involves the use of small molecules that bind MDM2 and neutralize its interaction with p53. MDM2 inhibits p53 activity by three mechanisms: 1) acting as an E3 ubiquitin ligase to promote p53 degradation; 2) binding to and blocking the p53 transcriptional activation domain; and 3) exporting p53 from the nucleus to the cytoplasm. All three of these mechanisms would be blocked by neutralizing the MDM2-p53 interaction. In particular, this therapeutic strategy could be applied to tumors that are $p53^{WT}$, and studies with small molecule MDM2 inhibitors have yielded promising reductions in tumor growth both *in vitro* and *in vivo*. Further, in patients with p53-inactivated tumors, stabilization of wild type p53 in normal tissues by MDM2 inhibition might allow selective protection of normal tissues from mitotic poisons. As used herein, MDM2 means a human MDM2 protein and p53 means a human p53 protein. It is noted that human MDM2 can also be referred to as HDM2 or hMDM2. Several MDM2 inhibitors are in human clinical trials for the treatment of various cancers.

The present invention relates to combination therapy with an MDM2 inhibitor and one or more additional pharmaceutically active agents, which particular combinations show enhanced anti-cancer activity in certain types of cancers over what is expected when the individual members of the combination therapy are used alone.

SUMMARY

In one aspect, the present disclosure provides a use of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid in the manufacture of a medicament for use in combinatorial therapy for treating acute myelogenous leukemia, wherein said medicament is to be administered in combination with decitabine.

In another aspect, the present disclosure provides a use of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid in the manufacture of a medicament for use in combinatorial therapy for treating acute myelogenous leukemia, wherein said medicament is to be administered in combination with cytarabine.

In yet another aspect, the present disclosure provides a use of a pharmaceutical composition comprising 2-((3R,5R,6S)-5-(3- chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2- oxopiperidin-3-yl)acetic acid and decitabine in the manufacture of a medicament for treating acute myelogenous leukemia.

In yet another aspect, the present disclosure provides a use of a pharmaceutical composition comprising 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-

(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2- oxopiperidin-3-yl)acetic acid and cytarabine in the manufacture of a medicament for treating acute myelogenous leukemia.

In yet another aspect, the present disclosure provides a use of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid in the manufacture of a first medicament and use of decitabine in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy for treating acute myelogenous leukemia.

In a further aspect, the present disclosure provides a use of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid in the manufacture of a first medicament and cytarabine in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy for treating acute myelogenous leukemia.

In example 1, the present disclosure provides a method of treating melanoma, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a BRAF inhibitor.

In example 2, the present disclosure provides a method of example 1 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 3, the present disclosure provides a method of example 1 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 4, the present disclosure provides a method of any one of examples 1 to 3 wherein the BRAF inhibitor is dabrafenib.

In example 5, the present disclosure provides a method of any one of examples 1 to 3 wherein the BRAF inhibitor is AMG 2112819 or vemurafenib.

In example 6, the present disclosure provides a method of treating melanoma, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a pan-Raf inhibitor.

In example 7, the present disclosure provides a method of example 6 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 8, the present disclosure provides a method of example 6 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert -butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 9, the present disclosure provides a method of any one of examples 6 to 8 wherein the pan-RAF inhibitor is RAF265 or MLN-2480.

In example 10, the present disclosure provides a method of treating melanoma, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a MEK inhibitor.

In example 11, the present disclosure provides a method of example 10 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 12, the present disclosure provides a method of example 10 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3 –fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 13, the present disclosure provides a method of any one of examples 10 to 12 wherein the MEK inhibitor is trametinib.

In example 14, the present disclosure provides a method of any one of examples 10 to 12 wherein the MEK inhibitor is pimasertib, PD0325901, MEK162, TAK-733, GDC-0973 or AZD8330.

In example 15, the present disclosure provides a method of any one of examples 1 to 14 wherein the melanoma has a BRAF V600E or V600K mutation.

In example 16, the present disclosure provides a method of treating colon cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a BRAF inhibitor.

In example 17, the present disclosure provides a method of example 16 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 18, the present disclosure provides a method of example 16 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2- (tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-

chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 19, the present disclosure provides a method of any one of examples 16 to 18 wherein the BRAF inhibitor is dabrafenib.

In example 20, the present disclosure provides a method of any one of examples 16 to 18 wherein the BRAF inhibitor is AMG 2112819 or vemurafenib.

In example 21, the present disclosure provides a method of treating colon cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a pan-Raf inhibitor.

In example 22, the present disclosure provides a method of example 21 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 23, the present disclosure provides a method of example 21 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 24, the present disclosure provides a method of any one of examples 21 to 23 wherein the pan-RAF inhibitor is RAF265 or MLN-2480.

In example 25, the present disclosure provides a method of treating colon cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a MEK inhibitor.

In example 26, the present disclosure provides a method of example 25 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 27, the present disclosure provides a method of example 25 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3 –fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 28, the present disclosure provides a method of any one of examples 25 to 27 wherein the MEK inhibitor is trametinib.

In example 29, the present disclosure provides a method of any one of examples 25 to 27 wherein the MEK inhibitor is pimasertib, PD0325901, MEK162, TAK-733, GDC-0973 or AZD8330.

In example 30, the present disclosure provides a method of any one of examples 16 to 29 wherein the colon cancer has a BRAF V600E or V600K mutation.

In example 31, the present disclosure provides a method of treating liver cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a BRAF inhibitor.

In example 32, the present disclosure provides a method of example 31 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 33, the present disclosure provides a method of example 31 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 34, the present disclosure provides a method of any one of examples 31 to 33 wherein the BRAF inhibitor is dabrafenib, or a pharmaceutically acceptable salt thereof.

In example 35, the present disclosure provides a method of any one of examples 31 to 33 wherein the BRAF inhibitor is AMG 2112819 or vemurafenib.

In example 36, the present disclosure provides a method of treating liver cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a pan-Raf inhibitor.

In example 37, the present disclosure provides a method of example 36 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 38, the present disclosure provides a method of example 36 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 39, the present disclosure provides a method of any one of examples 36 to 38 wherein the pan-RAF inhibitor is RAF265 or MLN-2480.

