US 20150225483 A1 describes administration of the Trap molecule at doses based on the patient's weight.

SUMMARY

[0004a] In one aspect, the present disclosure refers to the use of a protein comprising a first polypeptide and a second polypeptide in the manufacture of a medicament for treating cancer or inhibiting tumor growth in a subject in need thereof, wherein the use comprises that the subject is to be administered a dose of at least 500 mg of said protein, wherein the first polypeptide comprises: (a) at least a variable region of a heavy chain of an antibody that binds to human protein Programmed Death Ligand 1 (PD-L1); and (b) human Transforming Growth Factor β Receptor II (TGFβRII), or a fragment thereof, capable of binding Transforming Growth Factor β (TGFβ), wherein the second polypeptide comprises at least a variable region of a light chain of an antibody that binds PD-L1, and wherein the heavy chain of the first polypeptide and the light chain of the second polypeptide, when combined, form an antigen binding site that binds PD-L1. In another aspect, the present disclosure refers to an intravenous drug delivery formulation comprising 500 mg – 2400 mg of a protein comprising a first polypeptide and a second polypeptide, wherein the first polypeptide comprises: (a) at least a variable region of a heavy chain of an antibody that binds to human protein Programmed Death Ligand 1 (PD-L1); and (b) human Transforming Growth Factor β Receptor II (TGFβRII), or a fragment thereof, capable of binding Transforming Growth Factor β (TGFβ), wherein the second polypeptide comprises at least a variable region of a light chain of an antibody that binds PD-L1, and wherein the heavy chain of the first polypeptide and the light chain of the second polypeptide, when combined, form an antigen binding site that binds PD-L1. In another aspect, the present disclosur refers to drug delivery device comprising a formulation comprising 500 mg – 2400 mg of a protein comprising a first polypeptide and a second polypeptide, wherein the first polypeptide comprises: (a) at least a variable region of a heavy chain of an antibody that binds to human protein Programmed Death Ligand 1 (PD-L1); and (b) human Transforming Growth Factor β Receptor II (TGFβRII), or a fragment thereof, capable of binding Transforming Growth Factor β (TGFβ), wherein the second polypeptide comprises at least a variable region of a light chain of an antibody that binds PD-L1, and wherein the heavy chain of the first polypeptide and the light chain of the second polypeptide, when combined, form an antigen binding site that binds PD-L1. In yet another aspect, the present disclosure refers to a kit comprising one or more vessels collectively comprising a formulation comprising

500 mg – 2400 mg of a protein comprising a first polypeptide and a second polypeptide, wherein the first polypeptide comprises: (a) at least a variable region of a heavy chain of an antibody that binds to human protein Programmed Death Ligand 1 (PD-L1); and (b) human Transforming Growth Factor β Receptor II (TGFβRII), or a fragment thereof, capable of binding Transforming Growth Factor β (TGFβ), wherein the second polypeptide comprises at least a variable region of a light chain of an antibody that binds PD-L1, and wherein the heavy chain of the first polypeptide and the light chain of the second polypeptide, when combined, form an antigen binding site that binds PD-L1. In yet another aspect, the present disclosure refers the intravenous drug delivery formulation, the drug delivery device, or the kit as disclosed herein for use in therapy. In yet another aspect, the present disclosure refers to the use of the intravenous drug delivery formulation, the drug delivery device, or the kit as disclosed herein in the preparation of a medicament for treating cancer or inhibiting tumor growth in a subject in need thereof.

[0005] The present disclosure provides improved dosing regimens for administration of bifunctional proteins targeting PD-L1 and TGFβ. Specifically, body weight independent (BW-independent) dosing regimens and related dosage forms involving administration of at least 500 mg of the bifunctional protein administered at various dosing frequencies can be used as an anti-tumor and anti-cancer therapeutic. The BW-independent dosing regimen ensures that all patients, irrespective of their body weight, will have adequate drug exposure at the tumor site.

[0006] The bifunctional protein of the present disclosure (anti-PD-L1/TGFβ Trap molecule) includes a first and a second polypeptide. The first polypeptide includes: (a) at least a variable region of a heavy chain of an antibody that binds to human protein Programmed Death Ligand 1 (PD-L1); and (b) human Transforming Growth Factor β Receptor II (TGFβRII), or a fragment thereof, capable of binding Transforming Growth Factor β (TGFβ) (*e.g.*, a soluble fragment). The second polypeptide includes at least a variable region of a light chain of an antibody that binds PD-L1, in which the heavy chain of the first polypeptide and the light chain of the second polypeptide, when combined, form an antigen binding site that binds PD-L1 (*e.g.*, any of the antibodies or antibody fragments described herein). Because the bifunctional protein of the present disclosure binds to two targets, (1) PD-L1, which is largely membrane bound, and (2) TGFβ, which is soluble in blood and interstitium, the BW-independent dosing regimen requires a dose that is effective not only to inhibit PD-L1 at the tumor site but also sufficient to inhibit TGFβ.

