

CLAIMS

1. Use of an isoform-specific inhibitor of TGF β 1 in the manufacture of a medicament for the treatment of cancer or myelofibrosis, wherein the isoform-specific inhibitor is:

(a) an antibody or an antigen-binding fragment thereof which comprises a heavy chain variable region comprising a CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising a CDRL1, CDRL2, and CDRL3, wherein:

CDRH1 comprises a sequence as set forth in SEQ ID NO: 2;

CDRH2 comprises a sequence as set forth in SEQ ID NO: 4;

CDRH3 comprises a sequence as set forth in SEQ ID NO: 6;

CDRL1 comprises a sequence as set forth in SEQ ID NO: 8;

CDRL2, comprises a sequence as set forth in SEQ ID NO: 10; and

CDRL3 comprises a sequence as set forth in SEQ ID NO: 12;

(b) an antibody or an antigen-binding fragment thereof which comprises a heavy chain variable region comprising a CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising a CDRL1, CDRL2, and CDRL3, wherein:

CDRH1 comprises a sequence as set forth in SEQ ID NO: 1;

CDRH2 comprises a sequence as set forth in SEQ ID NO: 3;

CDRH3 comprises a sequence as set forth in SEQ ID NO: 5;

CDRL1 comprises a sequence as set forth in SEQ ID NO: 7;

CDRL2, comprises a sequence as set forth in SEQ ID NO: 9; and

CDRL3 comprises a sequence as set forth in SEQ ID NO: 11; or

(c) an antibody or an antigen-binding fragment thereof which competes or cross-competes with the antibody defined in part (a) or (b) for binding to TGF β 1 having the amino acid sequence of SEQ ID NO: 21;

wherein, a therapeutically effective dose of the inhibitor does not cause a cardiovascular toxicity associated with TGF β inhibition in a subject,

wherein the antibody or the antigen-binding fragment thereof specifically binds to all of the following pro/latent TGF β 1 complexes: a TGF β 1-LTBP1 complex, a TGF β 1-LTBP3 complex, a TGF β 1-GARP complex and a TGF β 1-LRRC33 complex, and inhibits release of mature TGF β 1 from the complexes; and

wherein the antibody or antigen-binding fragment thereof does not bind TGF β 2 having the amino acid sequence of SEQ ID NO: 22 or TGF β 3 having the amino acid sequence of SEQ ID NO: 23.

2. The use according to claim 1, wherein the antibody or the antigen-binding fragment of part (a) comprises a heavy chain variable region comprising a sequence as set forth in SEQ ID NO: 17 and a light chain variable region comprising a sequence as set forth in SEQ ID NO: 18 or wherein the antibody or antigen-binding fragment of part (b) comprises a heavy chain variable region comprising a

sequence as set forth in SEQ ID NO: 13 and a light chain variable region comprising a sequence as set forth in SEQ ID NO: 14.

3. The use according to claim 1 or claim 2, wherein the cancer is a cancer or tumor found in the colon, anus, bladder, bile duct, bone, brain, breast, cervix, rectum, endometrium, esophagus, eye, gallbladder, head and neck, liver, kidney, larynx, lung, mediastinum (chest), mouth, ovaries, pancreas, penis, prostate, skin, small intestine, stomach, spinal marrow, tailbone, testicles, thyroid or uterus.
4. The use according to claim 1, wherein the cardiovascular toxicity comprises heart valve lesions, wherein optionally the heart valve lesions include hemorrhage, inflammation, degeneration and/or proliferation of valvular interstitial cells.
5. The use according to claim 4, wherein the cardiovascular toxicities include valvulopathy.
6. The use according to any one of claims 1-5, wherein the inhibitor reduces tumor growth.
7. The use according to any one of claims 1-6, wherein the inhibitor reduces the suppressive activity of regulatory T cells.
8. The use according to any one of claims 1-7, wherein the therapeutically effective dose is from about 0.1 µg/kg to about 30 mg/kg.
9. The use according to any one of claims 1-8, wherein the inhibitor inhibits or decreases solid tumor growth.
10. The use according to any one of claims 1-9, further comprising an additional agent or therapy.
11. The use according to claim 10, wherein the additional therapy is radiation, a chemotherapeutic, or a combination thereof.
12. The use according to claim 10 or 11, wherein the additional agent is a checkpoint inhibitor.
13. The use according to claim 12, wherein the checkpoint inhibitor is selected from the group consisting of an anti-PD1 antibody, a PD-1 antagonist, a PDL1 antagonist, or a PD-L1 or PDL2 fusion protein, a CTLA4 antagonist, a GITR agonist, an anti-ICOS antibody, an anti-ICOSL antibody, an anti-B7H3 antibody, an anti-B7H4 antibody, an anti-TIM3 antibody, an anti-LAG3 antibody, an anti-OX40 antibody, an anti-CD27 antibody, an anti-CD70 antibody, an anti-CD47 antibody, an anti-41BB antibody, an oncolytic virus, and a PARP inhibitor.

