CLAIMS

1. An antibody or antigen binding fragment thereof that binds to CD70 for use in treating a myeloid malignancy in a human subject, who is resistant to BCL-2 inhibitor treatment.

2. The antibody or antigen binding fragment thereof that binds to CD70 for use according to claim 1, wherein the BCL-2 inhibitor is venetoclax or a pharmaceutically acceptable salt thereof.

3. The antibody or antigen binding fragment thereof that binds to CD70 for use according to claim 1 or 2, wherein the myeloid malignancy is selected from the group consisting of acute myeloid leukemia (AML), myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN), chronic myeloid leukemia (CML), and chronic myelomonocytic leukemia (CMML).

4. The antibody or antigen binding fragment thereof that binds to CD70 for use according to any one of claims 1-3, wherein the myeloid malignancy is AML.

5. The antibody or antigen binding fragment thereof that binds to CD70 for use according to claim 4, wherein the AML is monocytic AML.

6. The antibody or antigen binding fragment thereof that binds to CD70 for use according to any one of claims 1-3, wherein the myeloid malignancy is MDS.

7. The antibody or antigen binding fragment thereof that binds to CD70 for use according to claim 5, wherein the human subject is identified on the basis of different expression levels as having differentiated monocytic AML.

8. The antibody or antigen binding fragment thereof that binds to CD70 for use according to claim 7, wherein the treatment is preceded by a selection comprising the steps of:
(i) measuring the myeloid differentiation status of the human subject, and

(ii) determining whether the human subject has differentiated monocytic AML, and

wherein a therapeutically effective dose of the anti-CD70 antibody or anti-CD70-binding fragment thereof is administered to said human subject having differentiated monocytic AML.

9. The antibody or antigen binding fragment thereof that binds to CD70 for use according to claim 6 or claim 7, wherein the human subject is identified as having differentiated monocytic AML on the basis of differential expression level(s) of at least one marker selected from the group consisting of: BCL-2, CD117, CD11b, CD68, CD64, BCL2A1, and MCL1, of malignant myeloid cells of the human subject.

10. The antibody or antigen binding fragment thereof that binds to CD70 for use according to claim 9, wherein the expression level(s) of at least one of BCL-2 and CD117 is downregulated, and the expression level(s) of at least one of CD11b, CD68, CD64, CD70, BCL2A1, and MCL1 is upregulated.

11. The antibody or antigen binding fragment thereof that binds to CD70 for use according to any one of claims 5-10, wherein a CD70 expression level of malignant myeloid cells of the human subject is measured.

12. The antibody or antigen binding fragment thereof that binds to CD70 for use according to claim 11, wherein CD70 is upregulated compared to a CD70 expression level as measured before or during a BCL-2 inhibitor treatment.

13. The antibody or antigen binding fragment thereof that binds to CD70 for use according to any one of claims 1-12, wherein the human subject has a clinical history comprising:
    (a) treatment with a BCL-2 inhibitor; and
    (b) absence of a remission in response to the treatment with the BCL-2 inhibitor.

14. The antibody or antigen binding fragment thereof that binds to CD70 for use according to claim 13, wherein the historical treatment with the BCL-2 inhibitor further comprises treatment with a hypomethylating agent (HMA).

15. The antibody or antigen binding fragment thereof that binds to CD70 for use according to any one of claims 1-12, wherein the human subject has a clinical history comprising:

(a) treatment with a BCL-2 inhibitor;

(b) partial or complete remission; and

(c) partial or complete relapse.

16. The antibody or antigen binding fragment thereof that binds to CD70 for use according to claim 15, wherein the historical treatment with the BCL-2 inhibitor further comprises treatment with a hypomethylating agent (HMA).

17. The antibody or antigen binding fragment thereof that binds to CD70 for use according to any one of claims 1-16, wherein a hypomethylating agent (HMA) is co-administered with the antibody or antigen binding fragment thereof that binds to CD70.

18. The antibody or antigen binding fragment thereof that binds to CD70 for use according to any one of claims 1-17, wherein a BCL-2 inhibitor is co-administered with the antibody or antigen binding fragment thereof that binds to CD70.

