^{c2}R^{d2}$, $-S(O)_2R^{b2}$ and $-S(O)_2NR^{c2}R^{d2}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are each optionally substituted by 1, 2, 3, or 4 substituents independently selected from halo, $-CN$, $-NO_2$, $-OR^{a2}$, $-SR^{a2}$, $-C(O)R^{b2}$, $-C(O)NR^{c2}R^{d2}$, $-C(O)OR^{a2}$, $-OC(O)R^{b2}$, $-OC(O)NR^{c2}R^{d2}$, $-C(=NR^{c2})NR^{c2}R^{d2}$, $-NR^{c2}C(=NR^{c2})NR^{c2}R^{d2}$, $-NR^{c2}R^{d2}$, $-NR^{c2}C(O)R^{b2}$, $-NR^{c2}C(O)OR^{a2}$, $-NR^{c2}C(O)NR^{c2}R^{d2}$, $-NR^{c2}S(O)R^{b2}$, $-NR^{c2}S(O)_2R^{b2}$, $-NR^{c2}S(O)_2NR^{c2}R^{d2}$, $-S(O)R^{b2}$, $-S(O)NR^{c2}R^{d2}$, $-S(O)_2R^{b2}$, and $-S(O)_2NR^{c2}R^{d2}$;

Y is O, S, $CR^{Y1}R^{Y2}$ or NR^{Y3} , wherein R^{Y1} , R^{Y2} , and R^{Y3} are each independently selected from H and C_{1-4} alkyl;

Z is Cy^2 , halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-CN$, $-NO_2$, OR^{a3} , SR^{a3} , $C(O)R^{b3}$, $C(O)NR^{c3}R^{d3}$, $C(O)OR^{a3}$, $OC(O)R^{b3}$, $OC(O)NR^{c3}R^{d3}$, $C(=NR^{c3})NR^{c3}R^{d3}$, $NR^{c3}C(=NR^{c3})NR^{c3}R^{d3}$, $NR^{c3}R^{d3}$, $NR^{c3}C(O)R^{b3}$, $NR^{c3}C(O)OR^{a3}$, $NR^{c3}C(O)NR^{c3}R^{d3}$, $NR^{c3}S(O)R^{b3}$, $NR^{c3}S(O)_2R^{b3}$, $NR^{c3}S(O)_2NR^{c3}R^{d3}$, $S(O)R^{b3}$, $S(O)NR^{c3}R^{d3}$, $S(O)_2R^{b3}$, $S(O)_2NR^{c3}R^{d3}$, and $P(O)R^{c3}R^{d3}$ wherein said C_{1-6} alkyl, C_{2-6} alkenyl,

and C₂₋₆ alkynyl are each optionally substituted by 1, 2, 3, or 4 substituents independently selected from Cy², halo, CN, NO₂, OR^{a3}, SR^{a3}, C(O)R^{b3}, C(O)NR^{c3}R^{d3}, C(O)OR^{a3}, OC(O)R^{b3}, OC(O)NR^{c3}R^{d3}, C(=NR^{c3})NR^{c3}R^{d3}, NR^{c3}C(=NR^{c3})NR^{c3}R^{d3}, NR^{c3}R^{d3}, NR^{c3}C(O)R^{b3}, NR^{c3}C(O)OR^{a3}, NR^{c3}C(O)NR^{c3}R^{d3}, NR^{c3}S(O)R^{b3}, NR^{c3}S(O)₂R^{b3}, NR^{c3}S(O)₂NR^{c3}R^{d3}, S(O)R^{b3}, S(O)NR^{c3}R^{d3}, S(O)₂R^{b3}, and S(O)₂NR^{c3}R^{d3};

each R² and R³ is independently selected from H, halo, C₁₋₆ alkyl, C₁₋₄ haloalkyl, C₁₋₄ cyanoalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, CN, NO₂, OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4}, C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, C(=NR^{c4})NR^{c4}R^{d4}, NR^{c4}C(=NR^{c4})NR^{c4}R^{d4}, NR^{c4}R^{d4}, NR^{c4}C(O)R^{b4}, NR^{c4}C(O)OR^{a4}, NR^{c4}C(O)NR^{c4}R^{d4}, NR^{c4}S(O)R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, and S(O)₂NR^{c4}R^{d4}, wherein said C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are each optionally substituted by 1, 2, 3, or 4 substituents independently selected from halo, CN, NO₂, OR^{a4}, SR^{a4}, C(O)R^{b4}, C(O)NR^{c4}R^{d4}, C(O)OR^{a4}, OC(O)R^{b4}, OC(O)NR^{c4}R^{d4}, C(=NR^{c4})NR^{c4}R^{d4}, NR^{c4}C(=NR^{c4})NR^{c4}R^{d4}, NR^{c4}R^{d4}, NR^{c4}C(O)R^{b4}, NR^{c4}C(O)OR^{a4}, NR^{c4}C(O)NR^{c4}R^{d4}, NR^{c4}S(O)R^{b4}, NR^{c4}S(O)₂R^{b4}, NR^{c4}S(O)₂NR^{c4}R^{d4}, S(O)R^{b4}, S(O)NR^{c4}R^{d4}, S(O)₂R^{b4}, and S(O)₂NR^{c4}R^{d4};

each R^{A1} is independently selected from H, halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, amino, C₁₋₄ alkylamino, C₂₋₈ dialkylamino, CN, NO₂, and OH;

each R^{A2} is independently selected from H, halo, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, amino, C₁₋₄ alkylamino, C₂₋₈ dialkylamino, CN, NO₂, and OH;

each R^{A3} is independently selected from H, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, C(O)R^z, and C(O)OR^z, wherein said C₁₋₄ alkyl is optionally substituted by phenyl, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, CN, NO₂, or OH;

R^z is H, C₁₋₄ alkyl, or phenyl;

each Cy¹ is independently selected from C₆₋₁₄ aryl, C₃₋₁₈ cycloalkyl, 5-16 membered heteroaryl, and 4-18 membered heterocycle, each of which is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^{Cy1}, wherein the heteroaryl or heterocycle has 1-3 rings and 1-4 heteroatoms independently selected from nitrogen, sulfur, and oxygen;

each Cy² is independently selected from C₆₋₁₄ aryl, C₃₋₁₈ cycloalkyl, 5-16 membered heteroaryl, and 4-18 membered heterocycle, each of which is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R^{Cy2}, wherein the heteroaryl or has 1-3 rings and 1-4 heteroatoms independently selected from nitrogen, sulfur, and oxygen;

each R^{Cy1} and R^{Cy2} is independently selected from halo, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-4} cyanoalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycle, CN, NO_2 , OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $C(=NR^{c5})NR^{c5}R^{d5}$, $NR^{c5}C(=NR^{c5})NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)OR^{a5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}S(O)R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, and $S(O)_2NR^{c5}R^{d5}$, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, C_{3-7} cycloalkyl, 5-6 membered heteroaryl, and 4-7 membered heterocycle are each optionally substituted by 1, 2, 3, or 4 substituents independently selected from CN, NO_2 , OR^{a5} , SR^{a5} , $C(O)R^{b5}$, $C(O)NR^{c5}R^{d5}$, $C(O)OR^{a5}$, $OC(O)R^{b5}$, $OC(O)NR^{c5}R^{d5}$, $C(=NR^{c5})NR^{c5}R^{d5}$, $NR^{c5}C(=NR^{c5})NR^{c5}R^{d5}$, $NR^{c5}R^{d5}$, $NR^{c5}C(O)R^{b5}$, $NR^{c5}C(O)OR^{a5}$, $NR^{c5}C(O)NR^{c5}R^{d5}$, $NR^{c5}S(O)R^{b5}$, $NR^{c5}S(O)_2R^{b5}$, $NR^{c5}S(O)_2NR^{c5}R^{d5}$, $S(O)R^{b5}$, $S(O)NR^{c5}R^{d5}$, $S(O)_2R^{b5}$, and $S(O)_2NR^{c5}R^{d5}$, wherein the heteroaryl or heterocycle has 1-3 rings and 1-4 heteroatoms independently selected from nitrogen, sulfur, and oxygen;

each R^{a1} , R^{b1} , R^{c1} , R^{d1} , R^{a2} , R^{b2} , R^{c2} , R^{d2} , R^{a3} , R^{b3} , R^{c3} , R^{d3} , R^{a4} , R^{b4} , R^{c4} , R^{d4} , R^{a5} , R^{b5} , R^{c5} , and R^{d5} is independently selected from H, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycle, C_{6-10} aryl- C_{1-6} alkyl, C_{3-10} cycloalkyl- C_{1-6} alkyl, (5-10 membered heteroaryl)- C_{1-6} alkyl, and (4-10 membered heterocycle)- C_{1-6} alkyl, wherein said C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, C_{3-10} cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycle, C_{6-10} aryl- C_{1-6} alkyl, C_{3-10} cycloalkyl- C_{1-6} alkyl, (5-10 membered heteroaryl)- C_{1-6} alkyl, and (4-10 membered heterocycle)- C_{1-6} alkyl are each optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from R^E , wherein the heteroaryl or heterocycle has 1-3 rings and 1-4 heteroatoms independently selected from nitrogen, sulfur, and oxygen;

each R^{e1} , R^{e2} , R^{e3} , R^{e4} , and R^{e5} is independently selected from H, C_{1-4} alkyl, and CN;

each R^E is independently selected from the group consisting of OH, NO_2 , CN, halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, cyano- C_{1-3} alkyl, HO- C_{1-3} alkyl, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, thiol, C_{1-6} alkylthio, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, carboxy, aminocarbonyl, C_{1-6} alkylcarbonyl, and C_{1-6} alkoxycarbonyl;

n is 0 or 1;

m is 0 or 1;

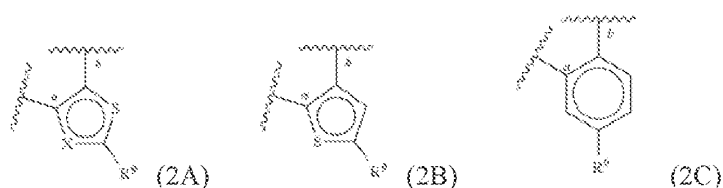
p is 0, 1, 2, or 3;

the dotted circle indicates that the ring is aromatic, R^1 and R^2 are each independently a hydrogen atom or a C_{1-6} alkyl group, one of R^3 and R^4 is a hydrogen atom, a hydroxy group, a halogen atom, a C_{1-6} alkoxy group, a di(C_{1-6} alkyl)carbamoyl group, or an oxazolyl group, and the other of R^3 and R^4 is a hydrogen atom, a hydroxy group, a halogen atom, or a C_{1-6} alkoxy group,

R^5 is a hydrogen atom, a C_{1-6} alkyl group, or a hydroxy C_{1-6} alkyl group,

R^6 is a hydrogen atom, a C_{1-6} alkyl group, a halogen atom, a C_{1-6} alkoxy group, an amino group, or a C_{1-6} alkylamino group,

R^7 and R^8 are taken together with the carbon atom to which R^7 is bonded and the carbon atom to which R^8 is bonded to form any of the following formulas (2A) to (2C):



wherein

the dotted circle indicates that the ring is aromatic,

the carbon atom marked with a is the carbon atom to which R^8 is bonded,

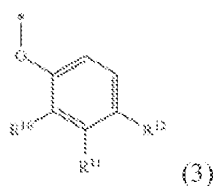
the carbon atom marked with b is the carbon atom to which R^7 is bonded,

X is CH or a nitrogen atom, and

R^9 is a halogen, C_{1-6} alkyl group, a C_{3-8} cycloalkyl group, a

C_{3-8} cycloalkyl C_{1-6} alkyl group, a C_{1-6} alkoxy C_{1-6} alkyl group, or an oxetanyl group, or

R^7 is a hydrogen atom, and R^8 is the following formula (3):



wherein

* indicates a bonding site,

R^{10} is a di(C_{1-6} alkyl) carbamoyl group, a (C_{1-6} alkyl)pyrimidinyl group, a (C_{1-6} alkyl)phenyl group, or a (C_{1-6} alkyl)pyrazolyl group,

R^{11} is a hydrogen atom or a halogen atom, and

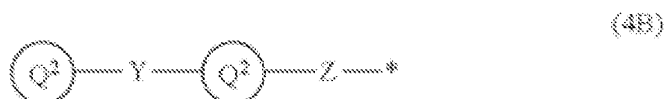
R^{12} is a halogen atom,

m is 1 or 0,

n is 1 or 2,

Ring Q^1 is a 6-membered aromatic ring optionally containing one nitrogen atom in the ring (the aromatic ring optionally has one or two substituents independently selected from the following Group A), a 5-membered aromatic heterocycle containing, in the ring, one or two heteroatoms independently selected from the group consisting of a nitrogen atom and a sulfur atom (the aromatic heterocycle optionally has one substituent independently selected from the following Group A), a C_{3-8} cycloalkane ring optionally having one substituent independently selected from the following Group A, a C_{4-8} cycloalkene ring optionally having one substituent independently selected from the following Group A, a 4- to 8-membered saturated heterocycle containing one nitrogen atom in the ring (the saturated heterocycle optionally has one substituent independently selected from the following Group A), or a 9-membered bicyclic aromatic heterocycle containing one nitrogen atom in the ring (the bicyclic aromatic heterocycle optionally has one or two substituents independently selected from the following Group B), and

W is the following formula (4A) or (4B):



wherein

* indicates a bonding site,

Ring Q^2 is a 6-membered aromatic ring optionally containing one nitrogen atom in the ring (the aromatic ring optionally has one to three substituents independently selected from the following Group C), a 6-membered aromatic heterocycle containing two nitrogen atoms in the ring (the aromatic heterocycle optionally has one to three substituents independently selected from the following Group C), a 5-membered aromatic heterocycle containing, in the ring, one to three heteroatoms independently selected from the group consisting of a nitrogen atom, an oxygen atom and a sulfur atom (the aromatic heterocycle optionally has one substituent independently selected from the following Group C), a 9- or 10-membered bicyclic aromatic or partially unsaturated heterocycle containing, in the ring, one to three heteroatoms independently selected from the group consisting of a nitrogen atom and an oxygen atom (the bicyclic aromatic or

partially unsaturated heterocycle optionally has one or two substituents independently selected from the following Group D), a 5- to 8-membered saturated heterocycle containing, in the ring, one or two heteroatoms independently selected from the group consisting of an oxygen atom and a nitrogen atom (the saturated heterocycle optionally has one substituent independently selected from the following Group E), or a C₃₋₈ cycloalkane ring optionally having one substituent independently selected from the following Group E, Ring Q³ is a 4- to 8-membered saturated heterocycle containing one nitrogen atom or one oxygen atom in the ring (the saturated heterocycle optionally has one C₁₋₆ alkylsulfonyl group), or a 6-membered aromatic ring optionally containing one nitrogen atom in the ring (the aromatic ring optionally has one substituent independently selected from the following Group F),

Y is a single bond or an oxygen atom, and

Z is a single bond, an oxygen atom, —NH—, —SO₂—, a C₁₋₆ alkylene group, *—R¹³—

NHC(=O)—**, *—R⁴—O—**, or *—R⁵—NH—**,

wherein * is bonded to Ring Q², ** is bonded to Ring Q¹, and R¹³, R¹⁴ and R¹⁵ are each independently a C₁₋₆ alkylene group,

Group A: a halogen atom, a hydroxy group, a C₁₋₆ alkyl group, a C₁₋₆ alkoxy group, a hydroxy C₁₋₆ alkoxy group, a vinylsulfonylamino(C₁₋₆ alkyl)carbamoyl group, and a prop-2-enoylamino(C₁₋₆ alkyl)carbamoyl group,

Group B: a cyano group, a C₁₋₆ alkyl group, a halogen atom, and a C₁₋₆ alkoxy group,

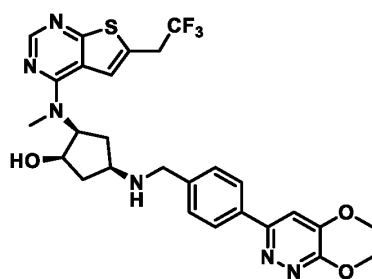
Group C: a halogen atom, a C₁₋₆ alkyl group, a C₁₋₆ alkoxy group, a C₁₋₆ alkyl(C₁₋₆ alkylsulfonyl)amino group, a cyano group, a C₁₋₆ alkylsulfonyl group, a C₁₋₆ alkylamino group, a di(C₁₋₆ alkyl)amino group, a halogeno C₁₋₆ alkyl group, a C₁₋₆ alkoxy C₁₋₆ alkoxy group, a halogeno C₁₋₆ alkoxy group, a C₁₋₆ alkylsulfonyl C₁₋₆ alkyl group, a di(C₁₋₆ alkyl)sulfamoyl group, a C₁₋₆ alkylendioxy group, a (C₁₋₆ alkyl)carbamoyl group, a hydroxy C₁₋₆ alkyl group, a 2-C₃₋₆ alkenoylamino group, a C₁₋₆ alkyl (2-C₃₋₆ alkenoyl)amino group, a hydroxy group, an oxo group, a —OC(=O)H group, and a —N[(C(=O)H)₂] group,

Group D: a halogen atom, a C₁₋₆ alkyl group, and a C₁₋₆ alkylsulfonyl group,

Group E: an oxo group, a hydroxy group, and a C₁₋₆ alkoxy group, and

Group F: a halogen atom, and a C₁₋₆ alkoxy group.

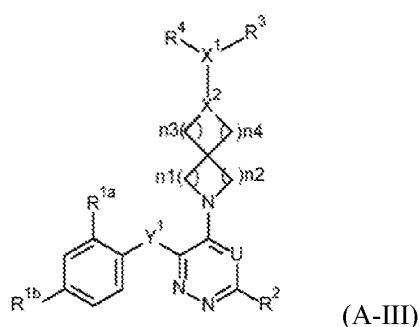
[0071] In some embodiments, the menin inhibitor is Compound A:



Compound A,

or a pharmaceutically acceptable form thereof.

