Summary

A combination of a FAK inhibitor (*e.g.*, VS-6063) and a dual RAF/MEK inhibitor (*e.g.*, CH5126766) may enhance the generation and effectiveness of tumor-specific cytotoxic lymphocytes and provide a promising approach for more effectively treating a disease or disorder described herein (*e.g.*, abnormal cell growth, *e.g.*, cancer (*e.g.*, a cancer described herein)). VS-6063, or a pharmaceutically acceptable salt thereof (a FAK inhibitor), may be used in combination with CH5126766, or a pharmaceutically acceptable salt thereof (a dual RAF/MEK inhibitor) to treat a disease or disorder described herein, *e.g.*, abnormal cell growth (*e.g.*, a cancer described herein).

Therefore, provided herein is a certain combination (*e.g.*, a combination as described herein (*e.g.*, a FAK inhibitor in combination with a dual RAF/MEK inhibitor)), which can be used, for example, to treat abnormal cell growth, such as cancer (*e.g.*, a cancer with a RAS mutation), in a subject (*e.g.*, humans).

In one aspect of the present disclosure, there is provided a use of CH5126766, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating ovarian cancer or non-small cell lung cancer in a subject in need thereof, wherein CH5126766, or a pharmaceutically acceptable salt thereof, is to be orally administered to the subject, in combination with an effective amount of defactinib, or a pharmaceutically acceptable salt thereof,

wherein CH5126766, or a pharmaceutically acceptable salt thereof, and defactinib, or a pharmaceutically acceptable salt thereof, are to be administered as a cycle, wherein CH5126766, or a pharmaceutically acceptable salt thereof, is to be administered twice a week and defactinib, or a pharmaceutically acceptable salt thereof, is to be administered twice daily for three weeks and then CH5126766, or a pharmaceutically acceptable salt thereof, and defactinib, or a pharmaceutically acceptable salt thereof, are not administered for one week.

Described herein is also a method of treating a subject having cancer, the method comprising administering to the subject a therapeutically effective amount of VS-6063, or a pharmaceutically acceptable salt thereof (a FAK inhibitor), in combination with CH5126766, or a pharmaceutically acceptable salt thereof (a dual RAF/MEK inhibitor),

thereby treating the subject, wherein the cancer is a cancer with a RAS mutation. In some examples, the RAS mutation is a KRAS mutation or NRAS mutation.

Described herein is a method of treating a subject having cancer, the method comprising administering to the subject a therapeutically effective amount of VS-6063, or a pharmaceutically acceptable salt thereof, in combination with a dual RAF/MEK inhibitor, wherein the dual RAF/MEK inhibitor is CH5126766, or a pharmaceutically acceptable salt thereof. In some examples, the cancer is caused by a mutation in RAS, BRAF, or NF-1. In some examples, the cancer is a cancer with a RAS mutation. In other examples, the cancer has a KRAS mutation or NRAS mutation.

Described herein is a use of VS-6063, or a pharmaceutically acceptable salt thereof, in combination with a dual RAF/MEK inhibitor, for treating cancer, wherein the dual RAF/MEK inhibitor is CH5126766, or a pharmaceutically acceptable salt thereof. In some examples, the cancer is caused by a mutation in RAS, BRAF, or NF-1. In

some examples, the cancer has a RAS mutation. In other examples, the cancer has a KRAS mutation or NRAS mutation.

Described herein is a method of treating a subject having cancer, the method comprising administering to the subject a therapeutically effective amount of CH5126766, or a pharmaceutically acceptable salt thereof, in combination with a FAK inhibitor, wherein the FAK inhibitor is VS-6063, or a pharmaceutically acceptable salt thereof. In some examples, the cancer is caused by a mutation in RAS, BRAF, or NF-1. In some examples, the cancer has a RAS mutation. In other examples, the cancer has a KRAS mutation or NRAS mutation.

Described herein is a use of CH5126766, or a pharmaceutically acceptable salt thereof, in combination with a FAK inhibitor, for treating cancer, wherein the FAK inhibitor is VS-6063, or a pharmaceutically acceptable salt thereof. In some examples, the cancer is caused by a mutation in RAS, BRAF, or NF-1. In some examples, the cancer has a RAS mutation. In other examples, the cancer has a KRAS mutation or NRAS mutation.

Described herein is a method of treating a subject having cancer, the method comprising administering to the subject a therapeutically effective amount of a dual RAF/MEK inhibitor, in combination with a FAK inhibitor, wherein the dual RAF/MEK inhibitor is CH5126766, or a pharmaceutically acceptable salt thereof, and the FAK inhibitor is VS-6063, or a pharmaceutically acceptable salt thereof.

Described herein is a use of a dual RAF/MEK inhibitor, in combination with a FAK inhibitor, for treating cancer, wherein the dual RAF/MEK inhibitor is CH5126766, or a pharmaceutically acceptable salt thereof, and the FAK inhibitor is VS-6063, or a pharmaceutically acceptable salt thereof.

In some examples, the cancer is caused by a mutation in RAS, BRAF, or NF-1.

In some examples, the cancer is selected from ovarian cancer, lung cancer, colon cancer, and pancreatic cancer. In some examples, the cancer is ovarian cancer. In some examples, the ovarian cancer is low grade serous ovarian cancer. In some examples, the cancer is lung cancer. In other examples, the cancer is colon cancer. In some examples, the cancer is pancreatic cancer. In some examples,

the cancer is selected from low grade serous ovarian cancer, lung cancer, colon cancer, and pancreatic cancer.

