Myelodysplastic syndrome

[0010] A myelodysplastic syndrome (MDS) is a group of symptoms that includes cancer of the blood and bone marrow. Myelodysplastic syndromes (MDS) includes diseases such as, refractory anemia, refractory anemia with excess blasts, refractory cytopenia with multilineage dysplasia, refractory cytopenia with unilineage dysplasia, and chronic myelomonocytic leukemia. The immature blood stem cells (blasts) do not become healthy red blood cells, white blood cells or platelets. The blast die in the bone marrow or soon after they travel to the blood. This leaves less room for healthy white cells, red cells and/or platelets to form in the bone marrow.

[0011] The myelodysplastic syndromes (MDS) are a collection of hematological medical conditions that involve ineffective production of the myeloid class of blood cells. Patients with MDS often develop severe anemia and require frequent blood transfusions. Bleeding and risk of infections also occur due to low or dysfunctional platelets and neutrophils, respectively. In some cases the disease worsens and the patient develops cytopenias (low blood counts) caused by progressive bone marrow failure. In some cases the disease transforms into acute myelogenous leukemia (AML). If the overall percentage of bone marrow myeloblasts rises over a particular cutoff (20% for WHO and 30% for FAB), then transformation to acute myelogenous leukemia (AML) is said to have occurred.

[0012] What is needed, therefore, are new treatments for myelodysplastic proliferative disorders or neoplasm such as ET, PV, MF, CML and AML, and for myelodysplastic syndrome which target the neoplastic progenitor cells responsible for the disease's malignant phenotype, particularly in individuals who are resistant to or experience adverse events as a result of taking commonly prescribed front-line therapies for this disorder.

[0013] Throughout this specification, various patents, patent applications and other types of publications (*e.g.*, journal articles) are referenced. The disclosure of all patents, patent applications, and publications cited herein are hereby incorporated by reference in their entirety for all purposes.

SUMMARY OF THE INVENTION

[0013a] In one aspect, there is provided the use of a telomerase inhibitor for the manufacture of a medicament for alleviating at least one symptom associated with myeloproliferative neoplasms or myelodysplastic syndrome in an individual in need thereof.

[0013b] In one aspect, there is provided the use of a telomerase inhibitor for the manufacture of a medicament for reducing neoplastic progenitor cell proliferation in an individual diagnosed with or suspected of having a myeloproliferative neoplasm or myelodysplastic syndrome.

[0013c] In one aspect, there is provided the use of a telomerase inhibitor for the manufacture of a medicament for maintaining blood platelet counts of between less than about 400 x 10^3 / µL in the blood of an individual diagnosed with or suspected of having essential thrombocythemia.

[0013d] In one aspect, there is provided the use of a telomerase inhibitor for the manufacture of a medicament for reducing bone marrow fibrosis in an individual diagnosed with or suspected of having a myeloproliferative neoplasm or myelodysplastic syndrome.

[0014] The ~~invention~~ disclosure provided herein discloses, *inter alia*, methods for using telomerase inhibitor compounds to treat and alleviate symptoms associated with myeloproliferative

neoplasms such as Essential Thrombocythemia (ET), Polycythemia Vera (PV), Myelofibrosis (MF), and Acute Myelogenous Leukemia (AML) by targeting the neoplastic progenitor cells characteristic of these diseases. The ~~invention~~ disclosure provided herein also discloses, *inter alia*, methods for using telomerase inhibitor compounds to treat and alleviate symptoms associated with myelodysplastic syndromes (MDS) such as, for example, refractory anemia, refractory anemia with excess blasts, refractory cytopenia with multilineage dysplasia, refractory cytopenia with unilineage dysplasia, and chronic myelomonocytic leukemia by targeting the neoplastic progenitor cells responsible for producing the abnormally high numbers of cells characteristic of these diseases.

[0015] Accordingly, in one ~~aspect~~ embodiment, provided herein are methods for alleviating at least one symptom associated with myeloproliferative neoplasms in an individual in need thereof, the method comprising: administering a clinically effective amount of a telomerase inhibitor to the individual, wherein administration of the telomerase inhibitor alleviates at least one symptom associated with myeloproliferative neoplasms. In some embodiments, the symptom comprises headache, dizziness or lightheadedness, chest pain, weakness, fainting, vision changes, numbness or tingling of extremities, redness, throbbing or burning pain in extremities (erythromelalgia), enlarged spleen, nosebleeds, bruising, bleeding from mouth or gums, bloody stool, or stroke. In some embodiments the myeloproliferative neoplasms are, for example, Essential Thrombocythemia (ET), Polycythemia Vera (PV), Myelofibrosis (MF), and Acute Myelogenous Leukemia (AML). In some embodiments of any of the embodiments herein, the telomerase inhibitor comprises an oligonucleotide. In some embodiments, the oligonucleotide is complementary to the RNA component of telomerase. In some embodiments, the oligonucleotide is 10-20 base pairs in length. In some embodiments, the oligonucleotide comprises the sequence TAGGGTTAGACAA. In some embodiments of any of the embodiments herein, the oligonucleotide comprises at least one N3'→ P5' thiophosphoramidate internucleoside linkage. In some embodiments of any of the embodiments herein, oligonucleotide comprises N3'→ P5' thiophosphoramidate internucleoside linkages. In some embodiments of any of the embodiments herein, the oligonucleotide further comprises a lipid moiety linked to the 5' and/or 3' end of the oligonucleotide. In some embodiments of any of the embodiments herein, the lipid moiety is linked to the 5' and/or 3' end of the oligonucleotide via a linker. In some embodiments, the linker is a glycerol or aminoglycerol linker. In some embodiments of any of the embodiments herein, the lipid moiety is a palmitoyl (C16) moiety. In

some embodiments of any of the embodiments herein, the telomerase inhibitor is imetelstat. In some embodiments of any of the embodiments herein, the telomerase inhibitor is administered with a pharmaceutically acceptable excipient. In some embodiments of any of the embodiments herein, the telomerase inhibitor is formulated for oral, intravenous, subcutaneous, intramuscular, topical, intraperitoneal, intranasal, inhalation, or intraocular administration. In some embodiments of any of the embodiments herein, administration of the therapeutically effective amount of the telomerase inhibitor comprises contacting one or more neoplastic progenitor cells with the telomerase inhibitor. In some embodiments of any of the embodiments herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 9.3 mg/kg. In some embodiments of any of the embodiments herein, the effective amount of a telomerase inhibitor is 9.5 mg/kg to 11.7 mg/kg. In some embodiments herein, the effective amount of a telomerase inhibitor is 6.5 mg/kg to 11.7 mg/kg. In some embodiments herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 11.7 mg/kg. In some embodiments herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 9.4 mg/kg. In some embodiments of any of the embodiments herein, administration of the telomerase inhibitor does not inhibit cytokine-dependent megakaryocyte growth. In some embodiments of any of the embodiments herein, the individual carries a V617F gain of function mutation in the Janus kinase 2 (JAK2) gene. In some embodiments, administration of the telomerase inhibitor decreases the percentage of JAK2 V617F allelic burden in the individual. In some embodiments of any of the embodiments herein, administration of the telomerase inhibitor inhibits cytokine-independent megakaryocyte growth. In some embodiments of any of the embodiments herein, administration of the telomerase inhibitor inhibits CFU-mega. In some embodiments, inhibition of CFU-Mega is independent of reduction in JAK2 allelic burden. In some embodiments, the individual is resistant or intolerant to a prior non- telomerase inhibitor-based therapy. In some embodiments, the individual is a human.

[0016] Accordingly, in one ~~aspect~~ embodiment, provided herein are methods for alleviating at least one symptom associated with essential thrombocythemia in an individual in need thereof, the method comprising: administering a clinically effective amount of a telomerase inhibitor to the individual, wherein administration of the telomerase inhibitor alleviates at least one symptom associated with essential thrombocythemia. In some embodiments, the symptom comprises headache, dizziness or lightheadedness, chest pain, weakness, fainting, vision changes, numbness or tingling of extremities, redness, throbbing or burning pain in extremities

administration of the telomerase inhibitor inhibits cytokine-independent megakaryocyte growth. In some embodiments of any of the embodiments herein, administration of the telomerase inhibitor inhibits CFU-mega. In some embodiments, inhibition of CFU-Mega is independent of reduction in JAK2 allelic burden. In some embodiments, the individual is resistant or intolerant to a prior non-telomerase inhibitor-based therapy. In some embodiments, the prior non- telomerase inhibitor-based therapy is hydroxyurea, anagrelide, or Interferon α-2B. In some embodiments, the individual is a human.

[0017] In another ~~aspect~~ embodiment, provided herein are methods for reducing neoplastic progenitor cell proliferation in an individual diagnosed with or suspected of having myeloproliferative neoplasms or myelodysplastic syndrome, the method comprising: administering a clinically effective amount of a telomerase inhibitor to the individual, wherein administration of the telomerase inhibitor reduces neoplastic progenitor cell proliferation in the individual. In some embodiments the myeloproliferative neoplasms are, for example, Essential Thrombocythemia (ET), Polycythemia Vera (PV), Myelofibrosis (MF), and Acute Myelogenous Leukemia (AML). In some embodiments,for ET reduced neoplastic progenitor cell proliferation results in platelet counts of less than about 600 x 10^3 / μL in the blood of the individual. In some embodiments, reduced neoplastic progenitor cell proliferation results in platelet counts of less than about 400 x 10^3 / μL in the blood of the individual. In some embodiments of any of the embodiment herein, the individual does not experience a thromboembolic event. In some embodiments of any of the embodiment herein, reduced neoplastic cell proliferation resulting in platelet counts of less than about 400 x 10^3 / μL in the blood of the individual occurs within 2 months or less following initiation of telomerase inhibitor administration. In some embodiments of any of the embodiment herein, reduced neoplastic cell proliferation resulting in platelet counts of less than about 400 x 10^3 / μL in the blood of the individual occurs within 1 month or less following initiation of telomerase inhibitor administration. In some embodiments, the individual is resistant or intolerant to a prior non- telomerase inhibitor-based therapy. In some embodiments, such as for MF, reduced neoplastic progenitor cell proliferation results in platelet counts of greater than about 100 x 10^9 / L in the blood of the individual. In some embodiments, such as for MF, reduced neoplastic progenitor cell proliferation results in modified hemoglobin level of at least 90g/L, or 100g/L or 110g/L or 120g/L. In some embodiments, such as for MF, reduced neoplastic progenitor cell proliferation results in modified absolute neutrophil count of at least 1.0 x 10^9/L or at least 2.0 x 10^9/L. In some embodiments of any of the embodiments herein, the

inhibitor inhibits CFU-mega. In some embodiments, inhibition of CFU-Mega is independent of reduction in JAK2 allelic burden. In some embodiments, the individual is a human.

[0018] In another ~~aspect~~ embodiment, provided herein are methods for reducing neoplastic progenitor cell proliferation in an individual diagnosed with or suspected of having essential thrombocythemia, the method comprising: administering a clinically effective amount of a telomerase inhibitor to the individual, wherein administration of the telomerase inhibitor reduces neoplastic progenitor cell proliferation in the individual. In some embodiments, reduced neoplastic progenitor cell proliferation results in platelet counts of less than about 600 x 10^3 / μL in the blood of the individual. In some embodiments, reduced neoplastic progenitor cell proliferation results in platelet counts of less than about 400 x 10^3 / μL in the blood of the individual. In some embodiments of any of the embodiment herein, the individual does not experience a thromboembolic event. In some embodiments of any of the embodiment herein, reduced neoplastic cell proliferation resulting in platelet counts of less than about 400 x 10^3 / μL in the blood of the individual occurs within 2 months or less following initiation of telomerase inhibitor administration. In some embodiments of any of the embodiment herein, reduced neoplastic cell proliferation resulting in platelet counts of less than about 400 x 10^3 / μL in the blood of the individual occurs within 1 month or less following initiation of telomerase inhibitor administration. In some embodiments, the individual is resistant or intolerant to a prior non-telomerase inhibitor-based therapy. In some embodiments, the prior non- telomerase inhibitor-based therapy is hydroxyurea, anagrelide, or Interferon α-2B. In some embodiments of any of the embodiments herein, the telomerase inhibitor comprises an oligonucleotide. In some embodiments, the oligonucleotide is complementary to the RNA component of telomerase. In some embodiments, the oligonucleotide is 10-20 base pairs in length. In some embodiments, the oligonucleotide comprises the sequence TAGGGTTAGACAA. In some embodiments of any of the embodiments herein, the oligonucleotide comprises at least one N3'→ P5' thiophosphoramidate internucleoside linkage. In some embodiments of any of the embodiments herein, oligonucleotide comprises N3'→ P5' thiophosphoramidate internucleoside linkages. In some embodiments of any of the embodiments herein, the oligonucleotide further comprises a lipid moiety linked to the 5' and/or 3' end of the oligonucleotide. In some embodiments of any of the embodiments herein, the lipid moiety is linked to the 5' and/or 3' end of the oligonucleotide via a linker. In some embodiments, the linker is a glycerol or aminoglycerol linker. In some embodiments of any of the embodiments herein, the lipid moiety is a palmitoyl

(C16) moiety. In some embodiments of any of the embodiments herein, the telomerase inhibitor is imetelstat. In some embodiments of any of the embodiments herein, the telomerase inhibitor is administered with a pharmaceutically acceptable excipient. In some embodiments of any of the embodiments herein, the telomerase inhibitor is formulated for oral, intravenous, subcutaneous, intramuscular, topical, intraperitoneal, intranasal, inhalation, or intraocular administration. In some embodiments of any of the embodiments herein, administration of the therapeutically effective amount of the telomerase inhibitor comprises contacting one or more neoplastic progenitor cells with the telomerase inhibitor. In some embodiments of any of the embodiments herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 9.3 mg/kg. In some embodiments of any of the embodiments herein, the effective amount of a telomerase inhibitor is 9.5 mg/kg to 11.7 mg/kg. In some embodiments herein, the effective amount of a telomerase inhibitor is 6.5 mg/kg to 11.7 mg/kg. In some embodiments herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 11.7 mg/kg. In some embodiments herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 9.4 mg/kg. In some embodiments of any of the embodiments herein, administration of the telomerase inhibitor does not inhibit cytokine-dependent megakaryocyte growth. In some embodiments of any of the embodiments herein, the individual carries a V617F gain of function mutation in the Janus kinase 2 (JAK2) gene. In some embodiments, administration of the telomerase inhibitor decreases the percentage of JAK2 V617F allelic burden in the individual. In some embodiments of any of the embodiments herein, administration of the telomerase inhibitor inhibits cytokine-independent megakaryocyte growth. In some embodiments of any of the embodiments herein, administration of the telomerase inhibitor inhibits CFU-mega. In some embodiments, inhibition of CFU-Mega is independent of reduction in JAK2 allelic burden. In some embodiments, the individual is a human.

[0019] In another ~~aspect~~ embodiment, provided herein are methods for maintaining blood platelet counts of less than about 400 x 10^3 / μL in the blood of an individual diagnosed with or suspected of having essential thrombocythemia, the method comprising: administering a clinically effective amount of a telomerase inhibitor to the individual, wherein administration of the telomerase inhibitor maintains blood platelet counts of less than about 400 x 10^3 / μL in the individual. In some aspects, the telomerase inhibitor is administered no more than once every two weeks. In other aspects, the telomerase inhibitor is administered to maintain blood platelet counts of between about 150 x 10^3 / μL to about 400 x 10^3 / μL in the blood of an individual. In some

In some embodiments of any of the embodiments herein, administration of the telomerase inhibitor inhibits CFU-mega. In some embodiments, inhibition of CFU-Mega is independent of reduction in JAK2 allelic burden. In some embodiments, the individual is resistant or intolerant to a prior non- telomerase inhibitor-based therapy. In some embodiments, the prior non-telomerase inhibitor-based therapy is hydroxyurea, anagrelide, or Interferon α-2B. In some embodiments, the individual is a human.

[0020] Accordingly, in one ~~aspect~~ embodiment, provided herein are methods for alleviating at least one symptom associated with polycythemia vera (PV) in an individual in need thereof, the method comprising: administering a clinically effective amount of a telomerase inhibitor to the individual, wherein administration of the telomerase inhibitor alleviates at least one symptom associated with polycythemia vera. In some embodiments, the symptom comprises headache, dizziness or lightheadedness, chest pain, weakness, fainting, vision changes, numbness or tingling of extremities, shortness of breath, weakness or feeling tired, enlarged spleen, nosebleeds, bruising, bleeding from mouth or gums, or bloody stool. In some embodiments of any of the embodiments herein, the telomerase inhibitor comprises an oligonucleotide. In some embodiments, the oligonucleotide is complementary to the RNA component of telomerase. In some embodiments, the oligonucleotide is 10-20 base pairs in length. In some embodiments, the oligonucleotide comprises the sequence TAGGGTTAGACAA. In some embodiments of any of the embodiments herein, the oligonucleotide comprises at least one N3'→ P5' thiophosphoramidate internucleoside linkage. In some embodiments of any of the embodiments herein, oligonucleotide comprises N3'→ P5' thiophosphoramidate internucleoside linkages. In some embodiments of any of the embodiments herein, the oligonucleotide further comprises a lipid moiety linked to the 5' and/or 3' end of the oligonucleotide. In some embodiments of any of the embodiments herein, the lipid moiety is linked to the 5' and/or 3' end of the oligonucleotide via a linker. In some embodiments, the linker is a glycerol or aminoglycerol linker. In some embodiments of any of the embodiments herein, the lipid moiety is a palmitoyl (C16) moiety. In some embodiments of any of the embodiments herein, the telomerase inhibitor is imetelstat. In some embodiments of any of the embodiments herein, the telomerase inhibitor is administered with a pharmaceutically acceptable excipient. In some embodiments of any of the embodiments herein, the telomerase inhibitor is formulated for oral, intravenous, subcutaneous, intramuscular, topical, intraperitoneal, intranasal, inhalation, or intraocular administration. In some embodiments of any of the embodiments herein, administration of the

therapeutically effective amount of the telomerase inhibitor comprises contacting one or more neoplastic progenitor cells with the telomerase inhibitor. In some embodiments of any of the embodiments herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 9.3 mg/kg. In some embodiments of any of the embodiments herein, the effective amount of a telomerase inhibitor is 9.5 mg/kg to 11.7 mg/kg. In some embodiments herein, the effective amount of a telomerase inhibitor is 6.5 mg/kg to 11.7 mg/kg. In some embodiments herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 11.7 mg/kg. In some embodiments herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 9.4 mg/kg. In some embodiments of any of the embodiments herein, administration of the telomerase inhibitor inhibits erythroid growth. In some embodiments of any of the embodiments herein, administration of the telomerase inhibitor inhibits CFU-erythroid. . In some embodiments of any of the embodiments herein, the individual carries a V617F gain of function mutation in the Janus kinase 2 (JAK2) gene. In some embodiments, administration of the telomerase inhibitor decreases the percentage of JAK2 V617F allelic burden in the individual. In some embodiments, the individual is resistant or intolerant to a prior non- telomerase inhibitor-based therapy. In some embodiments, the individual is a human.

[0021] Accordingly, in one ~~aspect~~ embodiment, provided herein are methods for alleviating at least one symptom associated with myelofibrosis in an individual in need thereof, the method comprising: administering a clinically effective amount of a telomerase inhibitor to the individual, wherein administration of the telomerase inhibitor alleviates at least one symptom associated with myelofibrosis. In some embodiments, the symptom comprises enlarged spleen and splenic pain, early satiety, anemia, bone pain, fatigue, fever, night sweats, weight loss, weakness, fainting, nosebleeds, bruising, bleeding from mouth or gums, bloody stool, or stroke. In some embodiments of any of the embodiments herein, the telomerase inhibitor comprises an oligonucleotide. In some embodiments, the oligonucleotide is complementary to the RNA component of telomerase. In some embodiments, the oligonucleotide is 10-20 base pairs in length. In some embodiments, the oligonucleotide comprises the sequence TAGGGTTAGACAA. In some embodiments of any of the embodiments herein, the oligonucleotide comprises at least one N3'→ P5' thiophosphoramidate internucleoside linkage. In some embodiments of any of the embodiments herein, oligonucleotide comprises N3'→ P5' thiophosphoramidate internucleoside linkages. In some embodiments of any of the embodiments herein, the oligonucleotide further comprises a lipid moiety linked to the 5' and/or

3' end of the oligonucleotide. In some embodiments of any of the embodiments herein, the lipid moiety is linked to the 5' and/or 3' end of the oligonucleotide via a linker. In some embodiments, the linker is a glycerol or aminoglycerol linker. In some embodiments of any of the embodiments herein, the lipid moiety is a palmitoyl (C16) moiety. In some embodiments of any of the embodiments herein, the telomerase inhibitor is imetelstat. In some embodiments of any of the embodiments herein, the telomerase inhibitor is administered with a pharmaceutically acceptable excipient. In some embodiments of any of the embodiments herein, the telomerase inhibitor is formulated for oral, intravenous, subcutaneous, intramuscular, topical, intraperitoneal, intranasal, inhalation, or intraocular administration. In some embodiments of any of the embodiments herein, administration of the therapeutically effective amount of the telomerase inhibitor comprises contacting one or more neoplastic progenitor cells with the telomerase inhibitor. In some embodiments of any of the embodiments herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 9.3 mg/kg. In some embodiments of any of the embodiments herein, the effective amount of a telomerase inhibitor is 9.5 mg/kg to 11.7 mg/kg. In some embodiments herein, the effective amount of a telomerase inhibitor is 6.5 mg/kg to 11.7 mg/kg. In some embodiments herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 11.7 mg/kg. In some embodiments herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 9.4 mg/kg. In some embodiments of any of the embodiments herein, administration of the telomerase inhibitor does not inhibit cytokine-dependent megakaryocyte growth. In some embodiments of any of the embodiments herein, the individual carries a V617F gain of function mutation in the Janus kinase 2 (JAK2) gene. In some embodiments, administration of the telomerase inhibitor decreases the percentage of JAK2 V617F allelic burden in the individual. In some embodiments of any of the embodiments herein, administration of the telomerase inhibitor inhibits cytokine-independent megakaryocyte growth. In some embodiments of any of the embodiments herein, administration of the telomerase inhibitor inhibits CFU-mega. In some embodiments, inhibition of CFU-Mega is independent of reduction in JAK2 allelic burden. In some embodiments, the individual is resistant or intolerant to a prior non- telomerase inhibitor-based therapy. In some embodiments, the individual is a human.

[0022] In another ~~aspect~~ embodiment provided herein are methods for reducing bone marrow fibrosis in an individual diagnosed with or suspected of having a myeloproliferative neoplasm or myelodysplastic syndrome, the method comprising administering a clinically effective amount

of a telomerase inhibitor to the individual, wherein administration of the telomerase inhibitor reduces bone marrow fibrosis in the individual. In another ~~aspect~~ embodiment, provided herein are methods in patients with MF for maintaining platelet counts of greater than about 100 x 10^9 / L in the blood of the individual the method comprising administering a clinically effective amount of a telomerase inhibitor to the individual, wherein administration of the telomerase inhibitor increases platelet counts. In another ~~aspect~~ embodiment, provided herein are methods in patients with MF for maintaining hemoglobin level of at least 90g/L, or 100g/L or 110g/L or 120g/L the method comprising administering a clinically effective amount of a telomerase inhibitor to the individual, wherein administration of the telomerase inhibitor increases hemoglobin levels. In another ~~aspect~~ embodiment, provided herein are methods in patients with MF for maintaining absolute neutrophil count of at least 1.0 x 10^9/L or at least 2.0 x 10^9/L the method comprising administering a clinically effective amount of a telomerase inhibitor to the individual, wherein administration of the telomerase inhibitor increases neutrophil counts. In some ~~aspects~~ embodiments, the telomerase inhibitor is administered no more than once every two weeks. In other ~~aspects~~ embodiments, the telomerase inhibitor is administered to maintain blood platelet counts of between about 150 x 10^3 / μL to about 400 x 10^3 / μL in the blood of an individual. In some embodiments of any of the embodiments herein, the telomerase inhibitor comprises an oligonucleotide. In some embodiments, the oligonucleotide is complementary to the RNA component of telomerase. In some embodiments, the oligonucleotide is 10-20 base pairs in length. In some embodiments, the oligonucleotide comprises the sequence TAGGGTTAGACAA. In some embodiments of any of the embodiments herein, the oligonucleotide comprises at least one N3'→ P5' thiophosphoramidate internucleoside linkage. In some embodiments of any of the embodiments herein, oligonucleotide comprises N3'→ P5' thiophosphoramidate internucleoside linkages. In some embodiments of any of the embodiments herein, the oligonucleotide further comprises a lipid moiety linked to the 5' and/or 3' end of the oligonucleotide. In some embodiments of any of the embodiments herein, the lipid moiety is linked to the 5' and/or 3' end of the oligonucleotide via a linker. In some embodiments, the linker is a glycerol or aminoglycerol linker. In some embodiments of any of the embodiments herein, the lipid moiety is a palmitoyl (C16) moiety. In some embodiments of any of the embodiments herein, the telomerase inhibitor is imetelstat. In some embodiments of any of the embodiments herein, the telomerase inhibitor is administered with a pharmaceutically acceptable excipient. In some embodiments of any of the embodiments herein, the telomerase inhibitor is formulated for oral, intravenous, subcutaneous, intramuscular, topical, intraperitoneal, intranasal, inhalation, or intraocular

administration. In some embodiments of any of the embodiments herein, administration of the therapeutically effective amount of the telomerase inhibitor comprises contacting one or more neoplastic progenitor cells with the telomerase inhibitor. In some embodiments of any of the embodiments herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 9.3 mg/kg. In some embodiments of any of the embodiments herein, the effective amount of a telomerase inhibitor is 9.5 mg/kg to 11.7 mg/kg. In some embodiments herein, the effective amount of a telomerase inhibitor is 6.5 mg/kg to 11.7 mg/kg. In some embodiments herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 11.7 mg/kg. In some embodiments herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 9.4 mg/kg.

[0023] Accordingly, in one ~~aspect~~ embodiment, provided herein are methods for alleviating at least one symptom associated with acute myeloid leukemia in an individual in need thereof, the method comprising: administering a clinically effective amount of a telomerase inhibitor to the individual, wherein administration of the telomerase inhibitor alleviates at least one symptom associated with acute myeloid leukemia. In some embodiments, the symptoms comprise enlarged spleen and splenic pain, anemia, bone pain, fatigue, fever, night sweats, weight loss, weakness, fainting, nosebleeds, bruising, bleeding from mouth or gums, bloody stool, or stroke. In some embodiments of any of the embodiments herein, the telomerase inhibitor comprises an oligonucleotide. In some embodiments, the oligonucleotide is complementary to the RNA component of telomerase. In some embodiments, the oligonucleotide is 10-20 base pairs in length. In some embodiments, the oligonucleotide comprises the sequence TAGGGTTAGACAA. In some embodiments of any of the embodiments herein, the oligonucleotide comprises at least one N3'→ P5' thiophosphoramidate internucleoside linkage. In some embodiments of any of the embodiments herein, oligonucleotide comprises N3'→ P5' thiophosphoramidate internucleoside linkages. In some embodiments of any of the embodiments herein, the oligonucleotide further comprises a lipid moiety linked to the 5' and/or 3' end of the oligonucleotide. In some embodiments of any of the embodiments herein, the lipid moiety is linked to the 5' and/or 3' end of the oligonucleotide via a linker. In some embodiments, the linker is a glycerol or aminoglycerol linker. In some embodiments of any of the embodiments herein, the lipid moiety is a palmitoyl (C16) moiety. In some embodiments of any of the embodiments herein, the telomerase inhibitor is imetelstat. In some embodiments of any of the embodiments herein, the telomerase inhibitor is administered with a pharmaceutically acceptable excipient. In some embodiments of any of the embodiments herein, the telomerase

inhibitor is formulated for oral, intravenous, subcutaneous, intramuscular, topical, intraperitoneal, intranasal, inhalation, or intraocular administration. In some embodiments of any of the embodiments herein, administration of the therapeutically effective amount of the telomerase inhibitor comprises contacting one or more neoplastic progenitor cells with the telomerase inhibitor. In some embodiments of any of the embodiments herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 9.3 mg/kg. In some embodiments of any of the embodiments herein, the effective amount of a telomerase inhibitor is 9.5 mg/kg to 11.7 mg/kg. In some embodiments herein, the effective amount of a telomerase inhibitor is 6.5 mg/kg to 11.7 mg/kg. In some embodiments herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 11.7 mg/kg. In some embodiments herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 9.4 mg/kg. In some embodiments herein, administration of the telomerase inhibitor does not inhibit cytokine-dependent megakaryocyte growth. In some embodiments herein, the individual carries a V617F gain of function mutation in the Janus kinase 2 (JAK2) gene. In some embodiments, administration of the telomerase inhibitor decreases the percentage of JAK2 V617F allelic burden in the individual. In some embodiments of any of the embodiments herein, administration of the telomerase inhibitor inhibits cytokine-independent megakaryocyte growth. In some embodiments of any of the embodiments herein, administration of the telomerase inhibitor inhibits CFU-mega. In some embodiments, inhibition of CFU-Mega is independent of reduction in JAK2 allelic burden. In some embodiments, the individual is resistant or intolerant to a prior non- telomerase inhibitor-based therapy. In some embodiments, the individual is a human.

[0024] Accordingly, in one ~~aspect~~ embodiment, provided herein are methods for alleviating at least one symptom associated with myelodysplastic syndrome, such as, for example, refractory anemia, refractory anemia with excess blasts, refractory cytopenia with multilineage dysplasia, refractory cytopenia with unilineage dysplasia, and chronic myelomonocytic leukemia. in an individual in need thereof, the method comprising: administering a clinically effective amount of a telomerase inhibitor to the individual, wherein administration of the telomerase inhibitor alleviates at least one symptom associated with myelodysplastic syndrome. In some embodiments, the symptoms comprise shortness of breath, fatigue, weakness, fainting, nosebleeds, bruising, bleeding from mouth or gums, bloody stool, petechiae, or stroke. In some embodiments of any of the embodiments herein, the telomerase inhibitor comprises an oligonucleotide. In some embodiments, the oligonucleotide is complementary to the RNA component of telomerase. In

CLAIMS

What is claimed is:

1. A method for alleviating at least one symptom associated with myeloproliferative neoplasms or myelodysplastic syndrome in an individual in need thereof, the method comprising: administering a clinically effective amount of a telomerase inhibitor to the individual, wherein administration of the telomerase inhibitor alleviates at least one symptom associated with myeloproliferative neoplasms or myelodysplastic syndrome.
2. The method of claim 1 wherein the myeloproliferative neoplasm is selected from the group consisting of Essential Thrombocythemia (ET), Polycythemia vera (PV), ChronicMyelogenous Leukemia (CML), myelofibrosis (MF), chronic neutrophilic leukemia, chronic eosinophilic leukemia and acute myelogenous leukemia (AML).
3. The method of claim 2, wherein the symptom comprises headache, dizziness or lightheadedness, chest pain, weakness, fainting, vision changes, numbness or tingling of extremities, redness, throbbing or burning pain in extremities (erythromelalgia), enlarged spleen, nosebleeds, bruising, bleeding from mouth or gums, bloody stool, or stroke.
4. The method of claim 2 wherein the the myeloproliferative neoplasm (MPN) is Essential Thrombocythemia (ET) or Polycythemia vera (PV).
5. The method of claim 2 wherein the myeloproliferative neoplasm (MPN) is myelofibrosis (MF).
6. The method of claim 2 wherein the myeloproliferative neoplasm (MPN) is acute myelogenous leukemia (AML).
7. The method of claim 1 wherein the myelodysplastic syndrome is selected from the group consisting of refractory anemia, refractory anemia with excess blasts, refractory cytopenia with multilineage dysplasia, refractory cytopenia with unilineage dysplasia, and chronic myelomonocytic leukemia (CMML).
8. The method of claim 7 wherein the myelodysplastic syndrome (MDS) is chronic myelomonocytic leukemia (CMML).
9. A method for reducing neoplastic progenitor cell proliferation in an individual diagnosed with or suspected of having a myeloproliferative neoplasm or myelodysplastic syndrome,

the method comprising: administering a clinically effective amount of a telomerase inhibitor to the individual, wherein administration of the telomerase inhibitor reduces neoplastic progenitor cell proliferation in the individual.

10. The method of claim 9 wherein the myeloproliferative neoplasm is selected from the group consisting of Essential Thrombocythemia (ET), Polycythemia vera (PV), ChronicMyelogenous Leukemia (CML), myelofibrosis (MF), chronic neutrophilic leukemia, chronic eosinophilic leukemia and acute myelogenous leukemia (AML).

11. The method of claim 10 wherein the myeloproliferative neoplasm (MPN) is Essential Thrombocythemia (ET) or Polycythemia vera (PV).

12. The method of claim 10 wherein the myeloproliferative neoplasm (MPN) is myelofibrosis (MF).

13. The method of claim 10 wherein the myeloproliferative neoplasm (MPN) is acute myelogenous leukemia (AML).

14. The method of claim 9 wherein the myelodysplastic syndrome is selected from the group consisting of refractory anemia, refractory anemia with excess blasts, refractory cytopenia with multilineage dysplasia, refractory cytopenia with unilineage dysplasia, and chronic myelomonocytic leukemia (CMML).

15. The method of claim 11wherein reduced neoplastic progenitor cell proliferation results in platelet counts of less than about 600 x 10^3 / μL in the blood of the individual

16. The method of claim 9, wherein the individual is resistant or intolerant to a prior non-telomerase inhibitor-based therapy.