In example 40, the present disclosure provides a method of treating liver cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a MEK inhibitor.

In example 41, the present disclosure provides a method of example 40 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 42, the present disclosure provides a method of example 40 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 43, the present disclosure provides a method of any one of examples 40 to 42 wherein the MEK inhibitor is trametinib.

In example 44, the present disclosure provides a method of any one of examples 40 to 42 wherein the MEK inhibitor is pimasertib, PD0325901, MEK162, TAK-733, GDC-0973 or AZD8330.

In example 45, the present disclosure provides a method of any one of examples 31 to 44 wherein the liver cancer has a BRAF V600E or V600K mutation.

In example 46, the present disclosure provides a method of treating bladder cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a MEK inhibitor.

In example 47, the present disclosure provides a method of example 46 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 48, the present disclosure provides a method of example 46 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 49, the present disclosure provides a method of any one of examples 46 to 48 wherein the MEK inhibitor is trametinib.

In example 50, the present disclosure provides a method of any one of examples 46 to 48 wherein the MEK inhibitor is pimasertib, PD0325901, MEK162, TAK-733, GDC-0973 or AZD8330.

In example 51, the present disclosure provides a method of treating AML, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a MEK inhibitor.

In example 52, the present disclosure provides a method of example 51 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 53, the present disclosure provides a method of example 51 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 54, the present disclosure provides a method of any one of examples 51 to 53 wherein the MEK inhibitor is trametinib.

In example 55, the present disclosure provides a method of any one of examples 51 to 53 wherein the MEK inhibitor is pimasertib, PD0325901, MEK162, TAK-733, GDC-0973 or AZD8330.

In example 56, the present disclosure provides a method of any one of examples 51 to 55 wherein the AML has a FLT3-ITD mutation.

In example 57, the present disclosure provides a method of treating NSCLC, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a pan-Raf inhibitor.

In example 58, the present disclosure provides a method of example 57 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 59, the present disclosure provides a method of example 57 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 60, the present disclosure provides a method of any one of examples 57 to 59 wherein the pan-RAF inhibitor is RAF265 or MLN-2480.

In example 61, the present disclosure provides a method of treating NSCLC, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a MEK inhibitor.

In example 62, the present disclosure provides a method of example 61 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 63, the present disclosure provides a method of example 61 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3 –fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 64, the present disclosure provides a method of any one of examples 61 to 63 wherein the MEK inhibitor is trametinib.

In example 65, the present disclosure provides a method of any one of examples 61 to 63 wherein the MEK inhibitor is pimasertib, PD0325901, MEK162, TAK-733, GDC-0973 or AZD8330, or a pharmaceutically acceptable salt thereof.

In example 66, the present disclosure provides a method of any one of examples 57 to 65 wherein the NSCLC had a KRAS mutation.

In example 67, the present disclosure provides a method of treating kidney cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a MEK inhibitor.

In example 68, the present disclosure provides a method of example 67 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 69, the present disclosure provides a method of example 67 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 70, the present disclosure provides a method of any one of examples 67 to 69 wherein the MEK inhibitor is trametinib.

In example 71, the present disclosure provides a method of any one of examples 67 to 69 wherein the MEK inhibitor is pimasertib, PD0325901, MEK162, TAK-733, GDC-0973 or AZD8330, or a pharmaceutically acceptable salt thereof.

In example 72, the present disclosure provides a method of treating stomach cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a MEK inhibitor.

In example 73, the present disclosure provides a method of example 72 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 74, the present disclosure provides a method of example 72 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 75, the present disclosure provides a method of any one of examples 72 to 74 wherein the MEK inhibitor is trametinib.

In example 76, the present disclosure provides a method of any one of examples 72 to 74 wherein the MEK inhibitor is pimasertib, PD0325901, MEK162, TAK-733, GDC-0973 or AZD8330.

In example 77, the present disclosure provides a method of any one of examples 72 to 76 wherein the stomach cancer had a KRAS mutation.

In example 78, the present disclosure provides a method of treating prostate cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a PI3K pathway inhibitor.

In example 79, the present disclosure provides a method of example 78 wherein the PI3K pathway inhibitor is a PI3Kα selective inhibitor.

In example 80, the present disclosure provides a method of example 79 wherein the PI3Kα selective inhibitor is AMG 511, AMG2520765 or BYL719.

In example 81, the present disclosure provides a method of example 78 wherein the PI3K pathway inhibitor is a pan-PI3K inhibitor.

In example 82, the present disclosure provides a method of example 81 wherein the pan-PI3K inhibitor is BKM120 or GDC-0941.

In example 83, the present disclosure provides a method of example 78 wherein the PI3K pathway inhibitor is an AKT inhibitor.

In example 84, the present disclosure provides a method of example 83 wherein the AKT inhibitor is MK-2206, GDC-0068 or AZD5363.

In example 85, the present disclosure provides a method of example 78 wherein the PI3K pathway inhibitor is a dual PI3K/mTOR inhibitor.

In example 86, the present disclosure provides a method of example 85 wherein the dual PI3K/mTOR inhibitor is GDC-0980.

In example 87, the present disclosure provides a method of example 78 wherein the PI3K pathway inhibitor is an mTOR inhibitor.

In example 88, the present disclosure provides a method of example 87 wherein the mTOR inhibitor is AZD2014 or MLN0128.

In example 89, the present disclosure provides a method of any one of examples 78 to 88 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 90, the present disclosure provides a method of any one of examples 78 to 88 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 91, the present disclosure provides a method of treating breast cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a PI3K pathway inhibitor.

In example 92, the present disclosure provides a method of example 91 wherein the PI3K pathway inhibitor is a PI3Kα selective inhibitor.

In example 93, the present disclosure provides a method of example 92 wherein the PI3Kα selective inhibitor is AMG 511, AMG2520765 or BYL719.

In example 94, the present disclosure provides a method of example 91 wherein the PI3K pathway inhibitor is a pan-PI3K inhibitor.

