

SUMMARY

[0006] In one aspect, the present disclosure refers to an antibody or antigen-binding fragment thereof that binds Six Trans-membrane Epithelial Antigen of the Prostate 1 (STEAP1) of SEQ ID NO: 2 and comprises heavy chain CDRs comprising amino acid sequences vhCDR1 SEQ ID NO: 14, vhCDR2 SEQ ID NO: 15 or vhCDR2 SEQ ID NO: 21, and vhCDR3 SEQ ID NO: 16; and light chain CDRs comprising amino acid sequences vlCDR1 SEQ ID NO: 11, vlCDR2 SEQ ID NO: 12, and vlCDR3 SEQ ID NO: 13. In another aspect, the present disclosure refers to a pharmaceutical composition comprising the antibody or antigen-binding fragment thereof of the disclosure and a physiologically acceptable carrier. In still another aspect, the present disclosure refers to a polynucleotide comprising a nucleic acid sequence encoding the light chain variable domain and/or heavy chain variable domain of the antibody or antigen-binding fragment thereof of the present disclosure. In still another aspect, the present disclosure refers to an expression vector comprising the polynucleotide of the present disclosure. In another aspect, the present disclosure refers to a composition comprising a polynucleotide comprising a nucleic acid sequence encoding the light chain variable domain of the antibody or antigen-binding fragment thereof of the present disclosure and a polynucleotide comprising a nucleic acid sequence encoding the heavy chain variable domain of the antibody or antigen-binding fragment thereof of the present disclosure. In another aspect, the present disclosure refers to a method of making an antibody or antigen-binding fragment thereof, the method comprising contacting a host cell with (i) a polynucleotide encoding light chain variable region of the present disclosure and a polynucleotide encoding the heavy chain variable region of the present disclosure or (ii) the composition of the present disclosure under conditions that allow expression of the light chain variable domain and the heavy chain variable domain. In another aspect, the present disclosure refers to a bispecific antibody or antigen binding fragment thereof comprising the antibody or antigen-binding fragment thereof of the present disclosure. In still

WHAT IS CLAIMED IS:

1. An antibody or antigen-binding fragment thereof that binds Six Trans-membrane Epithelial Antigen of the Prostate 1 (STEAP1) of SEQ ID NO: 2 and comprises heavy chain CDRs comprising amino acid sequences vhCDR1 SEQ ID NO: 14, vhCDR2 SEQ ID NO: 15 or vhCDR2 SEQ ID NO: 21, and vhCDR3 SEQ ID NO: 16; and light chain CDRs comprising amino acid sequences vlCDR1 SEQ ID NO: 11, vlCDR2 SEQ ID NO: 12, and vlCDR3 SEQ ID NO: 13.
2. The antibody or antigen-binding fragment thereof of claim 1, comprising
 - vhCDR1 comprising SEQ ID NO: 14,
 - vhCDR2 comprising SEQ ID NO: 15,
 - vhCDR3 comprising SEQ ID NO: 16,
 - vlCDR1 comprising SEQ ID NO: 11,
 - vlCDR2 comprising SEQ ID NO: 12, and
 - vlCDR3 comprising SEQ ID NO: 13.
3. The antibody or antigen-binding fragment thereof of claim 1, comprising
 - vhCDR1 comprising SEQ ID NO: 14,
 - vhCDR2 comprising SEQ ID NO: 21,
 - vhCDR3 comprising SEQ ID NO: 16,
 - vlCDR1 comprising SEQ ID NO: 11,
 - vlCDR2 comprising SEQ ID NO: 12, and
 - vlCDR3 comprising SEQ ID NO: 13.
4. The antibody or antigen-binding fragment thereof of claim 1, comprising a heavy chain variable domain comprising a sequence at least 90% identical to SEQ ID NO: 182 or SEQ ID NO: 184 and a light chain variable domain comprising an amino acid sequence at least 90% identical to SEQ ID NO: 183.

