TREATMENT OF HEMATOLOGICAL MALIGNANCIES WITH ANTIBODIES INHIBITING GALECTIN-9

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of the filing dates of U.S. Provisional Application No. 63/591,589, filed October 19, 2023, and U.S. Provisional Application No. 63/562,397, filed March 7, 2024, the entire contents of each of which are incorporated by reference herein.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been filed electronically in XML format and is hereby incorporated by reference in its entirety. Said XML copy, created on October 17, 2024, is named "063587-515001WO_SEQ-Listing_ST26.xml" and is 40,964 bytes in size.

BACKGROUND

Galectin-9 is a tandem-repeat lectin consisting of two carbohydrate recognition domains (CRDs) and was discovered and described for the first time in 1997 in patients suffering from Hodgkin's lymphoma (HL) (Tureci et al., J. Biol. Chem. 1997, 272, 6416–6422). Three isoforms exist and can be located within the cell or extracellularly. Elevated Galectin-9 levels have been in observed a wide range of cancers, including melanoma, Hodgkin's lymphoma, hepatocellular, pancreatic, gastric, colon and clear cell renal cell cancers (Wdowiak et al. Int. J. Mol. Sci. 2018, 19, 210). In renal cancer, patients with high Galectin-9 expression showed more advanced progression of the disease with larger tumor size (Kawashima et al.; BJU Int. 2014;113:320–332). In melanoma, Galectin-9 was expressed in 57% of tumors and was significantly increased in the plasma of patients with advanced melanoma compared to healthy controls (Enninga et al., Melanoma Res. 2016 Oct; 26(5): 429–441). A number of studies have shown utility for Galectin-9 as a prognostic marker, and more recently as a potential new drug target (Enninga et al., 2016; Kawashima et al. BJU Int 2014; 113: 320–332; Kageshita et al., Int J Cancer. 2002 Jun 20;99(6):809-16, and references therein).

Galectin-9 has been described to play an important role in in a number of cellular processes such as adhesion, cancer cell aggregation, apoptosis, and chemotaxis. Recent studies have shown a role for Galectin-9 in immune modulation in support of the tumor, e.g., through negative regulation of Th1 type responses, Th2 polarization and polarization of macrophages to

the M2 phenotype. This work also includes studies that have shown that Galectin-9 participates in direct inactivation of T cells through interactions with the T-cell immunoglobulin and mucin protein 3 (TIM-3) receptor (Dardalhon et al., *J Immunol.,* 2010, 185, 1383-1392; Sanchez-Fueyo et al., *Nat Immunol.,* 2003, 4, 1093-1101).

Galectin-9 has also been found to play a role in polarizing T cell differentiation into tumor suppressive phenotypes), as well as promoting tolerogenic macrophage programming and adaptive immune suppression (Daley et al., *Nat Med.,* 2017, 23, 556-567). In mouse models of pancreatic ductal adenocarcinoma (PDAC), blockade of the checkpoint interaction between Galectin-9 and the receptor Dectin-1 found on innate immune cells in the tumor microenvironment (TME) has been shown to increase anti-tumor immune responses in the TME and to slow tumor progression (Daley et al., *Nat Med., 2017, 23, 556-567*). Galectin-9 also has been found to bind to CD206, a surface marker of M2 type macrophages, resulting in a reduced secretion of CVL22 (MDC), a macrophage derived chemokine which has been associated with longer survival and lower recurrence risk in lung cancer (Enninga et al, J Pathol. 2018 Aug;245(4):468-477).

SUMMARY

The present disclosure is based, at least in part, on the development of treatment regimen for hematological malignancies such as acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS).

Accordingly, in one aspect, described herein is a use of an antibody that binds human galectin-9 (anti-Gal9 antibody) in the manufacture of a medicament for use in combination therapy for treating a hematologic malignancy in a subject in need thereof, wherein the medicament is to be administered in combination with: (i) venetoclax, (ii) a hypomethylating agent (HMA), or (iii) a combination thereofof (i) and (ii); wherein the anti-Gal9 antibody comprises: (a) a light chain comprising a light chain variable region (VL), which comprises a light chain (LC) complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 1, a LC complementarity determining region 2 (CDR2) comprising the amino acid sequence of SEQ ID NO: 2, and a LC complementarity determining region 3 (CDR3) comprising the amino acid sequence of SEQ ID NO: 3 and (b) a heavy chain comprising a heavy chain variable region (VH), which comprises a heavy chain (HC) complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 4, a HC complementarity determining region 2 (CDR2) comprising the amino acid sequence of SEQ ID NO: 5, and a HC complementarity determining region 3 (CDR3)

comprising the amino acid sequence of SEQ ID NO: 6.