[0007] In one example, the disclosure provides treatment of a cancer or inhibition of a tumor, *e.g.*, non-small cell lung cancer, melanoma, pancreatic cancer, colorectal cancer (*e.g.*, pretreated colorectal cancer (CRC)), ovarian cancer, glioblastoma, gastric cancer (*e.g.*, pretreated recurrent or refractory unresectable Stage IV gastric cancer), biliary tract cancer, esophageal cancer (squamous cell carcinoma or adenocarcinoma), adenoma of the head or the neck, and squamous carcinoma of the head or the neck.

[0008] The disclosure also features a bifunctional protein described above for use in treating cancer or for use in inhibiting tumor growth. The cancer or tumor may be selected from colorectal (*e.g.*, pretreated colorectal cancer (CRC)), breast, ovarian, pancreatic, gastric (*e.g.*, pretreated recurrent or refractory unresectable Stage IV gastric cancer), 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. The use may further include administration of radiation or administration of a chemotherapeutic, a biologic, or a vaccine.

[0009] The disclosure also features a method of promoting local depletion of TGFβ. The method includes administering a protein described above, where the protein binds TGFβ in solution, binds PD-L1 on a cell surface, and carries the bound TGFβ into the cell (*e.g.*, a cancer cell).

[0010] The disclosure also features a method of inhibiting SMAD3 phosphorylation in a cell (*e.g.*, a cancer cell or an immune cell), the method including exposing the cell in the tumor microenvironment to a protein described above.

[0011] The disclosure also features a method of inhibiting tumor growth or treating cancer. The method includes exposing the tumor to a protein described above. The method may further include exposing the tumor to radiation or to a chemotherapeutic, a biologic, or a vaccine. In certain examples, the tumor or cancer is selected from colorectal (*e.g.*, pretreated colorectal cancer (CRC)), breast, ovarian, pancreatic, gastric (*e.g.*, pretreated recurrent or refractory unresectable Stage IV gastric cancer), 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.

[0012] By "TGFβRII" or "TGFβ Receptor II" is meant a polypeptide having the wild-type human TGFβ Receptor Type 2 Isoform A sequence (*e.g.*, the amino acid sequence of NCBI Reference Sequence (RefSeq) Accession No. NP_001020018 (SEQ ID NO. 8)), or a

What is claimed is:

1. Use of a protein comprising a first polypeptide and a second polypeptide in the manufacture of a medicament for treating cancer or inhibiting tumor growth in a subject in need thereof, wherein the use comprises that the subject is to be administered a dose of at least 500 mg of said protein,

wherein the first polypeptide comprises: (a) at least a variable region of a heavy chain of an antibody that binds to human protein Programmed Death Ligand 1 (PD-L1); and (b) human Transforming Growth Factor β Receptor II (TGFβRII), or a fragment thereof, capable of binding Transforming Growth Factor β (TGFβ),

wherein the second polypeptide comprises at least a variable region of a light chain of an antibody that binds PD-L1, and

wherein the heavy chain of the first polypeptide and the light chain of the second polypeptide, when combined, form an antigen binding site that binds PD-L1.

2. The use of claim 1, wherein the first polypeptide comprises the amino acid sequence of SEQ ID NO: 3, and the second polypeptide comprises the amino acid sequence of SEQ ID NO: 1.

3. The use of claim 1 or 2, wherein the dose is 500 mg to 2400 mg.

4. The use of claim 1 or 2, wherein the dose is 1200 mg to 2400 mg.

5. The use of any one of claims 1-4, wherein the dose is 1200 mg.

6. The use of claim 1-4, wherein the dose is 2400 mg.

7. The use of any one of claims 1-6, wherein the dose is to be administered once every two weeks or once every three weeks.

8. The use of any one of claims 1-7, wherein the protein is to be administered by intravenous administration.

9. The use of claim 8, wherein the intravenous administration is performed with a prefilled bag, a prefilled pen, or a prefilled syringe comprising a formulation comprising the protein.

10. The use of claim 9, wherein the bag is connected to a channel comprising a tube and/or a needle.

11. The use of any one of claims 1-10, wherein the cancer or tumor is selected from the group consisting of: non-small cell lung cancer, melanoma, pancreatic cancer, colorectal cancer, ovarian cancer, glioblastoma, gastric cancer, biliary tract cancer, esophageal cancer (squamous cell carcinoma or adenocarcinoma), adenoma of the head or the neck, and squamous carcinoma of the head or the neck.

12. The use of any one of claims 1-10, wherein the cancer or tumor 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.

13. The use of any one of claims 1-10, wherein the tumor is an advanced solid tumor.

14. The use of claim 13, wherein the tumor is refractory and/or resistant to prior treatment.

15. An intravenous drug delivery formulation comprising 500 mg – 2400 mg of a protein comprising a first polypeptide and a second polypeptide,

wherein the first polypeptide comprises: (a) at least a variable region of a heavy chain of an antibody that binds to human protein Programmed Death Ligand 1 (PD-L1); and (b) human Transforming Growth Factor β Receptor II (TGFβRII), or a fragment thereof, capable of binding Transforming Growth Factor β (TGFβ),

wherein the second polypeptide comprises at least a variable region of a light chain of an antibody that binds PD-L1, and

wherein the heavy chain of the first polypeptide and the light chain of the second polypeptide, when combined, form an antigen binding site that binds PD-L1.