5. The antibody or antigen-binding fragment thereof of claim 1, comprising a heavy chain variable domain comprising SEQ ID NO: 184 and a light chain variable domain comprising SEQ ID NO: 183.
6. The antibody or antigen-binding fragment thereof of claim 1, comprising a heavy chain variable domain comprising SEQ ID NO: 182 and a light chain variable domain comprising SEQ ID NO: 183.
7. The antibody or antigen-binding fragment thereof of any one of claims 1-6, which is an antibody.
8. The antibody or antigen-binding fragment thereof of claim 7, which is a monoclonal antibody, a chimeric antibody, or a humanized antibody.
9. The antibody or antigen-binding fragment thereof of any one of claims 1-6, which is an antigen-binding antibody fragment.
10. The antibody or antigen-binding fragment thereof of any one of claims 1-6, comprising a single chain antibody, a diabody, a triabody, or a tetrabody.
11. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof of any one of claims 1-10 and a physiologically acceptable carrier.
12. The pharmaceutical composition of claim 11, further comprising an anti-PD-1 antibody or antigen-binding fragment thereof comprising a vhCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 189, a vhCDR2 comprising the amino acid sequence set forth in SEQ ID NO: 190, a vhCDR3 comprising the amino acid sequence set forth in SEQ ID NO: 191, a vlCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 192, a vhCDR2 comprising the amino acid sequence set forth in SEQ ID NO: 193, and a vl CDR3 comprising the amino acid sequence set forth in SEQ ID NO: 194.

13. A polynucleotide comprising a nucleic acid sequence encoding the light chain variable domain and/or heavy chain variable domain of the antibody or antigen-binding fragment thereof of any one of claims 1-6.

14. An expression vector comprising the polynucleotide of claim 13.

15. A composition comprising a polynucleotide comprising a nucleic acid sequence encoding the light chain variable domain of the antibody or antigen-binding fragment thereof of any one of claims 1-6 and a polynucleotide comprising a nucleic acid sequence encoding the heavy chain variable domain of the antibody or antigen-binding fragment thereof of any one of claims 1-6.

16. A method of making an antibody or antigen-binding fragment thereof, the method comprising contacting a host cell with (i) a polynucleotide encoding light chain variable region of any one of claims 1-6 and a polynucleotide encoding the heavy chain variable region of any one of claims 1-6 or (ii) the composition of claim 19 under conditions that allow expression of the light chain variable domain and the heavy chain variable domain.

17. A bispecific antibody or antigen-binding fragment thereof comprising the antibody or antigen-binding fragment thereof of any one of claims 1-6.

18. The bispecific antibody or antigen-binding fragment thereof of claim 17, which binds STEAP1 and CD3.

19. The bispecific antibody or antigen-binding fragment thereof of claim 18, comprising a CD3 binding domain comprising CDR sequences vLCDR1 SEQ ID NO: 174, vLCDR2 SEQ ID NO: 175, vLCDR3 SEQ ID NO: 176, vHCDR1 SEQ ID NO: 170, vHCDR2 SEQ ID NO: 171, and vHCDR3 SEQ ID NO: 172.

20. A heterodimeric antibody comprising:

a) a first monomer comprising a first heavy chain comprising:

1) a first variable heavy domain;

2) a first constant heavy chain comprising a first CH1 domain and a first Fc domain;

3) a scFv that binds human CD3 and comprises a scFv variable light domain, an scFv linker and a scFv variable heavy domain; wherein said scFv is covalently attached between the C-terminus of said CH1 domain and the N-terminus of said first Fc domain using domain linker(s);

b) a second monomer comprising a second heavy chain comprising a second variable heavy domain and a second constant heavy chain comprising a second Fc domain; and

c) a common light chain comprising a variable light domain and a constant light domain;

wherein said first variable heavy domain and said variable light domain bind human STEAP1, said second variable heavy domain and said variable light domain bind human STEAP1, and

wherein the first variable heavy domain and the second variable heavy domain comprise heavy chain CDRs comprising amino acid sequences vhCDR1 SEQ ID NO: 14, vhCDR2 SEQ ID NO: 15 or SEQ ID NO: 21, and vhCDR3 SEQ ID NO: 16, and the variable light domain comprises light chain CDRs comprising amino acid sequences vlCDR1 SEQ ID NO: 11, vlCDR2 SEQ ID NO: 12, and vlCDR3 SEQ ID NO: 13.

21. The heterodimeric antibody of claim 20, wherein the first variable heavy domain and the second variable heavy domain comprise an amino acid sequence at least 90% identical to SEQ ID NO: 182 or 184 and the variable light domain comprises an amino acid sequence at least 90% identical to SEQ ID NO: 183.

22. The heterodimeric antibody of claim 20 or claim 21, wherein said scFv comprises a variable heavy domain comprising heavy chain CDRs comprising amino acid sequences vhCDR1 SEQ ID NO: 170, vhCDR2 SEQ ID NO: 171, and vhCDR3 SEQ ID NO: 172, and a variable light domain comprising light chain CDRs comprising amino acid sequences vlCDR1 SEQ ID NO: 174, vlCDR2 SEQ ID NO: 175, and vlCDR3 SEQ ID NO: 176.

