An anti-CTLA-4 antibody and an anti-PD-1 antibody have been approved for treatment of metastatic melanoma and are currently in clinical trials for other cancers. Anti-PD-L1 antibody, directed to the ligand for PD-1, is also currently in clinical development.

[0010] Inhibition of FGFR signaling has been reported to improve anti-tumor immunity and impair metastasis in breast cancer. (*See, e.g.,* T. Ye et al., *Breast Cancer Res. Treat.* 143: 435-446 (2014).) Anti-FGFR2 antibodies have also been tested in models of gastric cancer, for example. However, whether co-administering an FGFR2 inhibitor with an immune checkpoint inhibitor such as a PD-1 or PD-L1 inhibitor would further improve treatment in a tumor model was unknown. The inventors herein have demonstrated that a combination of an FGFR2 inhibitory antibody and a PD-1 inhibitory antibody demonstrates at least additive effects in a mouse breast tumor model. The inventors further show that treatment with an FGFR2 inhibitory antibody alone leads to an increase in PD-L1-expressing cells, NK cells, and CD3+, CD8+, and CD4+ T cells in tumor tissue in a mouse breast tumor model, and results in an increased lymphoid to myeloid cell ratio in the tumor tissue. In addition, an FGFR2 inhibitor given alone has also benefitted a human bladder cancer subject. The results herein, taken together, indicate that FGFR2 inhibitors may alter the tumor microenvironment and may therefore enhance tumor-killing immune responses, either alone or in combination with a PD-1/PD-L1 inhibitor.

SUMMARY

[0011] In one aspect, there is provided the use of an anti-fibroblast growth factor receptor 2 (FGFR2) -IIIb antibody and a programmed cell death 1 (PD-1) / programmed cell death ligand 1 (PD-L1) inhibitor for preparation of a medicament for treatment of cancer in a subject, wherein the PD-1/PD-L1 inhibitor is an anti-PD-1 antibody, and wherein the anti-FGFR2-IIIb antibody comprises a heavy chain variable region comprising: (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 6; (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 7; and (iii) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 8; and the anti-FGFR2-IIIb antibody comprises a light chain variable region comprising (iv) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 9; (v) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 10 and (vi) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 11.

In a further aspect, there is provided the use of an anti-FGFR2 antibody-IIIb for preparation of a medicament for treatment of cancer in a subject, wherein, if the subject is determined to have an increased number of NK cells and/or PD-L1 positive cells and/or CD8+ T cells relative to a sample prior to administration of the antibody, the treatment comprises further that at least one PD-1/PD-L1 inhibitor is to be administered to the subject, wherein the anti-FGFR2-IIIb antibody is an antibody as defined in the present disclosure, and wherein the at least one PD-1/PD-L1 inhibitor comprises an anti-PD-1 antibody. In a further aspect, there is provided a pharmaceutical kit comprising an anti-FGFR2-IIIb antibody and at least one PD-1/PD-L1 inhibitor, wherein the at least one PD-1/PD-L1 inhibitor comprises an anti-PD-1 antibody, and wherein the anti-FGFR2-IIIb antibody comprises a heavy chain variable region comprising: (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 6; (ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 7; and (iii) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 8; and the anti-FGFR2-IIIb antibody comprises a light chain variable region comprising: (iv) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 9; (v) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 10 and (v) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 11. . In some examples, methods of treating cancer in a subject are provided, comprising administering to the subject an FGFR2 inhibitor such as an anti-FGFR2 antibody or FGFR2 ECD or FGFR2 ECD fusion molecule in combination with at least one immune stimulating agent. In some examples, the immune stimulating agent is a PD-1/PD-L1 inhibitor such as an anti-PD-1 antibody, anti-PD-L1 antibody, PD-1 fusion molecule, or PD-1 polypeptide. In some examples, the immune stimulating agent comprises one or more of the agents described in the section below entitled "combinations with other immune stimulating agents." In some examples, the FGFR2 inhibitor is an antibody. In some examples, the FGFR2 inhibitor is an antibody that recognizes FGFR2-IIIb. In some examples, the FGFR2-IIIb antibody

Claims:

1. Use of an anti-fibroblast growth factor receptor 2 (FGFR2)-IIIb antibody and a programmed cell death 1 (PD-1) / programmed cell death ligand 1 (PD-L1) inhibitor for preparation of a medicament for treatment of cancer in a subject, wherein the PD-1/PD-L1 inhibitor is an anti-PD-1 antibody, and wherein the anti-FGFR2-IIIb antibody comprises a heavy chain variable region comprising:

(i) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 6;

(ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 7; and

(iii) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 8;

and the anti-FGFR2-IIIb antibody comprises a light chain variable region comprising:

(iv) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 9;

(v) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 10; and

(vi) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 11.

