BRIEF SUMMARY

[0008] Provided herein are methods for treating or delaying progression of cancer in an individual comprising administering to the individual an effective amount of a PD-1 axis binding antagonist and a MEK inhibitor, wherein the individual has cancer or is at risk of developing cancer that is resistant to a B-raf antagonist. In some embodiments, the method further comprises diagnosing the individual as having a cancer that is resistant to a B-raf antagonist, wherein the diagnosing occurs prior to administering the effective amount of the PD-1 axis binding antagonist and the MEK inhibitor. In some embodiments, the method further comprises selecting an individual for treatment based on the individual having cancer that is resistant to a B-raf antagonist or assessing that the individual is at risk of developing cancer that is resistant to a B-raf antagonist, wherein the selecting occurs prior to administering the effective amount of the PD-1 axis binding antagonist and the MEK inhibitor. In some embodiments, the individual has not been previously treated with a B-raf antagonist. In some embodiments, the individual has been previously treated with a B-raf antagonist.

[0008a] In one aspect, provided herein is use of an effective amount of: a PD-L1 antagonist for the manufacture of a first medicament, and a MEK inhibitor for the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination for treating or delaying progression of melanoma that is resistant to a B-raf antagonist in an individual, wherein the individual has been previously treated with the B-raf antagonist for melanoma, wherein the B-raf antagonist is vemurafenib, wherein the PD-L1 antagonist is an anti-PD-L1 antibody, and wherein the MEK inhibitor is GDC-0973, or a pharmaceutically acceptable salt or solvate thereof.

[0008b] In one aspect, provided herein is use of an effective amount of a PD-L1 antagonist in the manufacture of a medicament for treating or delaying progression of melanoma that is resistant to a B-raf antagonist in an individual, wherein the medicament is to be used in combination with a MEK inhibitor, wherein the individual hasbeen previously treated with the B-raf antagonist for melanoma, wherein the B-raf antagonist is vemurafenib, wherein the PD-L1 antagonist is an anti-PD-L1 antibody, and wherein the MEK inhibitor is GDC-0973, or a pharmaceutically acceptable salt or solvate thereof.

[0008c] In one aspect, provided herein is use of an effective amount of a MEK inhibitor in the manufacture of a medicament for treating or delaying progression of melanoma that is resistant to a B-raf antagonist in an individual, wherein the medicament is to be used in combination with a PD-L1 antagonist, wherein the individual has been previously treated with the B-raf antagonist for melanoma, wherein the B-raf antagonist is vemurafenib, wherein the PD-L1 antagonist is an anti-PD-L1 antibody, and wherein the MEK inhibitor is GDC-0973, or a pharmaceutically acceptable salt or solvate thereof.

[0008d] Provided herein is a pharmaceutical composition comprising a PD-1 axis binding antagonist in combination with a MEK inhibitor for use in treating or delaying progression of cancer in an individual, wherein the individual has cancer or is at risk of developing cancer that is resistant to a B-raf antagonist.

[0008e] Provided herein is a pharmaceutical composition comprising a PD-1 axis binding antagonist for use in treating or delaying progression of cancer in an individual in combination with a MEK inhibitor, wherein the individual has cancer or is at risk of developing cancer that is resistant to a B-raf antagonist.

[0008f] Provided herein is a pharmaceutical composition comprising a MEK inhibitor for use in treating or delaying progression of cancer in an individual in combination with a PD-1 axis binding antagonist wherein the individual has cancer or is at risk of developing cancer that is resistant to a B-raf antagonist.

[0009] Provided herein are methods for treating or delaying progression of cancer in an individual comprising (a) diagnoising the individual as having a cancer that is resistant to a B-raf antagonist; and (b) administering to the individual an effective amount of a PD-1 axis binding antagonist and a MEK inhibitor, wherein the administering occurs after diagnosing the individual. In some embodiments, the individual has not been previously treated with a B-raf antagonist. In some embodiments, the individual has been previously treated with a B-raf antagonist.

[0010] Provided herein are methods for treating or delaying progression of cancer in an individual comprising (a) selecting an individual for treatment based on the individual having cancer that is resistant to a B-raf antagonist or assessing that the individual is at risk of developing cancer that is resistant to a B-raf antagonist; and (b) administering to the individual an effective amount of a PD-1 axis binding antagonist and a MEK inhibitor, wherein the administering occurs after selecting the individual. In some embodiments, the individual has not been previously treated with a B-raf antagonist. In some embodiments, the individual has been previously treated with a B-raf antagonist.