23. The heterodimeric antibody of claim 22, wherein said scFv comprises a variable heavy domain comprising an amino acid sequence at least 90% identical to SEQ ID NO:169 and a variable light domain comprising an amino acid sequence at least 90% identical to SEQ ID NO: 173.

24. The heterodimeric antibody of any one of claims 20-22, wherein said scFv comprises a variable heavy region and a variable light region of SEQ ID NO:169 and SEQ ID NO:173.

25. The heterodimeric antibody of any one of claims 20-24, wherein said scFv has a charged scFv linker.

26. The heterodimeric antibody of claim 25, wherein the charged scFv linker has a positive charge from 3 to 8 and is selected from the group consisting of SEQ ID NOs: 143 to 153.

27. The heterodimeric antibody of claim 25, wherein the scFv linker comprises SEQ ID NO: 152.

28. The heterodimeric antibody of any one of claims 20-24, wherein said scFv comprises the sequence of SEQ ID NO: 44.

29. The heterodimeric antibody of any one of claims 20-28, wherein the first variable heavy domain and the second variable heavy domain comprise CDR sequences vhCDR1 comprising SEQ ID NO: 14, vhCDR2 comprising SEQ ID NO: 15, vhCDR3 comprising SEQ ID NO: 16, and wherein the variable light domain comprises CDR sequences vlCDR1 comprising SEQ ID NO: 11, vlCDR2 comprising SEQ ID NO: 12, and vlCDR3 comprising SEQ ID NO: 13.

30. The heterodimeric antibody of any of claims 20-28, wherein the first variable heavy domain and the second variable heavy domain comprise SEQ ID NO: 182 and the variable light domain comprises SEQ ID NO: 183.

31. The heterodimeric antibody of any one of claims 20-28, wherein the first variable heavy domain and the second variable heavy domain comprise CDR sequences vhCDR1 comprising SEQ ID NO: 14, vhCDR2 comprising SEQ ID NO: 21, vhCDR3 comprising SEQ ID NO: 16, and

wherein the variable light domain comprises CDR sequences vlCDR1 comprising SEQ ID NO: 11, vlCDR2 comprising SEQ ID NO: 12, and vlCDR3 comprising SEQ ID NO: 13.

32. The heterodimeric antibody of any of claims 20-28, wherein the first variable heavy domain and the second variable heavy domain comprise SEQ ID NO: 184 and the variable light domain comprises SEQ ID NO: 183.

33. The heterodimeric antibody of any one of claims 20-28 comprising the amino acid substitution N67Q and/or a substitution at one or more of positions 292, 297, or 302 in the first and/or second monomer in the EU numbering of IgG1.

34. The heterodimeric antibody of any one of claims 20-30, wherein the first monomer comprises amino acid substitutions E233P, L235V, G236A, S267K, R292C, N297G, V302C, E357Q, and S364K; the second monomer comprises the amino acid substitutions N208D, E233P, L235V, G236A, S267K, R292C, Q295E, N297G, V302C, L368D, K370S, N384D, Q418E, and N421D; and both monomers comprise a deletion at position 234 in the EU numbering of IgG1.

35. A heterodimeric antibody comprising a first monomer comprising the sequence of SEQ ID NO: 19, a second monomer comprising the sequence of SEQ ID NO: 18, and a common light chain comprising the sequence of SEQ ID NO: 17.

36. A heterodimeric antibody comprising a first monomer comprising the sequence of SEQ ID NO: 202, a second monomer comprising the sequence of SEQ ID NO: 201, and a common light chain comprising the sequence of SEQ ID NO: 200.

37. A heterodimeric antibody comprising a first monomer comprising the sequence of SEQ ID NO: 207, a second monomer comprising the sequence of SEQ ID NO: 203, and a common light chain comprising the sequence of SEQ ID NO: 200.

38. A nucleic acid composition comprising:

a) a first nucleic acid encoding the first monomer of any one of claims 20-37;

- b) a second nucleic acid encoding the second monomer of any one of claims 20-37; and
- c) a third nucleic acid encoding the common light chain of any one of claims 20-37.

39. A nucleic acid composition comprising:

- a) a first expression vector comprising a first nucleic acid encoding the first monomer of any one of claims 20-37;
- b) a second expression vector comprising a second nucleic acid encoding the second monomer of any one of claims 20-37; and
- c) a third expression vector comprising a third nucleic acid encoding the common light chain of any one of claims 20-37.

