CLAIMS

1. An antibody or an antigen-binding fragment thereof that binds each of the following antigen complexes with a KD of ≤ 5 nM, as measured by biolayer interferometry:

i) human LTBP1-proTGFβ1;

ii) human LTBP3-proTGFβ1;

iii) human GARP-proTGFβ1; and,

iv) human LRRC33-proTGFβ1;

wherein the antibody or the fragment thereof inhibits TGFβ1 activation;

wherein the antibody or the fragment thereof is a fully human or humanized antibody or fragment thereof;

wherein the antibody or the fragment thereof comprises:

an H-CDR1 represented by the formula FTF(X_1)(X_2)(X_3)(X_4)M(X_5), wherein: X_1 is S, G or A; X_2 is S or F; X_3 is F or Y; X_4 is S or A; and X_5 is D, N or Y (SEQ ID NO: 143);

an H-CDR2 represented by the formula YI(X_1)(X_2)(X_3)A(X_4)TIYYA(X_5)SVKG, wherein: X_1 is S or H; X_2 is P or S; X_3 is S or D; X_4 is D or S; and X_5 is D or G (SEQ ID NO: 144);

an H-CDR3 represented by the formula (X_1)R(X_2)(X_3)(X_4)D(X_5)GDML(X_6)P, wherein: X_1 is A or V; X_2 is G or A; X_3 is V or T; X_4 is L or W; X_5 is Y or M; and X_6 is M or D (SEQ ID NO: 145);

an L-CDR1 set forth in SEQ ID NO: 105;

an L-CDR2 set forth in SEQ ID NO: 106; and

an L-CDR3 set forth in SEQ ID NO: 12.

2. An antibody or an antigen-binding fragment thereof that binds each of the following antigen complexes with a KD of ≤ 0.5 nM, as measured by biolayer interferometry:

i) human LTBP1-proTGFβ1;

ii) human LTBP3-proTGFβ1;

iii) human GARP-proTGFβ1; and,

iv) human LRRC33-proTGFβ1;

wherein the antibody or the fragment thereof inhibits TGFβ1 activation;

wherein the antibody or the fragment thereof is a fully human or humanized antibody or fragment thereof;

wherein the antibody or the fragment thereof comprises a heavy chain variable domain (V_H) having at least 90% sequence identity to SEQ ID NO: 13 and a light chain variable domain (V_L) having at least 90% sequence identity to SEQ ID NO: 15.

3. The antibody or antigen-binding fragment thereof of claim 1, wherein the H-CDR1 is SEQ ID NO: 107; the H-CDR2 is SEQ ID NO: 103; and the H-CDR3 is SEQ ID NO: 6.

4. The antibody or antigen-binding fragment thereof of claim 1 or 3, which binds each of the antigen complexes with a KD of ≤ 1 nM, optionally ≤ 0.5 nM, as measured by biolayer interferometry.

5. The antibody or the antigen-binding fragment of any one of the preceding claims; which binds an epitope that includes one or more amino acid residues of SEQ ID NO: 169.

6. The antibody or the antigen-binding fragment thereof of any one of the preceding claims, wherein the antibody or the antigen-binding fragment thereof further binds a portion of the growth factor domain.

7. The antibody or antigen-binding fragment thereof of any one of the preceding claims, comprising a V_H according to SEQ ID NO: 13 and a V_L according to SEQ ID NO: 15.

8. The antibody or the antigen-binding fragment thereof of any one of the preceding claims, which is of human IgG4 or IgG1 subtype.

9. A composition comprising the antibody, or the antigen-binding fragment thereof, of any one of the preceding claims, and an excipient.

10. Use of the antibody or the antigen-binding fragment thereof according to claims 1-8, or the composition according to claim 9 in the manufacture of a medicament for treating a proliferative and/or fibrotic disorder in a subject.

11 The use according to claim 10, wherein the disorder is cancer.

12. The use according to claim 10, wherein the disorder is myelofibrosis.

13. The use according to claim 11, wherein the subject has primary or acquired resistance to a cancer therapy, wherein optionally the cancer therapy is checkpoint inhibition therapy, chemotherapy and/or radiation therapy.

14. The use according to claim 13, wherein the composition of claim 9 is to be administered in conjunction with additional cancer therapy, selected from the group consisting of checkpoint inhibitor, chemotherapy and radiation therapy and/or cancer vaccine.

15. A method for manufacturing a pharmaceutical composition comprising:

i) providing an antibody or antigen-binding fragment thereof according to any one of claims 1-8;

ii) formulating the antibody or the antigen-binding fragment thereof into a pharmaceutical composition with a pharmaceutically acceptable carrier.

16. The antibody or the antigen-binding fragment thereof according to claims 1-8, or the composition according to claim 9 for use in therapy.