19. The antibody or antigen binding fragment thereof that binds to CD70 for use according to any one of claims 1-18, wherein the antibody or antibody binding fragment that binds to CD70 comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, wherein
the amino acid sequence of HCDR1 consists of SEQ ID NO: 1;
the amino acid sequence of HCDR2 consists of SEQ ID NO: 2;
the amino acid sequence of HCDR3 consists of SEQ ID NO: 3;
the amino acid sequence of LCDR1 consists of SEQ ID NO: 4;
the amino acid sequence of LCDR2 consists of SEQ ID NO: 5; and
the amino acid sequence of LCDR3 consists of SEQ ID NO: 6.

20. The antibody or antigen binding fragment thereof that binds to CD70 for use according to any one of claims 1-19, wherein the antibody or antibody binding

fragment that binds to CD70 comprises a variable heavy chain domain (VH) comprising an amino acid sequence at least 90 % identical to SEQ ID NO: 7 and a variable light chain domain (VL) comprising an amino acid sequence at least 90 % identical to SEQ ID NO: 8.

21. The antibody or antigen binding fragment thereof that binds to CD70 for use according to claim 20, wherein the antibody or antibody binding fragment that binds to CD70 comprises a variable heavy chain domain (VH) comprising an amino acid sequence identical to SEQ ID NO: 7 and a variable light chain domain (VL) comprising an amino acid sequence identical to SEQ ID NO: 8.

22. The antibody or antigen binding fragment thereof that binds to CD70 for use according to claim 20, wherein the amino acid sequence which is at least 90 % identical to the VH consisting of SEQ ID NO: 7 comprises HCDR1, HCDR2, and HCDR3, wherein
the amino acid sequence of HCDR1 consists of SEQ ID NO: 1;
the amino acid sequence of HCDR2 consists of SEQ ID NO: 2; and
the amino acid sequence of HCDR3 consists of SEQ ID NO: 3; and
wherein the amino acid sequence which is at least 90 % identical to the VL consisting of SEQ ID NO: 8 comprises LCDR1, LCDR2, and LCDR3, wherein
the amino acid sequence of LCDR1 consists of SEQ ID NO: 4;
the amino acid sequence of LCDR2 consists of SEQ ID NO: 5; and
the amino acid sequence of LCDR3 consists of SEQ ID NO: 6.

23. The antibody or antigen binding fragment thereof that binds to CD70 for use according to any one of claims 16 to 22, wherein the HMA is selected from the group consisting of azacitidine, decitabine, and guadecitabine.

24. The antibody or antigen binding fragment thereof that binds to CD70 for use according to any one of claims 18 to 23, wherein the BCL-2 inhibitor is venetoclax or a pharmaceutically acceptable salt thereof.

25. The antibody or antigen binding fragment thereof that binds to CD70 for use according to any one claims 1-24, wherein the antibody that binds to CD70 is cusatuzumab.

26. Use of an antibody or antigen binding fragment thereof that binds to CD70 in the manufacture of a medicament for the treatment of a myeloid malignancy in a human subject, comprising the steps of:
    (a) selecting a human subject having a myeloid malignancy that has a reduced sensitivity or is refractory to a BCL-2 inhibitor; and
    (b) administering to the human subject an antibody or antigen binding fragment thereof that binds to CD70.

27. The use of claim 26, wherein the BCL-2 inhibitor is venetoclax or a pharmaceutically acceptable salt thereof.

28. The use of claim 26 or 27, wherein the myeloid malignancy is selected from the group consisting of acute myeloid leukemia (AML), myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN), chronic myeloid leukemia (CML), and chronic myelomonocytic leukemia (CMML).

29. The use of any one of claims 26-28, wherein the myeloid malignancy is AML.

30. The use of claim 29, wherein the AML is monocytic AML.

31. The use of any one of claims 26 to 28, wherein the myeloid malignancy is MDS.

32. The use of any one of claims 26-31, wherein step (a) comprises determining an expression level of at least one marker selected from the group consisting of: BCL-2, CD117, CD11b, CD68, CD64, BCL2A1, and MCL1, of malignant myeloid cells of the human subject.

33. The use of claim 32, wherein at least one of BCL-2 and CD117 is downregulated, and at least one of CD11b, CD68, CD64, CD70, BCL2A1, and MCL1 is upregulated.

34. The use of any one of claims 26-33, wherein step (a) comprises determining a CD70 expression level of malignant myeloid cells of the human subject.

35. The use of claim 34, wherein CD70 is upregulated compared to a CD70 expression level as measured before or during a BCL-2 inhibitor treatment.

36. The use of any one of claims 26-35, wherein the human subject has a clinical history comprising:
    (a) treatment with a BCL-2 inhibitor; and
    (b) absence of a remission in response to the treatment with the BCL-2 inhibitor.