2. The use of claim 1, wherein the anti-FGFR2-IIIb antibody has one or more of the following properties:

a. binds to FGFR2-IIIb with higher affinity than to FGFR2-IIIc or does not detectably bind to FGFR2-IIIc;

b. inhibits binding of FGF2 to human FGFR2;

c. inhibits binding of FGF7 to human FGFR2;

d. inhibits growth of a human tumor in a mouse tumor model;

e. induces an ADCC activity;

f. possesses enhanced ADCC activity;

g. is afucosylated; and

h. is capable of increasing the number of one or more of PD-L1 positive cells, NK cells, CD3+ T cells, CD4+ T cells, CD8+ T cells, and macrophages in tumor tissue in a mouse tumor model compared to a control.

3. The use of claim 1 or 2, wherein the heavy chain variable domain of the anti-FGFR2-IIIb antibody comprises the amino acid sequence of SEQ ID NO: 4 and the light chain

variable domain of the anti-FGFR2-IIIb antibody comprises the amino acid sequence of SEQ ID NO: 5.

4. The use of claim 3, wherein the heavy chain of the anti-FGFR2-IIIb antibody comprises the amino acid sequence of SEQ ID NO: 2 and the light chain of the anti-FGFR2-IIIb antibody comprises the amino acid sequence of SEQ ID NO: 3.

5. The use of any one of claims 1-4, wherein the anti-FGFR2-IIIb antibody is chimeric, humanized, or human.

6. The use of any one of claims 1-5, wherein the anti-FGFR2-IIIb antibody is afucosylated.

7. The use of any one of claims 1-3 or 5-6, wherein the anti-FGFR2-IIIb antibody is selected from a Fab, an Fv, an scFv, a Fab', and a $(Fab')_2$.

8. The use any one of claims 1-7, wherein the anti-FGFR2-IIIb antibody is to be administered at a dose of 15 mg/kg every 2 weeks.

9. The use of any one of claims 1-8, wherein the PD-1/PD-L1 inhibitor is selected from nivolumab, pidilizumab, and pembrolizumab.

10. The use of any one of claims 1-9, wherein the anti-FGFR2-IIIb antibody and the PD-1/PD-L1 inhibitor are to be administered concurrently or sequentially.

11. The use of any one of claims 1-10, wherein the cancer is selected from breast cancer, gastric cancer, non-small cell lung cancer, melanoma, squamous cell carcinoma of the head and neck, ovarian cancer, pancreatic cancer, renal cell carcinoma, hepatocellular carcinoma, bladder cancer, cholangiocarcinoma, esophageal cancer, and endometrial cancer.

12. The use of claim 11, wherein the cancer is gastric or bladder cancer.

13. The use of any one of claims 1-13, wherein the cancer overexpresses FGFR2-IIIb.

14. The use of any one of claims 1-13, wherein the cancer has previously been determined to overexpress FGFR2-IIIb, either in the presence or in the absence of FGFR2 gene amplification.

15. The use of claim 13 or 14, wherein FGFR2-IIIb overexpression is determined by immunohistochemistry (IHC).

16. The use of claim 15, wherein the overexpression is determined by an IHC signal of 1+, 2+, or 3+ in a sample of the cancer.

17. The use of claim 14, 15 or 16, wherein FGFR2 gene amplification is determined by obtaining the ratio of FGFR2 to chromosome 10 centromere (CEN10) using fluorescence in situ hybridization (FISH), wherein the FGFR2 gene is considered amplified if the FGFR2/CEN10 ratio determined by FISH is greater than or equal to 2.

