SUMMARY

[0009] The present 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. In some examples the method further comprises administering a VEGF antagonist.

[0010a] In one aspect, the present disclosure refers to use of an effective amount of an anti-PD-L1 antibody in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the medicament is to be administered with an anti-VEGF antibody, oxaliplatin, leucovorin, and 5-FU.

[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 examples, the subject treated is a human.

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

[0013] In some examples, 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 examples, the PD-1 binding antagonist inhibits binding of PD-1 to PD-L1 and/or binding of PD-1 to PD-L2. In some examples, 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 examples, the PD-L1 binding antagonist inhibits binding of PD-L1 to PD-1 and/or binding of PD-L1 to B7-1. In some examples, 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 examples, the PD-L2 binding antagonist inhibits binding of PD-L2 to PD-1. In some examples, 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 examples, the VEGF antagonist is an antibody, e.g., a monoclonal antibody. In some examples 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 examples the anti-VEGF antibody is bevacizumab. In some examples 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, the present disclosure refers to a kit comprising an anti-PD-L1 antibody and a package insert comprising instructions for using the anti-PD-L1 antibody in combination with an anti-VEGF antibody, oxaliplatin, leucovorin and 5-FU to treat or delay progression of cancer in an individual.

[0013b] In one aspect, the present disclosure refers to a kit comprising an anti-VEGF antibody and a package insert comprising instructions for using the anti-VEGF antibody in combination with an anti-PD-L1antibody, oxaliplatin, leucovorin and 5-FU to treat or delay progression of cancer in an individual.

[0014] In another example, 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. Use of an effective amount of an anti-PD-L1 antibody in the manufacture of a medicament for treating or delaying progression of cancer in an individual, wherein the medicament is to be administered with an anti-VEGF antibody, oxaliplatin, leucovorin, and 5-FU.

2. The use of Claim 1, wherein the anti-PD-L1 antibody is a PD-L1 binding antagonist.

3. The use of Claim 2, wherein the anti-PD-L1 antibody inhibits the binding of PD-L1 to PD-1.

4. The use of Claim 2, wherein the anti-PD-L1 antibody inhibits the binding of PD-L1 to B7-1.

5. The use of Claim 2, wherein the anti-PD-L1 antibody inhibits the binding of PD-L1 to both PD-1 and B7-1.

6. The use of any one of claims 1-5, wherein the anti-PD-L1 antibody is a monoclonal antibody.

7. The use of any one of claims 1-6, 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.

8. The use of any one of claims 1-7, wherein the anti-PD-L1 antibody is a humanized antibody.

9. The use of any one of claims 1-7, wherein the anti-PD-L1 antibody is a human antibody.

10. The use of Claim 1, wherein the anti-PD-L1 antibody is selected from the group consisting of: YW243.55.S70 and MDX-1105.

11. The use of Claim 10, wherein the anti-PD-L1 antibody is YW243.55.S70.

12. The use of Claim 10, wherein the anti-PD-L1 antibody is MDX-1105.

13. The use of any one of claims 1-6, wherein the anti-PD-L1 antibody comprises a heavy chain variable region and a light chain variable region, wherein:

(a) the heavy chain variable region comprises an HVR-H1, HVR-H2 and HVR-H3, and wherein:

(i) the HVR-H1 comprises the amino acid sequence of SEQ ID NO: 15;

(ii) the HVR-H2 comprises the amino acid sequence of SEQ ID NO: 16;

(iii) the HVR-H3 comprises the amino acid sequence of SEQ ID NO: 3; and

(b) the light chain variable region comprises an HVR-L1, HVR-L2 and HVR-L3, and wherein:

(iv) the HVR-L1 comprises the amino acid sequence of SEQ ID NO: 17;

(v) the HVR-L2 comprises the amino acid sequence of SEQ ID NO: 18; and

(vi) the HVR-L3 comprises the amino acid sequence of SEQ ID NO: 19.