In one example, described herein is a method for treating a hematologic malignancy, comprising administering to a subject in need thereof an antibody that binds human galectin-9 (anti-Gal9 antibody), and one or more chemotherapeutics such as venetoclax, a hypomethylating agent, or a combination thereof. The anti-Gal9 antibody comprises: (a) a light chain comprising a light chain variable region (V_L), which comprises a light chain (LC) complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 1, a LC complementarity determining region 2 (CDR2) comprising the amino acid sequence of SEQ ID NO: 2, and a LC complementarity determining region 3 (CDR3) comprising the amino acid sequence of SEQ ID NO: ,3 and (b) a heavy chain comprising a heavy chain variable region (V_H), which comprises a heavy chain (HC) complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 4, a HC complementarity determining region 2 (CDR2) comprising the amino acid sequence of SEQ ID NO: 5, and a HC complementarity determining region 3 (CDR3) comprising the amino acid sequence of SEQ ID NO: 6.

In some examples, the anti-Gal9 antibody may be administered to the subject at a dose of about 2 mg/kg to about 16 mg/kg once every week (QW) by intravenous infusion. In one example, the anti-Gal9 antibody disclosed herein (*e.g.*, G9.2-17 (IgG4)) may be administered to the subject at a dose of about 2 mg/kg to about 4 mg/kg once every week by intravenous infusion (*e.g.*, about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, or any increment therein). In another example, the anti-Gal9 antibody disclosed herein (*e.g.*, G9.2-17 (IgG4)) may be administered to the subject at a dose of about 4 mg/kg to 7.5 mg/kg once every week by intravenous infusion (*e.g.*, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about 7.5 mg/kg, or any increment therein). In still another example, the anti-Gal9 antibody disclosed herein (*e.g.*, G9.2-17 (IgG4)) may be administered to the subject at a dose of about 7.5 mg/kg to 12 mg/kg once every week by intravenous infusion (*e.g.*, about 7.5 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg, about 11 mg/kg, about 12 mg/kg, or any increment therein). In yet another example, the anti-Gal9 antibody disclosed herein (*e.g.*, G9.2-17 (IgG4)) may be administered to the subject at a dose of about 12 mg/kg to about 16 mg/kg once every week by intravenous infusion (*e.g.*, about 12 mg/kg, about 13 mg/kg, about 14 mg/kg, about 15 mg/kg, about 16 mg/kg, or any increment therein). In some specific examples, the anti-Gal9 antibody may be administered to the subject at a dose of about 2 mg/kg, about 4 mg/kg, about 7.5 mg/kg, about 12 mg/kg, or about 16 mg/kg once every week by intravenous infusion.

Alternatively, the anti-Gal9 antibody may be administered to the subject at a dose of about 2 mg/kg to about 16 mg/kg once every 2 weeks (Q2W) by intravenous infusion. In one example, the anti-Gal9 antibody disclosed herein (*e.g.*, G9.2-17 (IgG4)) may be administered to the subject at a dose of about 2 mg/kg to about 4 mg/kg once every 2 weeks by intravenous infusion (*e.g.*, about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, or any increment therein). In another example, the anti-Gal9 antibody disclosed herein (*e.g.*, G9.2-17 (IgG4)) may be administered to the subject at a dose of about 4 mg/kg to 7.5 mg/kg once every 2 weeks by intravenous infusion (*e.g.*, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about 7.5 mg/kg, or any increment therein). In still another example, the anti-Gal9 antibody disclosed herein (*e.g.*, G9.2-17 (IgG4)) may be administered to the subject at a dose of about 7.5 mg/kg to 12 mg/kg once every 2 weeks by intravenous infusion (*e.g.*, about 7.5 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg, about 11 mg/kg, about 12 mg/kg, or any increment therein). In yet another example, the anti-Gal9 antibody disclosed herein (*e.g.*, G9.2-17 (IgG4)) may be administered to the subject at a dose of about 12 mg/kg to about 16 mg/kg once every 2 weeks by intravenous infusion (*e.g.*, about 12 mg/kg, about 13 mg/kg, about 14 mg/kg, about 15 mg/kg, about 16 mg/kg, or any increment therein). In some specific examples, the anti-Gal9

antibody may be administered to the subject at a dose of about 2 mg/kg, about 4 mg/kg, about 7.5 mg/kg, about 12 mg/kg, or about 16 mg/kg once every 2 weeks by intravenous infusion.