[0011] Provided herein are methods for treating or delaying progression of cancer in an individual comprising administering to the individual an effective amount of a PD-1

axis binding antagonist and a MEK inhibitor, wherein the individual has been previously treated with a B-raf antagonist for cancer.

[0011a] Provided herein is use of an effective amount of a PD-1 axis binding antagonist and a MEK inhibitor for the manufacture of a first medicament comprising the PD-1 axis binding antagonist and a second medicament comprising the MEK inhibitor for treating or delaying progression of cancer in an individual, wherein the individual has been previously treated with a B-raf antagonist for cancer.

[0011b] Provided herein is use of an effective amount of a PD-1 axis binding antagonist in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the PD-1 axis binding agent is used in combination with a MEK inhibitor, wherein the individual has been previously treated with a B-raf antagonist for cancer.

[0011c] Provided herein is use of an effective amount of a MEK inhibitor in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the MEK inhibitor is used in combination with a PD-1 axis binding antagonist, wherein the individual has been previously treated with a B-raf antagonist for cancer.

[0011d] Provided herein is a pharmaceutical composition comprising a PD-1 axis binding antagonist in combination with a MEK inhibitor for use in treating or delaying progression of cancer in an individual, wherein the individual has been previously treated with a B-raf antagonist for cancer.

[0011e] Provided herein is a pharmaceutical composition comprising a PD-1 axis binding antagonist for use in treating or delaying progression of cancer in an individual in combination with a MEK inhibitor, wherein the individual has been previously treated with a B-raf antagonist for cancer.

[0011f] Provided herein is a pharmaceutical composition comprising a MEK inhibitor for use in treating or delaying progression of cancer in an individual in combination with a PD-1 axis binding antagonist wherein the individual has been previously treated with a B-raf antagonist for cancer.

some embodiments, the PD-1 axis binding antagonist and/or the MEK inhibitor is administered intravenously, intramuscularly, subcutaneously, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally.

[0016] Provided herein are kits comprising a PD-1 axis binding antagonist and a package insert comprising instructions for using the PD-1 axis binding antagonist in combination with a MEK inhibitor to treat or delay progression of cancer in an individual, wherein the individual has cancer or is at risk of developing cancer that is resistant to a B-raf antagonist. Provided herein are kits comprising a PD-1 axis binding antagonist and a MEK inhibitor, and a package insert comprising instructions for using the PD-1 axis binding antagonist and the MEK inhibitor to treat or delay progression of cancer in an individual, wherein the individual has cancer or is at risk of developing cancer that is resistant to a B-raf antagonist. Provided herein are kits comprising a MEK inhibitor and a package insert comprising instructions for using the MEK inhibitor in combination with a PD-1 axis binding antagonist to treat or delay progression of cancer in an individual, wherein the individual has cancer or is at risk of developing cancer that is resistant to a B-raf antagonist. Provided herein are kits comprising a PD-1 axis binding antagonist and a package insert comprising instructions for using the PD-1 axis binding antagonist in combination with a MEK inhibitor to treat or delay progression of cancer in an individual, wherein the individual has been previously treated with a B-raf antagonist for cancer. Provided herein are kits comprising a PD-1 axis binding antagonist and a MEK inhibitor, and a package insert comprising instructions for using the PD-1 axis binding antagonist and the MEK inhibitor to treat or delay progression of cancer in an individual, wherein the individual has been previously treated with a B-raf antagonist for cancer. Provided herein are kits comprising a MEK inhibitor and a package insert comprising instructions for using the MEK inhibitor in combination with a PD-1 axis binding antagonist to treat or delay progression of cancer in an individual, wherein the individual has been previously treated with a B-raf antagonist for cancer.

[0017] In some embodiments, the individual is a human.

