

being developed as therapeutic agents. Accordingly, there exists a need for compositions and methods for use in identifying biomarkers of IFN γ production in IFN γ -related disorders.

Summary

[0004] The compositions and methods provided herein use a fully human IgG1 anti-interferon gamma (IFN γ) monoclonal antibody (mAb) referred to herein as NI-0501, which binds and neutralizes IFN γ . NI-0501 binds to soluble and receptor (IFN γ R1)-bound forms of IFN γ . The compositions and methods provided herein are useful in the treatment of hemophagocytic lymphohistiocytosis (HLH).

[0005] The anti-IFN γ antibody referred to herein as NI-051 comprises a variable heavy chain complementarity determining region 1 (VH CDR1) comprising the amino acid sequence of SYAMS (SEQ ID NO: 1); a variable heavy chain complementarity determining region 2 (VH CDR2) comprising the amino acid sequence of AISGSGGSTYYADSVKG (SEQ ID NO: 2); and a variable heavy chain complementarity determining region 3 (VH CDR3) comprising the amino acid sequence of DGSSGWYVPHWFDP (SEQ ID NO: 3); a variable light chain complementarity determining region 1 (VL CDR1) comprising the amino acid sequence of TRSSGSIASNYVQ (SEQ ID NO: 4); a variable light chain complementarity determining region 2 (VL CDR2) region comprising the amino acid sequence of EDNQRPS (SEQ ID NO: 5); and a variable light chain complementarity determining region 3 (VL CDR3) region comprising the amino acid sequence of QSYDGSNRWM (SEQ ID NO: 6). The NI-0501 comprises the heavy chain variable amino acid sequence to the amino acid sequence of SEQ ID NO: 47, and the light chain variable amino acid sequence to the amino acid sequence of SEQ ID NO: 48.

[0005a] In one aspect, the present disclosure refers to use of a therapeutically effective amount of an antibody or antigen-binding fragment thereof that binds interferon gamma (IFN γ) and comprises a variable heavy chain complementarity determining region 1 (VH CDR1) comprising the amino acid sequence of SYAMS (SEQ ID NO: 1); a variable heavy chain complementarity determining region 2 (VH CDR2) comprising the amino acid sequence of AISGSGGSTYYADSVKG (SEQ ID NO: 2); and a variable heavy chain complementarity determining region 3 (VH CDR3) comprising the amino acid sequence of DGSSGWYVPHWFDP (SEQ ID NO: 3); a variable light chain complementarity determining region 1 (VL CDR1) comprising the amino acid sequence of TRSSGSIASNYVQ (SEQ ID NO: 4); a variable light chain complementarity determining

region 2 (VL CDR2) region comprising the amino acid sequence of EDNQRPS (SEQ ID NO: 5); and a variable light chain complementarity determining region 3 (VL CDR3) region comprising the amino acid sequence of QSYDGSNRWM (SEQ ID NO: 6) in the manufacture of a medicament for treating hemophagocytic lymphohistiocytosis (HLH) in a human subject in need thereof and wherein the antibody is to be administered to a subject in need thereof by IV infusion within a period of one hour at an initial dose of 1 mg/kg body weight.

[0006] In the compositions and methods provided herein, NI-0501 is formulated as a sterile concentrate for infusion (per mL). In some examples, NI-0501 is formulated as follows: 5 mg of NI-051, 1.55 mg L-histidine, 3.14 mg L-histidine monohydrochloride, monohydrate, 7.31 mg sodium chloride (NaCl), and 0.05 mg Polysorbate 80, where the pH is between 5.8 and 6.2. In some examples, NI-0501 is formulated as follows: 5 mg of NI-051, 1.55 mg L-histidine, 3.14 mg L-histidine monohydrochloride, monohydrate, 7.31 mg sodium chloride (NaCl), and 0.05 mg Polysorbate 80, where the pH is 6.0.

[0007] In the compositions and methods provided herein, NI-0501 is administered to a subject in need thereof for treating, preventing and/or delaying the onset or progression of, or alleviating a symptom associated with HLH. In some examples, NI-0501 is

[0018] In some examples, after 4 weeks, NI-0501 treatment is continued for up to an additional 4 weeks (i.e., up to SD56) as maintenance as needed until MAS remission is achieved. In some examples, after 4 weeks, NI-0501 treatment is continued for up to an additional 4 weeks (i.e., up to SD56) as maintenance as needed until MAS remission is achieved, with the possibility of decreasing the dose to 1 mg/kg and elongating the interval between infusion to weekly administration.

[0019] In the compositions and methods provided herein, NI-0501 is administered to a subject in need thereof for treating, preventing and/or delaying the onset or progression of, or alleviating a symptom associated with HLH, where the subject has been administered a background of dexamethasone. In some examples, the subject is a treatment-naïve patient (i.e., has not previously been treated for HLH), and the dexamethasone is administered at a dose of at least 10 mg/m². In some examples, the subject is receiving NI-0501 as a second line HLH treatment, and the dexamethasone is administered at a dose of in the range of 10 mg/m² to 5 mg/m². In some examples, the subject is receiving NI-0501 as a second line HLH treatment, and the dexamethasone is administered at a dose of at least 5 mg/m². In some examples, the subject is receiving NI-0501 as a second line HLH treatment, and the dexamethasone is administered at a dose of less than 5 mg/m².