In some examples, the subject for treatment by any of the methods disclosed herein is a human patient having a leukemia or lymphoma. In some instances, the hematologic malignancy is refractory and/or relapsed.

In some instances, the human patient has acute myeloid leukemia (AML). In some specific examples, the human patient has relapsed and/or refractory AML post at least one line of prior therapy. In some instances, the human patient has a myelodysplastic syndrome. In some specific examples, the human patient has relapsed and/or refractory MDS post at least one line of prior therapy. Alternatively or in addition, the human patient does not have acute promyelocytic leukemia (APL).

In some instances, the human patient (AML patients or MDS patients) for treatment by any of the methods disclosed herein may carry one or more biomarkers, for example, a mutation in at least one of the following genes: ABL1, ASXL1, BCOR, BCORL1, BRAF, CBFBMYH1, CBL, CBLB, CEBPA, CSF3R, CUX1, DDX41, DNMT3A, EZH2, GATA2, IDH2, JAK2, KRAS, MPL, MUTYH, NF1, NPM1, NRAS, NSD1, p53, PHF6, PMLRARA, PD_1, RAD21, RUNX1, RUNX1T1; SETBP1, SF3B1, SRFS2, SRSF2, STAG2, TBL1XR1/MECOM fusion, TET2, U2AF1, WT1, and ZRSR2. Patients with such genetic mutations are known to be difficult to treat. The anti-Gal9 antibody, either alone or in combination with the chemotherapeutics described herein showed promising treatment efficacy in such patients.

In some examples, the human patient who has AML is administered the anti-Gal9 antibody, a B-cell lymphoma-2 (BCL-2) inhibitor such as venetoclax (*e.g.*, VENCLEXTA®), and a hypomethylating agent (HMA), which is azacytidine (*e.g.*, Vidaza®) or decitabine (*e.g.*, DACOGEN®).

The amount of venetoclax to be given to a human patient depends on many factors, including height and weight, general health or other health problems, and the type of cancer to be treated, which would be within the knowledge of a medical practitioner following guidance described by the Food and Drug Administration (*e.g.*, see the drug labels of approved venetoclax products). In some examples, a human patient may be administered with venetoclax orally at a dose of 100 mg on Day 1, at 200 mg on Day 2, and at 400 mg on each day of Days 3-28 for a treatment cycle of 28 days. If one or more adverse effects occur, the dose of venetoclax may be reduced or the treatment may be withheld. More details for managing adverse effects associated with venetoclax treatment are described in **Example 1** below.

The amount of azacytidine to be given to a human patient depends on many factors, including height and weight, general health or other health problems, and the type of cancer to be treated, which would be within the knowledge of a medical practitioner following guidance described by the Food and Drug Administration (*e.g.*, see the drug labels of approved azacytidine products). In some examples, a human patient may be administered with azacytidine subcutaneously or intravenously at a dose of 75 mg/m^2 on each of Days 1-7 for a treatment cycle of 28 days. In some specific examples, a human patient may be administered with azacytidine subcutaneously at a dose of 75 mg/m^2 on each of Days 1-7 for a treatment cycle of 28 days. If one or more adverse effects occur, the dose of azacytidine may be reduced or the treatment may be withheld. More details for managing adverse effects associated with azacytidine treatment are described in **Example 1** below.

The amount of decitabine to be given to a human patient depends on many factors, including height and weight, general health or other health problems, and the type of cancer to be treated, which would be within the knowledge of a medical practitioner following guidance described by the Food and Drug Administration (*e.g.*, see the drug labels of approved decitabine products). In some examples, a human patient may be administered with decitabine intravenously at a dose of 75 mg/m^2 on each day of Days 1-5 for a treatment cycle of 28 days. If one or more adverse effects occur, the dose of decitabine may be reduced or the treatment may be withheld. More details for managing adverse effects associated with decitabine treatment are described in **Example 1** below.