In some examples, the dual RAF/MEK inhibitor (*e.g.*, CH5126766) is dosed twice a week. In some examples, the FAK inhibitor (*e.g.*, VS-6063) is dosed twice daily. In other examples, the FAK inhibitor (*e.g.*, VS-6063) is dosed once daily. In some examples, the dual RAF/MEK inhibitor (*e.g.*, CH5126766) and the FAK inhibitor (*e.g.*, VS-6063) are dosed for at least three weeks. In some examples, the dual RAF/MEK inhibitor (*e.g.*, CH5126766) and the FAK inhibitor (*e.g.*, VS-6063) are independently dosed cyclically for three weeks on and then one week off. In some examples, both of the dual RAF/MEK inhibitor (*e.g.*, CH5126766) and the FAK inhibitor (*e.g.*, VS-6063) are simultaneously dosed cyclically for three weeks on and then one week off.

In some examples, the dual RAF/MEK inhibitor (*e.g.*, CH5126766) is dosed at about 0.5 mg to about 10 mg. In further examples, the dual RAF/MEK inhibitor (*e.g.*, CH5126766) is dosed at about 4 mg. In other examples, the dual RAF/MEK inhibitor (*e.g.*, CH5126766) is dosed at 3.2 mg. In some examples, the FAK inhibitor (*e.g.*, VS-6063) is dosed at about 100 mg to about 400 mg. In some examples, the FAK inhibitor (*e.g.*, VS-6063) is dosed at about 100 mg to about 500 mg. In further examples, the FAK inhibitor (*e.g.*, VS-6063) is dosed at about 200 mg to about 500 mg. In other examples, the FAK inhibitor (*e.g.*, VS-6063) is dosed at about 200 mg to about 600 mg. In some examples, the dual RAF/MEK inhibitor (*e.g.*, CH5126766) is dosed at about 0.5 mg to about 10 mg and the FAK inhibitor (*e.g.*, VS-6063) is dosed at about 100 mg to about 400 mg. In some examples, the dual RAF/MEK inhibitor (*e.g.*, CH5126766) is dosed at about 4 mg twice a week and the FAK inhibitor (*e.g.*, VS-6063) is dosed at about 200 mg twice daily. In some examples, the dual RAF/MEK inhibitor (*e.g.*, CH5126766) is dosed at 3.2 mg twice a week and the FAK inhibitor (*e.g.*, VS-6063) is dosed at 200 mg twice daily. In some examples, the dual RAF/MEK inhibitor (*e.g.*, CH5126766) is dosed at about 4 mg twice a week and the FAK inhibitor (*e.g.*, VS-6063) is dosed at about 400 mg twice daily. In some examples, the dual RAF/MEK inhibitor (*e.g.*, CH5126766) is dosed at 3.2 mg twice a week and the FAK inhibitor (*e.g.*, VS-6063) is dosed at 400 mg twice daily.

CLAIMS

1. Use of CH5126766, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating ovarian cancer or non-small cell lung cancer in a subject in need thereof, wherein CH5126766, or a pharmaceutically acceptable salt thereof, is to be orally administered to the subject, in combination with an effective amount of defactinib, or a pharmaceutically acceptable salt thereof,

wherein CH5126766, or a pharmaceutically acceptable salt thereof, and defactinib, or a pharmaceutically acceptable salt thereof, are to be administered as a cycle, wherein CH5126766, or a pharmaceutically acceptable salt thereof, is to be administered twice a week and defactinib, or a pharmaceutically acceptable salt thereof, is to be administered twice daily for three weeks and then CH5126766, or a pharmaceutically acceptable salt thereof, and defactinib, or a pharmaceutically acceptable salt thereof, are not administered for one week.

2. The use of claim 1, wherein CH5126766, or a pharmaceutically acceptable salt thereof, is to be administered at a dose of 0.5 mg to 10 mg per administration.

3. The use of claim 2, wherein CH5126766, or a pharmaceutically acceptable salt thereof, is to be administered at a dose of 3.2 mg per administration.

4. The use of claim 2, wherein CH5126766, or a pharmaceutically acceptable salt thereof, is to be administered at a dose of 4 mg per administration.

5. The use of claim 1, wherein defactinib, or a pharmaceutically acceptable salt thereof, is to be administered at a dose of 100 mg to 500 mg per administration.

6. The use of claim 5, wherein defactinib , or a pharmaceutically acceptable salt thereof, is to be administered at a dose of 200 mg per administration.

7. The use of claim 5, wherein defactinib, or a pharmaceutically acceptable salt thereof, is to be administered at a dose of 400 mg per administration.

8. The use of claim 1, wherein the cancer is characterized as having a mutation in EGFR, FGFR, ALK, ROS1, PI3K, NF-1, BRAF, HRAS, KRAS or NRAS.

9. The use of claim 1, wherein the cancer is characterized as having a mutation in RAS, BRAF, or NF-1.

10. The use of claim 9, wherein the mutation in RAS is a mutation in HRAS, KRAS, or NRAS.

11. The use of claim 1, wherein the ovarian cancer is low grade serous ovarian cancer.

12. The use of claim 1, wherein CH5126766, or a pharmaceutically acceptable salt thereof, is a potassium salt of CH5126766.