14. Use of an effective amount of ~~a combination of~~ an isoform-specific inhibitor of TGFβ1 ~~and a checkpoint inhibitor~~ in the manufacture of a medicament for reducing tumor growth in a subject, wherein the isoform-specific inhibitor of TGFβ1 is an antibody, or an antigen binding fragment thereof; wherein the antibody, or the antigen-binding fragment thereof, competes or cross-competes with the antibody defined in part (a) or (b) of claim 1 for binding to TGFβ1 having the amino acid sequence of SEQ ID NO: 21, specifically binds to all of the following pro/latent TGFβ1 complexes: a TGFβ1-LTBP1 complex, a TGFβ1-LTBP3 complex, a TGFβ1-GARP complex and a TGFβ1-LRRC33 complex, inhibits the release of mature TGFβ1 from the complexes, and does not bind TGFβ2 having the amino acid sequence of SEQ ID NO: 22 or TGFβ3 having the amino acid sequence of SEQ ID NO: 23; wherein a therapeutically effective dose of the isoform-specific inhibitor of TGFβ1 does not cause a cardiovascular toxicity associated with TGFβ inhibition in a subject; and wherein ~~the subject is administered a checkpoint inhibitor in conjunction with the isoform-specific inhibitor of TGFβ1, wherein~~ the checkpoint inhibitor is a PD-1 antagonist or PD-L1 antagonist.

15. Use of an effective amount of a checkpoint inhibitor in the manufacture of a medicament for reducing tumor growth in a subject who is administered an isoform-specific inhibitor of TGFβ1 in conjunction with the checkpoint inhibitor, wherein the checkpoint inhibitor therapy is a PD-1 antagonist or PD-L1 antagonist, and wherein the isoform-specific inhibitor of TGFβ1 is an antibody, or an antigen binding fragment thereof; wherein the antibody, or the antigen-binding fragment thereof, competes or cross-competes with the antibody defined in part (a) or (b) of claim 1 for binding to TGFβ1 having the amino acid sequence of SEQ ID NO: 21, specifically binds to all of the following pro/latent TGFβ1 complexes: a TGFβ1-LTBP1 complex, a TGFβ1-LTBP3 complex, a TGFβ1-GARP complex and a TGFβ1-LRRC33 complex, inhibits the release of mature TGFβ1 from the complexes, and does not bind TGFβ2 having the amino acid sequence of SEQ ID NO: 22 or TGFβ3 having the amino acid sequence of SEQ ID NO: 23, and wherein a therapeutically effective dose of the isoform-specific inhibitor does not cause a cardiovascular toxicity associated with TGFβ inhibition in a subject.
~~The use according to claim 14, wherein the isoform-specific inhibitor of TGFβ1 and the checkpoint inhibitor are formulated as a single formulation or as separate formulations.~~

16. The use according to any one of claims 14-15, wherein the checkpoint inhibitor is a PD-1 antibody.

17. The use according to any one of claims 14-16, wherein the ~~cancer or~~ tumor is a solid tumor.