Use of azacytidine and decitabine is generally interchangeable. For patients who are resistant to or do not respond to azacytidine, decitabine can be used as an alternative. Likewise, for patients who are resistant to or do not respond to decitabine, azacytidine can be used as an alternative.

In some specific examples, the treatment regimen comprises one or more of a cycle of 28 days, wherein in each cycle: the anti-Gal9 antibody is administered to the human patient on Day 1, Day 8, Day 15, and Day 22 at a dose of about 4 mg/kg, about 7.5 mg/kg, about 12 mg/kg, or about 16 mg/kg once every week by intravenous infusion; the venetoclax is administered to the human patient orally at 100 mg on Day 1, at 200 mg on Day 2, and at 400 mg on each day of Days 3-28; and the azacytidine at 75 mg/m^2 subcutaneously or intravenously on each of Days 1-7.

In other specific examples, the treatment regimen comprises one or more of a cycle of 28 days, wherein in each cycle: the anti-Gal9 antibody is administered to the human patient on Day 1, Day 8, Day 15, and Day 22 at a dose of about 4 mg/kg, about 7.5 mg/kg, about 12

mg/kg, or about 16 mg/kg once every week by intravenous infusion; the venetoclax is administered to the human patient orally at 100 mg on Day 1, at 200 mg on Day 2, and at 400 mg on each of Days 3-28; and the decitabine at 20 mg/m2 intravenously on each day of Days 1-5. For this regimen, the administration of the decitabine is repeated every 28 days.

In any of the methods of treating AML described herein, venetoclax is administered at a reduced dose or is terminated when severe venetoclax-associated toxicity is occurred.

In some instances, the human patient has myelodysplastic syndrome (MDS) and high risk or very high risk MDS. In some specifically examples, the human patient has relapsed and/or refractory MDS post at least one line of prior therapy. Alternatively or in addition, the human patient does not have acute promyelocytic leukemia (APL).

In some examples, the human patient who has MDS is administered the anti-Gal9 antibody and a hypomethylating agent (HMA), which is azacytidine or decitabine (*e.g.*, DACOGEN®).

In some specific examples, the treatment regimen comprises one or more of a cycle of 28 days, wherein in each cycle: the anti-Gal9 antibody is administered to the human patient on Day 1, Day 8, Day 15, and Day 22 at a dose of about 4 mg/kg, about 7.5 mg/kg, about 12 mg/kg, or about 16 mg/kg once every week by intravenous infusion; and the azacytidine at 75 mg/m^2 subcutaneously or intravenously on each of Days 1-7.

In other specific examples, the treatment regimen comprises one or more of a cycle of 28 days, wherein in each cycle: the anti-Gal9 antibody is administered to the human patient on Day 1, Day 8, Day 15, and Day 22 at a dose of about 4 mg/kg, about 7.5 mg/kg, about 12 mg/kg, or about 16 mg/kg once every week by intravenous infusion; and the decitabine at 20 mg/m2 intravenously on each day of Days 1-5. For this regimen, the administration of the decitabine is repeated every 28 days.

In any of the methods of treating MDS described herein, azacytidine or decitabine is administered at a reduced dose or terminated when drug-related toxicity is occurred.

For any of the treatment methods described herein, the subject is free of a treatment comprising an immunosuppressant CYP3A4 substrate, which optionally is tacrolimus, cyclosporine, everolimus, or sirolimus.

In some examples, the anti-Gal9 antibody used in any of the treatment methods described herein may comprise the V_L, which comprises the amino acid sequence of SEQ ID NO:8, and the V_H, which comprises the amino acid sequence of SEQ ID NO: 7.

Any of the anti-Gal9 antibodies for use in the method disclosed herein may be an IgG1 molecule. Alternatively, the antibody may be an IgG4 molecule. In some examples, the

anti-Gal9 antibody can be an IgG4 molecule (e.g., a human IgG4 molecule) comprising a modified Fc region relative to the wild-type IgG4 counterpart (e.g., the wild-type human IgG4 counterpart). In some examples, the modified Fc region comprises the amino acid sequence of SEQ ID NO: 14. In one example, the anti-Gal9 antibody comprises a heavy chain, which comprises the amino acid sequence of SEQ ID NO: 19, and a light chain, which comprises the amino acid sequence of SEQ ID NO: 15. Such an anti-Gal9 antibody may be G9.2-17 (IgG4).

