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 refers to the use of 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 trametinib in the manufacture of a medicament for treating melanoma in a patient in need thereof. In still another aspect, the present disclosure refers to the use of 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 trametinib in the manufacture of a medicament for treating AML in a patient in need thereof. In example 1, the present disclosure provides a method of treating melanoma, the method comprising

CLAIMS

1. Use of 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 trametinib in the manufacture of a medicament for treating melanoma in a patient in need thereof.

2. The use of claim 1, further comprising a therapeutically effective amount of dabrafenib.

3. The use of claim 1, wherein the melanoma has a BRAF V600E or V600K mutation.

4. The use of claim 2, wherein the melanoma has a BRAF V600E or V600K mutation.

5. Use of 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 trametinib in the manufacture of a medicament for treating AML in a patient in need thereof.

6. The use of claim 5, wherein the AML has a FLT3-ITD mutation.