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 ~~embodiment~~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 ~~embodiment~~examples, the cancer is caused by a mutation in RAS, BRAF, or NF-1. In some ~~embodiment~~examples, the cancer is a cancer with a RAS mutation. In other ~~aspects~~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 ~~embodiment~~examples, the cancer is caused by a mutation in RAS, BRAF, or NF-1. In

some ~~embodiment~~examples, the cancer has a RAS mutation. In other ~~aspect~~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 ~~embodiment~~examples, the cancer is caused by a mutation in RAS, BRAF, or NF-1. In some ~~embodiment~~examples, the cancer has a RAS mutation. In other ~~aspect~~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 ~~embodiment~~examples, the cancer is caused by a mutation in RAS, BRAF, or NF-1. In some ~~embodiment~~examples, the cancer has a RAS mutation. In other ~~aspect~~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 ~~embodiment~~examples, the cancer is caused by a mutation in RAS, BRAF, or NF-1.

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

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

In some ~~aspect~~examples, the dual RAF/MEK inhibitor (*e.g.*, CH5126766) is dosed twice a week. In some ~~aspect~~examples, the FAK inhibitor (*e.g.*, VS-6063) is dosed twice daily. In other ~~aspect~~examples, the FAK inhibitor (*e.g.*, VS-6063) is dosed once daily. In some ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~aspect~~examples, the dual RAF/MEK inhibitor (*e.g.*, CH5126766) is dosed at about 0.5 mg to about 10 mg. In further ~~embodiment~~examples, the dual RAF/MEK inhibitor (*e.g.*, CH5126766) is dosed at about 4 mg. In other ~~embodiment~~examples, the dual RAF/MEK inhibitor (*e.g.*, CH5126766) is dosed at 3.2 mg. In some ~~embodiment~~examples, the FAK inhibitor (*e.g.*, VS-6063) is dosed at about 100 mg to about 400 mg. In some ~~embodiment~~examples, the FAK inhibitor (*e.g.*, VS-6063) is dosed at about 100 mg to about 500 mg. In further ~~embodiment~~examples, the FAK inhibitor (*e.g.*, VS-6063) is dosed at about 200 mg to about 500 mg. In other ~~embodiment~~examples, the FAK inhibitor (*e.g.*, VS-6063) is dosed at about 200 mg to about 600 mg. In some ~~aspect~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~embodiment~~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 ~~A method of~~ treating ovarian cancer or non-small cell lung cancer in a subject ~~having cancer~~in need thereof, wherein CH5126766, or a pharmaceutically acceptable salt thereof, is to be ~~the method comprising~~ orally administer~~ed~~~~ing~~ to the subject ~~a therapeutically effective amount of~~ , in combination with an effective amount of defactinib~~VS-6063~~, or a pharmaceutically acceptable salt thereof, ~~in combination with CH5126766, or a pharmaceutically acceptable salt thereof, thereby treating the subject, wherein the cancer is a cancer with a RAS mutation~~

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 method of claim 1, wherein the CH5126766 or pharmaceutically acceptable salt thereof is a potassium salt of CH5126766.~~

~~3. The method of claim 1 or 2, wherein the cancer is selected from the group consisting of ovarian cancer, lung cancer, colon cancer, and pancreatic cancer.~~

~~4. The method of any one of claims 1-3, wherein the cancer is ovarian cancer.~~

~~5. The method of claim 4, wherein the ovarian cancer is low grade serous ovarian cancer.~~

~~6. The method of any one of claims 1-3, wherein the cancer is lung cancer.~~

~~7. The method of any one of claims 1-3, wherein the cancer is colon cancer.~~

~~8. The method of any one of claims 1-3, wherein the cancer is pancreatic cancer.~~

~~9. The method of any one of claims 1-8, wherein the CH5126766 or pharmaceutically acceptable salt thereof is dosed twice a week.~~

~~10. The method of any one of claims 1-9, wherein the VS-6063 or pharmaceutically acceptable salt thereof is dosed twice daily.~~

~~11. The method of any one of claims 1-9, wherein the VS-6063 or pharmaceutically acceptable salt thereof is dosed once daily.~~

