

SUMMARY

[0016] Provided herein is a method of treating a CD70-expressing cancer in a subject, the method comprising administering to the subject a therapeutically effective amount of a nonfucosylated anti-CD70 antibody, wherein the method results in a depletion of cancer cells in the subject, wherein the method does not result in a depletion of CD70+ T regulatory cells (CD70+ Tregs) in the subject, wherein the anti-CD70 antibody comprises a heavy chain variable region comprising the three CDRs of SEQ ID NO:1, a light chain variable region comprising the three CDRs of SEQ ID NO:2, wherein the CDRs of the anti-CD70 antibody are defined by the Kabat numbering scheme, and an Fc domain, and wherein the cancer is selected from the group consisting of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). In one aspect, the present disclosure refers to use of a therapeutically effective amount of a nonfucosylated anti-CD70 antibody for the manufacture of a medicament for the treatment of a CD70-expressing cancer in a subject, wherein the use results in a depletion of cancer cells in the subject, wherein the use does not result in a depletion of CD70+ T regulatory cells (CD70+ Tregs) in the subject, wherein the anti-CD70 antibody comprises a heavy chain variable region comprising three CDRs of SEQ ID NO:1, a light chain variable region comprising three CDRs of SEQ ID NO:2, wherein the CDRs of the anti-CD70 antibody are defined by the Kabat numbering scheme, and an Fc domain, and wherein the cancer is selected from the group consisting of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). In some embodimentexamples, the anti-CD70 antibody comprises a heavy chain variable region comprising an amino acid sequence at least 85% identical to the amino acid sequence of SEQ ID NO:1 and a light chain variable region comprising an amino acid sequence at least 85% identical to the amino acid sequence of SEQ ID NO:2. In some embodimentexamples, the anti-CD70 antibody a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:1 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:2. In some embodimentexamples, the Fc domain is an antibody effector domain mediating one or more of antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement-dependent cellular cytotoxicity (CDC). In some embodimentexamples, the Fc domain is an antibody effector domain mediating ADCC. In some embodimentexamples, the Fc domain is a human Fc domain. In some embodimentexamples, the anti-CD70 antibody is vorsetuzumab. In some embodimentexamples, the antibody is conjugated to a therapeutic agent. In some embodimentexamples, the therapeutic agent is a chemotherapeutic agent or an immunomodulatory agent. In some embodimentexamples, the therapeutic agent is a chemotherapeutic agent. In some embodimentexamples, the chemotherapeutic agent is monomethyl auristatin E (MMAE) or monomethyl auristatin F (MMAF). In some embodimentexamples, the method comprises administering a population of anti-CD70 antibodies, wherein each antibody in the population of anti-CD70 antibodies comprises a heavy chain variable region comprising the three CDRs of SEQ ID NO:1, a light chain variable region comprising the three CDRs of SEQ ID NO:2, wherein the CDRs of the anti-CD70 antibody are defined by the Kabat numbering scheme, and an Fc domain, wherein at least 50% of the anti-CD70 antibodies in the population of the anti-CD70 antibodies lack core fucosylation. In some embodimentexamples, at least