In example 95, the present disclosure provides a method of example 94 wherein the pan-PI3K inhibitor is BKM120 or GDC-0941.

In example 96, the present disclosure provides a method of example 91 wherein the PI3K pathway inhibitor is an AKT inhibitor.

In example 97, the present disclosure provides a method of example 96 wherein the AKT inhibitor is MK-2206, GDC-0068 or AZD5363.

In example 98, the present disclosure provides a method of example 91 wherein the PI3K pathway inhibitor is a dual PI3K/mTOR inhibitor.

In example 99, the present disclosure provides a method of example 98 wherein the dual PI3K/mTOR inhibitor is GDC-0980.

In example 100, the present disclosure provides a method of example 91 wherein the PI3K pathway inhibitor is an mTOR inhibitor.

In example 101, the present disclosure provides a method of example 100 wherein the mTOR inhibitor is AZD2014 or MLN0128.

In example 102, the present disclosure provides a method of any one of examples 91 to 101 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 103, the present disclosure provides a method of any one of examples 91 to 101 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 104, the present disclosure provides a method of any one of examples 91 to 103 wherein the breast cancer has a PI3K mutation.

In example 105, the present disclosure provides a method of treating endometrial cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a PI3K pathway inhibitor.

In example 106, the present disclosure provides a method of example 105 wherein the PI3K pathway inhibitor is a PI3Kα selective inhibitor.

In example 107, the present disclosure provides a method of example 106 wherein the PI3Kα selective inhibitor is AMG 511, AMG252076 or BYL719.

In example 108, the present disclosure provides a method of example 105 wherein the PI3K pathway inhibitor is a pan-PI3K inhibitor.

In example 109, the present disclosure provides a method of example 108 wherein the pan-PI3K inhibitor is BKM120 or GDC-0941.

In example 110, the present disclosure provides a method of example 105 wherein the PI3K pathway inhibitor is an AKT inhibitor.

In example 111, the present disclosure provides a method of example 110 wherein the AKT inhibitor is MK-2206, GDC-0068 or AZD5363.

In example 112, the present disclosure provides a method of example 105 wherein the PI3K pathway inhibitor is a dual PI3K/mTOR inhibitor.

In example 113, the present disclosure provides a method of example 112 wherein the dual PI3K/mTOR inhibitor is GDC-0980.

In example 114, the present disclosure provides a method of example 105 wherein the PI3K pathway inhibitor is an mTOR inhibitor.

In example 115, the present disclosure provides a method of example 114 wherein the mTOR inhibitor is AZD2014 or MLN0128.

In example 116, the present disclosure provides a method of any one of examples 105 to 115 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 117, the present disclosure provides a method of any one of examples 105 to 115 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 118, the present disclosure provides a method of treating NSCLC, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a PI3K pathway inhibitor.

In example 119, the present disclosure provides a method of example 118 wherein the PI3K pathway inhibitor is a PI3Kα selective inhibitor.

In example 120, the present disclosure provides a method of example 119 wherein the PI3Kα selective inhibitor is AMG 511, AMG2520765 or BYL719.

In example 121, the present disclosure provides a method of example 118 wherein the PI3K pathway inhibitor is a pan-PI3K inhibitor.

In example 122, the present disclosure provides a method of example 121 wherein the pan-PI3K inhibitor is BKM120 or GDC-0941.

In example 123, the present disclosure provides a method of example 118 wherein the PI3K pathway inhibitor is an AKT inhibitor.

In example 124, the present disclosure provides a method of example 123 wherein the AKT inhibitor is MK-2206, GDC-0068 or AZD5363.

In example 125, the present disclosure provides a method of example 118 wherein the PI3K pathway inhibitor is a dual PI3K/mTOR inhibitor.

In example 126, the present disclosure provides a method of example 125 wherein the dual PI3K/mTOR inhibitor is GDC-0980.

In example 127, the present disclosure provides a method of example 118 wherein the PI3K pathway inhibitor is an mTOR inhibitor.

In example 128, the present disclosure provides a method of example 127 wherein the mTOR inhibitor is AZD2014 or MLN0128.

In example 129, the present disclosure provides a method of any one of examples 118 to 128 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 130, the present disclosure provides a method of any one of examples 118 to 128 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 131, the present disclosure provides a method of treating head and neck cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a PI3K pathway inhibitor.

In example 132, the present disclosure provides a method of example 131 wherein the PI3K pathway inhibitor is a PI3Kα selective inhibitor.

In example 133, the present disclosure provides a method of example 132 wherein the PI3Kα selective inhibitor is AMG 511, AMG2520765 or BYL719.

In example 134, the present disclosure provides a method of example 131 wherein the PI3K pathway inhibitor is a pan-PI3K inhibitor.

In example 135, the present disclosure provides a method of example 134 wherein the pan-PI3K inhibitor is BKM120 or GDC-0941.

In example 136, the present disclosure provides a method of example 131 wherein the PI3K pathway inhibitor is an AKT inhibitor.

In example 137, the present disclosure provides a method of example 136 wherein the AKT inhibitor is MK-2206, GDC-0068 or AZD5363.

In example 138, the present disclosure provides a method of example 131 wherein the PI3K pathway inhibitor is a dual PI3K/mTOR inhibitor.

In example 139, the present disclosure provides a method of example 138 wherein the dual PI3K/mTOR inhibitor is GDC-0980.

In example 140, the present disclosure provides a method of example 131 wherein the PI3K pathway inhibitor is an mTOR inhibitor.

In example 141, the present disclosure provides a method of example 140 wherein the mTOR inhibitor is AZD2014 or MLN0128.

In example 142, the present disclosure provides a method of any one of examples 131 to 141 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 143, the present disclosure provides a method of any one of examples 131 to 141 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 144, the present disclosure provides a method of treating DLBCL, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a PI3K pathway inhibitor.

In example 145, the present disclosure provides a method of example 144 wherein the PI3K pathway inhibitor is a PI3Kα selective inhibitor.

In example 146, the present disclosure provides a method of example 145 wherein the PI3Kα selective inhibitor is AMG 511, AMG2520765 or BYL719.

