

FOLR1 is expressed on tumor cells of various origins, e.g., ovarian and lung cancer. Several approaches to target FOLR1 with therapeutic antibodies, such as farletuzumab, antibody drug conjugates, or adoptive T cell therapy for imaging of tumors have been described (Kandalafi et al., *J Transl Med.* 2012 Aug 3;10:157. doi: 10.1186/1479-5876-
5 10-157; van Dam et al., *Nat Med.* 2011 Sep 18;17(10):1315-9. doi: 10.1038/nm.2472; Clifton et al., *Hum Vaccin.* 2011 Feb;7(2):183-90. Epub 2011 Feb 1; Kelemen et al., *Int J Cancer.* 2006 Jul 15;119(2):243-50; Vaitilingam et al., *J Nucl Med.* 2012 Jul;53(7); Teng et al., 2012 Aug;9(8):901-8. doi: 10.1517/17425247.2012.694863. Epub 2012 Jun 5.

Some attempts have been made to target folate receptor-positive tumors with constructs
10 that target the folate receptor and CD3 (Kranz et al., *Proc Natl Acad Sci U S A.* Sep 26, 1995; 92(20): 9057–9061; Roy et al., *Adv Drug Deliv Rev.* 2004 Apr 29;56(8):1219-31; Huiting Cui et al *Biol Chem.* Aug 17, 2012; 287(34): 28206–28214; Lamers et al., *Int. J. Cancer.* 60(4):450 (1995); Thompson et al., *MAbs.* 2009 Jul-Aug;1(4):348-56. Epub 2009 Jul 19; Mezzanzanica et al., *Int. J. Cancer,* 41, 609–615 (1988).

15 There remains a need for such an optimal therapy for treating, stabilizing, preventing, and/or delaying development of various cancers.

SUMMARY

Broadly, the present disclosure relates to bispecific antibodies combining a Folate Receptor 1 (FolR1) targeting antigen binding site with a second antigen binding site that
20 targets CD3 and their use in combination with a PD-1 axis binding antagonist, e.g., for the treatment of cancer. In one embodiment, the combination further comprises a TIM3 antagonist. The methods and combinations of the present disclosure enable enhanced immunotherapy. The advantage over conventional treatment is the specificity of inducing T cell activation only at the site where FolR1 is expressed as well as the reduction and/or
25 reversal of low T cell mediated activity also termed T cell exhaustion due to the combination with a PD-1 axis binding antagonist, and, optionally, a TIM3 antagonist.

Accordingly, the present disclosure provides a method for treating or delaying progression of a cancer in an individual comprising administering to the individual an effective amount of a T cell activating bispecific antigen binding molecule and a PD-1
30 axis binding antagonist. In one aspect, the present disclosure provides use of a T cell activating bispecific antigen binding molecule and a PD-1 axis binding antagonist in the manufacture of a medicament for the treatment of or delaying the

progression of a cancer, wherein the T cell activating bispecific antigen binding molecule comprises a first Fab fragment capable of specific binding to CD3, a second Fab fragment capable of specific binding to Folate Receptor 1 (FolR1), wherein the PD-1 axis binding antagonist inhibits the binding of PD-1 to its ligand binding partners, wherein the PD-1 axis binding antagonist is selected from the group consisting of an anti-PD-1 antibody, an anti-PD-L1 antibody and an anti-PD-L2 antibody.

In one embodiment, the T cell activating bispecific antigen binding molecule comprises a first antigen binding moiety capable of specific binding to CD3 and a second antigen binding moiety capable of specific binding to Folate Receptor 1 (FolR1). In one embodiment, the first antigen binding moiety comprises at

Claims

1. Use of a T cell activating bispecific antigen binding molecule and a PD-1 axis binding antagonist in the manufacture of a medicament for the treatment of or delaying the progression of a cancer,
wherein the T cell activating bispecific antigen binding molecule comprises a first Fab fragment capable of specific binding to CD3, a second Fab fragment capable of specific binding to Folate Receptor 1 (FolR1), wherein the PD-1 axis binding antagonist inhibits the binding of PD-1 to its ligand binding partners, wherein the PD-1 axis binding antagonist is selected from the group consisting of an anti-PD-1 antibody, an anti-PD-L1 antibody and an anti-PD-L2 antibody.
2. The use of claim 1, wherein the first Fab fragment comprises the heavy chain CDR1 SEQ ID NO: 37, the heavy chain CDR2 of SEQ ID NO: 38, the heavy chain CDR3 of SEQ ID NO: 39, the light chain CDR1 of SEQ ID NO: 32, the light chain CDR2 of SEQ ID NO: 33, and the light chain CDR3 of SEQ ID NO: 34.
3. The use of claim 1, wherein the first Fab fragment comprises a variable heavy chain comprising an amino acid sequence of SEQ ID NO: 36 and a variable light chain comprising an amino acid sequence of SEQ ID NO: 31.
4. The use of any one of claims 1-3, wherein the T cell activating bispecific antigen binding molecule further comprises a third Fab fragment capable of specific binding to FolR1.
5. The use of claim 4, wherein the second and third Fab fragment capable of specific binding to FolR1 comprise identical heavy chain complementarity determining region (CDR) and light chain CDR sequences.
6. The use of claim 5, wherein the third Fab fragment is identical to the second Fab fragment.

