~~BRIEF~~ SUMMARY ~~OF THE INVENTION~~

[0009] The present ~~invention~~ disclosure describes a combination treatment comprising oxaliplatin, leucovorin and 5-FU and a PD-1 axis binding antagonist with or without a VEGF antagonist.

[0010] Provided herein are methods for treating cancer or slowing progression of cancer in an individual comprising administering to the individual an effective amount of a PD-1 axis binding antagonist and oxaliplatin, leucovorin and 5-FU.

[0010a] In one aspect, there is provided 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 medicament is to be administered with oxaliplatin, leucovorin and 5-FU.

In some ~~aspects~~ embodiments the method
further comprises administering a VEGF antagonist.

[0011] The cancer may be a melanoma, a colorectal cancer, a non-small cell lung cancer, an ovarian cancer, a breast cancer, a prostate cancer, a pancreatic cancer, hematological malignancy or a renal cell carcinoma. The cancer may be at early stage or at late stage. In some embodiments, the subject treated is a human.

[0012] In some embodiments, the treatment results in sustained response in the individual after cessation of the treatment. In some embodiments, the treatment produces a complete response, a partial response, or stable disease in the subject.

[0013] In some embodiments, the PD-1 axis binding antagonist is a PD-1 binding antagonist, a PD-L1 binding antagonist or a PD-L2 binding antagonist. In some embodiments, the PD-1 binding antagonist inhibits binding of PD-1 to PD-L1 and/or binding of PD-1 to PD-L2. In some embodiments, the PD-1 binding antagonist is an antibody (e.g., antibody MDX-1106, CT-011 and Merck 3745 described herein), an antigen binding fragments thereof, an immunoadhesin, a fusion protein, or an oligopeptide. In some embodiments, the PD-L1 binding antagonist inhibits binding of PD-L1 to PD-1 and/or binding of PD-L1 to B7-1. In some embodiments, the PD-L1 binding antagonist is an antibody (e.g., antibody YW243.55.S70 and MDX-1105 described herein), an antigen binding fragments thereof, an immunoadhesin, a fusion protein, or an oligopeptide. In some embodiments, the PD-L2 binding antagonist inhibits binding of PD-L2 to PD-1. In some embodiments, the PD-L2 binding antagonist is an

antibody, an antigen binding fragments thereof, an immunoadhesin (e.g., AMP-224 described herein), a fusion protein, or an oligopeptide.

In some embodiments, the VEGF antagonist is an antibody, e.g., a monoclonal antibody. In some embodiments the anti-VEGF antibody binds the same epitope as the monoclonal anti-VEGF antibody A4.6.1 produced by hybridoma ATCC HB 10709. The anti-VEGF

antibody may be a humanized antibody or a human antibody. In some embodiments the anti-VEGF antibody is bevacizumab. In some embodiments the anti-VEGF antibody has a heavy chain variable region comprising the following amino acid sequence:

EVQLVESGGG LVQPGGSLRL SCAASGYTFT NYGMNWVRQA PGKGLEWVGW INTYTGEPTY AADFKRRFTF SLDTSKSTAY LQMNSLRAED TAVYYCAKYP HYYGSSHWYF DVWGQGTLVT VSS (SEQ ID NO:22)

and a light chain variable region comprising the following amino acid sequence:

DIQMTQSPSS LSASVGDRVT ITCSASQDIS NYLNWYQQKP GKAPKVLIYF TSSLHSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YSTVPWTFGQ GTKVEIKR (SEQ ID NO:23).

[0013a] In one aspect, there is provided a kit comprising a PD-1 axis binding antagonist and a package insert comprising instructions for using the PD-1 axis binding antagonist in combination with oxaliplatin, leucovorin and 5-FU to treat or delay progression of cancer in an individual.

[0013b] In one aspect, there is provided a kit comprising a PD-1 axis binding antagonist, oxaliplatin, leucovorin and 5-FU, and a package insert comprising instructions for using the PD-1 axis binding antagonist and the oxaliplatin, leucovorin and 5-FU to treat or delay progression of cancer in an individual.

[0014] In another ~~aspect~~embodiment, provided is a kit comprising a PD-1 axis binding antagonist, oxaliplatin, leucovorin and 5-FU with or without a VEGF antagonist for treating or delaying progression of a cancer in an individual or enhancing immune function in an individual having cancer. The kit may comprise a PD-1 axis binding antagonist and a package insert comprising instructions for using the PD-1 axis binding antagonist in combination with oxaliplatin, leucovorin and 5-FU with or without a VEGF antagonist to treat or delay progression of cancer in an individual, or enhancing immune function in an individual having cancer. The kit may comprise a VEGF antagonist and a package insert comprising instructions for using the VEGF antagonist in combination with a PD-1 axis binding antagonist and oxaliplatin, leucovorin and 5-FU to treat or delay progression of cancer in an individual, or to enhance immune function in an individual having cancer. The kit may comprise a PD-1 axis binding antagonist and a VEGF antagonist, and a package insert comprising instructions for using the PD-1 axis binding antagonist and the VEGF antagonist to treat or delay progression of cancer in an individual, or to enhance immune function in an individual having cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] **Figure 1** is a graph depicting changes in tumor volume with anti-PD-L1 antibodies and FOLFOX co-treatment. The data demonstrate a significant reduction of tumor growth and sustained anti-tumor effect as compared to anti-PD-L1 antibodies or FOLFOX treatment alone.

[0016] **Figure 2** is a graph showing changes in body weight for the treatment groups shown in Figure 1.