[0072] In some embodiments, the menin inhibitor is a menin inhibitor described in PCT Publ. No. WO2021/121327, which disclosure is incorporated by reference herein. In some embodiments, the menin inhibitor is a compound of Formula (A-III):



(A-III)

or a pharmaceutically acceptable form thereof, wherein

R^{1a} represents $-C(=O)-NR^{xa}R^{xb}$; Het; or  $NR^{xa}R^{xb}$;

Het represents a 5- or 6-membered monocyclic aromatic ring containing one, two or three nitrogen atoms and optionally a carbonyl moiety;

wherein said 5- or 6-membered monocyclic aromatic ring is optionally substituted with one or two substituents selected from the group consisting of C_{3-6} cycloalkyl and C_{1-4} alkyl;

R^{xa} and R^{xb} are each independently selected from the group consisting of hydrogen, C_{1-4} alkyl and C_{3-6} cycloalkyl;

R^{1b} represents F or Cl;

Y^1 represents $-CR^{5a}R^{5b}$, $-O-$ or $-NR^{5c}$;

R^2 is selected from the group consisting of hydrogen, halo, C_{1-4} alkyl, $-O-C_{1-4}$ alkyl, and $-NR^{7a}R^{7b}$;

U represents N or CH;

$n1$, $n2$, $n3$ and $n4$ are each independently selected from 1 and 2;

X¹ represents CH, and X² represents N;

R⁴ represents isopropyl;

R^{5a}, R^{5b}, R^{5c}, R^{7a}, and R^{7b}, are each independently selected from the group consisting of hydrogen, C₁₋₄alkyl and C₃₋₆cycloalkyl;

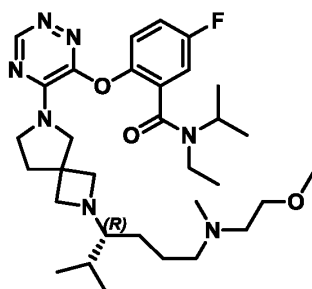
R³ represents -C₁₋₆alkyl-NR^{8a}R^{8b}, C₁₋₆alkyl-C(=O)-NR^{9a}R^{9b}, -C₁₋₆alkyl-OH, or -C₁₋₆alkyl-NR¹¹-C(=O)-O-C₁₋₄alkyl-O-C(=O)-C₁₋₄alkyl;

wherein each of the C₁₋₄alkyl or C₁₋₆alkyl moieties in the R³ definitions independently of each other may be substituted with one, two or three substituents each independently selected from the group consisting of cyano, halo, -OH, and -O-C₁₋₄alkyl;

R^{8a} and R^{8b} are each independently selected from the group consisting of hydrogen; C₁₋₆alkyl; -C(=O)-C₁₋₄alkyl; -C(=O)-O-C₁₋₄alkyl; -C(=O)-NR^{12a}R^{12b}; and C₁₋₆alkyl substituted with one, two or three substituents each independently selected from the group consisting of -OH, cyano, halo, -S(=O)₂-C₁₋₄alkyl, -O-C₁₋₄alkyl, -C(=O)-NR^{10a}R^{10b}, and -NR^{10c}-C(=O)-C₁₋₄alkyl;

R^{9a}, R^{9b}, R^{10a}, R^{10b}, R^{10c}, R¹¹, R^{12a}, and R^{12b} are each independently selected from the group consisting of hydrogen and C₁₋₆alkyl.

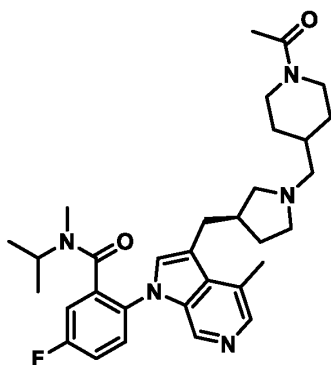
[0073] In one embodiment, the menin inhibitor is Compound B1:



Compound B1,

or a pharmaceutically acceptable form thereof.

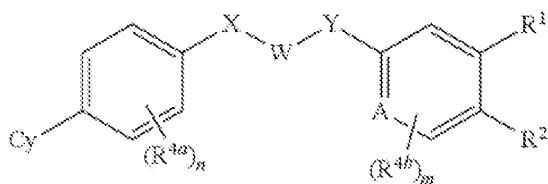
[0074] In one embodiment, the menin inhibitor is Compound B2:



Compound B2,

or a pharmaceutically acceptable form thereof.

[0075] In some embodiments, the menin inhibitor is a menin inhibitor described in U.S. Patent No. 11,084,825, which disclosure is incorporated by reference herein. In some embodiments, the menin inhibitor is a compound of Formula (A-IV):



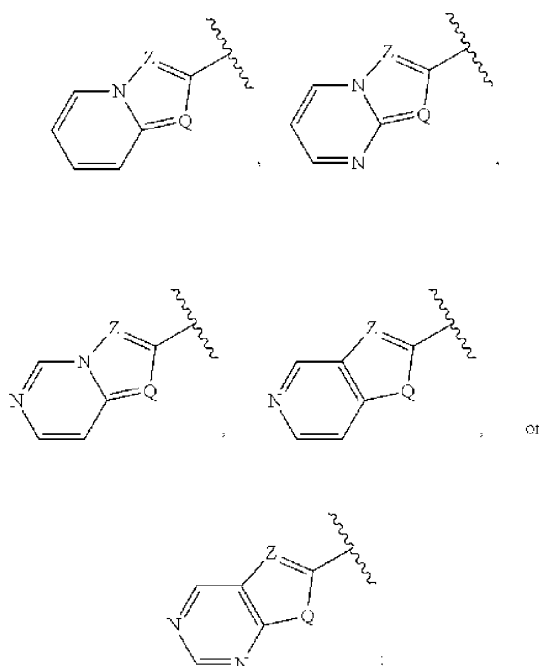
(A-IV)

or a pharmaceutically acceptable form thereof,

wherein:

A is N ;

Cy is:



wherein:

Q is =N— , —NH— , —O— , or —S— ; and

Z is $\text{—CR}^{5a}\text{=}$ or —N= ;

wherein Cy is optionally substituted with one or more independently selected R^7 substituents;

X is $\text{—C(R}^{3b})_2\text{—}$, $\text{—NR}^{3a}\text{—}$, or —O— ;

W is —C(O)— , —S(O)— , or $\text{—S(O)}_2\text{—}$;

Y is a single bond, $\text{—C(R}^{3b})_2\text{—}$, $\text{—NR}^{3a}\text{—}$, or —O— ;

(i) R^1 is H, halo, CN, C_{1-6} alkyl, or C_{1-6} haloalkyl; and

R^2 is $\text{CH}_2\text{—Cy}^2\text{—NHC(O)—C(R}^{6a})\text{=C(R}^{6b})(\text{R}^{6c})$ or $\text{Cy}^2\text{—NHC(O)—C(R}^{6a})\text{=C(R}^{6b})(\text{R}^{6c})$; or

(ii) R^1 is $\text{CH}_2\text{—Cy}^2\text{—NHC(O)—C(R}^{6a})\text{=C(R}^{6b})(\text{R}^{6c})$ or $\text{Cy}^2\text{—NHC(O)—C(R}^{6a})\text{=C(R}^{6b})(\text{R}^{6c})$; and

R^2 is H, halo, CN, C_{1-6} alkyl, or C_{1-6} haloalkyl;

each R^{3a} is independently H or C_{1-6} alkyl;

each R^{3b} is independently H or C_{1-6} alkyl;

each R^{4a} is independently H, halo, CN, C_{1-6} alkyl, C(O)R , C(O)N(R)_2 , C(O)OR , N(R)_2 ,

NRC(O)R , OR , $\text{S(O)}_2\text{R}$, C_{3-7} cycloalkyl, a 4- to 7-membered heterocycloalkyl ring, phenyl, an 8- to 10-membered bicyclic aryl ring, or a 5- or 6-membered heteroaryl ring, wherein the 4- to 7-membered heterocycloalkyl ring has 1 or 2 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, and the 5- or 6-membered heteroaryl ring has 1, 2, 3,

or 4 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur;

each R^{4b} is independently H, halo, CN, C_{1-6} alkyl, $C(O)R$, $C(O)N(R)_2$, $C(O)OR$, $N(R)_2$, $NRC(O)R$, OR , $S(O)_2R$, C_{3-7} cycloalkyl, a 4- to 7-membered heterocycloalkyl ring, phenyl, an 8- to 10-membered bicyclic aryl ring, or a 5- or 6-membered heteroaryl ring, wherein the 4- to 7-membered heterocycloalkyl ring has 1 or 2 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, and the 5- or 6-membered heteroaryl ring has 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur;

each R^7 is independently a 4- to 7-membered heterocycloalkyl ring, phenyl, an 8- to 10-membered bicyclic aryl ring, or a 5- or 6-membered heteroaryl ring, wherein each 4- to 7-membered heterocycloalkyl ring independently has 1 or 2 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, and each 5- or 6-membered heteroaryl ring independently has 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, and further wherein each 4- to 7-membered heterocycloalkyl ring, phenyl, 8- to 10-membered bicyclic aryl ring, and 5- or 6-membered heteroaryl ring is optionally and independently substituted with one or more substituents independently selected from the group consisting of halo, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, NH_2 , $NH(C_{1-6} \text{ alkyl})$, $N(C_{1-6} \text{ alkyl})_2$, OH , and $O(C_{1-6} \text{ alkyl})$;

each R is independently H, C_{1-6} aliphatic, a saturated or partially unsaturated 4- to 7-membered heterocyclic ring, phenyl, an 8- to 10-membered bicyclic aryl ring, or a 5- or 6-membered heteroaryl ring, wherein the saturated or partially unsaturated 4- to 7-membered heterocyclic ring has 1 or 2 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, and the 5- or 6-membered heteroaryl ring has 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur; or two geminal R groups, together with the nitrogen atom to which they are attached, form a saturated or partially unsaturated 4- to 7-membered heterocyclic ring or a 5- or 6-membered heteroaryl ring, wherein the 4- to 7-membered heterocyclic ring or the 5- or 6-membered heteroaryl ring has 0, 1, 2, or 3 additional heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur;

R^{5a} is H, halo, CN, C_{1-6} alkyl, or C_{1-6} haloalkyl;

R^{6a} is H or C_{1-6} alkyl;

R^{6b} is H or C_{1-6} alkyl; or

R^{6a} and R^{6b} , joined together, form a single bond;

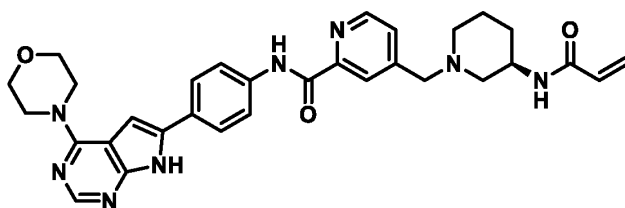
R^{6c} is H or C_{1-6} alkyl, wherein the C_{1-6} alkyl is optionally substituted with $N(CH_3)_2$;

Cy^2 is a 4- to 7-membered heterocycloalkyl ring, phenyl, or pyridyl, wherein the 4- to 7-membered heterocycloalkyl ring has 1 or 2 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur;

m is 1, 2, or 3; and

n is 1, 2, 3, or 4.

[0076] In one embodiment, the menin inhibitor is Compound C:

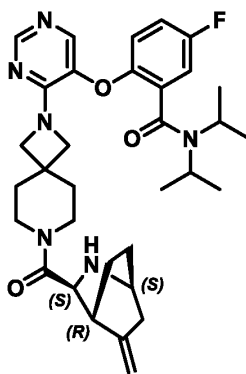


Compound C,

or a pharmaceutically acceptable form thereof.

[0077] In some embodiments, the menin inhibitor is ziftomenib, SNDX-5613 (revumenib), VTP-50469, JNJ-75276617, DS-1594, DS-1594a, DS-1594b, DSP-5336, MI-3454, M-808, A300-105A, BN104, Compound A, Compound B1, Compound B2, or Compound C, or a pharmaceutically acceptable form thereof.

[0078] The compound DSP-5336 has the following structure:



[0079] In some embodiments, the menin inhibitor is ziftomenib, SNDX-5613 (revumenib), VTP-50469, Compound A, Compound B1, Compound B2, or Compound C, or a pharmaceutically acceptable form thereof.

[0080] In some embodiments, the menin inhibitor is ziftomenib, SNDX-5613 (revumenib), VTP-50469, Compound A, Compound B1, Compound B2, or Compound C, or a pharmaceutically acceptable form thereof.

[0081] In some embodiments, the menin inhibitor is ziftomenib, SNDX-5613 (revumenib), VTP-50469, or Compound A, or a pharmaceutically acceptable form thereof.

[0082] The compound of Formula (I-A), Formula (I-B), Formula (II-A), Formula (III-A), Formula (IV-A), or Formula (VI-B) (e.g., ziftomenib) may be synthesized by methods described in U.S. Pat. No. 10,781,218, which disclosure is incorporated by reference herein.

Ziftomenib and Pharmaceutically Acceptable Forms

[0083] Ziftomenib (KO-539; alternatively named as (*S*)-4-methyl-5-((4-((2-(methylamino)-6-(2,2,2-trifluoroethyl)thieno[2,3-*d*]pyrimidin-4-yl)amino)piperidin-1-yl)methyl)-1-(2-(4-(methylsulfonyl)piperazin-1-yl)propyl)-1*H*-indole-2-carbonitrile) is potent and selective inhibitor of the menin-KMT2A(MLL) complex that has downstream effects on *HOXA9/MEIS1* expression. (Burrows et al., Proceedings of the AACR EORTC International Conference: Molecular Targets and Cancer Therapeutics; 2017 Oct 26-30; Philadelphia, PA. Philadelphia (PA): AACR; Mol Cancer Ther 2018;17(1 Suppl): Abstract nr LB-A27.) Ziftomenib is in clinical development for the treatment of acute leukemias, including *NPM1*-mutated (*NPM1*-m) and *KMT2A*-rearranged (*KMT2A*-r) AML. (See <https://kuraoncology.com/clinical-trials/clinical-trials-komet-001/>.)

[0084] In some embodiments, the menin inhibitor described herein is ziftomenib or a pharmaceutically acceptable form thereof. In some embodiments, the methods described herein employ a pharmaceutically acceptable form of ziftomenib. In some embodiments, the methods described herein employ ziftomenib or a pharmaceutically acceptable salt thereof. In some embodiments, the methods described herein employ ziftomenib or a solvate thereof. In certain embodiments, ziftomenib comprises the free base form or a solvate thereof. Also included, in some embodiments, are stereoisomers and/or metabolites of ziftomenib.

KIT Inhibitors

[0085] In some embodiments, the methods provided herein comprise administering a KIT inhibitor to an individual. In some embodiments, the KIT inhibitor is imatinib, sunitinib, regorafenib, ripretinib, dasatinib, avapritinib, masitinib, or nilotinib, or a pharmaceutically acceptable form thereof. In some embodiments, the KIT inhibitor is midostaurin. In some embodiments, the KIT inhibitor is imatinib or a pharmaceutically acceptable form thereof. In some embodiments, the KIT inhibitor is imatinib mesylate. In some embodiments, the KIT inhibitor is sunitinib or a pharmaceutically acceptable form thereof. In some embodiments, the

KIT inhibitor is sunitinib malate. In some embodiments, the KIT inhibitor is regorafenib. In some embodiments, the KIT inhibitor is ripretinib. In some embodiments, the concomitant KIT inhibitor and/or prior KIT inhibitor are each independently selected from imatinib, sunitinib, regorafenib, ripretinib, dasatinib, avapritinib, masitinib, nilotinib, cabozantinib, pazopanib, ponatinib, sorafenib, elenestatinib, chiauranib (CS2164), CS-2660, lenvatinib, pexidartinib (PLX-3397), tyrphostin AG 1288, midostaurin, linifanib, sitravatinib (MGCD516), dovitinib (CHIR-258), AST 487, flumatinib (HHGV678), bezuclastinib (CGT9486), amuvatinib (MP470), barzolvolimab (CDX 0159), ISCK0, SU14813, vimseltinib (DCC-3014), AZD3229, motesanib (AMG 706), M4205, tandutinib (MLN518), seralutinib (GB002), PLX647, OCI-930, toceranib (SU11654), Ki20227, dovitinib, SU14813, SU11642, motesanib, PD180970, AC710, AZD2932, SKLB4771, telatinib, KG5, labuxtinib, JNJ-38158471, sitravatinib, CHMFL-ABL/KIT-155, CHMFL-KIT-033, KBP-7018, apatinib, PLX647, APcK110, JI6, GW694590A (UNC10112731), henatinib, toceranib, tafetinib, dasatinib, pembrolizumab, ipilimumab, PTK787/ZK222584, AMNN207, and AMG706, and pharmaceutically acceptable forms thereof.

Doses and Dosing Regimens of Menin Inhibitors and KIT Inhibitors

[0086] In certain embodiments, dosages, treatment regimens, and effective amounts vary depending on the severity of the disease, the age and relative health of the subject, the potency of the compound(s) used and other factors. In some embodiments, the methods provided herein comprise administering a menin inhibitor to an individual. In some embodiments, the methods provided herein comprise administering an effective amount of a menin inhibitor to an individual.

[0087] In some embodiments, the amount of the menin inhibitor administered in the methods provided herein is from 5 mg/day up to, and including, 2000 mg/day, or up to, and including, 3000 mg/day. In some embodiments, the daily dosage of the menin inhibitor is between about 50 mg to about 800 mg. In some embodiments, the daily dosage of the menin inhibitor is from about 100 mg to about 3000 mg, or about 100 mg to about 2000 mg, or about 100 to about 1600 mg, or about 200 to about 1200 mg, or about 600 to about 1200 mg, or about 500 to about 1000 mg. In some embodiments, the daily dosage of the menin inhibitor is about 50 mg. In some embodiments, the daily dosage of the menin inhibitor is about 100 mg. In some embodiments, the daily dosage of the menin inhibitor is about 200 mg. In some embodiments, the daily dosage of the menin inhibitor is about 400 mg. In some embodiments, the daily dosage of the menin inhibitor is about 600 mg. In some embodiments, the daily dosage of the menin inhibitor is

about 800 mg. In some embodiments, the daily dosage of the menin inhibitor is about 900 mg. In some embodiments, the daily dosage of the menin inhibitor is about 1000 mg. In some embodiments, the daily dosage of the menin inhibitor is about 1100 mg. In some embodiments, the daily dosage of the menin inhibitor is about 1200 mg. In some embodiments, the daily dosage of the menin inhibitor is about 1300 mg. In some embodiments, the daily dosage of the menin inhibitor is about 1400 mg. In some embodiments, the daily dosage of the menin inhibitor is about 1500 mg. In some embodiments, the daily dosage of the menin inhibitor is about 1600 mg. In some embodiments, the menin inhibitor is ziftomenib and the daily dosage is about 200, 400, 600, or 800 mg. In some embodiments, the menin inhibitor is ziftomenib and the daily dosage is about 1000 mg, 1200 mg, 1400 mg, or 1600 mg. In some embodiments, the menin inhibitor is ziftomenib and the daily dosage is about 200, 600, 900, or 1200 mg. In some embodiments, the menin inhibitor is administered at a dose of about 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 250, 300, 350, 360, 400, 450, 500, 550, 600, or 800 mg/day. In some embodiments, the menin inhibitor is administered at a dose of about 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, or 1600 mg/day. In some embodiments, the menin inhibitor is administered as a dose of about 1000 to about 3000 mg/day.