16. The intravenous drug delivery formulation of claim 15, wherein the first polypeptide comprises the amino acid sequence of SEQ ID NO: 3, and the second polypeptide comprises the amino acid sequence of SEQ ID NO: 1.

17. The intravenous drug delivery formulation of claim 15 or 16 comprising 1200 mg of the protein.

18. The intravenous drug delivery formulation of claim 15 or 16 comprising 1200 mg to 2400 mg of the protein.

19. The intravenous drug delivery formulation of claim 15 or 16 comprising 2400 mg of the protein.

20. The intravenous drug delivery formulation of any one of claims 15-19, wherein the formulation is contained in a bag, a pen, or a syringe.

21. The intravenous drug delivery formulation of claim 20, wherein the bag is connected to a channel comprising a tube and/or a needle.

22. The intravenous drug delivery formulation of any one of claims 15-21, wherein the formulation is a lyophilized formulation or a liquid formulation.

23. A drug delivery device comprising a formulation comprising 500 mg – 2400 mg of a protein comprising a first polypeptide and a second polypeptide,

wherein the first polypeptide comprises: (a) at least a variable region of a heavy chain of an antibody that binds to human protein Programmed Death Ligand 1 (PD-L1); and (b) human Transforming Growth Factor β Receptor II (TGFβRII), or a fragment thereof, capable of binding Transforming Growth Factor β (TGFβ),

wherein the second polypeptide comprises at least a variable region of a light chain of an antibody that binds PD-L1, and

wherein the heavy chain of the first polypeptide and the light chain of the second polypeptide, when combined, form an antigen binding site that binds PD-L1.

24. The drug delivery device of claim 23, wherein the first polypeptide comprises the amino acid sequence of SEQ ID NO: 3, and the second polypeptide comprises the amino acid sequence of SEQ ID NO: 1.

25. The drug delivery device of claim 23 or 24 comprising 1200 mg of the protein.

26. The drug delivery device of claim 23 or 24 comprising 1200 mg to 2400 mg of the protein.

27. The drug delivery device of claim 23 or 24 comprising 2400 mg of the protein.

28. The drug delivery device of any one of claims 23-27, wherein the device is a bag, a pen, or a syringe.

29. The drug delivery device of claim 28, wherein the bag is connected to a channel comprising a tube and/or a needle.

30. A kit comprising one or more vessels collectively comprising a formulation comprising 500 mg – 2400 mg of a protein comprising a first polypeptide and a second polypeptide,

wherein the first polypeptide comprises: (a) at least a variable region of a heavy chain of an antibody that binds to human protein Programmed Death Ligand 1 (PD-L1); and (b) human Transforming Growth Factor β Receptor II (TGFβRII), or a fragment thereof, capable of binding Transforming Growth Factor β (TGFβ),

wherein the second polypeptide comprises at least a variable region of a light chain of an antibody that binds PD-L1, and

wherein the heavy chain of the first polypeptide and the light chain of the second polypeptide, when combined, form an antigen binding site that binds PD-L1.

31. The kit of claim 30, wherein the first polypeptide comprises the amino acid sequence of SEQ ID NO: 3, and the second polypeptide comprises the amino acid sequence of SEQ ID NO: 1.

32. The kit of claim 30 or 31, wherein the vessels collectively comprise 1200 mg of the protein.

33. The kit of claim 30 or 31, wherein the vessels collectively comprise 1200 to 2400 mg of the protein.

34. The kit of claim 30 or 31, wherein the vessels collectively comprise 2400 mg of the protein.

35. The kit of any one of claims 30-34, wherein the formulation is a lyophilized formulation or a liquid formulation.

36. The intravenous drug delivery formulation of any one of claims 15-22, the drug delivery device of any one of claims 23-29, or the kit of any one of claims 30-35, for use in therapy.

37. Use of the intravenous drug delivery formulation of any one of claims 15-22, the drug delivery device of any one of claims 23-29, or the kit of any one of claims 30-35, in the preparation of a medicament for treating cancer or inhibiting tumor growth in a subject in need thereof.

38. The use of claim 37, wherein the cancer or tumor is selected from the group consisting of: non-small cell lung cancer, melanoma, pancreatic cancer, colorectal cancer, ovarian cancer, glioblastoma, gastric cancer, biliary tract cancer, esophageal cancer (squamous cell carcinoma or adenocarcinoma), adenoma of the head or the neck, and squamous carcinoma of the head or the neck.

39. The use of claim 37, wherein the cancer or tumor 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.

40. The use of claim 37, wherein the tumor is an advanced solid tumor.

41. The use of claim 37, wherein the tumor is refractory to prior treatment.

42. The use of any one of claims 37-41, wherein the formulation is to be administered to the subject once every two weeks.