70% of the anti-CD70 antibodies in the population of the anti-CD70 antibodies lack core fucosylation. In some [embodimentexamples](#), at least 90% of the anti-CD70 antibodies in the population of the anti-CD70 antibodies lack core fucosylation. In some [embodimentexamples](#), the cancer is MDS. In some [embodimentexamples](#), the MDS is relapsed or refractory MDS. In some [embodimentexamples](#), the subject experienced treatment failure after prior hypomethylating agent (HMA) therapy for the MDS. In some [embodimentexamples](#), the cancer is AML. In some [embodimentexamples](#), the AML is relapsed or refractory AML. In some [embodimentexamples](#), the subject received 2 prior treatment regimens to treat the AML. In some [embodimentexamples](#), the subject received 3 prior treatment regimens to treat the AML. In some [embodimentexamples](#), at least about 0.1%, at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80% of the cancer cells express CD70. In some [embodimentexamples](#), administering the nonfucosylated anti-CD70 antibody to the subject results in a depletion of cancer cells by at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, or about 100% compared to the amount of cancer cells before administering the nonfucosylated anti-CD70 antibody to the subject. In some [embodimentexamples](#), administering the nonfucosylated anti-CD70 antibody to the subject results in a depletion of CD70+ Tregs of no more than about 20%, about 10%, about 9%, about 8%, about 7%, about 6%, about 5%, about 4%, about 3%, about 2%, about 1%, or about 0.1% compared to the amount of CD70+ Tregs before administering the afucosylated anti-CD70 antibody to the subject. In some [embodimentexamples](#), one or more therapeutic effects in the subject is improved after administration of the nonfucosylated anti-CD70 antibody relative to a baseline. In some [embodimentexamples](#), the one or more therapeutic effects is selected from the group consisting of: objective response rate, duration of response, time to response, progression free survival and overall survival. In some [embodimentexamples](#), the objective response rate is at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80%. In some

embodimentexamples, the subject exhibits progression-free survival of at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after administration of the nonfucosylated anti-CD70 antibody. In some embodimentexamples, the subject exhibits overall survival of at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after administration of the nonfucosylated anti-CD70 antibody. In some embodimentexamples, the duration of response to the anti-CD70 antibody is at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after administration of the nonfucosylated anti-CD70 antibody. In some embodimentexamples, the route of administration for the anti-CD70 antibody is intravenous. In some embodimentexamples, the subject is a human. In some embodimentexamples, the anti-CD70 antibody is administered in combination with azacitidine. In some embodimentexamples, the anti-CD70 antibody is administered in combination with venetoclax. In some embodimentexamples, the anti-CD70 antibody is administered in combination with azacitidine and venetoclax. In some embodimentexamples, the anti-CD70 antibody is administered in combination with fluoroquinolone.

[0017] Also provided herein is a pharmaceutical composition for the treatment of a CD70-expressing cancer, the composition comprising a nonfucosylated anti-CD70 antibody, wherein the anti-CD70 antibody comprises a heavy chain variable region comprising the three CDRs of SEQ ID NO:1, a light chain variable region comprising the three CDRs of SEQ ID NO:2, wherein the CDRs of the anti-CD70 antibody are defined by the Kabat numbering scheme, and an Fc domain, and at least one pharmaceutically compatible ingredient, wherein the composition is for use in the method of any of the embodimentexamples herein. In one aspect, the present disclosure refers to a pharmaceutical composition for the treatment of a CD70-expressing cancer, the composition comprising a nonfucosylated anti-CD70 antibody, wherein the anti-CD70 antibody comprises a heavy chain variable region comprising three CDRs of SEQ ID NO:1, a light chain variable region comprising three CDRs of SEQ ID NO:2, wherein the CDRs of the anti-CD70 antibody are defined by the Kabat numbering scheme, and an Fc domain, and at least one pharmaceutically compatible ingredient, wherein the composition is for use as disclosed herein. In one aspect, the present disclosure refers to use of a pharmaceutical composition comprising a nonfucosylated anti-CD70 antibody and at least one pharmaceutically compatible ingredient for the manufacture of a medicament for the treatment of a CD70-expressing cancer, wherein the anti-CD70 antibody comprises a heavy chain variable region comprising three CDRs of SEQ ID NO:1, a light chain variable region comprising three CDRs of SEQ ID NO:2, wherein the CDRs of the anti-CD70 antibody are defined by the Kabat numbering scheme, and an Fc domain.

[0018] Also provided herein is a kit comprising a nonfucosylated anti-CD70 antibody, wherein the anti-CD70 antibody comprises a heavy chain variable region comprising the three CDRs of SEQ ID NO:1, a light chain variable region comprising the three CDRs of SEQ ID NO:2, wherein the CDRs of the anti-CD70 antibody are defined by the Kabat numbering scheme, and an Fc domain, and instructions for using the anti-CD70 antibodies in the method of any of the ~~embodiment~~examples herein. In one aspect, the present disclosure refers to a kit comprising a nonfucosylated anti-CD70 antibody, wherein the anti-CD70 antibody comprises a heavy chain variable region comprising the three CDRs of SEQ ID NO:1, a light chain variable region comprising the three CDRs of SEQ ID NO:2, wherein the CDRs of the anti-CD70 antibody are defined by the Kabat numbering scheme, and an Fc domain, and instructions for using the anti-CD70 antibodies as disclosed herein.

[0019] It is to be understood that one, some, or all of the properties of the various ~~embodiment~~examples described herein may be combined to form other ~~embodiment~~examples of the present ~~invention~~disclosure. These and other ~~aspect~~examples of the ~~invention~~disclosure will become apparent to one of skill in the art. These and other ~~embodiment~~examples of the ~~invention~~disclosure are further described by the detailed description that follows.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0021] FIG. 1 is a series of sensograms of SGN-70 (fucosylated h1F6) and SEA-CD70 (nonfucosylated h1F6) binding to various Fcγ receptors. SGN-70 is labeled as h1F6 WT and SEA-CD70 is labeled as h1F6 SEA in FIG. 1. Biolayer interferometry (BLI) was used to assess the binding kinetics and affinity of SGN-70 and SEA-CD70 to FcγR I, IIa, IIIa, IIb, and FcRN.

[0022] FIG. 2A-2B is a series of graphs assessing the binding of SGN-70 and SEA-CD70 (labeled as SEA-70 in FIG. 2A-2B) to the high affinity human FcγRIIIa receptor (158V) (FIG. 2A) or the cynomolgus FcγRIIIa receptor (FIG. 2B) using flow cytometry.

[0023] FIG. 3A-3B is a series of graphs showing the ADCC activity of SGN-70 and SEA-CD70 in two CD70+ AML cell lines, MOLM-13 (FIG. 3A) and NOMO-1 (FIG. 3B).

[0024] FIG. 4A-4D is a series of graphs assessing the impact of SGN-70 (labeled as SGN-CD70 in FIG. 4A-4D) and SEA-CD70 on CD70+ Tregs and CD8 T cells in cells from donors homozygous for high affinity FcγRIIIa receptor (V/V 158) or homozygous for low affinity FcγRIIIa receptor (F/F 158).

CLAIMS

What is claimed is:

1. ~~A method of treating a CD70-expressing cancer in a subject, the method comprising administering to the subject~~Use of a therapeutically effective amount of a nonfucosylated anti-CD70 antibody ~~for the manufacture of a medicament for the treatment of a CD70-expressing cancer in a subject~~, wherein the ~~usemethod~~ results in a depletion of cancer cells in the subject, wherein the ~~usemethod~~ does not result in a depletion of CD70+ T regulatory cells (CD70+ Tregs) in the subject,

wherein the anti-CD70 antibody comprises a heavy chain variable region comprising ~~the~~ three CDRs of SEQ ID NO:1, a light chain variable region comprising ~~the~~ three CDRs of SEQ ID NO:2, wherein the CDRs of the anti-CD70 antibody are defined by the Kabat numbering scheme, and an Fc domain, and

wherein the cancer is selected from the group consisting of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML).
2. The ~~usemethod~~ of claim 1, wherein the anti-CD70 antibody comprises a heavy chain variable region comprising an amino acid sequence at least 85% identical to the amino acid sequence of SEQ ID NO:1 and a light chain variable region comprising an amino acid sequence at least 85% identical to the amino acid sequence of SEQ ID NO:2.
3. ~~The method of claim 1, wherein the anti-CD70 antibody a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:1 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:2.~~
43. The ~~usemethod~~ of ~~any one of claims 1-3~~claim 1 or 2, wherein the Fc domain is an antibody effector domain mediating one or more of antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement-dependent cellular cytotoxicity (CDC).