[0088] In some embodiments, a daily dose is given once a day, or is divided and given twice a day, three times per day, four times per day to equal the daily dose. In some embodiments, any of the daily doses described herein may be given once daily. In some embodiments, any of the daily doses described herein may be divided and given twice a day. In some embodiments, the menin inhibitor is administered at a unit dose of 25 mg, 50 mg, or 200 mg. In some embodiments, the menin inhibitor is administered at a unit dose of about 50 to about 400 mg, or about 200 to about 300 mg. In some embodiments, the unit dose(s) is given once a day, given twice a day, given three times per day, or given four times per day. In some embodiments, one unit dose is given per day, two unit doses are given per day, three unit doses are given per day, or four unit doses are given per day. In some embodiments, two unit doses are given twice per day. In some embodiments, three unit doses are given once per day. In some embodiments, four unit doses are given once per day. In some embodiments, the menin inhibitor is ziftomenib, which is administered at a dose of 200 mg once per day. In some embodiments, the 200 mg comprises one 200 mg unit dose. In some embodiments, the menin inhibitor is ziftomenib, which is administered at a dose of 400 mg once per day. In some embodiments, the 400 mg comprises two 200 mg unit doses. In some embodiments, the menin inhibitor is ziftomenib,

which is administered at a dose of 600 mg once per day. In some embodiments, the 600 mg comprises three 200 mg unit doses, or comprises two 300 mg unit doses. In some embodiments, the menin inhibitor is ziftomenib, which is administered at a dose of 900 mg once per day. In some embodiments, the 900 mg comprises four 200 mg unit doses and two 50 mg unit doses, or comprises three 300 mg unit doses. In some embodiments, the menin inhibitor is ziftomenib, which is administered at a dose of 1200 mg once per day. In some embodiments, the 1200 mg comprises six 200 mg unit doses or comprises four 300 mg unit doses.

[0089] In some embodiments, the menin inhibitor is SNDX-5613 (revumenib) and the amount administered is 75 mg, 113 mg, 163 mg, 164 mg, or 226 mg once or twice per day. In some embodiments, the menin inhibitor is Compound C and the amount administered is 25, 50, 75, 100, 15, 175, 200, 325, 500, or 650 mg once per day. In some embodiments, the menin inhibitor is Compound B1 or Compound B2 and the daily dose is 5 to 1000 mg/day.

[0090] In some embodiments, the daily dose of the KIT inhibitor that is administered is from 50 mg/day up to, and including, 1000 mg/day. In some embodiments, a daily dose is given once a day, or is divided and given twice a day, three times per day, four times per day to equal the daily dose. In some embodiments, the daily dose of the KIT inhibitor is administered according to approved labeling for the target indication or for other indications. In some embodiments, the amount of the KIT inhibitor that is administered is about 50 mg/day, or about 100 mg/day, or about 150 mg/day, or about 200 mg/day, or about 250 mg/day, or about 300 mg/day, or about 350 mg/day, or about 400 mg/day, or about 500 mg/day. In some embodiments, the KIT inhibitor is administered once daily. In some embodiments, the KIT inhibitor is administered twice daily.

[0091] In some embodiments, the KIT inhibitor is imatinib (e.g., imatinib mesylate), and is administered at a daily dose of 100, 200, 300, 400, 600, or 800 mg/day, or 100 mg/day, or 200 mg/day, or 400 mg/day. In some embodiments, the imatinib (e.g., imatinib mesylate) is administered in 100 mg or 400 mg tablets. In some embodiments, the imatinib (e.g., imatinib mesylate) is administered at a daily dose of 800 mg, for example, as 400 mg, such as a 400 mg tablet, twice a day. In some embodiments, the daily dose of imatinib (e.g., imatinib mesylate) is administered once a day (e.g., 100 mg or 400 mg once daily). In some embodiments, where imatinib is the prior KIT inhibitor and the concomitant KIT inhibitor, the combination treatment may employ the same dosage of imatinib that was used as a monotherapy, without need for dose reduction or dose increase. In some embodiments, where an individual received imatinib at a

reduced dose (relative to the label-indicated dose) for monotherapy, that dose is maintained for the combination of imatinib and the menin inhibitor.

[0092] In some embodiments, the KIT inhibitor is sunitinib (e.g., sunitinib malate), and is administered at a daily dose of 25, 37.5, or 50 mg/day. In some embodiments, the sunitinib (e.g., sunitinib mesylate) is administered at a daily dose of 50 mg/day. In some embodiments, the 25 mg is administered as a 25 mg capsule, the 37.5 mg is administered as one 25 mg capsule and one 12.5 mg capsule, and the 50 mg is administered as a 50 mg capsule. In some embodiments, the daily dose of sunitinib (e.g., sunitinib malate) is administered once a day. In some embodiments, the sunitinib (e.g., sunitinib malate) is administered once a day, for four weeks, followed by two weeks off (a 6-week cycle), for at least one cycle.

[0093] In some embodiments, the KIT inhibitor is regorafenib, and is administered at a daily dose of 80, 120, or 160 mg/day. In some embodiments, the regorafenib daily dose is 160 mg/day. In some embodiments, the regorafenib is administered once daily. In some embodiments, the regorafenib is administered in 40 mg tablets. In some embodiments, the regorafenib is administered on days 1 to 21 of a 28-day cycle, for at least one cycle.

[0094] In some embodiments, the KIT inhibitor is ripretinib, and is administered at a daily dose of 100 or 150 mg/day, or at a daily dose of 150 mg/day. In some embodiments, the ripretinib is administered at a dose of 150 mg once daily. In some embodiments, the ripretinib is administered in 50 mg tablets.

[0095] In some embodiments, the administering of ziftomenib or the pharmaceutically acceptable form thereof comprises administering to the individual for at least 3 days, or for at least 5 days, or for at least 7 days, or for at least 10 days, or for at least 14 days, or for at least 21 days, or for at least 28 days, or for a cycle comprising at least 28 days, or for a cycle comprising 28 days.

[0096] In certain embodiments, ziftomenib or a pharmaceutically acceptable form thereof is administered daily to the individual for a cycle comprising at least 28 days, for N cycles, wherein N is at least 1. In certain embodiments, N is at least 2. In certain embodiments, N is at least 3. In certain embodiments, N is at least 4. In certain embodiments, N is 2. In certain embodiments, N is 3. In certain embodiments, N is 4. In certain embodiments, N is 5. In certain embodiments, N is 6. In certain embodiments, N is 7. In certain embodiments the cycles are continuous (i.e., 0 days between cycles).

[0097] In certain embodiments, ziftomenib or a pharmaceutically acceptable form thereof is administered orally.

[0098] In some embodiments, administering daily is administering once or twice daily. In some embodiments, administering daily is once daily.

[0099] Dose amounts of the menin inhibitors (such as ziftomenib) or KIT inhibitors as presented herein refer to the free base amount (if using the free form) or to the free base equivalent amount (if using a salt and/or solvate). Thus, for example, if a salt form were used, the total amount of a given agent that is administered would exceed the dose of active form, but would be used in a scaled amount to provide the target dose of active agent.

KIT Positive Cancers

[0100] In some embodiments, the KIT positive cancer is sarcoma (optionally, sarcoma, gastrointestinal stromal tumor (GIST), or soft tissue sarcoma), melanoma (optionally, melanoma, mucosal melanoma, acral lentiginous melanoma, or chronically sun-damaged melanoma), blood-related cancer (optionally, leukemia, acute leukemia, acute myeloid leukemia, myelodysplastic syndrome, chronic myeloid leukemia, multiple myeloma, chronic myelomonocytic leukemia, myelodysplastic/myeloproliferative neoplasm, chronic lymphocytic leukemia, myelofibrosis, or T-cell and NK-cell neoplasm), solid tumor (optionally, solid tumor, malignant solid tumor, non-small cell lung carcinoma, pancreatic carcinoma, colorectal carcinoma, bladder carcinoma, head and neck squamous cell carcinoma, ovarian carcinoma, adenocarcinoma of the gastroesophageal junction, head and neck carcinoma, breast carcinoma, gastric adenocarcinoma, esophageal carcinoma, gastric carcinoma, bile duct carcinoma, cholangiocarcinoma, prostate carcinoma, malignant salivary gland neoplasm, urothelial carcinoma, nasal cavity and paranasal sinus carcinoma, nasopharyngeal carcinoma, penile carcinoma, small cell lung carcinoma, oropharyngeal carcinoma, oropharyngeal squamous cell carcinoma, gallbladder carcinoma, lung carcinoma, lip and oral cavity carcinoma, malignant uterine neoplasm, malignant laryngeal neoplasm, cervical carcinoma, hepatobiliary neoplasm, malignant hepatobiliary neoplasm, malignant germ cell tumor, or thymic carcinoma), lymphoma (optionally, lymphoma, non-Hodgkin lymphoma, small lymphocytic lymphoma, anaplastic large cell lymphoma, B-cell non-Hodgkin lymphoma, follicular lymphoma, or diffuse large B-cell lymphoma), systemic mastocytosis (optionally, systemic mastocytosis (SM) or SM with an associated hematological neoplasm (SM-AHN)), or brain cancer (optionally, brain cancer, glioblastoma, malignant glioma, or anaplastic astrocytoma). In some embodiments, the KIT positive cancer is GIST. In some embodiments, the KIT positive cancer is melanoma. In some embodiments, the KIT positive cancer is systemic mastocytosis.

Alterations and Mutations in KIT Positive Cancers

[0101] In some embodiments, the KIT positive cancer comprises KIT with an activating KIT alteration. In some embodiments, the activating KIT alteration is encoded by a *KIT* mutation, optionally wherein the *KIT* mutation is a deletion, point mutation, or duplication, or a combination thereof. In some embodiments, the activating KIT alteration is encoded by *KIT* exon 11. In some embodiments, the activating KIT alteration is between positions Lys550 and Glu561, optionally wherein the KIT alteration comprises an alteration at position Trp557, Val559, Val560, or Leu576, optionally wherein the KIT alteration is Trp557_Lys558del, Asp579del, Lys550_Lys558del, Trp557Arg, Val559Asp, Val559Ala, Val559Gly, Val560Asp, Val560Gly, Leu576Pro, Val560del, Gln575_Leu576dup, or Asp579del. In some embodiments, the activating KIT alteration is encoded by *KIT* exon 9. In some embodiments, the activating KIT alteration is at position Ala502 or Tyr503, or is Ala_Tyr503dup or Phe504_Phe508dup. In some embodiments, the activating KIT alteration is T670X. In some embodiments, the activating KIT alteration is not T670X.

[0102] In some embodiments, wherein the KIT positive cancer comprises KIT with a secondary KIT inhibitor-resistant alteration. In some embodiments, the secondary KIT inhibitor-resistant alteration is an imatinib-resistant alteration. In some embodiments, wherein the secondary KIT inhibitor-resistant alteration is encoded by *KIT* exon 13, exon 14, or exon 17. In some embodiments, the secondary KIT inhibitor-resistant alteration is encoded by *KIT* exon 13. In some embodiments, the secondary KIT inhibitor-resistant alteration is encoded by *KIT* exon 17. In some embodiments, wherein the secondary KIT inhibitor-resistant alteration is encoded by *KIT* exon 18. In some embodiments, the secondary KIT inhibitor-resistant alteration is encoded by *KIT* exon 13. In some embodiments, wherein the secondary KIT inhibitor-resistant alteration is encoded by *KIT* exon 14. In some embodiments, the secondary KIT inhibitor-resistant alteration is at position Val654 (e.g., Val654Ala), Thr670 (e.g., Thr670Ile), Asp816, Asp820, Asn822, or Tyr823 (e.g., Tyr823Asp). In some embodiments, wherein the secondary KIT inhibitor-resistant alteration is encoded by *KIT* exon 17 and/or exon 18 and the concomitant KIT inhibitor is ripretinib. In some embodiments, wherein the secondary KIT inhibitor-resistant alteration is encoded by *KIT* exon 13 and/or exon 14 and the concomitant KIT inhibitor is sunitinib.

[0103] In some embodiments, the KIT positive cancer has amplified KIT and/or overexpressed KIT, in addition to the alteration.

[0104] In certain instances, characterization of a KIT alteration, or of an activating *KIT* mutation (e.g., a point mutation, duplication, or deletion), can be achieved via collection of a patient sample, such as a bone marrow sample (BM aspirate), a whole blood sample, and/or tumor sample, or cell-free DNA, exosomes, or circulating tumor cells, followed by analysis of nucleic acids or protein sequences in the sample. In certain embodiments, a *KIT* mutation, such as a deletion, substitution, or duplication, is detected by sequencing (e.g., genomic sequencing), for example, by next-generation sequencing (NGS), polymerase chain reaction (PCR), RT-PCR, quantitative PCR (qPCR), or SNP array, such as by a companion diagnostic assay or a CLIA-validated, next-generation sequencing assay. In certain embodiments, a particular mutation is detected by molecular testing, such as by PCR (e.g., followed by fragment analysis and/or capillary gel electrophoresis). In certain embodiments, a mutation is detected by PCR using primers that are specific to the mutation and not the wild-type DNA sequence (e.g., allele-specific PCR). In certain embodiments, a mutation is detected by RT-PCR or qPCR. In certain embodiments, qPCR and RT-qPCR include quantifying mutations, duplications, or substitutions. In some embodiments, the methods provided herein comprise detecting a mutation, such as a duplication, deletion, or substitution, or receiving an identification of the mutation, optionally by a next-generation sequencing assay or a PCR assay, prior to administering the menin inhibitor.

Efficacy/Clinical Activity/Safety

[0105] Clinical activity of the treatments described herein may be evaluated according to rates of clinical benefit rate (CBR) (defined as patients achieving CR, PR, or SD based on mRECIST criteria, where SD must have been maintained, or that lasts, for at least 16 weeks), CR, ORR (CR + PR), DCR, duration of response (DoR), PR, SD, PFS, or OS, or a combination thereof, according to the ELN 2022 or RECIST v1.1 criteria, as applicable for the particular cancer type. Alternatively, the Choi criteria (measure of size and density of tumors) or radiographic determination (e.g., PET-CT scan) may be used to assess response. In some embodiments, the combination of a menin inhibitor, such as ziftomenib, and a concomitant KIT inhibitor, provides greater clinical activity than either agent alone. In some embodiments, the combination of a menin inhibitor, such as ziftomenib, and a concomitant KIT inhibitor provides greater than additive clinical activity, or synergistic activity.

[0106] Safety of the treatments described herein may be evaluated according to rates of dose-limiting toxicity or descriptive statistics of adverse events per the NCI-CTCAE v. 5.0.

Pharmaceutical Compositions

[0107] In some embodiments, provided herein is a pharmaceutical composition comprising a menin inhibitor, such as ziftomenib or a pharmaceutically acceptable form thereof, and a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition comprises ziftomenib or a pharmaceutically acceptable salt thereof, or a solvate thereof. In some embodiments, provided herein is a pharmaceutical composition comprising a menin inhibitor, such as ziftomenib or a pharmaceutically acceptable form thereof, and a KIT inhibitor, such as imatinib (e.g., imatinib mesylate), sunitinib (e.g., sunitinib malate), regorafenib, ripretinib, dasatinib, avapritinib, masitinib, or nilotinib, and a pharmaceutically acceptable excipient. In some embodiments, the methods provided herein comprise administering such pharmaceutical compositions.

[0108] Pharmaceutical compounds are formulated according to several factors well within the purview of those of ordinary skill in the art. These include, without limitation: the type and nature of the active agent being formulated; the subject to which the agent-containing composition is to be administered; the intended route of administration of the composition; and the therapeutic indication being targeted.

[0109] The pharmaceutical compositions are intended to be administered by a suitable route, including but not limited to orally, parenterally, rectally, topically, locally, intradermally, intramuscularly, intraperitoneally, percutaneously, intravenously, subcutaneously, intranasally, epidurally, sublingually, intracerebrally, intravaginally, transdermally, mucosally, by inhalation, or topically to the ears, nose, eyes, or skin. The pharmaceutical compositions are in liquid, semi-liquid or solid form and are formulated in a manner suitable for each route of administration. In some embodiments, the pharmaceutical compositions provided herein are administered orally. For oral administration, capsules and tablets can be formulated.

[0110] In some embodiments, the pharmaceutical compositions are provided for administration to a subject in dosage forms such as tablets, capsules, microcapsules, pills, powders, granules, troches, suppositories, injections, syrups, patches, creams, lotions, ointments, gels, sprays, sterile parenteral solutions or suspensions, and oral solutions or suspensions, and oil water emulsions containing suitable quantities of the compounds or pharmaceutically acceptable forms thereof. In some embodiments, the pharmaceutical compositions provided herein are in the form of a tablet. In some embodiments, the pharmaceutical compositions provided herein are in the form of a capsule.

Kits

[0111] For use in the therapeutic applications described herein, kits and articles of manufacture are also provided. In some embodiments, such kits comprise a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers are formed from a variety of materials such as glass or plastic.

[0112] In yet another aspect, the present disclosure provides a kit comprising (1) an effective amount of a pharmaceutical composition comprising a menin inhibitor and a pharmaceutically acceptable carrier or excipient, in a first dosage form; and (2) a composition comprising a KIT inhibitor and a pharmaceutically acceptable carrier or excipient, in a second dosage form.

[0113] The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products include those found in, e.g., U.S. Pat. Nos. 5,323,907, 5,052,558 and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment. For example, the container(s) includes a menin inhibitor (e.g., ziftomenib), or a pharmaceutically acceptable form thereof, optionally in a composition or in combination with another agent as disclosed herein. The container(s) optionally have a sterile access port (for example the container is an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). Such kits optionally comprising a compound with an identifying description or label or instructions relating to its use in the methods described herein.

[0114] For example, a kit typically includes one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for use of a compound described herein. Non-limiting examples of such materials include, but not limited to, buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use. A set of instructions will also typically be included. A label is optionally on or associated with the container. For example, a label is on a container when letters, numbers or other characters forming the label are attached, molded, or etched into the container itself, a label is associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. In addition, a label is

used to indicate that the contents are to be used for a specific therapeutic application. In addition, the label indicates directions for use of the contents, such as in the methods described herein. In certain embodiments, the pharmaceutical composition is presented in a pack or dispenser device which contains one or more unit dosage forms containing a compound provided herein. The pack, for example, contains metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may be accompanied by a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, is the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. In some embodiments, compositions containing a compound provided herein formulated in a compatible pharmaceutical carrier are prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

Definitions

[0115] Compounds of the present disclosure also include crystalline and amorphous forms of those compounds, pharmaceutically acceptable salts, and active metabolites of these compounds having the same type of activity, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrides), conformational polymorphs, and amorphous forms of the compounds, as well as mixtures thereof.

[0116] As used herein, a “pharmaceutically acceptable form” of a compound disclosed herein includes a tautomer, stereoisomer, mixture of stereoisomers, or racemic mixture thereof, or an isotopologue thereof, a pharmaceutically acceptable salt of any of the preceding forms, or a solvate of any of the preceding forms. In some embodiments, ziftomenib or a “pharmaceutically acceptable form” thereof includes, but is not limited to, ziftomenib or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[0117] The compounds described herein may exhibit their natural isotopic abundance, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. All isotopic variations of the compounds of the present disclosure, whether radioactive or not, are encompassed within the scope of the present disclosure. For example, hydrogen has three naturally occurring isotopes, denoted ^1H (protium),

²H (deuterium), and ³H (tritium). Protium is the most abundant isotope of hydrogen in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increased in vivo half-life and/or exposure, or may provide a compound useful for investigating in vivo routes of drug elimination and metabolism. Isotopically enriched compounds may be prepared by conventional techniques well known to those skilled in the art.

[0118] The term “isotopolog” refers to an isotopically enriched compound. The term “isotopically enriched” refers to an atom having an isotopic composition other than the natural isotopic composition of that atom. “Isotopolog” can also refer to a compound containing at least one atom having an isotopic composition other than the natural isotopic composition of that atom. The term “isotopic composition” refers to the amount of each isotope present for a given atom. Radiolabeled and isotopically enriched compounds are useful as therapeutic agents, e.g., multiple myeloma therapeutic agents, research reagents, e.g., binding assay reagents, and diagnostic agents, e.g., in vivo imaging agents. All isotopic variations of the compounds described herein, whether radioactive or not, are intended to be encompassed within the scope of the embodiments provided herein.

[0119] “Isomers” are different compounds that have the same molecular formula. “Stereoisomers” are isomers that differ only in the way the atoms are arranged in space. “Enantiomers” are a pair of stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a “racemic” mixture. The term “(±)” is used to designate a racemic mixture where appropriate. “Diastereoisomers” or “diastereomers” include stereoisomers that have at least two asymmetric atoms but are not mirror images of each other. The absolute stereochemistry is specified according to the Cahn-Ingold-Prelog R-S system. When a compound is a pure enantiomer, the stereochemistry at each chiral carbon can be specified by either R or S. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) in which they rotate plane polarized light at the wavelength of the sodium D line. Certain compounds described herein contain one or more asymmetric centers and can thus give rise to enantiomers, diastereomers, and other stereoisomeric forms, the asymmetric centers of which can be defined, in terms of absolute stereochemistry, as (R)- or (S)-. The present chemical entities, pharmaceutical compositions and methods are meant to include all such possible stereoisomers, including racemic mixtures, optically pure forms, mixtures of diastereomers and intermediate mixtures. Optically active (R)- and (S)-isomers can be prepared using chiral synthons or chiral reagents or can be resolved using conventional techniques. The optical activity of a compound

can be analyzed via any suitable method, including but not limited to chiral chromatography and polarimetry, and the degree of predominance of one stereoisomer over the other isomer can be determined.

[0120] Chemical entities having carbon-carbon double bonds or carbon-nitrogen double bonds may exist in Z- or E- form (or cis- or trans- form). Furthermore, some chemical entities may exist in various tautomeric forms. Unless otherwise specified, chemical entities described herein are intended to include all Z-, E- and tautomeric forms as well.

[0121] The term “solvate” generally refers to a compound (e.g., free base) or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of solvent bound by non-covalent intermolecular forces. Wherein the solvent is water, the solvate is a hydrate.

[0122] The term “salt” or “pharmaceutically acceptable salt” refers to salts derived from a variety of organic and inorganic counter ions well known in the art. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. In some embodiments, the pharmaceutically acceptable base addition salt is chosen from ammonium, potassium, sodium, calcium, and magnesium salts.

[0123] The term “pharmaceutical composition” generally refers to a composition comprising a therapeutic agent and a pharmaceutically acceptable excipient. A “pharmaceutically acceptable excipient” refers to media generally accepted in the art for the delivery of biologically active agents to an individual, including, e.g., adjuvants, vehicles, diluents, preserving agents, fillers, flow regulating agents, disintegrating agents, wetting agents, emulsifying agents, suspending agents, sweetening agents, flavoring agents, perfuming agents, antibacterial agents, antifungal

agents, lubricating agents and dispensing agents, depending on the nature of the mode of administration and dosage forms. Suitable carriers include without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye, colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals. Descriptions of suitable pharmaceutically acceptable excipients, and factors involved in their selection, are found in a variety of readily available sources such as, for example, Allen, L. V., Jr. et al., Remington: The Science and Practice of Pharmacy (2 Volumes), 22nd Edition, Pharmaceutical Press (2012).

[0124] As used herein, “treatment” or “treating” refers to an approach for obtaining beneficial or desired results with respect to a disease, disorder, or medical condition (e.g., AML) including but, in certain instances, not limited to a therapeutic benefit and/or a prophylactic benefit.

Therapeutic benefit refers to eradication or amelioration of the underlying disorder being treated. A therapeutic benefit is also achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the individual, notwithstanding that the individual may still be afflicted with the underlying disorder. In certain embodiments, for prophylactic benefit, the compositions are administered to an individual at risk of developing a particular disease, or to an individual reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease may not have been made.

[0125] As used herein, the term “effective amount” in connection with a compound means an amount capable of treating, preventing, or managing a disorder, disease, or condition, or one or more symptoms thereof.

[0126] “Individual” refers to an animal, such as a mammal, for example a human. The methods described herein can be useful in both human therapeutics and veterinary applications. In some embodiments, the individual is a mammal, and in some embodiments, the individual is human. “Mammal” includes humans and both domestic animals such as laboratory animals and household pets (e.g., cats, dogs, swine, cattle, sheep, goats, horses, rabbits), and non-domestic animals such as wildlife and the like. In some embodiments, the human is ≥ 18 years of age. In some embodiments, the human is less than 18 years of age, less than 12 years of age, less than 6, 5, 4, 3, 2, or 1 year of age.

[0127] Clinical terms used herein include the following: “CR” means a complete remission; the CR rate is defined as the population of patients achieving a best overall response of CR; “PR” means partial response; “SD” means stable disease without progression; “ORR” means overall response rate; “DCR” means disease control rate; “DoR” means duration of response; “PFS” means progression-free survival; “OS” means overall survival; and “CBR” means clinical benefit rate.

[0128] The term “combination,” “administered in combination with,” “concomitant,” and their grammatical equivalents, as used herein, encompass administration of two or more agents to an animal, including humans, so that both agents and/or their metabolites are present in the individual at the same time. Concomitant administration includes administration in separate compositions or administration in a composition in which both agents are present.

[0129] The term “inhibitor” refers to a compound having the ability to inhibit a biological function (e.g., activity, expression, binding, protein-protein interaction) of a target protein (e.g., menin, MLL1, MLL2, and/or an MLL fusion protein, or KIT). Preferably, the biological activity inhibited by an inhibitor is associated with the development, growth, or spread of a tumor.

[0130] As used herein, a “sample” includes and/or refers to any fluid or liquid sample which is being analyzed in order to detect and/or quantify an analyte. In some embodiments, a sample is a biological sample. Examples of samples include without limitation a bodily fluid, an extract, a solution containing proteins and/or DNA, a cell extract, a cell lysate, or a tissue lysate. Non-limiting examples of bodily fluids include urine, saliva, blood, serum, plasma, cerebrospinal fluid, tears, semen, sweat, pleural effusion, liquified fecal matter, and lacrimal gland secretion.

[0131] The term “in vivo” refers to an event that takes place in an individual’s body.

[0132] The term “in vitro” refers to an event that takes places outside of an individual’s body. For example, an in vitro assay encompasses any assay run outside of an individual. In vitro assays encompass cell-based assays in which cells alive or dead are employed. In vitro assays also encompass a cell-free assay in which no intact cells are employed.

[0133] As used herein, “KIT positive cancer” refers to a cancer characterized by at least one activating KIT alteration.

[0134] As used herein, a “KIT alteration” is a change in the protein sequence of the KIT protein relative to the wild-type sequence.

[0135] As used herein, an “activating KIT alteration” refers to a change in the KIT protein sequence that is a gain-of-function change. In some aspects, a KIT positive cancer is driven by

or dependent on activating KIT alteration such as an activating KIT mutation. An activating KIT alteration may be an amino acid deletion, point mutation, or duplication relative to the wild-type protein sequence. Examples of activating KIT alterations include alterations encoded by mutations in *KIT* exon 11 (such as, but not limited to, KIT alterations between positions Lys550 and Glu561, optionally at position Trp557, Val559, Val560, or Leu576, optionally wherein the KIT alteration is Trp557_Lys558del, Asp579del, Lys550_Lys558del, Trp557Arg, Val559Asp, Val559Ala, Val559Gly, Val560Asp, Val560Gly, Leu576Pro, Val560del, Gln575_Leu576dup, or Asp579del) or exon 9 (such as, but not limited to, KIT alteration at position Ala502 or Tyr503, or is Ala_Tyr503dup or Phe504_Phe508dup). A mutation in *KIT* exons can be, for example, a deletion, point mutation, or duplication in the genetic sequence of *KIT*.

[0136] As used herein, “secondary KIT inhibitor-resistant alteration” refers to a KIT alteration that is induced by treatment with a KIT inhibitor. In some aspects, the inhibitory activity of the KIT inhibitor against KIT bearing the secondary KIT inhibitor-resistant alteration is reduced relative to the inhibitory activity against KIT without the secondary KIT inhibitor-resistant alteration. As used herein, “imatinib-resistant alteration” refers to a KIT alteration that is induced by treatment with imatinib (e.g., imatinib mesylate). In some aspects, KIT inhibition by imatinib is reduced in KIT with an imatinib-resistant alteration relative to KIT without the imatinib-resistant alteration. In some aspects, the secondary KIT inhibitor-resistant alteration is encoded by *KIT* exon 13, exon 14, or exon 17, or in exon 18. In some aspects, the secondary inhibitor-resistant alteration is at KIT position Val654 (e.g., Val654Ala), Thr670 (e.g., Thr670Ile), Asp816, Asp820, Asn822, or Tyr823 (e.g., Tyr823Asp).

[0137] As used herein, “amplified” refers to a cell with at least 4 copies, or at least 6 copies, or at least 8 copies of a particular gene. Amplification can occur due to overexpression or by epigenetic support or both. As used herein, “overexpressed” refers to production of an excess of a protein due to activation of the relevant gene.

[0138] As used herein, “concomitant KIT inhibitor” refers to a KIT inhibitor that is administered in combination with a menin inhibitor. The two agents may be administered according to coincident regimens, such that the agents may both be administered on the same days, or on most of the same days, taking into account any on/off regimens for one or both agents.

[0139] As used herein a “prior KIT inhibitor” refers to a KIT inhibitor that has been administered to the individual prior to the methods described herein. In some instances, the prior KIT inhibitor and the concomitant KIT inhibitor can be the same KIT inhibitor. For

example, in some instances, an individual is treated with a KIT inhibitor, and the menin inhibitor is added to the treatment. In some instances, an individual is treated with a KIT inhibitor, and then the individual is treated with a menin inhibitor and a different KIT inhibitor. Preferably, the prior KIT inhibitor and the concomitant KIT inhibitor are different KIT inhibitors.

[0140] As used herein, “progression” of a cancer refers to disease progression as determined by: (a) radiographic progression or clinical progression or both; (b) increased burden of disease; or (c) symptomatic deterioration (e.g., increase in abdominal pain, nausea, vomiting, nerve pain, or pruritis, or negative laboratory test changes); or a combination thereof. Progression can occur while off a treatment, during a particular treatment, or after a particular treatment.

[0141] As used herein, “refractory” refers to a cancer that does not respond or has stopped responding to treatment.

[0142] As used herein, “relapsed” after or “failed” on a particular treatment refer to a cancer that initially responded to the particular treatment, but subsequently the cancer returned or progressed, either during the particular treatment or after the particular treatment was stopped. Initial active responses to a particular treatment may include stable disease (SD), partial response (PR), or complete response (CR). “Relapse” or “failure” includes, for example, an initial response of SD, PR, or CR followed by disease progression, or initial response of PR or CR followed by SD or disease progression.

[0143] As used herein, where a cancer “responds insufficiently to” a KIT inhibitor, the cancer has not achieved a complete response or has not achieved a partial response, or has not achieved stable disease, or has achieved stable disease, and then progressed, or has achieved a complete response, partial response, or stable disease for at least 3 months, or at least 6 months, or at least 12 months (at which time the cancer is at increased risk of progression).

[0144] As used herein, a “line” of treatment is a course of treatment with a particular therapy or combination of therapies. For example, imatinib (imatinib mesylate) is approved as a first-line or first line of treatment for GIST. A subsequent treatment would be referred to as a second-line or second line of treatment. Sunitinib (sunitinib malate) is approved as a second-line or second line of treatment for GIST. A subsequent treatment would be referred to as a third-line or third line of treatment.

[0145] As used herein, “safety risk” refers to the risk of an individual suffering from one or more adverse events, such as a treatment-related or treatment-associated adverse event, or a severe treatment-related or treatment-associated adverse event (e.g., an event at greater than or equal to Grade 3 severity). Exemplary safety risks for KIT inhibitors include edema, fluid

retention, cytopenias (e.g., anemia, neutropenia, thrombocytopenia), congestive heart failure, left ventricular dysfunction, hepatotoxicity, hemorrhage, gastrointestinal perforation, nausea, vomiting, muscle cramps, musculoskeletal pain, diarrhea, rash, fatigue, abdominal pain, decreased appetite, hypertension, infection, dysphonia, hyperbilirubinemia, fever, and mucositis.

[0146] As used herein, the words “comprising” (and any form of comprising, such as “comprise” and “comprises”), “having” (and any form of having, such as “have” and “has”), “including” (and any form of including, such as “include” and “includes”) or “containing” (and any form of containing, such as “contain” and “contains”), are inclusive or open-ended and do not exclude additional, unrecited elements or process steps. As also used herein, in any instance or embodiment described herein, “comprising” may be replaced with “consisting essentially of” and/or “consisting of”. used herein, in any instance or embodiment described herein, “comprises” may be replaced with “consists essentially of” and/or “consists of”.

[0147] As used herein, the term “and/or” is to be taken as specific disclosure of each of the two specified features or components with or without the other. For example, “A and/or B” is to be taken as specific disclosure of each of (i) A, (ii) B and (iii) A and B, just as if each were set out individually herein.

[0148] As used herein, the term “about,” when used in connection with doses, amounts, or weight percentages, mean a dose, amount, or weight percent within 10%, or within 5%, or within 2%, or within 1% of the stated amount.

[0149] Where a numerical value is used herein, such a value may encompass a range that is $\pm$ 5% of the stated numerical value.

EXAMPLES

[0150] The following examples are included for illustrative purposes only and are not intended to limit the scope of the present disclosure.

Patient-Derived Xenograft (PDX) Models

[0151] Human gastrointestinal stromal tumor (GIST) patient-derived xenograft (PDX) models GS11331, GS5106, and GS5108, and human melanoma models ME12098 and ME3332 (Crown Bioscience, Beijing) were used for the following studies. The KIT alterations, alteration types, amplification status, KIT expression status, and imatinib status (sensitive or resistant to imatinib) for each model is listed in **Table 1**. All models expressed KIT at an elevated level of at least 7.5 fragments per kilobase of transcript per million mapped reads (FPKM).

Table 1. Exemplary PDX Model Characteristics

Model	KIT Alterations	Alt. Type	Amplification	Imatinib
GS11331	W557_K558del, V654A	Ex11 del, Ex 13 heterozygous	No	resistant
GS5106	K642E, N822K	Ex13, Ex17	No	resistant
GS5108	W557-K558del, Y823D	Ex11 del, Ex17	No	resistant
GS11338	WT, low expression	NA	No	NA
GS11341	V559, low expression	Ex11	No	NA
GS11360	V559G	Ex11	No	sensitive
ME3332	L567P	Ex11	No (3 copies)	sensitive
ME12098	L567P	Ex11	Yes (7 copies)	sensitive
ME6928	L567P	Ex11	Yes (18 copies)	sensitive
ME12172	WT	Not overexpressed	Yes (8 copies)	resistant
GIST-T1	V560_Y578del	Ex11 del	No	sensitive

[0152] For efficacy studies, randomization was performed based on the “matched distribution” method (StudyDirector™ software, version 3.1.399.19). The date of randomization was denoted as Day 0. The treatment was initiated on the same day of randomization (Day 0) as per the study design. After tumor inoculation, the animals were checked daily for morbidity and mortality. During routine monitoring, the animals were checked for any effects of tumor growth and treatments on behavior such as mobility, food and water consumption, body weight gain/loss (body weights were measured twice per week after randomization), eye/hair matting, and any other abnormalities. Mortality and observed clinical signs were recorded for individual animals in detail. Tumor volumes were measured twice per week after randomization in two dimensions using a caliper, and the volume was expressed in mm³ using the formula: $V = (L \times W \times W)/2$, where V is tumor volume, L is tumor length (the longest tumor dimension), and W is tumor width (the longest tumor dimension perpendicular to L). Dosing as well as tumor measurements were conducted in a Laminar Flow Cabinet. The tumor volumes were measured by using StudyDirector™ software (version 3.1.399.19). Tumor growth inhibition (TGI) was calculated as $TGI\% = (1 - Ti/Vi) \times 100$, with Ti as the mean tumor volume of the treatment group on the measurement day and Vi as the mean tumor volume of control group at the measurement day. P-values are based on two-tailed unpaired t-test.

