

clinical trials further signify its coming of age (Pardoll, D.M., Nat Immunol. 2012; 13:1129-32). However, ipilimumab therapy is limited by its toxicity profile, presumably because anti-CTLA-4 treatment, by interfering with the primary T cell inhibitory checkpoint, can lead to the generation of new autoreactive T cells. While inhibiting the PD-L1/PD-1 interaction results in disinhibiting existing chronic immune responses in exhausted T cells that are mostly antiviral or anticancer in nature (Wherry, E.J., Nat Immunol. 2011; 12:492-9), anti-PD-1 therapy can nevertheless sometimes result in potentially fatal lung-related autoimmune adverse events. Despite the promising clinical activities of anti-PD1 and anti-PD-L1 so far, increasing the therapeutic index, either by increasing therapeutic activity or decreasing toxicity, or both, remains a central goal in the development of immunotherapeutics.

SUMMARY OF THE INVENTION

[0006] The present invention is based on the discovery of a combination therapy for cancer that includes administration of a bifunctional protein containing at least a portion of TGF β Receptor II (TGF β RII) that is capable of binding TGF β and an antibody, or antigen-binding fragment, that binds to an immune checkpoint protein such as human protein Programmed Death Ligand 1 (PD-L1). The combination therapy also includes administration of an anti-cancer therapeutic agent such as, for example, radiation, chemotherapeutic agents, a biologic and/or a vaccine. The combination therapy exhibits a synergistic effect as compared to the effect of administering the individual agents separately.

[0007] Accordingly, in a first aspect, the present invention features a method of treating cancer in a subject that includes (i) administration of a bifunctional protein comprising a human TGF β RII, or a fragment thereof capable of binding TGF β (*e.g.*, a soluble fragment), and an antibody, or an antigen-binding fragment thereof, that binds PD-L1 (*e.g.*, any of the antibodies or antibody fragments described herein); and (ii) administration of at least one additional second anti-cancer therapeutic agent.

[0007a] In another aspect of the disclosure, there is provided the use of a pharmaceutical composition comprising a protein comprising a human TGF β RII, or fragment thereof capable of binding TGF β ; and an antibody, or antigen-binding fragment thereof, that binds human protein Programmed Death Ligand 1 (PD-L1) in the manufacture of a medicament for treating cancer in combination with an effective amount of at least one additional anti-cancer agent, wherein said protein used in combination with said anti-cancer agent has an enhanced therapeutic effect

compared to the effect of the protein and the at least one additional anti-cancer agent each administered alone.

[0007b] In yet another aspect of the disclosure, there is provided the use of a pharmaceutical composition comprising a protein comprising a first moiety comprising a human TGF β RII, or fragment thereof capable of binding TGF β , and an antibody, or antigen-binding fragment thereof, that binds human protein Programmed Death Ligand 1 (PD-L1) in the manufacture of a medicament for inhibiting tumor growth in combination with an effective amount of at least one additional anti-cancer agent, wherein said protein used in combination with said anti-cancer agent has an enhanced therapeutic effect compared to the effect of the protein and the at least one additional anti-cancer agent each administered alone.

[0008] In certain embodiments, the combination treatment method of the invention features the use of a polypeptide including (a) at least a variable domain of a heavy chain of an antibody that binds PD-L1 (*e.g.*, amino acids 1-120 of SEQ ID NO: 2); and (b) human TGF β RII, or a soluble fragment thereof capable of binding TGF β (*e.g.*, a human TGF β RII extra-cellular domain (ECD), amino acids 24-159 of SEQ ID NO: 9, or any of those described herein) in combination with at least one additional anti-cancer therapeutic agent. The polypeptide may further include an amino acid linker connecting the C-terminus of the variable domain to the N-terminus of the human TGF β RII or soluble fragment thereof capable of binding TGF β . The polypeptide may

WHAT IS CLAIMED:

1. Use of a pharmaceutical composition comprising:
a protein comprising a human TGF β RII, or fragment thereof capable of binding TGF β ; and an antibody, or antigen-binding fragment thereof, that binds human protein Programmed Death Ligand 1 (PD-L1) in the manufacture of a medicament for treating cancer in combination with an effective amount of at least one additional anti-cancer agent,
wherein said protein used in combination with said anti-cancer agent has an enhanced therapeutic effect compared to the effect of the protein and the at least one additional anti-cancer agent each administered alone.
2. Use of a pharmaceutical composition comprising:
a protein comprising a first moiety comprising a human TGF β RII, or fragment thereof capable of binding TGF β , and an antibody, or antigen-binding fragment thereof, that binds human protein Programmed Death Ligand 1 (PD-L1) in the manufacture of a medicament for inhibiting tumor growth in combination with an effective amount of at least one additional anti-cancer agent,
wherein said protein used in combination with said anti-cancer agent has an enhanced therapeutic effect compared to the effect of the protein and the at least one additional anti-cancer agent each administered alone.
3. The use of claim 1 or 2, wherein the antibody, or antigen-binding fragment thereof, that binds PD-L1 comprises amino acids 1-120 of SEQ ID NO:2.
4. The use of claim 1 or 2, wherein the antibody, or antigen-binding fragment thereof, that binds PD-L1 comprises the amino acid sequence of SEQ ID NO:2 except that the C-terminal lysine has been mutated to alanine.
5. The use of claim 1 or 2, wherein the antibody, or antigen-binding fragment thereof, that binds PD-L1 comprises the amino acid sequences SYIMM (HVR-H1), SIYPSGGITFYADTVKG (HVR-H2) and IKLGTVTTVDY (HVR-H3).
6. The use of claim 1 or 2, wherein the human TGF β RII, or fragment thereof capable of binding TGF β comprises the amino acid sequence of SEQ ID NO:10.

7. The use of claim 1 or 2, wherein the protein comprises the amino acid sequence of SEQ ID NO:1 and SEQ ID NO:3.
8. The use of claim 1 or 2, where the anti-cancer agent is a chemotherapeutic agent.
9. The use of claim 1 or 2, wherein the anti-cancer agent is radiation.
10. The use of claim 8, wherein the chemotherapeutic agent is an alkylating agent.
11. The use of claim 10, wherein the alkylating agent is 5-FU.
12. The use of claim 8, wherein the chemotherapeutic agent is a platinum-based agent.
13. The use of claim 12, wherein the platinum based agent is oxaliplatin.
14. The use of claim 1 or 2, wherein the cancer is selected from the group consisting of colorectal, breast, ovarian, pancreatic, gastric, prostate, renal, cervical, myeloma, lymphoma, leukemia, thyroid, endometrial, uterine, bladder, neuroendocrine, head and neck, liver, nasopharyngeal, testicular, small cell lung cancer, non-small cell lung cancer, melanoma, basal cell skin cancer, squamous cell skin cancer, dermatofibrosarcoma protuberans, Merkel cell carcinoma, glioblastoma, glioma, sarcoma, mesothelioma, and myelodysplastic syndromes.
15. The use of claim 1 or 2, wherein the protein is to be provided in a dosage selected from the group consisting of (i) a dosage known to be used for treatment of said cancer and (ii) a lower dosage compared to the concentration known to be used for treating said cancer.
16. The use of claim 8, wherein the protein is to be provided in a dosage selected from the group consisting of (i) a dosage known to be used for treatment of said cancer and (ii) a lower dosage compared to the concentration known to be used for treating said cancer.
17. The use of claim 9, wherein the radiation is to be provided in a dosage selected from the group consisting of (i) a dosage known to be used for treatment of said cancer and (ii) a lower dosage compared to the concentration known to be used for treating said cancer.
18. The use of claim 16, wherein the protein is to be provided in a dosage between 2 to 10 times lower than the dosage known to be used for treating said cancer.

19. The use of claim 9, wherein said protein to be used in combination with radiation of a primary tumor inhibits the growth of a secondary tumor or metastasis distal to the primary tumor to be treated with radiation.
20. The use of claim 8, wherein the protein is to be administered after an initial dose of said chemotherapeutic agent.
21. The use of claim 9, wherein the protein is to be administered after an initial dose of radiation.
22. The use of claim 8, wherein multiple doses of said chemotherapeutic agent are to be administered.
23. The use of claim 9, wherein multiple doses of radiation are to be administered.
24. The use of claim 1 or 2, wherein multiple doses of the protein are to be administered.
25. The use of claim 1 or 2, wherein the protein and one additional anti-cancer agent are to be administered sequentially.