[0018] It is to be understood that one, some, or all of the properties of the various embodiments described herein may be combined to form other embodiments of the present disclosure. These and other aspects of the invention will become apparent to one of skill in the

CLAIMS

What is claimed is:

1. Use of an effective amount of:
a PD-L1 antagonist for the manufacture of a first medicament, and
a MEK inhibitor for the manufacture of a second medicament,
wherein the first and second medicaments are to be used in combination for treating or delaying progression of melanoma that is resistant to a B-raf antagonist in an individual,
wherein the individual has been previously treated with the B-raf antagonist for melanoma,
wherein the B-raf antagonist is vemurafenib,
wherein the PD-L1 antagonist is an anti-PD-L1 antibody, and
wherein the MEK inhibitor is GDC-0973, or a pharmaceutically acceptable salt or solvate thereof.

2. Use of an effective amount of a PD-L1 antagonist in the manufacture of a medicament for treating or delaying progression of melanoma that is resistant to a B-raf antagonist in an individual, wherein the medicament is to be used in combination with a MEK inhibitor for treating or delaying progression of melanoma that is resistant to a B-raf antagonist in an individual, wherein the individual has been previously treated with the B-raf antagonist for melanoma,
wherein the B-raf antagonist is vemurafenib,
wherein the PD-L1 antagonist is an anti-PD-L1 antibody, and
wherein the MEK inhibitor is GDC-0973, or a pharmaceutically acceptable salt or solvate thereof.

3. Use of an effective amount of a MEK inhibitor in the manufacture of a medicament for treating or delaying progression of melanoma that is resistant to a B-raf antagonist in an individual, wherein the medicament is to be used in combination with a PD-L1 antagonist for treating or delaying progression of melanoma that is resistant to a B-raf antagonist in an individual, wherein the individual has been previously treated with the B-raf antagonist for melanoma,
wherein the B-raf antagonist is vemurafenib,
wherein the PD-L1 antagonist is an anti-PD-L1 antibody, and
wherein the MEK inhibitor is GDC-0973, or a pharmaceutically acceptable salt or solvate thereof.

4. The use of any one of claims 1-3, wherein the melanoma in the individual has progressed within 1 month, 6 months, 1 year, or 5 years after completing a B-raf antagonist-based therapy regimen.

5. The use of any one of claims 1-4, wherein the melanoma contains a BRAF V600E mutation.

6. The use of any one of claims 1-5, wherein the treatment results in a sustained response in the individual after cessation of the treatment.

7. The use of any one of claims 1-6, wherein the melanoma is metastatic.

8. The use of any one of claims 1-7, wherein the PD-L1 antagonist inhibits the binding of PD-L1 to PD-1, PD-L1 to B7-1, or PD-L1 to both PD-1 and B7-1.

9. The use of any one of claims 1-8, wherein the anti-PD-L1 antibody is a monoclonal antibody.

10. The use of any one of claims 1-8, wherein the anti-PD-L1 antibody is an antibody fragment selected from the group consisting of Fab, Fab'-SH, Fv, scFv, and $(Fab')_2$ fragments.

11. The use of any one of claims 1-10, wherein the anti-PD-L1 antibody is a humanized antibody or a human antibody.

12. The use of any one of claims 1-9 and 11, wherein the anti-PD-L1 antibody is selected from the group consisting of: YW243.55.S70, atezolizumab, durvalumab, MDX-1105, and avelumab.

13. The use of any one of claims 1-12, wherein the antibody comprises a heavy chain comprising HVR-H1 sequence of SEQ ID NO:15, HVR-H2 sequence of SEQ ID NO:16, and HVR-H3 sequence of SEQ ID NO:3; and a light chain comprising HVR-L1 sequence of SEQ ID NO:17, HVR-L2 sequence of SEQ ID NO:18, and HVR-L3 sequence of SEQ ID NO:19.

14. The use of any one of claims 1-12, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:24 or SEQ ID NO:28 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:21.

15. The use of any one of claims 1-14, wherein the MEK inhibitor is administered continuously.

16. The use of any one of claims 1-14, wherein the MEK inhibitor is administered intermittently.

17. The use of any one of claims 1-14, wherein the MEK inhibitor is to be administered before the PD-L1 antagonist.

18. The use of any one of claims 1-14, wherein the MEK inhibitor is to be administered

simultaneous with the PD-L1 antagonist.

19. The use of any one of claims 1-14, wherein the MEK inhibitor is to be administered after the PD-L1 antagonist.

20. The use of any one of claims 1-19, wherein the PD-L1 antagonist and/or the MEK inhibitor is to be administered intravenously, intramuscularly, subcutaneously, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally.