

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.

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 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, 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, 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.

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-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, 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 22, 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, 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.
25. The pharmaceutical composition of claim 24, 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 26, wherein the medicament is for treatment of ovarian cancer, lung cancer, breast cancer, renal cancer, colorectal cancer, endometrial cancer.