18. The use of any one of claims 1-17, wherein:

a) the cancer is gastric cancer, and a sample of the cancer has an FGFR2-IIIb IHC signal of 2+ or 3+ in at least 10% of tumor cells;

b) the cancer is gastric cancer, and a sample of the cancer has an FGFR2-IIIb IHC signal of 3+ in at least 10% of tumor cells, and wherein the FGFR2 gene is amplified;

c) the cancer is gastric cancer, and a sample of the cancer has an FGFR2-IIIb IHC signal of 3+ in at least 10% of tumor cells, and wherein the FGFR2 gene is not amplified;

d) the cancer is bladder cancer, and a sample of the cancer has an FGFR2-IIIb IHC signal of 2+ or 3+ in at least 10% of tumor cells;

e) the cancer is bladder cancer that has an H score of 20 or greater; or

f) the cancer is bladder cancer that has an H score of 10-19.

19. The use of any one of claims 1-18, wherein the subject is a PD-1/PD-L1 inhibitor inadequate responder.

20. The use of any one of claims 1-19, wherein administration of the anti-FGFR2-IIIb antibody and the PD-1/PD-L1 inhibitor in a mouse tumor model of the cancer results in either additive or synergistic inhibition of tumor growth.

21. The use of any one of claims 1-18, wherein administration of the anti-FGFR2-IIIb antibody in a mouse tumor model:

a. increases the number of NK cells in tumor tissue compared to a control,

b. increases the number of PD-L1 positive cells in tumor tissue compared to a control,

c. increases the number of CD3+, CD8+, and/or CD4+ T cells in tumor tissue compared to a control, and/or

d. increases the ratio of lymphoid cells to myeloid cells in tumor tissue compared to a control.

22. Use of an anti-FGFR2-IIIb antibody for preparation of a medicament for treatment of cancer in a subject, wherein, if the subject is determined to have an increased number of NK cells and/or PD-L1 positive cells and/or CD8+ T cells relative to a sample prior to administration of the antibody, the treatment comprises further that at least one PD-1/PD-L1 inhibitor is to be administered to the subject, wherein the anti-FGFR2-IIIb antibody is an antibody as defined in any one of claims 1-7, and wherein the at least one PD-1/PD-L1 inhibitor comprises an anti-PD-1 antibody.

23. The use of claim 22, wherein the at least one PD-1/PD-L1 inhibitor comprises nivolumab, pidilizumab, or pembrolizumab.

24. A pharmaceutical kit comprising an anti-FGFR2-IIIb antibody and at least one PD-1/PD-L1 inhibitor, wherein the at least one PD-1/PD-L1 inhibitor comprises an anti-PD-1 antibody, and wherein the anti-FGFR2-IIIb antibody comprises a heavy chain variable region comprising:

(i) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 6;

(ii) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 7; and

(iii) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 8;

and the anti-FGFR2-IIIb antibody comprises a light chain variable region comprising:

(iv) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 9;

(v) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 10; and

(vi) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 11.

25. The pharmaceutical kit of claim 24, wherein the anti-FGFR2-IIIb antibody and the at least one PD-1/PD-L1 inhibitor are comprised within separate containers or compartments of the kit.

26. The pharmaceutical kit of claim 24 or 25, further comprising instructions for use in cancer treatment.

27. The pharmaceutical kit of any one of claims 24-26, wherein the heavy chain variable domain of the anti-FGFR2-IIIb antibody comprises the amino acid sequence of SEQ ID

NO: 4 and the light chain variable domain of the anti-FGFR2-IIIb antibody comprises the amino acid sequence of SEQ ID NO: 5.

28. The pharmaceutical kit of claim 27, wherein the heavy chain of the anti-FGFR2-IIIb antibody comprises the amino acid sequence of SEQ ID NO: 2 and the light chain of the anti-FGFR2-IIIb antibody comprises the amino acid sequence of SEQ ID NO: 3.

29. The pharmaceutical kit of any one of claims 24-28, wherein the at least one PD-1/PD-L1 inhibitor comprises nivolumab, pidilizumab, or pembrolizumab.

30. The pharmaceutical kit of any one of claims 24-29, wherein the anti-FGFR2-IIIb antibody is chimeric, humanized, or human.

31. The pharmaceutical kit of any one of claims 24-30, wherein the anti-FGFR2-IIIb antibody is afucosylated.

32. The pharmaceutical kit of any one of claims 24-27 or 29-31, wherein the anti-FGFR2-IIIb antibody is selected from a Fab, an Fv, an scFv, a Fab', and a $(Fab')_2$.