~~12. The method of any one of claims 1-11, wherein the CH5126766 or pharmaceutically acceptable salt thereof and the VS-6063 or pharmaceutically acceptable salt thereof are dosed for at least three weeks.~~

~~13. The method of any one of claims 1-12, wherein the CH5126766 or pharmaceutically acceptable salt thereof and the VS-6063 or pharmaceutically acceptable salt thereof are independently dosed cyclically for three weeks on and then one week off.~~

~~14. The method of any one of claims 1-12, wherein the CH5126766 or pharmaceutically acceptable salt thereof and the VS-6063 or pharmaceutically acceptable salt thereof are simultaneously dosed cyclically for three weeks on and then one week off.~~

~~15~~2. The use of claim 1~~method of any one of claims 1-14~~, wherein ~~the~~ CH5126766, or a pharmaceutically acceptable salt thereof, is to be administered at a dose of ~~dosed at about~~ 0.5 mg to ~~about~~ 10 mg per administration.

~~16. The method of any one of claims 1-14, wherein the CH5126766 or pharmaceutically acceptable salt thereof is dosed at about 4 mg.~~

~~17~~3. The use of claim 2~~method of any one of claims 1-14~~, wherein ~~the~~ CH5126766, or a pharmaceutically acceptable salt thereof, is to be administered at a dose of ~~dosed at~~ 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.

~~18. The method of any one of claims 1-17, wherein the VS-6063 or pharmaceutically acceptable salt thereof is dosed at about 100 mg to about 400 mg.~~

~~19~~5. The use of claim 1~~method of any one of claims 1-17~~, wherein defactinib~~the VS-6063~~, or a pharmaceutically acceptable salt thereof, is to be administered at a dose of ~~dosed at about~~ 100 mg to ~~about~~ 500 mg per administration.

~~20~~6. The use of claim 5~~method of any one of claims 1-17~~, wherein defactinib ~~the VS-6063~~, or a pharmaceutically acceptable salt thereof, is to be administered at a dose of ~~dosed at about~~ 200 mg ~~to about 500 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.

~~21. The method of any one of claims 1-17, wherein the VS-6063 or pharmaceutically acceptable salt thereof is dosed at about 200 mg to about 600 mg.~~

~~22. The method of any one of claims 1-14, wherein the CH5126766 or pharmaceutically acceptable salt thereof is dosed at about 0.5 mg to about 10 mg and the VS-6063 or pharmaceutically acceptable salt thereof is dosed at about 100 mg to about 400 mg.~~

~~23. The method of any one of claims 1-14, wherein the CH5126766 or pharmaceutically acceptable salt thereof is dosed at about 4 mg twice a week and the VS-6063 or pharmaceutically acceptable salt thereof is dosed at about 200 mg twice daily.~~

~~24. The method of any one of claims 1-14, wherein the CH5126766 or pharmaceutically acceptable salt thereof is dosed at 3.2 mg twice a week and the VS-6063 or pharmaceutically acceptable salt thereof is dosed at 200 mg twice daily.~~

~~25. The method of any one of claims 1-14, wherein the CH5126766 or pharmaceutically acceptable salt thereof is dosed at about 4 mg twice a week and the VS-6063 or pharmaceutically acceptable salt thereof is dosed at about 400 mg twice daily.~~

~~26. The method of any one of claims 1-14, wherein the CH5126766 or pharmaceutically acceptable salt thereof is dosed at 3.2 mg twice a week and the VS-6063 or pharmaceutically acceptable salt thereof is dosed at 400 mg twice daily.~~

~~27. 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 VS-6063, or a pharmaceutically acceptable salt thereof.~~

~~28. The method of claim 27, wherein the cancer is selected from the group consisting of ovarian cancer, lung cancer, colon cancer, and pancreatic cancer.~~

~~29. The method of claim 27 or 28, wherein the cancer is ovarian cancer.~~

~~30. The method of claim 29, wherein the ovarian cancer is low-grade serous ovarian cancer.~~