37. The use of claim 36, wherein the historical treatment with the BCL-2 inhibitor further comprises treatment with a hypomethylating agent (HMA).

38. The use of any one of claims 26 through 35, wherein the human subject has a clinical history comprising:
    (a) treatment with a BCL-2 inhibitor;
    (b) partial or complete remission; and
    (c) partial or complete relapse.

39. The use of claim 38, wherein the historical treatment with the BCL-2 inhibitor further comprises treatment with a hypomethylating agent (HMA).

40. The use of any one of claims 26-39, wherein a hypomethylating agent (HMA) is to be co-administered with the antibody or antigen binding fragment thereof that binds to CD70.

41. The use of any one of claims 26-40, wherein a BCL-2 inhibitor is to be co-administered with the antibody or antigen binding fragment thereof that binds to CD70.

42. The use of any one of claims 26-41, wherein the antibody or antibody binding fragment that binds to CD70 comprises HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3, wherein

the amino acid sequence of HCDR1 consists of SEQ ID NO: 1;
the amino acid sequence of HCDR2 consists of SEQ ID NO: 2;
the amino acid sequence of HCDR3 consists of SEQ ID NO: 3;
the amino acid sequence of LCDR1 consists of SEQ ID NO: 4;
the amino acid sequence of LCDR2 consists of SEQ ID NO: 5; and
the amino acid sequence of LCDR3 consists of SEQ ID NO: 6.

43. The use of any one of claims 26-42, wherein the antibody or antibody binding fragment that binds to CD70 comprises a variable heavy chain domain (VH) comprising an amino acid sequence at least 90 % identical to SEQ ID NO: 7 and a variable light chain domain (VL) comprising an amino acid sequence at least 90 % identical to SEQ ID NO: 8.

44. The use of claim 43, wherein the antibody or antibody binding fragment that binds to CD70 comprises a variable heavy chain domain (VH) comprising an amino acid sequence identical to SEQ ID NO: 7 and a variable light chain domain (VL) comprising an amino acid sequence identical to SEQ ID NO: 8.

45. The use of claim 43, wherein the amino acid sequence which is at least 90 % identical to the VH consisting of SEQ ID NO: 7 comprises HCDR1, HCDR2, and HCDR3, wherein
the amino acid sequence of HCDR1 consists of SEQ ID NO: 1;
the amino acid sequence of HCDR2 consists of SEQ ID NO: 2; and
the amino acid sequence of HCDR3 consists of SEQ ID NO: 3; and
wherein the amino acid sequence which is at least 90 % identical to the VL consisting of SEQ ID NO: 8 comprises LCDR1, LCDR2, and LCDR3, wherein
the amino acid sequence of LCDR1 consists of SEQ ID NO: 4;
the amino acid sequence of LCDR2 consists of SEQ ID NO: 5; and
the amino acid sequence of LCDR3 consists of SEQ ID NO: 6.

46. The use of any one of claims 39 to 45, wherein the HMA is selected from the group consisting of azacitidine, decitabine, and guadecitabine.

47. The use of any one of claims 41 to 46, wherein the BCL-2 inhibitor is venetoclax or a pharmaceutically acceptable salt thereof.

48. The use of any one of claims 26-47, wherein the antibody that binds to CD70 is cusatuzumab.

49. Use of an anti-CD70 antibody or CD70-binding fragment thereof in the manufacture of a medicament for the treatment of myeloid malignancy, in a patient, comprising the steps of:

(i) measuring the myeloid differentiation status of the patient;

(ii) determining whether the patient has differentiated monocytic AML, wherein a patient having differentiated monocytic AML is identified as a patient to be treated with the anti-CD70 antibody or CD70-binding fragment thereof; and

(iii) administering the anti-CD70 antibody or CD70-binding fragment thereof to the patient identified as a patient to be treated with the anti-CD70 antibody or CD70-binding fragment thereof.

50. The use of claim 49, wherein a bone marrow sample of the patient comprises $CD45^{bright}/SSC^{high}/CD38^{+}/CD34^{-}/CD33^{+}/CD11b^{+}/CD70^{+}$ phenotype cells or $CD45^{bright}/SSC^{high}/CD34^{-}/CD117^{-}/CD11b^{+}/CD68^{+}/CD14^{+}/CD64^{+}$ phenotype cells.