~~54~~. The usemethod of ~~any one of claims 1-3~~claim 1 or 2, wherein the Fc domain is an antibody effector domain mediating ADCC.

~~65~~. The usemethod of any one of claims ~~1-51~~4, wherein the Fc domain is a human Fc domain.

~~76~~. The usemethod of any one of claims ~~1-61~~5, wherein the anti-CD70 antibody is vorsetuzumab.

~~87~~. The usemethod of any one of claims ~~1-71~~6, wherein the antibody is conjugated to a therapeutic agent.

~~98~~. The usemethod of claim ~~87~~, wherein the therapeutic agent is a chemotherapeutic agent or an immunomodulatory agent.

~~109~~. The usemethod of claim ~~87~~, wherein the therapeutic agent is a chemotherapeutic agent.

~~110~~. The usemethod of claim ~~910~~, wherein the chemotherapeutic agent is monomethyl auristatin E (MMAE) or monomethyl auristatin F (MMAF).

~~1211~~. The usemethod of claim ~~87~~, wherein the therapeutic agent is an immunomodulatory agent.

~~1312~~. The usemethod of any one of claims ~~1-121-11~~, wherein the usemethod comprises administeringadministration of a population of anti-CD70 antibodies,

wherein each antibody in the population of anti-CD70 antibodies comprises a heavy chain variable region comprising ~~the~~ three CDRs of SEQ ID NO:1, a light chain variable region comprising ~~the~~ three CDRs of SEQ ID NO:2, wherein the CDRs of the anti-CD70 antibody are defined by the Kabat numbering scheme, and an Fc domain,

wherein at least 50% of the anti-CD70 antibodies in the population of the anti-CD70 antibodies lack core fucosylation.

~~1413~~. The ~~usemethod~~ of claim ~~1213~~, wherein at least 70% of the anti-CD70 antibodies in the population of the anti-CD70 antibodies lack core fucosylation.

~~15~~. The ~~method~~ of claim ~~13~~, wherein at least 90% of the anti-CD70 antibodies in the population of the anti-CD70 antibodies lack core fucosylation.

~~1614~~. The ~~usemethod~~ of any one of claims ~~1-151-13~~, wherein the cancer is MDS.

~~1715~~. The ~~usemethod~~ of claim ~~1614~~, wherein the MDS is relapsed or refractory MDS.

~~1816~~. The ~~usemethod~~ of claim ~~1715~~, wherein the subject experienced treatment failure after prior hypomethylating agent (HMA) therapy for the MDS.

~~1917~~. The ~~usemethod~~ of any one of claims ~~1-151-13~~, wherein the cancer is AML.

~~2018~~. The ~~usemethod~~ of claim ~~1917~~, wherein the AML is relapsed or refractory AML.

~~2119~~. The ~~usemethod~~ of claim ~~2018~~, wherein the subject received 2 prior treatment regimens to treat the AML.

~~2220~~. The ~~usemethod~~ of claim ~~2018~~, wherein the subject received 3 prior treatment regimens to treat the AML.

~~2321~~. The ~~usemethod~~ of any one of claims ~~1-221-20~~, wherein at least about 0.1%, at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80% of the cancer cells express CD70.

~~2422~~. The ~~use method~~ of any one of claims ~~1-231-21~~, wherein ~~administration of administering~~ the nonfucosylated anti-CD70 antibody to the subject results in a depletion of cancer cells by at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, or about 100% compared to the amount of cancer cells before ~~administration of administering~~ the nonfucosylated anti-CD70 antibody to the subject.