Any of the methods disclosed herein may effectively reduce or eliminate Gal9+ hematological cancer cells, for example, leukemia or lymphoma cells. Alternatively or in addition, the method disclosed herein may effectively modulate immune responses targeting the cancer cells.

Any of the methods disclosed herein may further comprise monitoring occurrence of an adverse event in the course of the treatment. In some instances, the dose of the anti-Gal9 antibody may be reduced when the adverse event occurs.

Also within the scope of the present disclosure are anti-Gal9 antibody such as G9.2-17 (IgG4) and one or more chemotherapeutics such as venetoclax and/or a hypomethylating agent (*e.g.*, those disclosed herein) for use in a method for treating hematological malignancies such as acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS), as well as use of the combination of the anti-Gal9 antibody and the chemotherapeutics for manufacturing one or more medicaments for treating the hematological malignancies.

The details of one or more examples of the invention are set forth in the description below. Other features or advantages of the present invention are to be apparent from the following drawing and detailed description of several examples, and also from the appended claims.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present disclosure, which can be better understood by reference to the drawing in combination with the detailed description of specific embodiments presented herein.

FIG. 1 is a diagram depicting a study schematic of using anti-Gal9 antibody G9.2-17(IgG4) (single agent), combination of G9.2-17(IgG4), venetoclax and azacytidine, and combination of G9.2-17(IgG4) and decitabine for treating hematologic malignancy such as relapsed/refractory AML and high risk MDS. RP2D = recommended phase 2 dose. PK = pharmacokinetics. PD = pharmacodynamics.

WHAT IS CLAIMED IS:

1. Use of an antibody that binds human galectin-9 (anti-Gal9 antibody) in the manufacture of a medicament for use in combination therapy for treating a hematologic malignancy in a subject in need thereof, wherein the medicament is to be administered in combination with: (i) venetoclax, (ii) a hypomethylating agent (HMA), or (iii) a combination of (i) and (ii);

wherein the anti-Gal9 antibody comprises:

(a) a light chain comprising a light chain variable region (V_L), which comprises a light chain (LC) complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 1, a LC complementarity determining region 2 (CDR2) comprising the amino acid sequence of SEQ ID NO: 2, and a LC complementarity determining region 3 (CDR3) comprising the amino acid sequence of SEQ ID NO: 3 and

(b) a heavy chain comprising a heavy chain variable region (V_H), which comprises a heavy chain (HC) complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO: 4, a HC complementarity determining region 2 (CDR2) comprising the amino acid sequence of SEQ ID NO: 5, and a HC complementarity determining region 3 (CDR3) comprising the amino acid sequence of SEQ ID NO: 6.

2. The use of claim 1, wherein the medicament is to be administered to the subject at a dose of:

about 2 mg/kg to about 16 mg/kg of the anti-Gal9 antibody once every week by intravenous infusion;

optionally about 4 mg/kg to about 16 mg/kg of the anti-Gal9 antibody once every week by intravenous infusion or about 7.5 mg/kg to about 16 mg/kg of the anti-Gal9 antibody once every week by intravenous infusion;

optionally about 4 mg/kg, about 7.5 mg/kg, about 12 mg/kg, or about 16 mg/kg of the anti-Gal9 antibody once every week by intravenous infusion.

3. The use of claim 1 or 2, wherein the subject is a human patient having a leukemia or lymphoma; optionally wherein the hematologic malignancy is refractory and/or relapsed.

4. The use of any one of claims 1 to 3, wherein the subject is a human patient

having acute myeloid leukemia (AML), optionally wherein the human patient has relapsed and/or refractory AML post at least one line of prior therapy; and wherein the medicament is to be administered in combination with venetoclax, and the HMA, which is azacytidine or decitabine.