Example 1 – GS11331 (Ex11del, V654A) GIST PDX Studies

Efficacy Assessments

[0153] Tumor fragments from stock mice were harvested and used for inoculation into female Balb/c nude mice. Each mouse was inoculated subcutaneously in the right upper flank with primary human tumor xenograft model tumor fragment (2-3 mm in diameter) for tumor development. Randomization started when the mean tumor size reached approximately 275 – 277 mm³.

[0154] Study 1: Animals were randomly allocated to 4 study groups, with 5 mice in each group. GS11331 xenograft mice (model of a second-line treatment in imatinib-resistant disease) were treated orally with: control vehicle (20% w/v hydroxypropyl- β -cyclodextrin, pH 2.5), QD; ziftomenib, 2X mg/kg (aqueous solution), QD; imatinib, 100 mg/kg (solution in 2% DMSO+30% PEG 300 + 2% Tween 80 + ddH₂O), QD; ziftomenib, 2X mg/kg, QD, plus imatinib, 100 mg/kg, QD; sunitinib, 10 mg/kg (solution in 10% w/v 2-hydroxypropyl- β -cyclodextrin), QD, 5-days ON + 2-days OFF; or ziftomenib, 2X mg/kg, QD, plus sunitinib, 10 mg/kg, QD, 5-days ON + 2-days OFF. Mice were treated with vehicle or test agents for 4 weeks (28 days) and tumor growth was observed for another 4 weeks (regrowth observation period). Animals were terminated on Day 56. As shown in **FIG. 2**, as of Day 28, imatinib single agent treatment slowed tumor growth (TGI 56.7%; standard error, 9.98; p-value vs. vehicle, 1.71E-02), but only induced tumor stasis and did not achieve tumor regression. This result was not unexpected given that GS11331 model carries an imatinib-resistant KIT protein mutation. Ziftomenib single agent treatment did not show significant anti-tumor effects (TGI, -8.54%; standard error, 20.8; p-value vs. vehicle, not significant (ns)). The combination treatment of ziftomenib and imatinib showed significant tumor regression at Day 28 (TGI, 99.62%; standard error, 0.226; p-value vs. vehicle, 2.82e-08) and this change was statistically significant relative to TGI for imatinib alone (p-value = 0.0001). In the combination group, 3 out of 5 animals achieved a complete response as indicated by tumor volume measuring 0.00 mm³. As of Day 28, sunitinib single agent treatment slowed tumor growth (TGI 72.9%; standard error, 9.18; p-value vs. vehicle, 1.32E-03), but only induced tumor stasis and did not achieve tumor regression. The combination treatment of ziftomenib and sunitinib showed significant tumor regression at Day 28 (TGI, 99.34%; standard error, 0.168; p-value vs. vehicle, 1.566E-07) and this change was statistically significant relative to TGI for sunitinib alone (p-value = 5.41E-03). In the ziftomenib/sunitinib combination group, 4 out of 5 animals achieved a complete response as indicated by tumor volume measuring 0.00 mm³. These results indicate that the mechanism of action of the combination depends on the synthetic lethality in which ziftomenib targets the vulnerability of GIST tumors created by the TKI treatments. Animals stayed as complete

response for 2 weeks for the sunitinib combination and 4 weeks for the imatinib combination during the regrowth observation period, indicating durability of the response to the combination following the end of treatment.

[0155] Study 2: Animals were randomly allocated to 10 study groups with 5 mice in each group. GS11331 xenograft mice were treated orally with: control vehicle (20% w/v hydroxypropyl- β -cyclodextrin, pH 2.5), QD; ziftomenib, 2X mg/kg (aqueous solution), QD; imatinib, 100 mg/kg (solution in 2% DMSO+30% PEG 300 + 2% Tween 80 + ddH₂O), QD; revumenib, 50 mg/kg (solution in 20% w/v hydroxypropyl- β -cyclodextrin, pH 5.0), BID; regorafenib, 3 mg/kg (2% DMSO + 30% PEG 300 + 5% Tween 80 + ddH₂O), QD, 5-days ON + 2-days OFF; ziftomenib, 2X mg/kg, QD, plus imatinib, 100 mg/kg, QD; ziftomenib, 1X mg/kg, QD, plus imatinib, 100 mg/kg, QD; ziftomenib, 0.5X mg/kg, QD, plus imatinib, 100 mg/kg, QD; revumenib, 50 mg/kg, BID, plus imatinib, 100 mg/kg, QD; or ziftomenib, 2X mg/kg, QD, plus regorafenib, 3 mg/kg (2% DMSO + 30% PEG 300 + 5% Tween 80 + ddH₂O), QD, 5-days ON + 2-days OFF. Mice were treated with vehicle or test agents for 4 weeks, and tumor growth was observed for another 2 weeks (regrowth observation period). Animals were terminated on Day 42.

[0156] As shown in **FIG. 3**, as of Day 28, imatinib single agent treatment slowed tumor growth (TGI 61.1%; standard error, 6.70; p-value vs. vehicle, 4.85E-04), but only induced tumor stasis and did not achieve tumor regression, as expected. Two menin inhibitors, ziftomenib and revumenib, as single agents, did not induce significant anti-tumor effects by Day 28 (ziftomenib: TGI, 20.7%; standard error, 14.1; p-value vs. vehicle, ns; revumenib: TGI, 20.3%; standard error, 10.3; p value vs. vehicle, ns). In contrast, combinations of ziftomenib or revumenib with imatinib both showed significant tumor regression at Day 28 (ziftomenib: TGI, 99.4%; standard error, 0.26; p value vs. vehicle, 4.71E-13; revumenib: TGI, 74.9%; standard error, 4.69; p-value vs. vehicle, 7.18E-06), indicating a mechanism-based effect for the combination of a menin inhibitor with a KIT inhibitor. For the combinations, the TGI at Day 28 was also statistically significant relative to imatinib single agent treatment (ziftomenib combination, p-value < 0.0001; revumenib combination, p-value < 0.01). In the ziftomenib-imatinib combination group, 1 out of 5 animals achieved a complete response by Day 28, as indicated by tumor volume measuring 0.00 mm³, and maintained the complete response for 11 days, and two more animals achieved complete responses during the regrowth observation period. These results indicate the durability of the effect of the combination extends beyond the end of treatment. Regorafenib data are described below.

[0157] Shown in **FIG. 4** are data extracted from **FIG. 3** showing results from the study for different doses of ziftomenib (2X mg/kg, 1X mg/kg and 0.5X mg/kg, QD) in combination with imatinib (100 mg/kg, QD) that were studied to identify the saturating ziftomenib dose in the combination. By Day 28, all doses of the combination treatments produced significant TGI (2X mg/kg combo: TGI 99.4%, standard error 0.258, p-value vs. vehicle 4.707E-13; 1X mg/kg combo: TGI 99.5%, standard error 0.153, p-value vs. vehicle 4.772E-13; 0.5X mg/kg combo: TGI 98.0%, standard error 0.466, p-value vs. vehicle 4.766E-12). In the 2X mg/kg and 1X mg/kg combination groups, one animal in each group had achieved a complete response on Day 28. Tumors in the 0.5X mg/kg group showed significant regression but without any complete responses. After dosing was stopped, the 0.5X mg/kg group showed substantial tumor regrowth (p-value vs. 2X mg/kg combo 5.590e-05) during the tumor regrowth period (14 days), while the 1X mg/kg group did not show a significant difference in tumor volume compared to the 2X mg/kg group. These observations suggest that 1X mg/kg of ziftomenib is sufficient to saturate the response of the ziftomenib-imatinib combination in this model.

[0158] Shown in **FIG. 5** are data extracted from **FIG. 3** for regorafenib single agent, ziftomenib (2X mg/kg) plus imatinib, and ziftomenib (2X mg/kg) plus regorafenib groups. All treatments produced significant tumor regression on Day 28 (regorafenib: TGI 95.2%, standard error 0.646, p-value vs. vehicle 5.881e-09; ziftomenib-imatinib combo: TGI 99.4%, standard error 0.258, p-value vs. vehicle 4.707e-13; ziftomenib-regorafenib combo: TGI 99.8%, standard error 0.113, p-value vs. vehicle 4.641e-13). On Day 28, 1 animal in the ziftomenib-imatinib group, 2 in the ziftomenib-regorafenib group, and 0 in the regorafenib group had achieved a complete response. Both ziftomenib combinations showed superior efficacies compared to regorafenib single agent (regorafenib vs. (a) ziftomenib-imatinib combo, p-value 2.033e-04; and (b) ziftomenib-regorafenib combo, 1.611e-06). During the regrowth observation period, regorafenib group animals relapsed, while the animals in both combination groups maintained the efficacies measured by tumor volume on Day 42 (regorafenib vs. (a) ziftomenib-imatinib combo, p-value 7.298e-05; and (b) ziftomenib-regorafenib combo, p-value 6.558e-06).

[0159] The combination of ziftomenib with various TKIs such as imatinib, regorafenib, and sunitinib significantly improved the anti-tumor effect of TKIs in KIT-mutated GIST tumors. In addition, our data suggests that combining ziftomenib with 1L therapy imatinib seems to be superior to later lines of therapies (sunitinib and regorafenib).

Pharmacodynamics Analysis

[0160] To address the molecular mechanism of synthetic lethality demonstrated by the combination treatment in the GS11331 PDX studies, GS11331 tumor samples were harvested and subjected to western blot.

[0161] Tumor fragments from stock mice were harvested and used for inoculation into female Balb/c nude mice. Each mouse was inoculated subcutaneously in the right upper flank with primary human tumor xenograft model tumor fragment (2-3 mm in diameter) for tumor development. Randomization started when the mean tumor size reached approximately 464 mm³. Animals were randomly allocated to 4 study groups, with 6 mice in each group. GS11331 xenograft mice were treated orally with: control vehicle (20% w/v hydroxypropyl- β -cyclodextrin, pH 2.5), QD; ziftomenib, 2X mg/kg (aqueous solution), QD; imatinib, 100 mg/kg (solution in 2% DMSO+30% PEG 300 + 2% Tween 80 + ddH₂O), QD; or ziftomenib, 2X mg/kg, QD, plus imatinib, 100 mg/kg, QD. Three animals from each group were sacrificed and tumors harvested on Day 5 (when tumors in the combination group were about to regress) and the other three animals from each group were sacrificed and tumors harvested on Day 8 (when tumors were in the middle of regression). Tumor samples were collected from three animals for all groups the next day post the last dose. Tumor volume (TV) was measured for each animal, and mean tumor volumes for each test group are shown in **FIG. 6**.

[0162] Each tumor sample was split into two pieces, and half was snap-frozen for protein analysis. Snap-frozen tumor samples were cut into smaller pieces and lysed in 1X cell lysis buffer (Cell Signaling Technology #9803) supplemented with Halt protease inhibitor cocktail (Thermo Scientific #78430) using a Bead Mill Homogenizer 20 (Fisher Brand). Lysates were cleared by centrifugation (maximum speed, 10 min) and protein concentration was determined by bicinchoninic acid (BCA) assay (Pierce). Lysate (20-30 μ g) was loaded on to 4-12% Bis-Tris gels (NuPAGE, Invitrogen) for electrophoresis and immunoblotting.

[0163] Western blot analysis was performed to evaluate Day 5 samples for total KIT, phosphorylated KIT (Y803), total AKT, phosphorylated AKT (S473), total S6, phosphorylated S6 (S235/236), phosphorylated mTOR (S537), total ERK, phosphorylated ERK (T202/Y204), cleaved PARP, phosphorylated Rb (S807/811), with actin serving as a loading control. As shown in **FIG. 7**, total KIT protein was almost completely abolished by treatment with the combination. The single agents did not decrease the KIT protein level, suggesting that elimination of KIT protein is based on the synthetic lethality of the combination treatment. The phosphorylation level of KIT (Y703) showed a significant decrease in the samples treated with

the combination, reflecting the elimination of KIT protein. This effect on p-KIT (Y703) was much stronger compared to imatinib single agent treatment. The AKT pathway, which is one of the major pathways downstream of KIT in GIST, was significantly inhibited in the combination samples, as indicated by levels of p-AKT (S473) and p-S6 (S235/S236). Inhibition of the AKT pathway was much stronger for the combination compared to imatinib single agent treatment. Apoptosis was induced by the combination as indicated by the increase in levels of cleaved PARP, while single agent treatments failed to induce it. These observations suggest that the combination treatment of ziftomenib and imatinib eliminated KIT protein, shut down downstream oncogenic signals, and induced apoptosis.

[0164] Western blot analysis of the Day 8 tumor samples further demonstrated deepened antitumor effects (**FIG. 8**). Total KIT, phosphorylated KIT (Y803), total AKT, phosphorylated AKT (S473), total S6, phosphorylated S6 (S235/236), total mTOR, phosphorylated mTOR (S537), phosphorylated ERK (T202/Y204), cleaved PARP, phosphorylated Rb (S807/811) were blotted, and actin served as a loading control. The total KIT protein remained undetectable, and AKT pathways were impacted as shown by reduced p-AKT (S473), p-mTOR (S537) and p-S6 (S235/S236) levels. The MAPK pathway, another major pathway downstream of KIT, was almost completely inhibited in the combination samples as indicated by reduced levels of p-ERK1/2 (T202/Y204). While imatinib single agent treatment inhibited p-ERK (T202/Y204) to a significant extent in both Day 5 and Day 8 samples, the combination showed enhanced p-ERK inhibition on Day 8. Apoptotic signals were activated in all combination animals as indicated by the increased cleaved PARP level, while single agent treatments did not induce apoptosis. Cell proliferation was blocked by the combination as indicated by the significant decrease of p-Rb (S807/811). These observations suggest that the elimination of KIT protein by the combination of ziftomenib and imatinib further shuts down multiple oncogenic signals essential for proliferation and maintenance of GIST on Day 8, resulting in the cell cycle block and further induction of apoptosis.

[0165] RNA analysis of the snap-frozen tumor samples was performed. Snap-frozen tumor samples were pulverized on dry ice or liquid nitrogen and total RNAs were extracted using MagMAX™ mirVana™ Total RNA Isolation Kit for Tissues (Thermo Fisher, Cat. No. A27828). Total RNA quantity and quality were measured by NanoDrop spectrophotometer (ThermoFisher) and Bioanalyzer automated electrophoresis instrument (Agilent) to determine the concentration of RNA in extracted samples to inform subsequent RT-qPCR transcription analyses.

[0166] Transcription of KIT, POLR2A, and IPO8 genes in Day 5 tumor samples was evaluated by RT-qPCR using a TaqMan™ gene expression assay (Thermo Fisher). The expression levels of KIT and POLR2A were normalized by comparison to IPO8 expression levels, and expression levels among the treatments were compared to the average expression level of vehicle-treated animals in each group (defined as the control for each treatment at 100%). One-way ANOVA statistical analysis was performed. Results are shown in Table 2 (mRNA).

Table 2.

Agents	KIT mRNA (5-day)	POL2RA (5-day)	KIT mRNA (8-day)
Ziftomenib	71% (p 0.0048)	83% (p 0.73)	82% (p 0.14)
Imatinib	72% (p 0.0067)	82% (p 0.67)	123% (p 0.054)
Combination	3.1% (p < 0.0001)	67% (p 0.088)	5.3% (p < 0.0001)
Vehicle	100%	100%	100%

[0167] In samples of tumors that had been exposed to ziftomenib and imatinib single agent for 5 days, KIT mRNA levels were slightly reduced relative to vehicle, at 71% and 72%, respectively. For ziftomenib alone, moderately reduced KIT expression may be driven by the contribution of the menin/KMT2A complex to KIT gene transcription in GIST. For imatinib alone, reduced expression may result from down-regulation of KIT gene enhancer/transcription factors such as FOXF1. In contrast, samples from the combination-treated tumors showed a significant reduction in KIT mRNA levels (3.1% of control), suggesting a synergistic effect of the combination that leads to nearly complete abolition of KIT gene transcription. Negative control POL2RA mRNA levels were not impacted significantly by the combination relative to the single agents, suggesting that the reduction in KIT gene transcription observed for the combination was not due to global RNA degradation or other non-specific mechanisms.

[0168] The significant reduction in KIT mRNA observed for Day 5 samples from combination-treated tumors was reproduced in Day 8 samples, as KIT mRNA remained at 5.3%, suggesting that the effect of the combination treatment on KIT transcription persists. In contrast, KIT mRNA levels rebounded in the Day 8 samples for tumors treated with the single agents, indicating the presence of an adaptive feedback mechanism.

[0169] These results indicate that the combination treatment targets both KIT gene transcription as well as mutant KIT proteins in imatinib-resistant models.

[0170] In contrast, Hemming et al., reported the effects of the combination of imatinib and the menin inhibitor, VTP-50469, on levels of KIT expression in imatinib-sensitive GIST-T1 xenografts, where the combination produced only a modest decrease in KIT mRNA after 5 or 10 days of exposure (Hemming, *supra*, Fig. 7D).

Example 2 – GS5106 and GS5108 GIST PDX Studies

[0171] GS5106 (K642E/N822K; sensitive to imatinib; resistant to sunitinib; sensitive to regorafenib; model of tumor suitable for 3L treatment with regorafenib) and GS5108 (Y823D; resistant to imatinib and sunitinib; sensitive to regorafenib; model of tumor suitable for 3L treatment with regorafenib) tumor fragments from stock mice were harvested and used for inoculation into female NOD/SCID mice. Each mouse was inoculated subcutaneously in the right upper flank with primary human tumor xenograft model tumor fragment (2-3 mm in diameter) for tumor development. Randomization started when the mean tumor size reached approximately 262 mm³. For each model, animals were randomly allocated into 4 study groups with 5 mice in each group. GS5106 and GS5108 xenograft mice were treated orally for 4 weeks with: control vehicle (20% w/v hydroxypropyl- β -cyclodextrin, pH 2.5), QD; ziftomenib, 2X mg/kg (aqueous solution), QD; imatinib, 100 mg/kg (solution in 2% DMSO+30% PEG 300 + 2% Tween 80 + ddH₂O), QD; or ziftomenib, 2X mg/kg, QD plus imatinib, 100 mg/kg, QD. Animals were terminated on Day 28. The combination of ziftomenib and imatinib induced significant antitumor effects, with 89.0% TGI in the GS5106 model (standard error, 2.63; p-value = 0.00101 vs. vehicle; **FIG. 9**) and 91.1% TGI in the GS5108 model (standard error, 1.39; p-value = 0.0210 vs. vehicle; **FIG. 10**). In contrast, imatinib (GS5106: TGI, 32.2%; standard error, 11.25; p-value, ns; GS5108: 8.03% TGI; standard error, 14.7, p-value, ns) and ziftomenib (GS5106: TGI, 11.3%; standard error, 21.1; p-value, ns; GS5108: 1.38% TGI; standard error, 15.3, p-value, ns) single agent treatments did not induce significant TGI in either model. The effects of the combination were significantly superior to imatinib single agent treatment in both models (GS5106: p-value < 0.0001; GS5108: p-value < 0.0001). These results further confirm that ziftomenib in the combination treatment targets the vulnerability of GIST tumors that is created by imatinib treatment in these two models with different imatinib-resistant KIT alterations.