40. A host cell comprising the nucleic acid composition of claim 38 or claim 39.

41. A pharmaceutical composition comprising the heterodimeric antibody of any one of claims 20-37.

42. The heterodimeric antibody of any one of claims 20-37 or the pharmaceutical composition of claim 41 for use in treating a subject in need thereof.

43. Use of the heterodimeric antibody of any one of claims 20-37 or the pharmaceutical composition of claim 41 in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein the cancer expresses STEAP1.

44. The heterodimeric antibody or the pharmaceutical composition for use of claim 42, or the use of claim 43, further comprising an anti-PD-1 antibody or antigen-binding fragment thereof to be administered to the subject.

45. The use, or the heterodimeric antibody or the pharmaceutical composition for use of claim 44, wherein the anti-PD-1 antibody or antigen-binding fragment thereof comprises a vhCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 189, a vhCDR2 comprising the amino acid sequence set forth in SEQ ID NO: 190, a vhCDR3 comprising the amino acid sequence

set forth in SEQ ID NO: 191, a vlCDR1 comprising the amino acid sequence set forth in SEQ ID NO: 192, a vhCDR2 comprising the amino acid sequence set forth in SEQ ID NO: 193, and a vlCDR3 comprising the amino acid sequence set forth in SEQ ID NO: 194.

46. The use, or the heterodimeric antibody or the pharmaceutical composition for use of claim 45, wherein the anti-PD-1 antibody or antigen-binding fragment thereof comprises a heavy chain variable domain comprising an amino acid sequence of SEQ ID NO: 195 and a light chain variable domain comprising an amino acid sequence of SEQ ID NO: 196.

47. The use, or the heterodimeric antibody or the pharmaceutical composition for use of claim 45 or claim 46, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is an antigen-binding antibody fragment.

48. The use, or the heterodimeric antibody or the pharmaceutical composition for use claim 45 or claim 46, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is an antibody.

49. The use, or the heterodimeric antibody or the pharmaceutical composition for use of claim 45 or claim 46, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is a monoclonal antibody, a chimeric antibody, or a humanized antibody.

50. The use, or the heterodimeric antibody or the pharmaceutical composition for use of any one of claims 45-49, wherein the anti-PD-1 antibody or antigen-binding fragment thereof comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 197 and a light chain comprising the amino acid sequence of SEQ ID NO: 198.

51. The use, or the heterodimeric antibody or the pharmaceutical composition for use of any one of claims 45-49, wherein the anti-PD-1 antibody or antigen-binding fragment thereof comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 208 and a light chain comprising the amino acid sequence of SEQ ID NO: 209.

52. The use, or the heterodimeric antibody for use or the pharmaceutical composition for use of claim 44, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is pembrolizumab.

53. The use, or the heterodimeric antibody or the pharmaceutical composition for use of any one of claims 44-52, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is to be administered before the antigen-binding protein that binds STEAP1 or the heterodimeric antibody.

54. The use, or the heterodimeric antibody or the pharmaceutical composition for use of any one of claims 44-52, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is to be administered concurrently with the antibody or antigen-binding fragment thereof that binds STEAP1 or the heterodimeric antibody.

55. The use, or the heterodimeric antibody or the pharmaceutical composition for use of any one of claims 44-52, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is to be administered after the antibody or antigen-binding fragment thereof that binds STEAP1 or the heterodimeric antibody.

56. The use, or the heterodimeric antibody or the pharmaceutical composition for use of claim 42 or claim 43, wherein the subject is also to be administered an effective amount of abiraterone acetate or enzalutamide.

57. The use, or the heterodimeric antibody or the pharmaceutical composition for use of any one of claims 42-56, wherein the antibody or antigen-binding fragment thereof that binds STEAP1 or the heterodimeric antibody is to be administered subcutaneously.

58. The use, or the heterodimeric antibody or the pharmaceutical composition for use of any one of claims 43-57, wherein the cancer is prostate cancer.

59. The use, or the heterodimeric antibody or the pharmaceutical composition for use of any one of claims 43-57, wherein the cancer is Ewing sarcoma.

60. The antibody or antigen-binding fragment thereof of any one of claims 1-10, attached to a detectable label.

61. The antibody or antigen-binding fragment thereof of claim 60, wherein the label is radioactive.

62. The antibody or antigen-binding fragment thereof of any one of claims 60 or 61, which is a Fab fragment.

63. The antibody or antigen-binding fragment thereof of any one of claims 60 or 61, which is a F(ab')₂ fragment.