~~2523~~. The ~~use method~~ of any one of claims ~~1-241-22~~, wherein ~~administration of administering~~ the nonfucosylated anti-CD70 antibody to the subject results in a depletion of CD70+ Tregs of no more than about 20%, about 10%, about 9%, about 8%, about 7%, about 6%, about 5%, about 4%, about 3%, about 2%, about 1%, or about 0.1% compared to the amount of CD70+ Tregs before ~~administration of administering~~ the afucosylated anti-CD70 antibody to the subject.

~~2624~~. The ~~use method~~ of any one of claims ~~1-251-23~~, wherein one or more therapeutic effects in the subject is improved after administration of the nonfucosylated anti-CD70 antibody relative to a baseline.

~~2725~~. The ~~use method~~ of claim ~~2426~~, wherein the one or more therapeutic effects is selected from the group consisting of: objective response rate, duration of response, time to response, progression free survival and overall survival.

~~28. The method of any one of claims 1-27, wherein the objective response rate is at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80%.~~

~~29. The method of any one of claims 1-28, wherein the subject exhibits progression free survival of at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least~~

about 12 months, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after administration of the nonfucosylated anti-CD70 antibody.

~~30. The method of any one of claims 1-29, wherein the subject exhibits overall survival of at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after administration of the nonfucosylated anti-CD70 antibody.~~

~~31. The method of any one of claims 1-30, wherein the duration of response to the anti-CD70 antibody is at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after administration of the nonfucosylated anti-CD70 antibody.~~

~~32~~26. The ~~use~~method of any one of claims ~~1-31~~1-25, wherein the route of administration for the anti-CD70 antibody is intravenous.

~~33. The method of any one of claims 1-32, wherein the subject is a human.~~

~~34~~27. The ~~use~~method of any one of claims ~~1-33~~1-26, wherein the anti-CD70 antibody is to be administered in combination with ~~azacitidine~~azacytidine; venetoclax; azacitidine and venetoclax; or fluoroquinolone.

~~35. The method of any one of claims 1-33, wherein the anti-CD70 antibody is administered in combination with venetoclax.~~

~~36. The method of any one of claims 1-33, wherein the anti-CD70 antibody is administered in combination with azacitidine and venetoclax.~~

~~37. The method of any one of claims 1-35, wherein the anti-CD70 antibody is administered in combination with fluoroquinolone.~~

~~38~~28. A pharmaceutical composition for the treatment of a CD70-expressing cancer, the composition comprising a nonfucosylated anti-CD70 antibody, wherein the anti-CD70 antibody comprises a heavy chain variable region comprising ~~the~~ three CDRs of SEQ ID NO:1, a light chain variable region comprising ~~the~~ three CDRs of SEQ ID NO:2, wherein the CDRs of the anti-CD70 antibody are defined by the Kabat numbering scheme, and an Fc domain, and at least one pharmaceutically compatible ingredient, wherein the composition is for use according to ~~in the method of~~ any one of claims ~~1-37~~1-27.

~~39~~29. A kit comprising a nonfucosylated anti-CD70 antibody, wherein the anti-CD70 antibody comprises a heavy chain variable region comprising the three CDRs of SEQ ID NO:1, a light chain variable region comprising the three CDRs of SEQ ID NO:2, wherein the CDRs of the anti-CD70 antibody are defined by the Kabat numbering scheme, and an Fc domain, and instructions for using the anti-CD70 antibodies according to ~~in the method of~~ any one of claims ~~1-37~~1-27.

30. Use of a pharmaceutical composition comprising a nonfucosylated anti-CD70 antibody and at least one pharmaceutically compatible ingredient for the manufacture of a medicament for the treatment of a CD70-expressing cancer, wherein the anti-CD70 antibody comprises a heavy chain variable region comprising three CDRs of SEQ ID NO:1, a light chain variable region comprising three CDRs of SEQ ID NO:2, wherein the CDRs of the anti-CD70 antibody are defined by the Kabat numbering scheme, and an Fc domain.