In example 147, the present disclosure provides a method of example 144 wherein the PI3K pathway inhibitor is a pan-PI3K inhibitor.

In example 148, the present disclosure provides a method of example 147 wherein the pan-PI3K inhibitor is BKM120 or GDC-0941.

In example 149, the present disclosure provides a method of example 144 wherein the PI3K pathway inhibitor is an AKT inhibitor.

In example 150, the present disclosure provides a method of example 149 wherein the AKT inhibitor is MK-2206, GDC-0068 or AZD5363.

In example 151, the present disclosure provides a method of example 144 wherein the PI3K pathway inhibitor is a dual PI3K/mTOR inhibitor.

In example 152, the present disclosure provides a method of example 151 wherein the dual PI3K/mTOR inhibitor is GDC-0980.

In example 153, the present disclosure provides a method of example 144 wherein the PI3K pathway inhibitor is an mTOR inhibitor.

In example 154, the present disclosure provides a method of example 153 wherein the mTOR inhibitor is AZD2014 or MLN0128.

In example 155, the present disclosure provides a method of any one of examples 144 to 154 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 156, the present disclosure provides a method of any one of examples 144 to 154 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 157, the present disclosure provides a method of treating glioblastoma, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a PI3K pathway inhibitor.

In example 158, the present disclosure provides a method of example 157 wherein the PI3K pathway inhibitor is a PI3Kα selective inhibitor.

In example 159, the present disclosure provides a method of example 158 wherein the PI3Kα selective inhibitor is AMG 511, AMG2520765 or BYL719.

In example 160, the present disclosure provides a method of example 157 wherein the PI3K pathway inhibitor is a pan-PI3K inhibitor.

In example 161, the present disclosure provides a method of example 160 wherein the pan-PI3K inhibitor is BKM120 or GDC-0941.

In example 162, the present disclosure provides a method of example 157 wherein the PI3K pathway inhibitor is an AKT inhibitor.

In example 163, the present disclosure provides a method of example 162 wherein the AKT inhibitor is MK-2206, GDC-0068 or AZD5363.

In example 164, the present disclosure provides a method of example 157 wherein the PI3K pathway inhibitor is a dual PI3K/mTOR inhibitor.

In example 165, the present disclosure provides a method of example 164 wherein the dual PI3K/mTOR inhibitor is GDC-0980.

In example 166, the present disclosure provides a method of example 157 wherein the PI3K pathway inhibitor is an mTOR inhibitor.

In example 167, the present disclosure provides a method of example 166 wherein the mTOR inhibitor is AZD2014 or MLN0128.

In example 168, the present disclosure provides a method of any one of examples 157 to 167 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-

1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 169, the present disclosure provides a method of any one of examples 157 to 167 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 170, the present disclosure provides a method of treating bladder cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a PI3K pathway inhibitor.

In example 171, the present disclosure provides a method of example 170 wherein the PI3K pathway inhibitor is a PI3Kα selective inhibitor.

In example 172, the present disclosure provides a method of example 171 wherein the PI3Kα selective inhibitor is AMG 511, AMG2520765 or BYL719.

In example 173, the present disclosure provides a method of example 170 wherein the PI3K pathway inhibitor is a pan-PI3K inhibitor.

In example 174, the present disclosure provides a method of example 173 wherein the pan-PI3K inhibitor is BKM120 or GDC-0941.

In example 175, the present disclosure provides a method of example 170 wherein the PI3K pathway inhibitor is an AKT inhibitor.

In example 176, the present disclosure provides a method of example 175 wherein the AKT inhibitor is MK-2206, GDC-0068 or AZD5363.

In example 177, the present disclosure provides a method of example 170 wherein the PI3K pathway inhibitor is a dual PI3K/mTOR inhibitor.

In example 178, the present disclosure provides a method of example 177 wherein the dual PI3K/mTOR inhibitor is GDC-0980.

In example 179, the present disclosure provides a method of example 170 wherein the PI3K pathway inhibitor is an mTOR inhibitor.

In example 180, the present disclosure provides a method of example 179 wherein the mTOR inhibitor is AZD2014 or MLN0128.

In example 181, the present disclosure provides a method of any one of examples 170 to 180 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 182, the present disclosure provides a method of any one of examples 170 to 180 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 183, the present disclosure provides a method of treating AML, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a PI3K pathway inhibitor.

In example 184, the present disclosure provides a method of example 183 wherein the PI3K pathway inhibitor is a PI3Kα selective inhibitor.

In example 185, the present disclosure provides a method of example 184 wherein the PI3Kα selective inhibitor is AMG 511, AMG2520765 or BYL719.

In example 186, the present disclosure provides a method of example 183 wherein the PI3K pathway inhibitor is a pan-PI3K inhibitor.

In example 187, the present disclosure provides a method of example 186 wherein the pan-PI3K inhibitor is BKM120 or GDC-0941.

In example 188, the present disclosure provides a method of example 183 wherein the PI3K pathway inhibitor is an AKT inhibitor.

In example 189, the present disclosure provides a method of example 188 wherein the AKT inhibitor is MK-2206, GDC-0068 or AZD5363.

In example 190, the present disclosure provides a method of example 183 wherein the PI3K pathway inhibitor is a dual PI3K/mTOR inhibitor.

In example 191, the present disclosure provides a method of example 190 wherein the dual PI3K/mTOR inhibitor is GDC-0980.

In example 192, the present disclosure provides a method of example 183 wherein the PI3K pathway inhibitor is an mTOR inhibitor.

In example 193, the present disclosure provides a method of example 192 wherein the mTOR inhibitor is AZD2014 or MLN0128.

In example 194, the present disclosure provides a method of any one of examples 183 to 193 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 195, the present disclosure provides a method of any one of examples 183 to 193 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-

cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 196, the present disclosure provides a method of any one of examples 183 to 195 wherein the AML has a FLT3 ITD mutation.

In example 197, the present disclosure provides a method of treating bladder cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a Bcl2/BclxL inhibitor.

