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 (Kandalaft et al., J Transl Med. 2012 Aug 3;10:157. doi: 10.1186/1479-5876-10-157; van Dam et al., Nat Med. 2011 Sep 18;17(10):1315-9. doi: 10.1038/nm.2472; Cliftonet 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 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; Mezzanzanca et al., Int. J. Cancer, 41, 609–615 (1988).

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

SUMMARY

Broadly, the present dislcosure relates to bispecific antibodies combining a Folate Receptor 1 (FolR1) targeting antigen binding site with a second antigen binding site that 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 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 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 combination therapy in 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, and wherein the cancer is a FolR1-positive cancer.

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

2011/155607, WO 2013/006490, WO 03/063792, WO 2009/097394, and WO 2011/159877. In one embodiment, the anti-TIM3 antibody is F38-2E2.

In one embodiment, the cancer contains a KRAS wildtype. In one embodiment, the cancer contains an activating KRAS mutation.

In one embodiment, the treatment results in a sustained response in the individual after cessation of the treatment. In one embodiment, at least one of the T cell activating bispecific antigen binding molecule and the PD-1 axis binding antagonist is administered continuously. In one embodiment, at least one of the T cell activating bispecific antigen binding molecule and the PD-1 axis binding antagonist is administered intermittently. In one embodiment, the PD-1 axis binding antagonist is administered before the FolR1 TCB. In one embodiment, the PD-1 axis binding antagonist is administered simultaneous with the FolR1 TCB. In one embodiment, the PD-1 axis binding antagonist is administered after the FolR1 TCB. In one embodiment, the cancer is selected from the group consisting of ovarian cancer, lung cancer, breast cancer, renal cancer, colorectal cancer, endometrial cancer. In one embodiment, at least one of the T cell activating bispecific antigen binding molecule and the PD-1 axis binding antagonist is administered intravenously, intramuscularly, subcutaneously, topically, orally, transdermally, intraperitoneally, intraorbitally, by implantation, by inhalation, intrathecally, intraventricularly, or intranasally.

In one embodiment, T cells in the individual have enhanced activation, proliferation and/or effector function relative to prior to the administration of the combination. In one embodiment, T cells in the individual have enhanced activation, proliferation and/or effector function relative to administration of the T cell activating bispecific antigen binding molecule alone. In one embodiment, T cell effector function is secretion of at least one of IL-2, IFN-γ and TNF-α. In one embodiment, the individual comprises less than about 15% PD-1^{hi} expressing tumor-infiltrating T cells.

The disclosure provides for a method of enhancing immune function in an individual having a FolR1 positive cancer comprising administering to the individual an effective amount 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 one aspect, the disclosure provides for 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 combination therapy in enhancing immune function in an individual having a FolR1-positive cancer, wherein the PD-1 axis binding antagonist inhibits the binding of PD-1 to its ligand binding partners, and 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, T cells in the individual have enhanced activation, proliferation and/or effector function relative to prior to the administration of the combination. In one embodiment, T cells in the individual have enhanced activation,

proliferation and/or effector function relative to administration of the T cell activating bispecific antigen binding molecule alone. In one embodiment, T cell effector function is secretion of at least one of IL-2, IFN-γ and TNF-α.

In one embodiment, the individual comprises less than about 15% PD-1^{hi} expressing tumor-infiltrating T cells.

The disclosure provides for 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.

In another aspect, the disclosure provides for 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-1hi expressing T cells is selected for treatment with the combination, wherein the PD-1 axis binding antagonist inhibits the binding of PD-1 to its ligand binding partners, and 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.

The disclosure provides for 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. In one embodiment, the kit further comprises instructions for using the T cell activating bispecific antigen binding molecule with a TIM3 antagonist.

The disclosure provides for 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.

In another aspect, the disclosure provides 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 as a combined pharmaceutical formulation for use in treating or delaying progression of cancer in an individual, 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, wherein the cancer is a FolR1-positive cancer and 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 kit further comprises a TIM3 antagonist. In one embodiment, the PD-1 axis binding antagonist is an anti-PD-1 antibody or an anti-PDL-1 antibody. In one embodiment, the PD-1 axis binding antagonist is an anti-PD-1 immunoadhesin.

In another aspect, the disclosure provides for 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. In one embodiment, the pharmaceutical composition further comprises a TIM3 antagonist.

The disclosure provides for a 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.

In another aspect, the disclosure provides for a use 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 combination therapy in the treatment of cancer, wherein the cancer is a FolR1-positive cancer and 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 medicament is for treatment of ovarian cancer, lung cancer, breast cancer, renal cancer, colorectal cancer, endometrial cancer.

In certain embodiments of the present disclosure, advantageously said T cell activating bispecific antigen binding molecule and/or PD-1 axis binding antagonist is human or humanized.

In some embodiments, the bispecific antibody comprises an Fc domain, at least one Fab fragment comprising the antigen binding site specific for FolR1, and at least one Fab fragment comprising the antigen binding site specific for CD3.

The disclosure provides for 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 TIM3 antagonist. In some embodiments, the T cell activating bispecific antigen binding molecule comprises an Fc domain, two Fab fragments comprising each an antigen binding site specific for FolR1, and one Fab fragment comprising an antigen binding site specific for CD3.

The present disclosure provides the use of a combination of a T cell activating bispecific antigen binding molecule that binds to FolR1 and CD3, and a PD-1 axis binding antagonist in the manufacture of a medicament for the treatment of cancer.

The present disclosure provides the use of a combination of a T cell activating bispecific antigen binding molecule that binds to FolR1 and CD3, a PD-1 axis binding antagonist and a TIM3 antagonist in the manufacture of a medicament for the treatment of cancer.

Embodiments of the present disclosure will now be described by way of example and not limitation with reference to the accompanying figures. However various further aspects and embodiments of the present disclosure will be apparent to those skilled in the art in view of the present disclosure.

"and/or" where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. For example "A and/or B" is to be taken as specific disclosure of each of (i) A, (ii) B and (iii) A and B, just as if each is set out individually herein.

Unless context dictates otherwise, the descriptions and definitions of the features set out above are not limited to any particular aspect or embodiment of the disclosure and

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 combination therapy in 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, and wherein the cancer is a FolR1-positive cancer.

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-Hl 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-Ll 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, wherein the medicament further comprises 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 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 combination therapy in enhancing immune function in an individual having a FolR1-positive cancer, wherein the PD-1 axis binding antagonist inhibits the binding of PD-1 to its ligand binding partners, and 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.

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,
wherein the PD-1 axis binding antagonist inhibits the binding of PD-1 to its ligand binding partners, and 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.

22. 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 as a combined pharmaceutical formulation for use in treating or delaying progression of cancer in an individual, 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, wherein the cancer is a FolR1-positive cancer and 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.

23. The kit of Claim 24, further comprising a TIM3 antagonist.

24. 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.

25. The pharmaceutical composition of Claim 27, further comprising a TIM3 antagonist.

26. Use 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 combination therapy in the treatment of cancer, wherein the cancer is a FolR1-positive cancer and 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.

27. 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.