[0019a] In another example, the present disclosure provides use of an anti-interferon gamma (IFN γ) antagonist in the manufacture of a medicament for alleviating a symptom of HLH characterized by elevated CXCL9 levels, wherein a level of CXCL9, alone or in conjunction with one or more other biomarkers in a biological sample from a subject is to be detected, the detected level of CXCL9 is to be compared to a control level of expression, and when the detected level is elevated, the anti-interferon gamma (IFN γ) antagonist is to be administered in an amount sufficient to alleviate the symptom of the disorder to the subject.

[0020] In some examples, NI-0501 is administered before and/or during and/or after treatment in combination with one or more additional agents such as, by way of non-limiting example, a therapeutic agent, an anti-inflammatory agent, and/or an immunosuppressive agent. In some examples, the second agent is an agent known to be used in the treatment of HLH. In some examples, the additional agent includes at least etoposide. In some examples, NI-0501 and the additional agent are formulated into a single therapeutic composition, and NI-0501 and additional agent are administered simultaneously. Alternatively, NI-0501 and additional agent are separate

What is claimed is:

1. Use of a therapeutically effective amount of an antibody or antigen-binding fragment thereof that binds interferon gamma (IFN γ) and comprises a variable heavy chain complementarity determining region 1 (VH CDR1) comprising the amino acid sequence of SYAMS (SEQ ID NO: 1); a variable heavy chain complementarity determining region 2 (VH CDR2) comprising the amino acid sequence of AISGSGGSTYYADSVKG (SEQ ID NO: 2); and a variable heavy chain complementarity determining region 3 (VH CDR3) comprising the amino acid sequence of DGSSGWYVPHWFDP (SEQ ID NO: 3); a variable light chain complementarity determining region 1 (VL CDR1) comprising the amino acid sequence of TRSSGSIASNYVQ (SEQ ID NO: 4); a variable light chain complementarity determining region 2 (VL CDR2) region comprising the amino acid sequence of EDNQRPS (SEQ ID NO: 5); and a variable light chain complementarity determining region 3 (VL CDR3) region comprising the amino acid sequence of QSYDGSNRWM (SEQ ID NO: 6) in the manufacture of a medicament for treating hemophagocytic lymphohistiocytosis (HLH) in a human subject in need thereof and wherein the antibody is to be administered to a subject in need thereof by IV infusion within a period of one hour at an initial dose of 1 mg/kg body weight.
2. The use of claim 1, wherein the antibody comprises the heavy chain variable amino acid sequence to the amino acid sequence of SEQ ID NO: 47, and the light chain variable amino acid sequence to the amino acid sequence of SEQ ID NO: 48.
3. The use of claim 1 or 2, wherein the antibody is formulated in a pharmaceutical composition at a concentration of 5 mg/mL.
4. The use of claim 3, wherein the pharmaceutical composition comprises L-histidine, L-histidine monohydrochloride, monohydrate, sodium chloride (NaCl), and Polysorbate 80, wherein the pH of the pharmaceutical composition is between 5.8 and 6.2.
5. The use of claim 4, wherein the pH is 6.0.

6. The use of claim 1, wherein at least one additional IV infusion is to be administered to the subject after the initial IV infusion, wherein the additional infusion is to be administered within a period of one hour.
7. The use of claim 6, wherein the at least one additional IV infusion is at a dose that is higher than the initial dose of 1 mg/kg body weight.
8. The use of claim 7, wherein the at least one additional IV infusion is at a dose of 3 mg/kg body weight.
9. The use of any one of claims 6 to 8, wherein the at least one additional IV infusion is to be administered at least three days after the initial IV infusion.
10. The use of claim 1, wherein a series of twice weekly IV infusions of the antibody is to be administered to the subject.
11. The use of claim 10, wherein the series of twice weekly IV infusions is to be administered at a dose higher than the initial dose.
12. The use of claim 11, wherein the series of twice weekly IV infusions is to be administered at a dose of at least 3 mg/kg body weight.
13. The use of claim 1, wherein the subject has been administered dexamethasone at least one day prior to the administration of the antibody.
14. The use of claim 13, wherein the dexamethasone is to be administered at a dose of no more than 10 mg/m².
15. The use of claim 13, wherein the dexamethasone is to be administered at a dose of at least 5 mg/m².
16. The use of claim 1, wherein the use further comprises at least a second agent that is to be administered to the subject.

17. The use of claim 16, wherein the second agent is a therapeutic agent, an anti-inflammatory agent, and/or an immunosuppressive agent.
18. The use of claim 1, wherein the HLH is primary HLH.
19. The use of claim 1, wherein the human subject is a pediatric subject.