In example 198, the present disclosure provides a method of example 197 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 199, the present disclosure provides a method of example 197 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 200, the present disclosure provides a method of any one of examples 197 to 199 wherein the Bcl2/BclxL inhibitor is navitoclax.

In example 201, the present disclosure provides a method of treating glioblastoma, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a Bcl2/BclxL inhibitor.

In example 202, the present disclosure provides a method of example 201 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 203, the present disclosure provides a method of example 201 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 204, the present disclosure provides a method of any one of examples 201 to 203 wherein the Bcl2/BclxL inhibitor is navitoclax.

In example 205, the present disclosure provides a method of treating head and neck cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a Bcl2/BclxL inhibitor.

In example 206, the present disclosure provides a method of example 205 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 207, the present disclosure provides a method of example 205 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 208, the present disclosure provides a method of any one of examples 205 to 207 wherein the Bcl2/BclxL inhibitor is navitoclax.

In example 209, the present disclosure provides a method of treating kidney cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a Bcl2/BclxL inhibitor.

In example 210, the present disclosure provides a method of example 209 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 211, the present disclosure provides a method of example 209 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 212, the present disclosure provides a method of any one of examples 209 to 211 wherein the Bcl2/BclxL inhibitor is navitoclax.

In example 213, the present disclosure provides a method of treating liver cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a Bcl2/BclxL inhibitor.

In example 214, the present disclosure provides a method of example 213 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 215, the present disclosure provides a method of example 213 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 216, the present disclosure provides a method of any one of examples 213 to 215 wherein the Bcl2/BclxL inhibitor is navitoclax.

In example 217, the present disclosure provides a method of treating sarcoma, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a Bcl2/BclxL inhibitor.

In example 218, the present disclosure provides a method of example 217 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 219, the present disclosure provides a method of example 217 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 220, the present disclosure provides a method of any one of examples 217 to 219 wherein the Bcl2/BclxL inhibitor is navitoclax.

In example 221, the present disclosure provides a method of treating AML, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a Bcl2/BclxL inhibitor.

In example 222, the present disclosure provides a method of example 221 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 223, the present disclosure provides a method of example 221 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 224, the present disclosure provides a method of any one of examples 221 to 223 wherein the Bcl2/BclxL inhibitor is navitoclax.

In example 225, the present disclosure provides a method of any one of examples 221 to 224 wherein the AML has a FLT3 ITD mutation.

In example 226, the present disclosure provides a method of treating CML, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a Bcl2/BclxL inhibitor.

In example 227, the present disclosure provides a method of example 226 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 228, the present disclosure provides a method of example 226 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 229, the present disclosure provides a method of any one of examples 226 to 228 wherein the Bcl2/BclxL inhibitor is navitoclax.

In example 230, the present disclosure provides a method of any one of examples 226 to 229 where the CML has a BCR-ABL mutation.

In example 231, the present disclosure provides a method of treating DLBCL, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a Bcl2/BclxL inhibitor.

In example 32, the present disclosure provides a method of example 231 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 233, the present disclosure provides a method of example 231 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 234, the present disclosure provides a method of any one of examples 231 to 233 wherein the Bcl2/BclxL inhibitor is navitoclax.

In example 235, the present disclosure provides a method of treating sarcoma, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a BCL2 inhibitor.

In example 236, the present disclosure provides a method of example 235 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 237, the present disclosure provides a method of example 235 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-

chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 238, the present disclosure provides a method of any one of examples 235 to 237 wherein the BCL2 inhibitor is ABT-199.

In example 239, the present disclosure provides a method of treating AML, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a BCL2 inhibitor.

In example 240, the present disclosure provides a method of example 239 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 241, the present disclosure provides a method of example 239 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 242, the present disclosure provides a method of any one of examples 239 to 241 wherein the BCL2 inhibitor is ABT-199.

In example 243, the present disclosure provides a method of any one of examples 239 to 242 wherein the AML has a FLT3 ITD mutation.

In example 244, the present disclosure provides a method of treating CML, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a BCL2 inhibitor.

In example 245, the present disclosure provides a method of example 244 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 246, the present disclosure provides a method of example 244 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 247, the present disclosure provides a method of any one of examples 244 to 246 wherein the BCL2 inhibitor is ABT-199.

In example 248, the present disclosure provides a method of any one of examples 244 to 247 where the CML has a BCR-ABL mutation.

In example 249, the present disclosure provides a method of treating DLBCL, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a BCL2 inhibitor.

In example 250, the present disclosure provides a method of example 249 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 251, the present disclosure provides a method of example 249 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 252, the present disclosure provides a method of any one of examples 249 to 251 wherein the BCL2 inhibitor is ABT-199.

In example 253, the present disclosure provides a method of treating endometrial cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a BCR-ABL inhibitor.

In example 254, the present disclosure provides a method of example 253 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 255, the present disclosure provides a method of example 253 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 256, the present disclosure provides a method of any one of examples 253 to 255 wherein the BCR-ABL inhibitor is dasatinib.

In example 257, the present disclosure provides a method of treating glioblastoma, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a BCR-ABL inhibitor.

In example 258, the present disclosure provides a method of example 257 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 259, the present disclosure provides a method of example 257 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 260, the present disclosure provides a method of any one of examples 257 to 259 wherein the BCR-ABL inhibitor is dasatinib.

In example 261, the present disclosure provides a method of treating CML, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a BCR-ABL inhibitor.

In example 262, the present disclosure provides a method of example 261 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 263, the present disclosure provides a method of example 261 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 264, the present disclosure provides a method of any one of examples 261 to 263 wherein the BCR-ABL inhibitor is dasatinib.

In example 265, the present disclosure provides a method of any one of examples 261 to 264 where the CML has a BCR-ABL mutation.

In example 266, the present disclosure provides a method of treating endometrial cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a BCR-ABL inhibitor.

In example 267, the present disclosure provides a method of example 266 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 268, the present disclosure provides a method of example 266 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 269, the present disclosure provides a method of any one of examples 266 to 268 wherein the BCR-ABL inhibitor is dasatinib.

In example 270, the present disclosure provides a method of treating bladder cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a BCR-ABL inhibitor.