7. The use of any one of the preceding claims, wherein the Fab fragment capable of specific binding to Folate Receptor 1 (FolR1) comprises at least one heavy chain complementarity determining region (CDR) amino acid sequence selected from the group consisting of SEQ ID NO: 16, SEQ ID NO: 17 and SEQ ID NO: 18 and at least one light chain CDR selected from the group of SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34.
8. The use of claim 7, wherein the Fab fragment capable of specific binding to Folate Receptor 1 (FolR1) comprises a variable heavy chain comprising an amino acid sequence of SEQ ID NO: 15 and a variable light chain comprising an amino acid sequence of SEQ ID NO: 31.
9. The use of any one of claims 1-6, wherein the Fab fragment capable of specific binding to Folate Receptor 1 (FolR1) comprises at least one heavy chain complementarity determining region (CDR) amino acid sequence selected from the group consisting of SEQ ID NO: 8, SEQ ID NO: 56 and SEQ ID NO: 57 and at least one light chain CDR selected from the group of SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 65.
10. The use of claim 9, wherein the Fab fragment capable of specific binding to Folate Receptor 1 (FolR1) comprises a variable heavy chain comprising an amino acid sequence of SEQ ID NO: 55 and a variable light chain comprising an amino acid sequence of SEQ ID NO: 64.
11. The use of any one of claims 1-6, wherein the Fab fragment capable of specific binding to Folate Receptor 1 (FolR1) comprises at least one heavy chain complementarity determining region (CDR) amino acid sequence selected from the group consisting of SEQ ID NO: 16, SEQ ID NO: 402 and SEQ ID NO: 400 and at least one light chain CDR selected from the group of SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34.

12. The use of claim 11, wherein the Fab fragment capable of specific binding to FolR1 comprises:
 - a) a complementarity determining region heavy chain 1 (CDR-H1) amino acid sequences of SEQ ID NO: 16;
 - (b) a CDR-H2 amino acid sequence of SEQ ID NO: 402;
 - (c) a CDR-H3 amino acid sequence of SEQ ID NO: 400;
 - (d) a complementarity determining region light chain 1 (CDR-L1) amino acid sequence of SEQ ID NO: 32;
 - (e) a CDR-L2 amino acid sequence of SEQ ID NO: 33, and
 - (f) a CDR-L3 amino acid sequence of SEQ ID NO: 34.

13. The use of claim 12, wherein the Fab fragment capable of specific binding to FolR1 comprises a variable heavy chain comprising an amino acid sequence of SEQ ID NO: 401 and a variable light chain comprising an amino acid sequence of SEQ ID NO: 31.

14. The use of any one of the preceding claims, wherein the anti-PD-L1 antibody comprises a heavy chain comprising HVR-H1 sequence of SEQ ID NO:289, HVR-H2 sequence of SEQ ID NO:290, and HVR-H3 sequence of SEQ ID NO:291; and a light chain comprising HVR-L1 sequence of SEQ ID NO: 292, HVR-L2 sequence of SEQ ID NO: 293, and HVR-L3 sequence of SEQ ID NO: 294.
15. The use of any one of the preceding claims, wherein the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:280 or SEQ ID NO:281 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:383.
16. The use of any one of Claims 1-15, further comprising a T cell immunoglobulin mucin 3 (TIM3) antagonist.
17. The use of Claim 16, wherein the TIM3 antagonist is an anti-TIM3 antibody.

18. The use of Claim 17, wherein the anti-TIM3 antibody is F38-2E2.

19. The use of any one of Claims 1-18, wherein the cancer is selected from the group consisting of ovarian cancer, lung cancer, breast cancer, renal cancer, colorectal cancer, endometrial cancer.

20. Use of a combination of a T cell activating bispecific antigen binding molecule specific for Folate Receptor 1 (FolR1) and CD3, and a PD-1 axis binding antagonist in the manufacture of a medicament for enhancing immune function in an individual having a FolR1-positive cancer.
21. A method for selecting a patient for treatment with a combination of a T cell activating bispecific antigen binding molecule specific for Folate Receptor 1 (FolR1) and CD3, and a PD-1 axis binding antagonist comprising measuring the level of PD-1 expression, wherein a patient having less than about 15% PD-1^{hi} expressing T cells is selected for treatment with the combination.
22. A kit comprising a T cell activating bispecific antigen binding molecule specific for Folate Receptor 1 (FolR1) and CD3, and a package insert comprising instructions for using the T cell activating bispecific antigen binding molecule with a PD-1 axis binding antagonist to treat or delay progression of cancer in an individual.

23. The kit of Claim 22, further comprising instructions for using the T cell activating bispecific antigen binding molecule with a TIM3 antagonist.
24. A kit comprising a T cell activating bispecific antigen binding molecule specific for Folate Receptor 1 (FolR1) and CD3 and a PD-1 axis binding antagonist, and a package insert comprising instructions for using the T cell activating bispecific antigen binding molecule and the PD-1 axis binding antagonist to treat or delay progression of cancer in an individual.
25. The kit of Claim 24, further comprising a TIM3 antagonist.
26. The kit of any one of claims 22-24, wherein the PD-1 axis binding antagonist is an anti-PD-1 antibody or an anti-PDL-1 antibody.
27. A pharmaceutical composition comprising a T cell activating bispecific antigen binding molecule specific for Folate Receptor 1 (FolR1) and CD3, a PD-1 axis binding antagonist and a pharmaceutically acceptable carrier.
28. The pharmaceutical composition of Claim 27, further comprising a TIM3 antagonist.
29. Use of a combination of a T cell activating bispecific antigen binding molecule specific for Folate Receptor 1 (FolR1) and CD3 and a PD-1 axis binding antagonist in the manufacture of a medicament for the treatment of cancer.
30. Use of a combination of a T cell activating bispecific antigen binding molecule specific for Folate Receptor 1 (FolR1) and CD3, a PD-1 axis binding antagonist, and a TIM3 antagonist in the manufacture of a medicament for the treatment of cancer.

31. The use of claim 29 or 30, wherein the medicament is for treatment of ovarian cancer, lung cancer, breast cancer, renal cancer, colorectal cancer, endometrial cancer.