CLAIMS

What is claimed is:

1. ~~A method for treating or delaying progression of cancer in an individual comprising administering to the individual~~ Use of an effective amount of a PD-1 axis binding antagonist, ~~oxaliplatin, leucovorin and 5-FU~~ in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the medicament is to be administered with oxaliplatin, leucovorin and 5-FU.

2. The ~~method~~ use of claim 1, wherein the PD-1 axis binding antagonist is selected from the group consisting of a PD-1 binding antagonist, a PD-L1 binding antagonist and a PD-L2 binding antagonist.

3. The use~~method~~ of Claim 2, wherein the PD-1 axis binding antagonist is a PD-1 binding antagonist.

4. The use~~method~~ of Claim 3, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to its ligand binding partners.

5. The use~~method~~ of Claim 4, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L1.

6. The use~~method~~ of Claim 4, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to PD-L2.

7. The use~~method~~ of Claim 4, wherein the PD-1 binding antagonist inhibits the binding of PD-1 to both PD-L1 and PD-L2.

8. The use~~method~~ of Claim 4, wherein the PD-1 binding antagonist is an antibody.

9. The use~~method~~ of Claim 8, wherein the PD-1 binding antagonist is MDX-1106.

10. The use~~method~~ of Claim 8, wherein the PD-1 binding antagonist is Merck 3745.

11. The use~~method~~ of Claim 8, wherein the PD-1 binding antagonist is CT-011.

12. The use ~~method~~ of Claim 2, wherein the PD-1 axis binding antagonist is a PD-L1 binding antagonist.

13. The use~~method~~ of Claim 12, wherein the PD-L1 binding antagonist inhibits the binding of PD-L1 to PD-1.

14. The use ~~method~~ of Claim 12, wherein the PD-L1 binding antagonist inhibits the binding of PD-L1 to B7-1.

15. The use~~method~~ of Claim 12, wherein the PD-L1 binding antagonist inhibits the binding of PD-L1 to both PD-1 and B7-1.

16. The use~~method~~ of Claim 12, wherein the PD-L1 binding antagonist is an anti-PD-L1

antibody.

17. The use~~method~~ of claim 16, wherein the anti-PD-L1 antibody is a monoclonal antibody.

18. The use~~method~~ of claim 16, 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.

19. The use~~method~~ of claim 16, wherein the anti-PD-L1 antibody is a humanized antibody.

20. The use~~method~~ of claim 16, wherein the anti-PD-L1 antibody is a human antibody.

21. The use~~method~~ of Claim 16, wherein the PD-L1 binding antagonist is selected from the group consisting of: YW243.55.S70 and MDX-1105.

22. The use~~method~~ of Claim 21, wherein the PD-L1 binding antagonist is YW243.55.S70.

23. The use~~method~~ of Claim 21, wherein the PD-L1 binding antagonist is MDX-1105.

24. The use ~~method~~ of Claim 2, wherein the PD-1 axis binding antagonist is a PD-L2 binding antagonist.

25. The use~~method~~ of Claim 24, wherein the PD-L2 binding antagonist is an antibody.

26. The use~~method~~ of Claim 24, wherein the PD-L2 binding antagonist is an immunoadhesin.

27. The use~~method~~ of Claim 24, wherein the PD-L2 binding antagonist is AMP-224.

28. The use~~method~~ of claim 1, wherein ~~the method further comprises administering~~ the medicament is to be administered with a VEGF antagonist.

29. The use~~method~~ of claim 28, wherein the VEGF antagonist is an anti-VEGF antibody.

30. The use~~method~~ of claim 29, wherein said anti-VEGF antibody binds the same epitope as the monoclonal anti-VEGF antibody A4.6.1 produced by hybridoma ATCC HB 10709.

31. The use~~method~~ of claim 29, wherein the anti-VEGF antibody is a humanized antibody.

32. The use ~~method~~ of claim 29, wherein the anti-VEGF antibody is bevacizumab.

33. The use~~method~~ of claim 29, wherein wherein the anti-VEGF antibody has a heavy chain variable region comprising the following amino acid sequence:

EVQLVESGGG LVQPGGSLRL SCAASGYTFT NYGMNWVRQA PGKGLEWVGW INTYTGEPTY AADFKRRFTF SLDTSKSTAY LQMNSLRAED TAVYYCAKYP HYYGSSHWYF DVWGQGTLVT VSS (SEQ ID NO:22).

and a light chain variable region comprising the following amino acid sequence:

DIQMTQSPSS LSASVGDRVT ITCSASQDIS NYLNWYQQKP GKAPKVLIYF TSSLHSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YSTVPWTFGQ GTKVEIKR (SEQ ID NO:23).

34. The use~~method~~ of any one of claims 1-33, wherein the treatment results in a sustained response in the individual after cessation of the treatment.

35. The use~~method~~ of any one of claims 1-33, wherein the subject has colorectal cancer.

36. A kit comprising a PD-1 axis binding antagonist and a package insert comprising instructions for using the PD-1 axis binding antagonist in combination with oxaliplatin, leucovorin and 5-FU to treat or delay progression of cancer in an individual.

37. A kit comprising a PD-1 axis binding antagonist, oxaliplatin, leucovorin and 5-FU, and a package insert comprising instructions for using the PD-1 axis binding antagonist and the oxaliplatin, leucovorin and 5-FU to treat or delay progression of cancer in an individual.

38. The kit of claim 36 or 37, wherein the PD-1 axis binding antagonist is an anti-PD-L1 antibody.

39. The kit of claim 36 or 37, wherein the PD-1 axis binding antagonist is an anti-PD-1 antibody.

40. The kit of claim 36 or 37, wherein the PD-1 axis binding antagonist is a PD-L2 immunoadhesin.