In example 271, the present disclosure provides a method of example 270 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 272, the present disclosure provides a method of example 270 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 273, the present disclosure provides a method of any one of examples 270 to 272 wherein the BCR-ABL inhibitor is dasatinib.

In example 274, the present disclosure provides a method of treating head and neck cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a BCR-ABL inhibitor.

In example 275, the present disclosure provides a method of example 274 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 276, the present disclosure provides a method of example 274 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 277, the present disclosure provides a method of any one of examples 274 to 276 wherein the BCR-ABL inhibitor is dasatinib.

In example 278, the present disclosure provides a method of treating kidney cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a HDAC inhibitor.

In example 279, the present disclosure provides a method of example 278 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 280, the present disclosure provides a method of example 278 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 281, the present disclosure provides a method of any one of examples 278 to 280 wherein the HDAC inhibitor is panobinostat.

In example 282, the present disclosure provides a method of treating liver cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a HDAC inhibitor.

In example 283, the present disclosure provides a method of example 282 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 284, the present disclosure provides a method of example 282 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 285, the present disclosure provides a method of any one of examples 282 to 284 wherein the HDAC inhibitor is panobinostat.

In example 286, the present disclosure provides a method of treating melanoma, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and a HDAC inhibitor.

In example 287, the present disclosure provides a method of example 286 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 288, the present disclosure provides a method of example 286 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 289, the present disclosure provides a method of any one of examples 286 to 288 wherein the HDAC inhibitor is panobinostat.

In example 290, the present disclosure provides a method of treating AML, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and decitabine.

In example 291, the present disclosure provides a method of example 290 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 292, the present disclosure provides a method of example 290 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 293, the present disclosure provides a method of any one of examples 290 to 292 wherein the AML has a FLT3 ITD mutation.

In example 294, the present disclosure provides a method of treating AML, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and cytarabine.

In example 295, the present disclosure provides a method of example 294 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 296, the present disclosure provides a method of example 294 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 297, the present disclosure provides a method of any one of examples 294 to 296 wherein the AML has a FLT3 ITD mutation.

In example 298, the present disclosure provides a method of treating AML, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and doxorubicin.

In example 299, the present disclosure provides a method of example 298 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 300, the present disclosure provides a method of example 298 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 301, the present disclosure provides a method of any one of examples 298 to 300 wherein the AML has a FLT3 ITD mutation.

In example 302, the present disclosure provides a method of treating sarcoma, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and etoposide.

In example 303, the present disclosure provides a method of example 302 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 304, the present disclosure provides a method of example 302 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 305, the present disclosure provides a method of treating breast cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and doxorubicin.

In example 306, the present disclosure provides a method of example 305 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 307, the present disclosure provides a method of example 305 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 308, the present disclosure provides a method of treating AML, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and imatinib.

In example 309, the present disclosure provides a method of example 308 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-

(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 310, the present disclosure provides a method of example 308 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 311, the present disclosure provides a method of any one of examples 308 to 310 wherein the AML has a FLT3 ITD mutation.

In example 312, the present disclosure provides a method of treating AML, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and ponatinib.

In example 313, the present disclosure provides a method of example 312 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 314, the present disclosure provides a method of example 312 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 315, the present disclosure provides a method of any one of examples 312 to 314 wherein the AML has a FLT3 ITD mutation.

In example 316, the present disclosure provides a method of treating AML, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and bosutinib.

In example 317, the present disclosure provides a method of example 316 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 318, the present disclosure provides a method of example 316 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 319, the present disclosure provides a method of any one of examples 316 to 318 wherein the AML has a FLT3 ITD mutation

In example 320, the present disclosure provides a method of treating AML, the method comprising administering to a patient in need thereof a therapeutically effective amount of an MDM2 inhibitor and nilotinib.

In example 321, the present disclosure provides a method of example 320 wherein the MDM2 inhibitor is 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof.

In example 322, the present disclosure provides a method of example 320 wherein the MDM2 inhibitor is 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof.

In example 323, the present disclosure provides a method of any one of examples 320 to 322 wherein the AML has a FLT3 ITD mutation

In example 324, the present disclosure provides a method of treating melanoma, the method comprising administering to a patient in need thereof a therapeutically effective amount of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, dabrafenib and trametinib.

In example 325, the present disclosure provides a method of treating melanoma, the method comprising administering to a patient in need thereof a therapeutically effective amount of 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, dabrafenib and trametinib.

In example 326, the present disclosure provides a method of any one of examples 324 to 325 wherein the melanoma has a BRAF V600E or V600K mutation.

In example 327, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; dabrafenib; and a pharmaceutically acceptable excipient.

In example 328, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof; dabrafenib; and a pharmaceutically acceptable excipient.

In example 329, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; AMG 2112819; and a pharmaceutically acceptable excipient.

In example 330, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof; AMG 2112819; and a pharmaceutically acceptable excipient.

In example 331, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; RAF265; and a pharmaceutically acceptable excipient.

In example 332, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof; RAF265; and a pharmaceutically acceptable excipient.

In example 333, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; MLN-2480; and a pharmaceutically acceptable excipient.

In example 334, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof; MLN-2480; and a pharmaceutically acceptable excipient.

In example 335, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; trametinib; and a pharmaceutically acceptable excipient.

In example 336, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic

acid, or a pharmaceutically acceptable salt thereof; trametinib; and a pharmaceutically acceptable excipient.

In example 337, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; nilotinib; and a pharmaceutically acceptable excipient.

In example 338, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof; nilotinib; and a pharmaceutically acceptable excipient.

In example 339, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; pimasertinib; and a pharmaceutically acceptable excipient.

In example 340, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof; pimasertinib; and a pharmaceutically acceptable excipient.

In example 341, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; PD0325901; and a pharmaceutically acceptable excipient.

In example 342, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof; PD0325901; and a pharmaceutically acceptable excipient.

In example 343, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; MEK 162; and a pharmaceutically acceptable excipient.

In example 344, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof; MEK 162; and a pharmaceutically acceptable excipient.

In example 345, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; TAK-733; and a pharmaceutically acceptable excipient.

In example 346, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof; TAK-733; and a pharmaceutically acceptable excipient.

In example 347, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; GDC-0973; and a pharmaceutically acceptable excipient.

In example 348, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof; GDC-0973; and a pharmaceutically acceptable excipient.

In example 349, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; AZD 8330; and a pharmaceutically acceptable excipient.

In example 350, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof; AZD 8330; and a pharmaceutically acceptable excipient.

In example 351, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-

3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; vemurafenib; and a pharmaceutically acceptable excipient.

In example 352, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof; vemurafenib; and a pharmaceutically acceptable excipient.

In example 353, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; AMG 511; and a pharmaceutically acceptable excipient.

In example 354, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof; AMG 511; and a pharmaceutically acceptable excipient.

In example 355, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; AMG 2520765; and a pharmaceutically acceptable excipient.

In example 356, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof; AMG 2520765; and a pharmaceutically acceptable excipient.

In example 357, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; BYL719; and a pharmaceutically acceptable excipient.

In example 358, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof; BYL719; and a pharmaceutically acceptable excipient.

In example 359, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; BKM 120; and a pharmaceutically acceptable excipient.

In example 360, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof; BKM 120; and a pharmaceutically acceptable excipient.

In example 361, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; GDC-0941; and a pharmaceutically acceptable excipient.

In example 362, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof; GDC-0941; and a pharmaceutically acceptable excipient.

In example 363, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; MK-2206; and a pharmaceutically acceptable excipient.

In example 364, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof; MK-2206; and a pharmaceutically acceptable excipient.

In example 365, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; AZD 5363; and a pharmaceutically acceptable excipient.

In example 366, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic

acid, or a pharmaceutically acceptable salt thereof; AZD 5363; and a pharmaceutically acceptable excipient.

In example 367, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; GDC-0068; and a pharmaceutically acceptable excipient.

In example 368, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof; GDC-0068; and a pharmaceutically acceptable excipient.

In example 369, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; GDC-0980; and a pharmaceutically acceptable excipient.

In example 370, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof; GDC-0980; and a pharmaceutically acceptable excipient.

In example 371, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; AZD2014; and a pharmaceutically acceptable excipient.

In example 372, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof; AZD2014; and a pharmaceutically acceptable excipient.

In example 373, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; MLN0128; and a pharmaceutically acceptable excipient.

In example 374, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof; MLN0128; and a pharmaceutically acceptable excipient.

In example 375, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; navitoclax; and a pharmaceutically acceptable excipient.

In example 376, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof; navitoclax; and a pharmaceutically acceptable excipient.

In example 377, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; ABT-199; and a pharmaceutically acceptable excipient.

In example 378, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof; ABT-199; and a pharmaceutically acceptable excipient.

In example 379, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; dasatinib; and a pharmaceutically acceptable excipient.

In example 380, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof; dasatinib; and a pharmaceutically acceptable excipient.

In example 381, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-

3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; panobinostat; and a pharmaceutically acceptable excipient.

In example 382, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof; panobinostat; and a pharmaceutically acceptable excipient.

In example 383, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; decitabine; and a pharmaceutically acceptable excipient.

In example 384, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof; decitabine; and a pharmaceutically acceptable excipient.

In example 385, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; cytarabine; and a pharmaceutically acceptable excipient.

In example 386, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof; cytarabine; and a pharmaceutically acceptable excipient.

In example 387, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; doxorubicin; and a pharmaceutically acceptable excipient.

In example 388, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof; doxorubicin; and a pharmaceutically acceptable excipient.

In example 389, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; etoposide; and a pharmaceutically acceptable excipient.

In example 390, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof; etoposide; and a pharmaceutically acceptable excipient.

In example 391, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; imatinib; and a pharmaceutically acceptable excipient.

In example 392, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof; imatinib; and a pharmaceutically acceptable excipient.

In example 393, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; ponatinib; and a pharmaceutically acceptable excipient.

In example 394, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof; ponatinib; and a pharmaceutically acceptable excipient.

In example 395, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; bosutinib; and a pharmaceutically acceptable excipient.

In example 396, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic

acid, or a pharmaceutically acceptable salt thereof; bosutinib; and a pharmaceutically acceptable excipient.

In example 397, the present disclosure provides a pharmaceutical composition comprising: 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, or a pharmaceutically acceptable salt thereof; dabrafenib; trametinib; and a pharmaceutically acceptable excipient.

In example 398, the present disclosure provides a pharmaceutical composition comprising: 4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chloropheny1)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid, or a pharmaceutically acceptable salt thereof; dabrafenib; trametinib; and a pharmaceutically acceptable excipient.

In example 399, the present disclosure provides a method of treating melanoma comprising administering to a patient in need thereof a therapeutically effective amount of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid, and dabrafenib.

In example 400, the present disclosure provides a combination of an MDM2 inhibitor medicament and a MEK inhibitor medicament for treating a solid tumor.

In example 401, the present disclosure provides a combination of an MDM2 inhibitor medicament and a MEK inhibitor medicament for treating AML.

In example 402, the present disclosure provides a combination of an MDM2 inhibitor medicament and a BRAF inhibitor medicament for treating a solid tumor.

In example 403, the present disclosure provides a combination of an MDM2 inhibitor medicament and a BRAF inhibitor medicament for treating AML.

In example 404, the present disclosure provides a use of an MDM2 inhibitor in combination with a BRAF inhibitor for manufacture of a medicament for the management or treatment of melanoma, liver cancer, AML or colon cancer in a subject.

In example 405, the present disclosure provides a use of an MDM2 inhibitor in combination with a MEK inhibitor for manufacture of a medicament for the management or treatment of melanoma, liver cancer, AML or colon cancer in a subject.

A further example of the disclosure includes the use of a combination comprising an MDM2 inhibitor with another therapeutic agent selected from a RAF inhibitor, a MEK inhibitor, a Pi3K a selective inhibitor, an mTOR inhibitor, an AKT inhibitor or an Aurora kinase inhibitor. A further example of the disclosure includes the use of a combination for treatment of cancer, the combination comprising an MDM2 inhibitor with another therapeutic agent selected from a RAF

inhibitor, an MEK inhibitor, a Pi3K a selective inhibitor, an mTOR inhibitor, an AKT inhibitor or an Aurora kinase inhibitor. A further example of the disclosure includes a method of using a combination comprising an MDM2 inhibitor with another therapeutic agent selected from a RAF inhibitor, a MEK inhibitor, a Pi3K a selective inhibitor, an mTOR inhibitor, an AKT inhibitor or an Aurora kinase inhibitor, for the treatment of cancer. A further example of the disclosure includes the use of a combination for treatment of cancer, the combination comprising an MDM2 inhibitor with another therapeutic agent selected from a RAF inhibitor, an MEK inhibitor, a Pi3K a selective inhibitor, an mTOR inhibitor, an AKT inhibitor or an Aurora kinase inhibitor, wherein the use comprises self-administering the combination.

A further example of the disclosure includes a method of treating cancer comprising prescribing a combination further comprising an MDM2 inhibitor with another therapeutic agent selected from a RAF inhibitor, a MEK inhibitor, a Pi3K a selective inhibitor, an mTOR inhibitor, an AKT inhibitor or an Aurora kinase inhibitor. A further example of the disclosure includes a method of treating cancer comprising prescribing to a subject in need thereof, a combination further comprising an MDM2 inhibitor with another therapeutic agent selected from a RAF inhibitor, a MEK inhibitor, a Pi3K a selective inhibitor, an mTOR inhibitor, an AKT inhibitor or an Aurora kinase inhibitor. A further example of the disclosure includes a method of treating cancer comprising prescribing a combination containing an MDM2 inhibitor with another therapeutic agent selected from a RAF inhibitor, a MEK inhibitor, a Pi3K a selective inhibitor, an mTOR inhibitor, an AKT inhibitor or an Aurora kinase inhibitor.

A further example of the disclosure includes a method of treating cancer using a combination comprising an MDM2 inhibitor with another therapeutic agent selected from a RAF inhibitor, a MEK inhibitor, a Pi3K a selective inhibitor, an mTOR inhibitor, an AKT inhibitor or an Aurora kinase inhibitor, wherein such method further comprises listing said combination in a formulary and directing a patient in need of such cancer treatment to administer the combination. A further example of the disclosure includes a method of treating cancer using a combination comprising an MDM2 inhibitor with another therapeutic agent selected from a RAF inhibitor, a MEK inhibitor, a Pi3K a selective inhibitor, an mTOR inhibitor, an AKT inhibitor or an Aurora kinase inhibitor, wherein such method further comprises listing said combination in a formulary and directing a patient in need of such cancer treatment to self-administer the combination.

A further example of the disclosure includes a method of treating cancer using a combination comprising an MDM2 inhibitor with another therapeutic agent selected from a RAF inhibitor, a MEK inhibitor, a Pi3K a selective inhibitor, an mTOR inhibitor, an AKT inhibitor or

an Aurora kinase inhibitor, wherein such method further comprises selling said combination for self-administration to a patient in need of such cancer treatment.

A further example of the disclosure includes a method of using a combination comprising an MDM2 inhibitor with another therapeutic agent selected from a RAF inhibitor, a MEK inhibitor, a Pi3K a selective inhibitor, an mTOR inhibitor, an AKT inhibitor or an Aurora kinase inhibitor, for the treatment of cancer, wherein such method comprises purchasing said combination for self-administration by a patient in need of such cancer treatment. A further example of the disclosure includes a method of using a combination comprising an MDM2 inhibitor with another therapeutic agent selected from a RAF inhibitor, a MEK inhibitor, a Pi3K a selective inhibitor, an mTOR inhibitor, an AKT inhibitor or an Aurora kinase inhibitor, for the treatment of cancer, wherein such method comprises purchasing said combination for administration by a patient in need of such cancer treatment.

A further example of the disclosure includes a method of treating cancer comprising instructing a subject in need of such treatment to administer a combination comprising an MDM2 inhibitor with another therapeutic agent selected from a RAF inhibitor, a MEK inhibitor, a Pi3K a selective inhibitor, an mTOR inhibitor, an AKT inhibitor or an Aurora kinase inhibitor.

A further example of the disclosure includes a process of treating cancer comprising

A] prescribing

B] selling or advertising to sell,

C] purchasing,

D] instructing to self-administer, or

E] administering

of a combination described herein, wherein the combination has been approved by a regulatory agency for the treatment of cancer, to a subject in need of cancer treatment.

A further example of the disclosure includes a method of supplying a combination comprising an MDM2 inhibitor with another therapeutic agent selected from a RAF inhibitor, a MEK inhibitor, a Pi3K a selective inhibitor, an mTOR inhibitor, an AKT inhibitor or an Aurora kinase inhibitor for treating cancer, said method comprises reimbursing a physician, a formulary, a patient or an insurance company for the sale of said combination.

For clarity, the term “instructing” is meant to include information on a label approved by a regulatory agency, in addition to its commonly understood definition.

CLAIMS

What is claimed is:

1. Use of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid in the manufacture of a medicament for use in combinatorial therapy for treating acute myelogenous leukemia, wherein said medicament is to be administered in combination with decitabine.

2. Use of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid in the manufacture of a medicament for use in combinatorial therapy for treating acute myelogenous leukemia, wherein said medicament is to be administered in combination with cytarabine.

3. The use according to claim 1 or 2, wherein the acute myelogenous leukemia has a FLT3-ITD mutation.

4. Use of a pharmaceutical composition comprising 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid and decitabine in the manufacture of a medicament for treating acute myelogenous leukemia.

5. Use of a pharmaceutical composition comprising 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid and cytarabine in the manufacture of a medicament for treating acute myelogenous leukemia.

6. Use of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid in the manufacture of a first medicament and use of decitabine in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy for treating acute myelogenous leukemia.

7. Use of 2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl)acetic acid in the manufacture of a first medicament and cytarabine in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy for treating acute myelogenous leukemia.