Example 3 – GS11338 and GS11341 KIT-Independent GIST PDX Studies

[0172] The tumor volume inhibition effects of ziftomenib, imatinib, and the ziftomenib-imatinib combination were investigated in two GIST models, GS11338 and GS11341. These two models exhibit low KIT expression regardless of KIT mutation status, suggesting that they are KIT-independent models.

[0173] GS11341 tumor fragments from stock mice were harvested and used for inoculation into female NPG mice. Each mouse was inoculated subcutaneously in the right upper flank with primary human tumor xenograft model tumor fragment (2-3 mm in diameter) for tumor development. Randomization started when the mean tumor size reached approximately 265-267 mm³. Animals were randomly allocated to 4 study groups with 5 mice in each group. GS11341 xenograft mice were treated orally with: control vehicle (20% w/v hydroxypropyl- β -cyclodextrin, pH 2.5), QD; ziftomenib, 1X mg/kg (aqueous solution), QD; imatinib, 100 mg/kg (solution in 2% DMSO+30% PEG 300 + 2% Tween 80 + ddH₂O), QD; or ziftomenib, 1X mg/kg, QD plus imatinib, 100 mg/kg, QD, from Day 0 to Day 16.

[0174] GS11338 tumor fragments from stock mice were harvested and used for inoculation into female NOD/SCID mice. Each mouse was inoculated subcutaneously in the right upper flank with primary human tumor xenograft model tumor fragment (2-3 mm in diameter) for tumor development. Randomization started when the mean tumor size reached approximately 254-267 mm³. Animals were randomly allocated to 4 study groups with 5 mice in each group. GS11338 xenograft mice were treated orally with: control vehicle (20% w/v hydroxypropyl- β -cyclodextrin, pH 2.5), QD; ziftomenib, 2X mg/kg (aqueous solution), QD, from Day 0 to Day 2, and 1X mg/kg, QD, from Day 3 to Day 17; imatinib, 100 mg/kg (solution in 2% DMSO + 30% PEG 300 + 2% Tween 80 + ddH₂O), QD, from Day 0 to Day 15; or ziftomenib, 2X mg/kg, QD, from Day 0 to Day 2 and 1X mg/kg, QD, from Day 3 to Day 17, plus imatinib, 100 mg/kg, QD, from Day 0 to Day 17. Imatinib single agent group was terminated on Day 15 as tumors exceeded 3000 mm³.

[0175] As shown in **FIG. 11** (GS11341 (**FIG. 11A**) and GS11338 (**FIG. 11B**), all treatment groups showed similar rates of tumor growth in both models, with no regressions or evidence of tumor growth inhibition relative to vehicle, and faster tumor growth in the imatinib single agent group in the GS11338 model. These results suggest that combinations of ziftomenib with KIT inhibitors target KIT specifically in KIT positive cancers such as GIST, further supporting the proposed mechanism of action discussed herein.

Example 4 – GS11360 (Ex11del, V559G; imatinib-sensitive) GIST PDX Studies

[0176] Animals were randomly allocated to 4 study groups, with 5 mice in each group. GS11360 xenograft mice (model of a first-line treatment in imatinib-sensitive disease) were treated orally with: control vehicle (20% w/v hydroxypropyl- β -cyclodextrin, pH 2.5), QD; ziftomenib, 1X mg/kg (aqueous solution), QD; imatinib, 100 mg/kg (solution in 2% DMSO+30% PEG 300 + 2% Tween 80 + ddH₂O), QD; or ziftomenib, 1X mg/kg, QD, plus imatinib, 100 mg/kg, QD. Mice were treated with vehicle or test agents for 28 days and the vehicle animals and the ziftomenib single-agent treatment animals were sacrificed on Day 28. Mice in the imatinib monotherapy and combination groups were treated continuously until Day 32. In these two groups, tumor growth was monitored from Day 33 until Day 42 (regrowth observation period). On Day 43, the combination treatment (1X mg/kg ziftomenib, QD, and 100 mg/kg imatinib, QD) was resumed for both the imatinib monotherapy group and the combination group. Animals were terminated on Day 59.

[0177] As shown in **FIG. 12**, on Day 28, the ziftomenib group showed no significant tumor growth inhibitory effect compared to the vehicle group (TGI, 25.8%; standard error, 11.9; p-value vs. vehicle, not significant (ns)), while the imatinib group showed a significant effect compared to vehicle (TGI, 86.1%; standard error, 2.21; p-value vs. vehicle, 1.629e-04). The combination of ziftomenib and imatinib induced significant tumor regression compared to either vehicle or imatinib alone (TGI, 95.5%; standard error, 1.96; p-value vs. vehicle, 5.789e-07; p-value vs. imatinib, 1.970e-02). Notably, two animals in the combination group achieved a complete response (CR), while no animals achieved CR in the imatinib group, which is as expected as this model carries an exon 11 mutation (Ex11 V556G) and represents the first-line exon 11-mutated situation in the clinic, where imatinib monotherapy rarely achieves CR. Dosing of imatinib or the combination was continued to Day 32. As of Day 32, the combination treatment continued to induce tumor regression in all remaining animals while the two CR animals remained as CR. Although imatinib alone induced slow tumor regression, the combination treatment impact was superior ($p = 0.00728$, on Day 32), and none of the imatinib-treated animals achieved CR as of Day 32. Imatinib may inhibit KIT activity only to the level that blocks tumor cell proliferation, leaving GIST cancer cells to survive in a dormant or resting state. When ziftomenib is combined with imatinib, the combination may reduce KIT levels below a threshold that is required for not only the cell cycle but also for survival signaling in these cells and effectively kills them, leading to tumor regression.

[0178] On Day 33, dosing of the imatinib and combination groups was stopped and tumor regrowth was monitored for another 10 days. Imatinib-treated animals immediately relapsed and all animals in that group showed significant tumor regrowth by Day 42, suggesting that imatinib halts the cell cycle of cancer cells without killing them, which allows them to stay in a dormant state until imatinib exposure is withdrawn. In contrast, all but one of the combination-treated animals continued to show tumor regression after dosing was stopped, suggesting that the combination eliminated most of the GIST cells. Two animals that had achieved CR by Day 32 remained in CR throughout the regrowth observation period, indicating that the effects of the combination persisted after dosing was withdrawn ($p = 0.0026$ vs. imatinib). The results suggest that the combination may target survival mechanisms of dormant or slowly proliferating cancer cells while imatinib merely inhibits cell proliferation.

[0179] On Day 42, dosing with ziftomenib and imatinib was resumed for the two remaining groups. Animals in both groups showed a significant tumor regression, with one additional animal from the combination group achieving CR on Day 59 (3 out of 5 animals achieved CR for the combination group). These results suggest that the combination induces regressions in tumors that have relapsed following imatinib treatment, and indicate that the combination may target the mechanism used by GIST cancer cells to survive exposure to imatinib.

Example 5 -- Ziftomenib plus imatinib in GIST-T1 cell line-derived xenografts expressing *KIT*-mutant V654A, T670I, or Y823D

[0180] Without being limited by theory, in a possible mechanism of synergy between ziftomenib and imatinib in KIT positive GIST, imatinib binds KIT proteins with secondary mutations, which leads to KIT protein instability and accelerated degradation. However, secondary mutations that occur in the ATP binding pocket of *KIT*, such as V654A (exon 13) and the gatekeeper mutant T670I (exon 14), or in the activation loop, such as Y823D (exon 17), have been reported to directly impede imatinib binding. (McLean, S.R. et al., *Mol. Cancer Ther.* 2005, 4(12), 2008-15; Tamborini, E. et al., *Gastroenterology* 2004, 127(1), 294-9; Antonescu, C.R. et al., *Clin. Cancer Res.* 2005, 11(11), 4182-90.) *KIT* V654A, *KIT* T670I, and *KIT* Y823D are cloned in the GIST-T1 parental line using CRISPR then individual clones are established as xenografts by subcutaneous injection into mice. Vehicle, ziftomenib, imatinib, and the combination of ziftomenib and imatinib are dosed in these models using methods analogous to those described above. Greater tumor growth inhibition in the combination compared to either single agent suggests that imatinib induces stress to the cells through a mechanism that does not

require binding to KIT mutant protein. For example, treatment with TKIs can cause intracellular calcium level disturbances and endoplasmic reticulum (ER) stress that could further destabilize KIT proteins by inducing the unfolded protein response (UPR). (Rodriguez-Hernandez, M.A. et al., *Redox Biol.* 2020, 36, 101510.) To evaluate this possible scenario, ER stress response markers in lysates from the models are analyzed by immunoblotting against the following proteins: phosphorylated and total IRE1a, phosphorylated and total PERK, and cleaved ATF6. An increase in phosphorylated IRE1a, phosphorylated PERK or cleaved ATF6 indicate increased ER stress.

Example 6 – GIST-T1 CDX antitumor activity and PD studies

[0181] GIST-T1 tumor cells (KIT Exon 11 deletion, heterozygous; sensitive to imatinib, a model of newly diagnosed, KIT inhibitor-naïve disease) were maintained in cell culture medium containing RPMI1640 plus 10% heat-inactivated fetal bovine serum (FBS) and 1% Antibiotic-Antimycotic, at 37 °C in an atmosphere of 5% CO₂ in air. The tumor cells were routinely subcultured twice weekly. Cells growing in an exponential growth phase were harvested and counted for tumor inoculation. Female BALB/c mice were inoculated subcutaneously at the right flank with the GIST-T1 tumor cells (10 x10⁶) in 0.2 mL of PBS mixed with Matrigel (50:50) for tumor development. Treatment was initiated when the average tumor size reached approximately 252 mm³.

[0182] Animals were randomly allocated into 4 study groups with 5 mice in each group. GIST-T1 xenograft mice were treated orally for 4 weeks with: control vehicle (10% w/v hydroxypropyl-β-cyclodextrin + 1% Tween 80, pH 3.0), QD; ziftomenib, 1X mg/kg (aqueous solution), QD; imatinib, 100 mg/kg (solution in 2% DMSO+30% PEG 300 + 2% Tween 80 + ddH₂O), QD; or ziftomenib, 1X mg/kg, QD plus imatinib, 100 mg/kg, QD. Animals were terminated on Day 28. As shown in **FIG. 13**, the combination of ziftomenib and imatinib induced significant antitumor effects, with 113.9% TGI (p-value < 0.01 vs. vehicle). Imatinib (TGI, 102.35%; p-value, < 0.01 vs. vehicle) achieved tumor stasis, but not tumor regression. Ziftomenib (TGI, 48.7%; p-value, ns vs. vehicle) did not induce significant TGI. The effects of the combination were significantly superior to imatinib single agent treatment (p-value < 0.01).

Example 7 – GIST-T1 CDX PD study

[0183] Female BALB/c mice were inoculated with GIST-T1 tumor cells (KIT Exon 11 deletion, heterozygous; sensitive to imatinib, a model of newly diagnosed, KIT inhibitor-naïve

disease) as described in Example 6. The animals were randomized and treatment was initiated when the average tumor size reached approximately 456 mm³. Mice were treated orally for 7 days with: control vehicle (10% w/v hydroxypropyl- β -cyclodextrin + 1% Tween 80, pH 3.0), QD; ziftomenib, 1X mg/kg (aqueous solution), QD; imatinib, 100 mg/kg (solution in 2% DMSO+30% PEG 300 + 2% Tween 80 + ddH₂O), QD; or ziftomenib, 1X mg/kg, QD plus imatinib, 100 mg/kg, QD. Tumor samples were collected from three animals on day 7 (tumor volumes at day 7 as shown in **FIG. 14A**). Each tumor was split into 4 pieces and preserved with snap frozen in liquid N₂, RNAlater (Thermo Fisher, Cat. No. AM7020), or as FFPE blocks.

[0184] Snap-frozen tumor samples were cut into smaller pieces and lysed in 1X cell lysis buffer (Cell Signaling Technology #9803) supplemented with Halt protease inhibitor cocktail (Thermo Scientific #78430) using a Bead Mill Homogenizer 20 (Fisher Brand). Lysates were cleared by centrifugation (maximum speed, 10 min) and protein concentration was determined by bicinchoninic acid (BCA) assay (Pierce). Lysate (20-30 μ g) was loaded on to 4-12% Bis-Tris gels (NuPAGE, Invitrogen) for electrophoresis and immunoblotting.

[0185] Western blot analysis was performed to evaluate Day 7 samples for total KIT, phosphorylated KIT (Y803), total AKT, phosphorylated AKT (S473), phosphorylated ERK (T202/Y204), and phosphorylated Rb (S807/811), with actin serving as a loading control. As shown in **FIG. 14B**, total KIT protein was almost completely depleted by treatment with the combination. The single agents did not decrease the KIT protein level, suggesting that elimination of KIT protein is based on the synthetic lethality of the combination. The phosphorylation level of KIT (Y703) showed a significant decrease in the samples treated with the combination, reflecting elimination of KIT protein, and was much stronger compared to imatinib alone. The AKT pathway, one of the major pathways downstream of KIT in GIST, was significantly inhibited in the combination samples, as indicated by levels of p-AKT (S473). Imatinib dosing induced AKT and ERK activation, which could be due to an adaptive response to the strong tumor growth inhibition elicited by imatinib, while the combination reduced both kinase activities. Cell proliferation was blocked by the combination as indicated by the significant decrease of p-Rb (S807/811) compared to imatinib alone. These observations suggest that the combination of ziftomenib and imatinib eliminated KIT protein, shut down downstream oncogenic signals, and induced cell cycle block.

[0186] RNA analysis of the RNA-later tumor samples was performed. Tumor samples were pulverized on dry ice or liquid nitrogen and total RNAs were extracted using MagMAXTM mirVanaTM Total RNA Isolation Kit for Tissues (Thermo Fisher, Cat. No. A27828). Total RNA

quantity and quality were measured by NanoDrop spectrophotometer (ThermoFisher) and Bioanalyzer automated electrophoresis instrument (Agilent) to determine the concentration of RNA in extracted samples to inform subsequent RT-qPCR transcription analyses. Transcription of KIT, POLR2A, and IPO8 genes in Day 5 tumor samples was evaluated by RT-qPCR using a TaqMan™ gene expression assay (Thermo Fisher). The expression levels of KIT and POLR2A were normalized by comparison to IPO8 expression levels, and expression levels among the treatments were compared to the average expression level of vehicle-treated animals in each group (defined as the control for each treatment at 100%). One-way ANOVA statistical analysis was performed. Results are shown in **FIG. 14C**.

[0187] In samples of tumors that had been exposed to ziftomenib for 7 days, KIT mRNA levels were slightly reduced relative to vehicle. Moderately reduced KIT expression may be driven by the contribution of the menin/KMT2A complex to KIT gene transcription in GIST. Samples from the combination-treated tumors showed no reduction in KIT mRNA levels, while the combination treatment robustly depleted KIT proteins (demonstrated by western blot analysis, see **FIG. 14B**). Negative control POL2RA mRNA levels were little affected by the combination relative to the single agents.

[0188] In the GIST-T1 model, the ziftomenib-imatinib combination eliminated KIT proteins but did not reduce KIT mRNA levels, suggesting that the antitumor effects of the combination may be exerted through KIT protein destabilization without a need to target KIT gene transcription.

Example 8 – GS5108 PDX PD study

[0189] Fresh tumor tissues from mice bearing established primary human cancer tissues (GS5108) were harvested and cut into small pieces (approximately 2-3 mm in diameter). Each mouse was inoculated subcutaneously in the right front flank with a specific PDX tumor fragment (3x3x3 mm) for tumor development. The randomization started when the mean tumor size reached approximately 417 mm³. Mice (24 total) were allocated to 4 study groups with 3 mice per group per timepoint. The date of grouping was denoted as day 0. Mice were treated orally for 5 days or for 8 days with: control vehicle (10% w/v hydroxypropyl-β-cyclodextrin + 1% Tween 80, pH 3.0), QD; ziftomenib, 1X mg/kg (aqueous solution), QD; imatinib, 100 mg/kg (solution in 2% DMSO+30% PEG 300 + 2% Tween 80 + ddH₂O), QD; or ziftomenib, 1X mg/kg, QD plus imatinib, 100 mg/kg, QD. Each tumor was split into 3 pieces and preserved with snap frozen in liquid N₂, RNAlater (Thermo Fisher, Cat. No. AM7020), or as FFPE

(formalin-fixed paraffin-embedded) blocks. Results for tumor growth over time are shown in **FIG. 15A**.

[0190] Snap-frozen tumor samples were cut into smaller pieces and lysed in 1X cell lysis buffer (Cell Signaling Technology #9803) supplemented with Halt protease inhibitor cocktail (Thermo Scientific #78430) using a Bead Mill Homogenizer 20 (Fisher Brand). Lysates were cleared by centrifugation (maximum speed, 10 min) and protein concentration was determined by bicinchoninic acid (BCA) assay (Pierce). Lysate (20-30 µg) was loaded on to 4-12% Bis-Tris gels (NuPAGE, Invitrogen) for electrophoresis and immunoblotting.