14. The use of claim 13, wherein the anti-PD-L1 antibody comprises a heavy chain variable region and a light chain variable region, wherein:

(a) the heavy chain variable region amino acid sequence has at least 90% sequence identity to the heavy chain variable region amino acid sequence of SEQ ID NO:20, and

(b) the light chain variable region amino acid sequence has at least 90% sequence identity to the light chain variable region amino acid sequence of SEQ ID NO:21.

15. The use of claim 13, wherein the anti-PD-L1 antibody comprises a heavy chain variable region and a light chain variable region, wherein:

(a) the heavy chain variable region amino acid sequence has at least 95% sequence identity to the heavy chain variable region amino acid sequence of SEQ ID NO:20, and

(b) the light chain variable region amino acid sequence has at least 95% sequence identity to the light chain variable region amino acid sequence of SEQ ID NO:21.

16. The use of claim 13, wherein the anti-PD-L1 antibody comprises a heavy chain variable region and a light chain variable region, wherein:

(a) the heavy chain variable region amino acid sequence has at least 99% sequence identity to the heavy chain variable region amino acid sequence of SEQ ID NO:20, and

(b) the light chain variable region amino acid sequence has at least 99% sequence identity to the light chain variable region amino acid sequence of SEQ ID NO:21.

17. The use of claim 13, wherein the anti-PD-L1 antibody comprises a heavy chain variable region and a light chain variable region, wherein:

(a) the heavy chain variable region amino acid sequence has at least 99% sequence identity to the heavy chain variable region amino acid sequence of SEQ ID NO:20, and

(b) the light chain variable region comprises the amino acid sequence of SEQ ID NO:21.

18. The use of any one of claims 13-17, wherein the anti-PD-L1 antibody further comprises a human IgG1 constant region.

19. The use of claim 18, wherein the anti-PD-L1 antibody comprises an effector-less Fc mutation, wherein the effector-less Fc mutation is N297A.

20. The use of any one of claims 1-19, wherein said anti-VEGF antibody binds the same epitope as the monoclonal anti-VEGF antibody A4.6.1 produced by hybridoma ATCC HB 10709.

21. The use of any one of claims 1-20, wherein the anti-VEGF antibody is a humanized antibody.

22. The use of any one of claims 1-19, wherein the anti-VEGF antibody is bevacizumab.

23. The use of any one of claims 1-21, wherein the anti-VEGF antibody comprises a heavy chain variable region and a light chain variable region, wherein:

(a) the heavy chain variable region comprises a CDRH1, CDRH2 and CDRH3, and wherein:

(i) the CDRH1 comprises the amino acid sequence of SEQ ID NO: 24;

(ii) the CDRH2 comprises the amino acid sequence of SEQ ID NO:25; and

(iii) the CDRH3 comprises the amino acid sequence of SEQ ID NO:26;

(b) the light chain variable region comprises a CDRL1, CDRL2 and CDRL3, and wherein:

(iv) the CDRL1 comprises the amino acid sequence of SEQ ID NO:27;

(v) the CDRL2 comprises the amino acid sequence of SEQ ID NO:28; and

(vi) the CDRL3 comprises the amino acid sequence of SEQ ID NO:29.

24. The use of any one of claims 1-19, 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).

25. The use of any one of claims 1-24, wherein the treatment results in a sustained response in the individual after cessation of the treatment.

26. The use of any one of claims 1-25, wherein the individual has a cancer selected from the

group consisting of lung cancer, bladder cancer, breast cancer, colon cancer and colorectal cancer.

27. The use of any one of claims 1-25, wherein the individual has colorectal cancer.

28. A kit comprising an anti-PD-L1 antibody and a package insert comprising instructions for using the anti-PD-L1 antibody in combination with an anti-VEGF antibody, oxaliplatin, leucovorin and 5-FU to treat or delay progression of cancer in an individual.

29. The kit of claim 28, wherein the kit further comprises the anti-VEGF antibody, oxaliplatin, leucovorin and 5-FU.

30. A kit comprising an anti-VEGF antibody and a package insert comprising instructions for using the anti-VEGF antibody in combination with an anti-PD-L1 antibody, oxaliplatin, leucovorin and 5-FU to treat or delay progression of cancer in an individual.