~~31. The method of claim 27 or 28, wherein the cancer is lung cancer.~~

~~32. The method of claim 27 or 28, wherein the cancer is colon cancer.~~

~~33. The method of claim 27 or 28, wherein the cancer is pancreatic cancer.~~

~~34. The method of any one of claims 27-33, wherein the CH5126766 or pharmaceutically acceptable salt thereof is dosed twice a week.~~

~~35. The method of any one of claims 27-34, wherein the VS-6063 or pharmaceutically acceptable salt thereof is dosed twice daily.~~

~~36. The method of any one of claims 27-34, wherein the VS-6063 or pharmaceutically acceptable salt thereof is dosed once daily.~~

~~37. The method of any one of claims 27-36, wherein the CH5126766 or pharmaceutically acceptable salt thereof and the VS-6063 or pharmaceutically acceptable salt thereof are dosed for at least three weeks.~~

~~38. The method of any one of claims 27-37, wherein the CH5126766 or pharmaceutically acceptable salt thereof and the VS-6063 or pharmaceutically acceptable salt thereof are independently dosed cyclically for three weeks on and then one week off.~~

~~39. The method of any one of claims 27-37, wherein the CH5126766 or pharmaceutically acceptable salt thereof and the VS-6063 or pharmaceutically acceptable salt thereof are simultaneously dosed cyclically for three weeks on and then one week off.~~

~~40. The method of any one of claims 27-39, wherein the CH5126766 or pharmaceutically acceptable salt thereof is dosed at about 0.5 mg to about 10 mg.~~

~~41. The method of any one of claims 27-39, wherein the CH5126766 or pharmaceutically acceptable salt thereof is dosed at about 4 mg.~~

~~42. The method of any one of claims 27-39, wherein the CH5126766 or pharmaceutically acceptable salt thereof is dosed at 3.2 mg.~~

~~43. The method of any one of claims 27-42, wherein the VS-6063 or pharmaceutically acceptable salt thereof is dosed at about 100 mg to about 400 mg.~~

~~44. The method of any one of claims 27-42, wherein the VS-6063 or pharmaceutically acceptable salt thereof is dosed at about 100 mg to about 500 mg.~~

~~45. The method of any one of claims 27-42, wherein the VS-6063 or pharmaceutically acceptable salt thereof is dosed at about 200 mg to about 500 mg.~~

~~46. The method of any one of claims 27-42, wherein the VS-6063 or pharmaceutically acceptable salt thereof is dosed at about 200 mg to about 600 mg.~~

~~47. The method of any one of claims 27-39, wherein the CH5126766 or pharmaceutically acceptable salt thereof is dosed at about 0.5 mg to about 10 mg and the VS-6063 or pharmaceutically acceptable salt thereof is dosed at about 100 mg to about 400 mg.~~

~~48. The method of any one of claims 27-39, wherein the CH5126766 or pharmaceutically acceptable salt thereof is dosed at about 4 mg twice a week and the VS-6063 or pharmaceutically acceptable salt thereof is dosed at about 200 mg twice daily.~~

~~49. The method of any one of claims 27-39, wherein the CH5126766 or pharmaceutically acceptable salt thereof is dosed at 3.2 mg twice a week and the VS-6063 or pharmaceutically acceptable salt thereof is dosed at 200 mg twice daily.~~

~~50. The method of any one of claims 27-39, wherein the CH5126766 or pharmaceutically acceptable salt thereof is dosed at about 4.0 mg twice a week and the VS-6063 or pharmaceutically acceptable salt thereof is dosed at about 400 mg twice daily.~~

~~51. The method of any one of claims 27-39, wherein the CH5126766 or pharmaceutically acceptable salt thereof is dosed at 3.2 mg twice a week and the VS-6063 or pharmaceutically acceptable salt thereof is dosed at 400 mg twice daily.~~

~~52~~9. The ~~method of any one of claims 27-51~~use of claim 1, wherein the cancer is characterized as having ~~caused by~~ a mutation in RAS, ~~or~~ BRAF, or NF-1.

~~53~~10. The ~~method of any one of claims 27-51~~use of claim 9, wherein the mutation in RAS is a mutation in HRAS, ~~cancer is caused by a~~ KRAS, ~~mutation~~ or NRAS ~~mutation~~.

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.