[0191] Western blot analysis was performed to evaluate Day 8 samples for total KIT, phosphorylated KIT (Y803), total AKT, phosphorylated AKT (S473), phosphorylated ERK (T202/Y204), phosphorylated Rb (S807/811), with actin serving as a loading control. As shown in **FIG. 15B**, the total KIT protein with lower molecular weight (indicated by a box across the KIT lanes) was almost completely abolished by treatment with the combination though the heavier molecular weight KIT protein was not affected. The phosphorylation level of lower molecular weight KIT (Y703) (indicated by a box across the p-KIT lanes) showed a significant decrease in the samples treated with the combination, reflecting the elimination of KIT protein. The lower molecular weight KIT could represent an intermediate form that is not fully glycosylated, and thus does not localize in the plasma membrane but in endoplasmic reticulum or in Golgi bodies. It was reported that mutant KIT proteins are tethered to Golgi complex in GIST and activate the downstream oncogenic signals (Kwon, Y. et al., *Cell Death Differ.* 2023, 30, 2309–2321, Saito Y et al., *Br. J. Cancer* 2020, 122, 658-667). The localization of mutant KIT to Golgi body allows mutant KIT to escape from ER quality control mechanism which degrades mutant proteins in ER. As the Golgi-localized mutant KIT seemed to be depleted by the combination, the AKT and ERK pathways were significantly inhibited in the combination samples, as indicated by levels of p-AKT (S473) and p-ERK (Thr202/Tyr204). Inhibition of the AKT and ERK pathways was stronger for the combination compared to imatinib single agent. These observations suggest that the combination of ziftomenib and imatinib eliminated mislocalized mutant KIT protein and shut down downstream oncogenic signals. The single agents did not affect the KIT protein level, suggesting that elimination of KIT protein is based on the synthetic lethality of the combination treatment. KIT gene transcription factor ETV1 was significantly downregulated in the combination samples, suggesting the positive feedback loop mediated by oncogenic KIT was disrupted.

[0192] mRNA levels of KIT, ETV1 and POLR2A were measured by qPCR. As shown in FIG. 15C, KIT mRNA levels were not affected by the combination. ETV1 mRNA levels did not change across the treatments, despite the strong reduction in ETV1 protein levels in the combination samples (western blot), implying the involvement of protein destabilization mechanisms induced by the combination treatment. Negative control POLR2A mRNA levels were not affected by the combination relative to the single agents.

[0193] To investigate the mechanism of KIT protein destabilization, we performed western blot of chaperone proteins and the transcriptional regulators of chaperone genes. As shown in FIG. 15D, endoplasmic reticulum (ER) chaperone proteins, the central transcription factor (TF) of unfolded protein response (UPR) XBP-1s, HSP90 complex components (HSP40, HOP and HSP60) and the heat-shock response master transcription factor HSF1 were downregulated by the combination, while imatinib and ziftomenib single agents did not affect the levels of these proteins. The HSP90 complex depends on the tight regulation of the protein level of each component; if one component is missing, the HSP90 complex becomes ineffective even though other components abundantly exist. The combination of ziftomenib and imatinib appears to disrupt the tight regulation of stoichiometry and reduce the amount of functional HSP90 complexes. Mutant KIT proteins are highly unstable and require support from HSP90 chaperone complex (Kwon, Y et al., *supra*; Saito, Y. et al., *supra*; Honma, Y. et al., *J. Clin. Oncol.* 2021, 39(15 Suppl.), 11524). The western blot suggests that the combination may target mutant KIT protein by reducing the functional chaperone activities, not necessarily through the downregulation of KIT gene transcription. HSP90 inhibitors have been developed to induce RTK (and other oncogenic protein) destabilization. A recent clinical trial showed positive results with a HSP90 inhibitor in patients with refractory GISTs (Honma, Y. et al., *supra*). However, a major roadblock for HSP90 as a target is treatment-related ocular toxicity, whereas the ziftomenib-imatinib combination was well tolerated in all models tested.

Example 9 – ME12098 Melanoma PDX Study

[0194] ME12098 tumor fragments (harboring imatinib-sensitive oncogenic KIT mutation and 7 copies of KIT gene (amplified)) from stock mice were harvested and used for inoculation into female NOD/SCID mice. Each mouse was inoculated subcutaneously in the right upper flank with primary human tumor xenograft model tumor fragment (2-3 mm in diameter) for tumor development. Randomization started when the mean tumor size reached approximately 265-267 mm³. Animals were randomly allocated to 4 study groups with 5 mice in each group. ME12098

xenograft mice were treated orally with: control vehicle (20% w/v hydroxypropyl- β -cyclodextrin, pH 2.5), QD; ziftomenib, 2X mg/kg (solution in 20% w/v hydroxypropyl- β -cyclodextrin, pH 3.0), QD, from Day 0 to Day 13, and 1X mg/kg, QD, from Day 14 to Day 27; imatinib, 100 mg/kg (solution in 2% DMSO+30% PEG 300 + 2% Tween 80 + ddH₂O), QD; or ziftomenib, 2X mg/kg, QD, from Day 0 to Day 13 and 1X mg/kg, QD, from Day 14 to Day 27, plus imatinib, 100 mg/kg, QD, from Day 0 to Day 27. Animals were terminated on Day 28. As shown in **FIG. 16A** (mean tumor volume over time) and **FIG. 16B** (%TV change, Day 0 to Day 28), the combination of ziftomenib and imatinib induced significant tumor regression, with 2 out of 5 animals achieving complete response. Imatinib single agent treatment slowed tumor growth compared to vehicle treatment but did not induce tumor regression. Ziftomenib single agent treatment did not exhibit any tumor growth inhibition. The combination showed a significantly superior efficacy to the imatinib single agent treatment in %TV change (p-value < 0.0001) (**FIG. 16B**). These observations indicate that the combination treatment of ziftomenib and imatinib can target oncogenic KIT gene in melanoma, regardless of the copy number of KIT genes.

Example 10 – ME3332 Melanoma PDX Study

[0195] ME3332 tumor fragments (imatinib-sensitive oncogenic KIT mutation and 3 copies of KIT gene (not amplified)) from stock mice were harvested and used for inoculation into female Balb/c nude mice. Each mouse was inoculated subcutaneously in the right upper flank with primary human tumor xenograft model tumor fragment (2-3 mm in diameter) for tumor development. Randomization started when the mean tumor size reached approximately 267-269 mm³. Animals were randomly allocated to 4 study groups with 5 mice in each group. ME3332 xenograft mice were treated orally for 26 days with: control vehicle (20% w/v hydroxypropyl- β -cyclodextrin, pH 2.5), QD, from Day 0 to Day 26; ziftomenib, 2X mg/kg (aqueous solution), QD, from Day 0 to Day 3, and 1X mg/kg, QD, from Day 4 to Day 26; imatinib, 100 mg/kg (solution in 2% DMSO+30% PEG 300 + 2% Tween 80 + ddH₂O), QD, from Day 0 to Day 26; ziftomenib, 2X mg/kg, QD, from Day 0 to Day 3, and 1X mg/kg, QD, from Day 4 to day 26, plus imatinib, 100 mg/kg, QD, from Day 0 to Day 26. Dosing was stopped on Day 27. Tumor regrowth was observed for another 18 days (tumor regrowth period). Animals were terminated on Day 45. As shown in **FIG. 17A** (mean tumor volume over time) and **FIG. 17B** (%TV change, Day 0 to Day 28), the combination of ziftomenib and imatinib induced significant tumor regressions, with 4 out of 5 animals achieving complete responses as of Day 28. Imatinib single agent treatment showed comparable tumor regression, with 1 out of 5 animals achieving a

complete response on Day 28. All four of the combination-treated animals that had achieved a complete response during dosing maintained a complete response during the tumor regrowth period, and the fifth animal in the combination group achieved a complete response at the end of the tumor regrowth period, for a 100% overall complete response rate. In the imatinib group, the one animal that had achieved a complete response at the end of dosing relapsed during the tumor regrowth period and three other animals showed significant tumor regrowth (**FIG. 17C**). These results suggest that the combination treatment of ziftomenib and imatinib exhibits a more significant and durable antitumor effect than imatinib single agent treatment after the treatment is stopped.

Example 11 – ME6928 melanoma PDX study

[0196] ME6928 tumor fragments (imatinib-sensitive oncogenic KIT mutation (KIT/W577C in Exon 11) and 18 copies of KIT gene, over-expressed) from stock mice were harvested and used for inoculation into female NOD/SCID mice. Each mouse was inoculated subcutaneously in the right upper flank with primary human tumor xenograft model tumor fragment (2-3 mm in diameter) for tumor development. Randomization started when the mean tumor size reached approximately 250-300 mm³. Animals were randomly allocated to 4 study groups with 5 mice in each group. ME6928 xenograft mice were treated orally for 26 days with: control vehicle (10% w/v hydroxypropyl- β -cyclodextrin + 1% Tween 80, pH 3.0), QD, from Day 0 to Day 27; ziftomenib, 1X mg/kg (aqueous solution), QD, from Day 0 to Day 27; imatinib, 100 mg/kg (solution in 2% DMSO+30% PEG 300 + 2% Tween 80 + ddH₂O), QD, from Day 0 to Day 88, plus ziftomenib, 1X mg/kg, QD, from Day 60 to Day 88; ziftomenib, 1X mg/kg, QD, from Day 0 to day 60, plus imatinib, 100 mg/kg, QD, from Day 0 to Day 60. Dosing of the upfront combination group was stopped on Day 60. Tumor regrowth was observed for another 28 days (tumor regrowth period) from Day 60 to Day 88. Animals were terminated on Day 88. In the imatinib single agent group, ziftomenib (1X mg/kg, QD) was added to the ongoing imatinib single agent treatment on Day 60 and the resulting combination treatment was administered for 28 days for this group from Day 60 to Day 88. Animals were terminated on Day 88.

[0197] As shown in **FIG. 18** (mean tumor volume over time), the upfront combination of ziftomenib and imatinib induced significant tumor regressions (TGI, 100%; p-value < 0.0001 vs. vehicle), with 5 out of 5 animals achieving complete responses as of Day 28, for a 100% overall complete response rate. All upfront combination-treated animals maintained a complete response during the tumor regrowth period for 20 days (until Day 80), with two animals relapsed

at the end of the tumor regrowth period. Imatinib single agent showed tumor regression (TGI, 92.4%; p-value < 0.0001 vs. vehicle); however, tumors started to regrow by Day 34 and no animals achieved complete response during the imatinib monotherapy period, suggesting a lack of durability for imatinib in this model. The tumor volumes of the combination groups were significantly smaller than imatinib single agent group (p-value = 0.0216) on Day 28 even before the tumors started to regrow in the imatinib single agent group. These results suggest that the upfront combination of ziftomenib and imatinib exhibits a more significant and durable antitumor effect than imatinib single agent including the period after the dosing discontinuation. Imatinib single agent showed tumor regression initially, but tumor regrowth was observed during the dosing period. When ziftomenib was added to imatinib in the progressing group, tumors regressed significantly, and one animal achieved a complete response. This model mimics GIST patients who harbor KIT exon 11 mutations, who eventually stop responding to imatinib therapy.

Example 12 – ME12172 melanoma PDX study

[0198] Tumor growth inhibition effects of ziftomenib, imatinib, and the ziftomenib-imatinib combination were investigated in a ME12172 model (KIT wild-wild type, 8 copies, not overexpressed). This model exhibits low KIT expression level, despite KIT amplification status, suggesting that this is a KIT-independent melanoma model.

[0199] ME12172 tumor fragments from stock mice were harvested and used for inoculation into female NOD/SCID mice. Each mouse was inoculated subcutaneously in the right upper flank with primary human tumor xenograft model tumor fragment (2-3 mm in diameter) for tumor development. Randomization started when the mean tumor size reached approximately 250-300 mm³. Animals were randomly allocated to 4 study groups with 5 mice in each group and were treated orally with: control vehicle (10% w/v hydroxypropyl-β-cyclodextrin + 1% Tween 80, pH 3.0), QD; ziftomenib, 1X mg/kg (aqueous solution), QD; imatinib, 100 mg/kg (solution in 2% DMSO+30% PEG 300 + 2% Tween 80 + ddH₂O), QD; or ziftomenib, 1X mg/kg, QD plus imatinib, 100 mg/kg, QD. All animals were terminated on Day 21.

[0200] As shown in **FIG. 19**, none of the treatments showed meaningful antitumor effects, with ziftomenib single agent showing the best but modest tumor growth inhibition (TGI; 41.9%, p-value < 0.01 vs. vehicle). Imatinib had no antitumor effects, consistent with the characterization of the ME12172 model as a KIT-independent melanoma. The combination did not enhance the activity of ziftomenib single agent treatment (TGI; 34.1%, p-value < 0.05),

suggesting a lack of synergy. These results demonstrate that the combination of ziftomenib with imatinib targets KIT specifically in KIT positive cancers.

Example 13 -- Mechanism of action of ziftomenib plus imatinib in *KIT*-mutant GIST and melanoma

[0201] Further experiments and analyses aim to define the mechanism of synergistic activity by ziftomenib and imatinib in *KIT*-mutant GIST and melanoma. As menin is part of an epigenetic complex and inhibition of menin likely results in global transcriptional changes, RNA-sequencing was performed in GS5108 GIST (KIT) and ME12098 melanoma (KIT) PDX models following treatment with vehicle, ziftomenib, imatinib, or the combination. A large number of differentially expressed genes (DEGs) were observed in samples treated for five days with ziftomenib plus imatinib compared to either vehicle or imatinib single agent (**FIG. 20**). These results suggest that the synergistic antitumor efficacy observed in these models is mediated by epigenetic mechanisms. Of note, there were minimal changes in transcription with imatinib treatment in GS5108, but a significant number of genes changed with imatinib treatment in ME12098, which correlated well with the tumor growth inhibitory activity observed with imatinib in these models.

[0202] Gene set enrichment analysis (GSEA) of genes that change with ziftomenib plus imatinib compared to vehicle showed that in the GS5108 PDX model, genes that have functions in the proteasome complex and in glycolysis/gluconeogenesis are significantly enriched in the genes that are downregulated in combination (**FIG. 21**). A few reports in the literature suggest that changes in metabolism, specifically glucose uptake, may influence the resistance to imatinib in GIST. (Lewitowicz, P. et al., *Gastroenterology Res. Pract.* 2016, 6478374; Shima, T. et al., *Oncol. Rep.* 2022, 47(1), 7.)

[0203] RNA-seq data are validated by performing immunohistochemistry and/or immunoblotting of treated xenografts and qPCR using RNA extracted from treated xenografts with a focus on the following genes: *HK1*, *HK2*, *LDHA*, *PGAM4*, *PGK1*, *PKM2*, *ENO1*, *ENO2*, *GPI*, and *SLC2A1*. ChIP-seq in GS5108 is performed to confirm that these are direct targets of the menin-KMT2A complex and that treatment with ziftomenib displaces menin and KMT2A from the target loci. ChIP-seq in GS5108 is performed for the histone marks H3K4me3 and H3K27ac to assess the levels of these active modifications upon treatment with ziftomenib with or without imatinib. Upon loss of menin/KMT2A, H3K4me3 and/or H3K27ac would decrease, leading to loss of expression of the target genes. The ChIP-seq data will also enable

transcription factor motif analysis to find proteins that potentially collaborate with menin/KMT2A. Findings from this analysis are validated by immunoprecipitation to show that the proteins interact and/or ChIP-seq to show that the proteins overlap in binding on chromatin.

[0204] If the antitumor effects of menin inhibition stem from effects on the glycolysis/gluconeogenesis pathway, ziftomenib or another menin inhibitor may have broader impact as anticancer agents given the heavy dependence of cancer cells on this pathway to meet energy demands (so called Warburg effect). (Schwartz, L. et al., *Anticancer Agents Med. Chem.* 2017, 17(2), 164-70; Ganapathy-Kanniappan, S. and J.F.H. Geschwind, *Mol. Cancer* 2013, 12, 153.)

[0205] Because significant changes in transcription were not observed with imatinib treatment in GS5108 GIST PDX, imatinib may be rewiring crucial cellular processes in ways that make them particularly sensitive to menin inhibition and that could be identified by changes in either protein expression or protein activity. To evaluate this, protein arrays are performed using treated tumor lysates from GS5108 and GS11331 PDX models. The arrays include various kinases in their phosphorylated forms as well as proteins that are known to have roles in cellular stress response, including hypoxia, DNA damage, and oxidative stress. Immunoblotting of tumor lysates is conducted to validate the changes. Contribution of such proteins to the mechanism is assessed by pharmacologically inducing or blocking the protein activity in mouse xenograft models or in cell lines established from *in vivo* models.

[0206] Analogous experiments are conducted for ME12098, including ChIP-seq for menin/KMT2A, H3K4me3 and H3K27ac in ME12098 PDX treated with vehicle, ziftomenib, imatinib, or the combination, RNA-seq to identify direct menin target genes sensitive to ziftomenib (and imatinib) treatment, and GSEA to identify signaling pathways of interest for validation. Transcription motif analysis is performed, and the collaborating proteins validated, as described above.

Example 14 – Binding of Imatinib to KIT Protein with Secondary Mutation

[0207] Binding of imatinib in the ATP pocket of KIT has been shown to accelerate KIT degradation via a lysosomal pathway, but this increased degradation is blocked in cells bearing KIT protein with the gatekeeper mutation, T670I (exon 14) (D'allard, *supra*). The T670I and V654A (exon 13) mutations both reside in the ATP binding pocket, and both show reduced binding affinity with imatinib. However, the magnitude of the reduction in binding affinity in V654A KIT protein was shown to be 2-fold less than the reduction for T670I (ΔG_{bind} : WT, -

10.22; V654A, -8.70; T670I, -6.38) (Tamborini et al., *Oncogene* 2006, 1-7). In a cellular system, Tamborini et al., showed that imatinib inhibited phosphorylation of KIT (V654A) at high concentrations (6 μ M), but KIT (T670I) was insensitive to imatinib up to the same concentration. These results suggest that imatinib may bind to the V654A mutant form of KIT but not to the T670I mutant form.

[0208] To extend the observations reported by D'allard et al. from studies of KIT WT and KIT (T670I) in human acute leukemia models to KIT (V654A) to GIST models, GIST cell lines harboring a *KIT* exon 11 deletion and (a) KIT V654A or (b) KIT T670I are established by introducing point mutations into the *KIT* gene of GIST-T1 cells using a CRISPR knock-in system. The cell lines are treated with a combination of imatinib and ziftomenib to investigate if the combination treatment reduces KIT protein levels. As imatinib does not bind to T670I, as shown by Tamborini et al., KIT levels are not reduced by the combination. These GIST model cells are treated with cycloheximide (to inhibit de novo protein synthesis and production), imatinib, and the combination cycloheximide and imatinib to assess if degradation of KIT is accelerated by imatinib compared to cycloheximide alone.

Example 15 – Clinical Trial of Ziftomenib and Imatinib in KIT-mutant GIST

[0209] A Phase 1a/1b clinical trial of ziftomenib and imatinib in KIT-mutant GIST is conducted. Inclusion criteria include: adult patients (at least 18 years old) with KIT-mutant GIST who are newly diagnosed, or are progressing or have progressed on imatinib. In some aspects, the GIST will be locally advanced or metastatic. In some aspects, patients will have failed imatinib as their most recent therapy, e.g., where imatinib as current or prior front-line therapy (a “1L+” or “2L” setting). In some aspects, patients will have failed imatinib and will have received at least one other therapy (e.g., a KIT inhibitor such as sunitinib, regorafenib, or ripretinib) (a “3L+” setting). In some aspects, patients will be newly diagnosed and will be imatinib-naïve (a “1L” setting).

[0210] In Phase 1a, patients will receive imatinib at 400 mg QD or at the dose of imatinib the patient received previously, if applicable, and ziftomenib at a dose of 200, 600, 900, or 1200 mg QD, or of 200 to 3000 mg QD, or of 200 to 2000 mg QD. Two ziftomenib doses will be selected for further evaluation as potential “recommended phase 2 dose” (RP2D) candidates. In Phase 1b, one ziftomenib dose will be evaluated in a dose expansion portion. Phase 1b includes: (a) advanced GIST patients progressing or progressed on imatinib in their first line (1L) therapy;

and (b) advanced GIST patients progressing or progressed in their second line and beyond (2L+), e.g., where the second line or beyond is a KIT inhibitor other than imatinib.

[0211] Trial objectives and endpoints include:

- Dose Escalation: To determine the safety and tolerability of ziftomenib in combination with imatinib, as measured by the rate of dose-limiting toxicities (DLTs) and descriptive statistics of adverse events (AEs) per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v. 5.0.
- RP2D Determination:
 - To determine the RP2D of ziftomenib in the ziftomenib-imatinib combination, as defined by the totality of evidence (e.g., PK, safety, pharmacodynamics, and preliminary antitumor activity; in some aspects, the evidence for a particular dose is assessed relative to such evidence for alternative doses tested).
 - To determine the safety and tolerability of ziftomenib in combination with imatinib, as measured by descriptive statistics of AEs per the NCI-CTCAE v. 5.0.
- Dose Expansion:
 - To determine the preliminary antitumor activity of ziftomenib in combination with imatinib, as measured by clinical benefit rate (CBR; rate of CR + PR + SD, with at least SD maintained for at least 16 weeks) based on modified Response Criteria in Solid Tumors (mRECIST) criteria.
 - To determine the safety and tolerability of ziftomenib in combination with imatinib, as measured by descriptive statistics of AEs per the NCI-CTCAE v. 5.0.
- All portions:
 - To evaluate survival and disease control outcomes of ziftomenib in combination with imatinib, as measured by CBR (as above), ORR (CR+PR), PFS, Duration of Response (DoR), and OS.
 - To characterize the multiple-dose PK of ziftomenib and imatinib as measured by C_{max} , T_{max} , $AUC_{0 \rightarrow last}$, and AUC_{tau} . Previous analyses using physiologically based pharmacokinetic (PBPK) modeling indicated a low risk of PK interactions b/w these ziftomenib and imatinib. In this portion of the study, the potential for drug-drug interactions and exposure-response correlations are evaluated.
- Intensive PK samples are collected and used to conduct non-compartmental analysis and population PK analysis to investigate the PK profile of the test compounds such as dose proportionality of exposure, accumulation after multiple doses, and effect of

intrinsic/extrinsic covariates. A PBPK model is built and verified in simCYP® using available non-clinical physicochemical, ADME, and biopharmaceutics properties, and clinical PK data. The PBPK model is then applied to investigate various PK characteristics of the test compounds. In some aspects, a PBPK-pharmacodynamic model is constructed, using data in TKI-resistant GIST mouse (KIT/Ex11 del, V654A), and linked to a ziftomenib PBPK model and a published imatinib PBPK model. The model indicates low risk of PK-driven interactions between the test agents despite both being metabolic substrates for CYP3A4. PBPK-PD modeling based on the mouse tumor TKI-resistant GIST PDX xenograft data is used to calculate doses for clinical investigation.

[0212] While some embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. It is not intended that the invention be limited by the specific examples provided within the specification. While the invention has been described with reference to the aforementioned specification, the descriptions and illustrations of the embodiments herein are not meant to be construed in a limiting sense. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. Furthermore, it shall be understood that all aspects of the invention are not limited to the specific depictions, configurations, or relative proportions set forth herein which depend upon a variety of conditions and variables. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is therefore contemplated that the invention shall also cover any such alternatives, modifications, variations, or equivalents. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

What is claimed is:

1. A method of treating a KIT positive cancer in an individual comprising administering a menin inhibitor to the individual.
2. The method of claim 1, comprising administering a concomitant KIT inhibitor to the individual.
3. The method of claim 2, wherein the concomitant KIT inhibitor is imatinib, sunitinib, regorafenib, ripretinib, dasatinib, avapritinib, masitinib, nilotinib, or cabozantinib, or a pharmaceutically acceptable form thereof.
4. The method of claim 3, wherein the concomitant KIT inhibitor is imatinib or a pharmaceutically acceptable form thereof, optionally imatinib mesylate.
5. The method of claim 3, wherein the concomitant KIT inhibitor is sunitinib or a pharmaceutically acceptable form thereof, optionally sunitinib malate.
6. The method of claim 3, wherein the concomitant KIT inhibitor is regorafenib or ripretinib, or a pharmaceutically acceptable form thereof.
7. The method of any one of claims 1 to 6, wherein the KIT positive cancer is unresectable, recurrent, and/or metastatic, or wherein the individual has had a resection of the KIT positive cancer.
8. The method of any one of claims 1 to 6, wherein the KIT positive cancer is unresectable or metastatic.
9. The method of any one of claims 1 to 8, wherein the KIT positive cancer has relapsed after, or failed, or progressed on, or responded insufficiently to treatment with a prior KIT inhibitor.
10. The method of claim 9, wherein the KIT positive cancer has relapsed after, or failed, or progressed on, or responded insufficiently to one line of treatment with the prior KIT inhibitor.
11. The method of claim 9 or claim 10, wherein the prior KIT inhibitor is imatinib, sunitinib, regorafenib, ripretinib, dasatinib, avapritinib, masitinib, nilotinib, or cabozantinib, or a pharmaceutically acceptable form thereof, optionally wherein the prior KIT inhibitor and the concomitant KIT inhibitor are the same.
12. The method of claim 11, wherein the prior KIT inhibitor is imatinib or a pharmaceutically acceptable form thereof, optionally imatinib mesylate.
13. The method of any one of claims 9 to 12, wherein the KIT positive cancer has relapsed after, or failed, or progressed on, or responded insufficiently to at least two lines of treatment

with prior KIT inhibitors, or at least three lines of treatment with prior KIT inhibitors, or two lines of treatment with prior KIT inhibitors, or three lines of treatment with prior KIT inhibitors.

14. The method of claim 13, wherein the prior KIT inhibitors are independently selected from imatinib, sunitinib, regorafenib, ripretinib, dasatinib, avapritinib, masitinib, nilotinib, and cabozantinib, and pharmaceutically acceptable forms thereof.

15. The method of claim 14, wherein one of the prior KIT inhibitors is imatinib or a pharmaceutically acceptable form thereof, optionally imatinib mesylate.

16. The method of claim 14 or claim 15, wherein one of the prior KIT inhibitors is sunitinib, or pharmaceutically acceptable forms thereof, optionally sunitinib malate.

17. The method of any one of claims 1 to 16, wherein the KIT positive cancer is refractory to treatment with a prior KIT inhibitor.

18. The method of claim 17, wherein the prior KIT inhibitor is imatinib and/or sunitinib, or a pharmaceutically acceptable form thereof, optionally imatinib mesylate and/or sunitinib malate.

19. The method of any one of claims 1 to 8, wherein the KIT positive cancer has relapsed after, or failed, or progressed on, or responded insufficiently to treatment with a prior KIT inhibitor, optionally wherein:

- (a) treatment with the prior KIT inhibitor comprises one line of treatment with imatinib or a pharmaceutically acceptable form thereof;
- (b) treatment with the prior KIT inhibitor comprises two or three lines of treatment with imatinib, sunitinib, regorafenib, ripretinib, dasatinib, avapritinib, masitinib, nilotinib, or cabozantinib, or a pharmaceutically acceptable form thereof; or
- (c) the KIT positive cancer is newly diagnosed or untreated.

20. The method of any one of claims 1 to 19, wherein the KIT positive cancer is sarcoma (optionally, sarcoma, gastrointestinal stromal tumor (GIST), or soft tissue sarcoma), melanoma (optionally, melanoma, mucosal melanoma, acral lentiginous melanoma, or chronically sun-damaged melanoma), blood-related cancer (optionally, leukemia, acute leukemia, acute myeloid leukemia, myelodysplastic syndrome, chronic myeloid leukemia, multiple myeloma, chronic myelomonocytic leukemia, myelodysplastic/myeloproliferative neoplasm, chronic lymphocytic leukemia, myelofibrosis, or T-cell and NK-cell neoplasm), solid tumor (optionally, solid tumor, malignant solid tumor, non-small cell lung carcinoma, pancreatic carcinoma, colorectal carcinoma, bladder carcinoma, head and neck squamous cell carcinoma, ovarian carcinoma, adenocarcinoma of the gastroesophageal junction, head and neck carcinoma, breast carcinoma, gastric adenocarcinoma, esophageal carcinoma, gastric carcinoma, bile duct carcinoma,

cholangiocarcinoma, prostate carcinoma, malignant salivary gland neoplasm, urothelial carcinoma, nasal cavity and paranasal sinus carcinoma, nasopharyngeal carcinoma, penile carcinoma, small cell lung carcinoma, oropharyngeal carcinoma, oropharyngeal squamous cell carcinoma, gallbladder carcinoma, lung carcinoma, lip and oral cavity carcinoma, malignant uterine neoplasm, malignant laryngeal neoplasm, cervical carcinoma, hepatobiliary neoplasm, malignant hepatobiliary neoplasm, malignant germ cell tumor, or thymic carcinoma), lymphoma (optionally, lymphoma, non-Hodgkin lymphoma, small lymphocytic lymphoma, anaplastic large cell lymphoma, B-cell non-Hodgkin lymphoma, follicular lymphoma, or diffuse large B-cell lymphoma), systemic mastocytosis (optionally, systemic mastocytosis (SM) or SM with an associated hematological neoplasm (SM-AHN)), brain cancer (optionally, brain cancer, glioblastoma, malignant glioma, or anaplastic astrocytoma), or germ cell cancer (seminoma, testicular seminoma).

21. The method of claim 20, wherein the KIT positive cancer is GIST.
22. The method of claim 20, wherein the KIT positive cancer is melanoma.
23. The method of claim 20, wherein the KIT positive cancer is systemic mastocytosis.
24. The method of any one of claims 1 to 23, wherein the KIT positive cancer comprises KIT with an activating KIT alteration.
25. The method of claim 24, wherein the activating KIT alteration is encoded by a *KIT* mutation, optionally wherein the *KIT* mutation is a deletion, point mutation, or duplication, or a combination thereof.
26. The method of claim 24 or claim 25, wherein the activating KIT alteration is encoded by *KIT* exon 11.
27. The method of claim 26, wherein the activating KIT alteration is between positions Lys550 and Glu561, optionally wherein the KIT alteration comprises an alteration at position Trp557, Val559, Val560, or Leu576, optionally wherein the KIT alteration is Trp557_Lys558del, Asp579del, Lys550_Lys558del, Trp557Arg, Val559Asp, Val559Ala, Val559Gly, Val560Asp, Val560Gly, Leu576Pro, Val560del, Gln575_Leu576dup, or Asp579del.
28. The method of claim 24 or claim 25, wherein the activating KIT alteration is encoded by *KIT* exon 9.
29. The method of claim 28, wherein the activating KIT alteration is at position Ala502 or Tyr503, or is Ala_Tyr503dup or Phe504_Phe508dup.
30. The method of any one of claims 24 to 29, wherein the KIT positive cancer comprises KIT with a secondary KIT inhibitor-resistant alteration.

31. The method of claim 30, wherein the secondary KIT inhibitor-resistant alteration is an imatinib-resistant alteration.
32. The method of claim 30 or claim 31, wherein the secondary KIT inhibitor-resistant alteration is encoded by *KIT* exon 13, exon 14, exon 17, or exon 18.
33. The method of claim 32, wherein the secondary KIT inhibitor-resistant alteration is at position Val654 (e.g., Val654Ala), Thr670 (e.g., Thr670Ile), Asp816, Asp820, Asn822, or Tyr823 (e.g., Tyr823Asp).
34. A method of treating KIT positive GIST or melanoma in an individual comprising administering to the individual a menin inhibitor.
35. The method of claim 34, wherein the KIT positive GIST or melanoma comprises KIT with an activating KIT alteration, wherein the activating KIT alteration is encoded by a *KIT* mutation in exon 9 or exon 11.
36. The method of claim 34 or claim 35, comprising administering a concomitant KIT inhibitor to the individual.
37. The method of claim 36, wherein the concomitant KIT inhibitor is selected from imatinib, sunitinib, ripretinib, regorafenib, dasatinib, avapritinib, masitinib, nilotinib, and cabozantinib, and pharmaceutically acceptable forms thereof.
38. The method of claim 37, wherein the concomitant KIT inhibitor is imatinib or sunitinib, or a pharmaceutically acceptable form thereof, optionally imatinib mesylate or sunitinb malate.
39. The method of any one of claims 34 to 38, wherein the GIST or melanoma has relapsed after, or failed, or progressed on, or responded insufficiently to treatment with a prior KIT inhibitor, or is refractory to a prior KIT inhibitor.
40. The method of claim 39, wherein the prior KIT inhibitor is imatinib or a pharmaceutically acceptable form thereof, optionally imatinib mesylate.
41. The method of any one of claims 34 to 38, wherein the GIST or melanoma has relapsed after, or failed, or progressed on, or responded insufficiently to treatment with a prior KIT inhibitor, optionally wherein:
- (a) treatment with the prior KIT inhibitor comprises one line of treatment with imatinib or a pharmaceutically acceptable form thereof;
 - (b) treatment with the prior KIT inhibitor comprises two or three lines of treatment with imatinib, sunitinib, regorafenib, ripretinib, dasatinib, avapritinib, masitinib, nilotinib, or cabozantinib, or a pharmaceutically acceptable form thereof; or
 - (c) the GIST or melanoma is newly diagnosed or untreated.

42. The method of any one of claims 34 to 41, wherein the GIST or melanoma comprises KIT with a secondary KIT inhibitor-resistant alteration, optionally wherein the secondary KIT inhibitor-resistant alteration is an imatinib-resistant alteration.
43. The method of any one of claims 1 to 42, wherein the administering reduces the level of KIT in the KIT positive cancer, GIST, or melanoma.
44. The method of claim 43, wherein the level of KIT is reduced by at least 50%, or at least 60%, or at least 70%, or at least 75%, or at least 80%, or at least 85%, or at least 90%, or at least 95%.
45. The method of any one of claims 1 to 44, wherein the administering reduces *KIT* transcription in the KIT positive cancer, GIST, or melanoma.
46. The method of claim 45, wherein the *KIT* transcription is reduced by at least 50%, or at least 60%, or at least 70%, or at least 75%, or at least 80%, or at least 85%, or at least 90%, or at least 95%.
47. A method of reducing an effective amount of a KIT inhibitor for treating a KIT positive cancer in an individual comprising administering to the individual a menin inhibitor and a concomitant KIT inhibitor, wherein the effective amount of the concomitant KIT inhibitor is lower than the effective amount for the KIT inhibitor without the menin inhibitor.
48. A method of reducing a safety risk of treating an individual with a KIT positive cancer with a KIT inhibitor comprising administering to the individual a menin inhibitor and a concomitant KIT inhibitor, wherein the safety risk of the KIT inhibitor is lower when administered with the menin inhibitor than the safety risk of the KIT inhibitor administered without the menin inhibitor.
49. A method of reducing a level of KIT in a KIT positive cancer cell comprising contacting the KIT positive cancer cell with a menin inhibitor and a concomitant KIT inhibitor.
50. The method of claim 49, wherein the contacting reduces the level of KIT by at least 50%, or at least 60%, or at least 70%, or at least 75%, or at least 80%, or at least 85%, or at least 90%, or at least 95%.
51. A method of reducing *KIT* transcription in a KIT positive cancer cell comprising contacting the KIT positive cancer cell with a menin inhibitor, optionally in combination with a KIT inhibitor.
52. The method of claim 51, wherein the contacting reduces *KIT* transcription by at least 50%, or at least 60%, or at least 70%, or at least 75%, or at least 80%, or at least 85%, or at least 90%, or at least 95%.

53. A method of increasing or inducing apoptosis, reducing AKT levels, reducing S6 levels, inhibiting AKT signaling, reducing mTOR, increasing levels of cleaved PARP, reducing ERK1/2, reducing cell proliferation, or decreasing Rb levels, or a combination thereof, in a KIT positive cancer comprising contacting the KIT positive cancer cell with a menin inhibitor, optionally in combination with a KIT inhibitor.
54. A method of increasing or inducing apoptosis, reducing p-AKT levels, reducing p-S6 levels, inhibiting AKT signaling, reducing p-mTOR, increasing levels of cleaved PARP, reducing p-ERK1/2, reducing cell proliferation, or decreasing p-Rb levels, or a combination thereof, in a KIT positive cancer comprising contacting the KIT positive cancer cell with a menin inhibitor, optionally in combination with a KIT inhibitor.
55. The method of any one of claims 2 to 33 or 36 to 50, wherein the individual has had a resection of the KIT positive cancer and the concomitant KIT inhibitor is an adjuvant treatment.
56. The method of any one of claims 2 to 33 or 36 to 54, wherein the menin inhibitor and the KIT inhibitor exhibit a synergistic effect.
57. The method of any one of claims 1 to 56, wherein the menin inhibitor is ziftomenib, SNDX-5613 (revumenib), VTP-50469, JNJ-75276617, bleximenib, DS-1594, DS-1594a, DS-1594b, DSP-5336, MI-3454, M-808, A300-105A, BN104, Compound A, Compound B1, Compound B2, or Compound C, or a pharmaceutically acceptable form thereof.
58. The method of any one of claims 1 to 56, wherein the menin inhibitor is a compound of Formula (I-A), (I-B), (II-A), (III-A), or (IV-B), or a pharmaceutically acceptable form thereof.
59. The method of any one of claims 1 to 58, wherein the menin inhibitor is ziftomenib or a pharmaceutically acceptable form thereof.