5. The use of claim 4, which comprises one or more of a cycle of 28 days, wherein in each cycle:

the medicament is to be administered to the human patient on Day 1, Day 8, Day 15, and Day 22 at a dose of about 4 mg/kg, about 7.5 mg/kg, about 12 mg/kg, or about 16 mg/kg of the anti-Gal9 antibody once every week by intravenous infusion;

the venetoclax is to be administered to the human patient orally at 100 mg on Day 1, at 200 mg on Day 2, and at 400 mg on each day of Days 3-28; and

the azacytidine is to be administered to the human patient at 75 mg/m^2 subcutaneously or intravenously, optionally subcutaneously, on each of Days 1-7;

or

wherein in each cycle:

the medicament is to be administered to the human patient on Day 1, Day 8, Day 15, and Day 22 at a dose of about 4 mg/kg, about 7.5 mg/kg, about 12 mg/kg, or about 16 mg/kg of the anti-Gal9 antibody once every week by intravenous infusion;

the venetoclax is to be administered to the human patient orally at 100 mg on Day 1, at 200 mg on Day 2, and at 400 mg on each of Days 3-28; and

the decitabine is to be administered to the human patient at 20 mg/m2 intravenously on each day of Days 1-5.

6. The use of claim 5, wherein administration of the decitabine is to be repeated every 28 days; and/or wherein the venetoclax is to be administered at a reduced dose or is to be terminated when a severe venetoclax-associated toxicity has occurred.

7. The use of any one of claims 1 to 3, wherein the subject is a human patient having myelodysplastic syndrome (MDS), optionally relapsed or refractory, and high risk or very high risk MDS;

optionally wherein the human patient has relapsed and/or refractory MDS post at least one line of prior therapy; and

wherein the medicament is to be administered in combination with the HMA, which is azacytidine or decitabine.

8. The use of claim 7, which comprises one or more of a cycle of 28 days, wherein in each cycle:

the medicament is to be administered to the human patient on Day 1, Day 8, Day 15, and Day 22 at a dose of about 4 mg/kg, about 7.5 mg/kg, about 12 mg/kg, or about 16 mg/kg of the anti-Gal9 antibody once every week by intravenous infusion; and

the azacytidine is to be administered to the human patient at 75 mg/m^2 subcutaneously or intravenously, optionally subcutaneously, on each of Days 1-7;

or

wherein in each cycle:

the medicament is to be administered to the human patient on Day 1, Day 8, Day 15, and Day 22 at a dose of about 4 mg/kg, about 7.5 mg/kg, about 12 mg/kg, or about 16 mg/kg anti-Gal9 antibody once every week by intravenous infusion; and

the decitabine is to be administered to the human patient at 20 mg/m2 intravenously on each day of Days 1-5.

9. The use of claim 8, wherein administration of the decitabine is to be repeated every 28 days; and/or wherein the azacytidine or decitabine is to be administered at a reduced dose or is to be terminated when a drug-related toxicity has occurred.

10. The use of any one of claims 1 to 9, wherein the subject is free of a treatment comprising an immunosuppressant CYP3A4 substrate, which optionally is tacrolimus, cyclosporine, everolimus, or sirolimus; and/or wherein the subject is a human patient having AML or MDS and carries a mutation in at least one of ABL1, ASXL1, BCOR, BCORL1, BRAF, CBFBMYH1, CBL, CBLB, CEBPA, CSF3R, CUX1, DDX41, DNMT3A, EZH2, GATA2, IDH2, JAK2, KMT1A, KRAS, MPL, MUTYH, NF1, NPM1, NRAS, NSD1, p53, PHF6, PMLRARA, PD_1, RAD21, RUNX1, RUNX1T1; SETBP1, SF3B1, SRFS2, SRSF2, STAG2, TBL1XR1/MECOM fusion, TET2, U2AF1, WT1, and ZRSR2.

11. The use of any one of claims 1 to 10, wherein the anti-Gal9 antibody comprises

the V_L, which comprises the amino acid sequence of SEQ ID NO:8, and the V_H, which comprises the amino acid sequence of SEQ ID NO: 7.

12. The use of any one of claims 1 to 11, wherein the anti-Gal9 antibody is an IgG1 molecule or an IgG4 molecule.

13. The use of claim 12, wherein the anti-Gal9 antibody is an IgG4 molecule comprising a modified Fc region relative to the wild-type human IgG4 counterpart, optionally wherein the modified Fc region comprises the amino acid sequence of SEQ ID NO: 14.

14. The use of claim 13, wherein the anti-Gal9 antibody comprises a heavy chain, which comprises the amino acid sequence of SEQ ID NO: 19, and a light chain, which comprises the amino acid sequence of SEQ ID NO: 15.

15. The use of any one of claims 1 to 14, wherein the medicament is to be administered at a reduced dose of the anti-Gal9 antibody when the subject shows an adverse event.