17. A method for maintaining blood platelet counts of between less than about 400 x 10^3 / μL in the blood of an individual diagnosed with or suspected of having essential thrombocythemia, the method comprising: administering a clinically effective amount of a telomerase inhibitor to the individual, wherein administration of the telomerase inhibitor maintains blood platelet counts of less than about 400 x 10^3 / μL in the individual.

18. The method of claim 17, wherein the telomerase inhibitor is administered no more than once every two weeks.

19. A method for reducing bone marrow fibrosis in an individual diagnosed with or suspected of having a myeloproliferative neoplasm or myelodysplastic syndrome, the method comprising: administering a clinically effective amount of a telomerase inhibitor to the individual, wherein administration of the telomerase inhibitor reduces bone marrow fibrosis in the individual.

20. The method of claim 9, wherein the telomerase inhibitor comprises an oligonucleotide.

21. The method of claim 13, wherein the oligonucleotide is complementary to the RNA component of telomerase.

22. The method of claim 14, wherein the oligonucleotide is 10-20 base pairs in length.

23. The method of claim 15, wherein the oligonucleotide comprises the sequence TAGGGTTAGACAA.

24. The method of claims 20, wherein the oligonucleotide comprises at least one N3'→ P5' thiophosphoramidate internucleoside linkage.

25. The method of claims 24, wherein the oligonucleotide comprises N3'→ P5' thiophosphoramidate internucleoside linkages.

26. The method of claim 20, wherein the oligonucleotide further comprises a lipid moiety linked to the 5' and/or 3' end of the oligonucleotide.

27. The method of claims 26, wherein the lipid moiety is linked to the 5' and/or 3' end of the oligonucleotide via a linker.

28. The method of claim 27, wherein the linker is a glycerol or aminoglycerol linker.

29. The method of claim 27, wherein the lipid moiety is a palmitoyl (C16) moiety.

30. The method of any one of claims 9, wherein the telomerase inhibitor is imetelstat.

31. The method of claim 9, wherein the telomerase inhibitor is administered with a pharmaceutically acceptable excipient.

32. The method of claims 9, wherein the telomerase inhibitor is formulated for oral, intravenous, subcutaneous, intramuscular, topical, intraperitoneal, intranasal, inhalation, or intraocular administration.

33. The method of claims 9, wherein administration of the therapeutically effective amount of the telomerase inhibitor comprises contacting one or more neoplastic progenitor cells with the telomerase inhibitor.

34. The method of claims 30, wherein the effective amount of a telomerase inhibitor is 7.5 mg/kg to 9.3 mg/kg.

35. The method of claim 30, wherein the effective amount of a telomerase inhibitor is 9.5 mg/kg to 11.7 mg/kg.

36. The method of claim 9, wherein administration of the telomerase inhibitor does not inhibit cytokine-dependent megakaryocyte growth.

37. The method of claim 9, wherein the individual carries a V617F gain of function mutation in the Janus kinase 2 (JAK2) gene.

38. The method of claim 37, wherein administration of the telomerase inhibitor decreases the percentage of JAK2 V617F allelic burden in the individual.

39. The method of claim 9, wherein administration of the telomerase inhibitor inhibits cytokine-independent megakaryocyte growth.

40. The method of claims 9, wherein administration of the telomerase inhibitor inhibits CFU-mega.

41. The method of claim 40, wherein inhibition of CFU-Mega is independent of reduction in JAK2 allelic burden.

Claims

What is claimed is:

1. Use of a telomerase inhibitor for the manufacture of a medicament for alleviating at least one symptom associated with myeloproliferative neoplasms or myelodysplastic syndrome in an individual in need thereof.
2. The use of a telomerase inhibitor according to claim 1 wherein the myeloproliferative neoplasm is selected from the group consisting of Essential Thrombocythemia (ET), Polycythemia vera (PV), ChronicMyelogenous Leukemia (CML), myelofibrosis (MF), chronic neutrophilic leukemia, chronic eosinophilic leukemia and acute myelogenous leukemia (AML).
3. The use of a telomerase inhibitor according to claim 2, wherein the symptom comprises headache, dizziness or lightheadedness, chest pain, weakness, fainting, vision changes, numbness or tingling of extremities, redness, throbbing or burning pain in extremities (erythromelalgia), enlarged spleen, nosebleeds, bruising, bleeding from mouth or gums, bloody stool, or stroke.
4. The use of a telomerase inhibitor according to claim 2 wherein the myeloproliferative neoplasm (MPN) is Essential Thrombocythemia (ET) or Polycythemia vera (PV).
5. The use of a telomerase inhibitor according to claim 2 wherein the myeloproliferative neoplasm (MPN) is myelofibrosis (MF).
6. The use of a telomerase inhibitor according to claim 2 wherein the myeloproliferative neoplasm (MPN) is acute myelogenous leukemia (AML).
7. The use of a telomerase inhibitor according to claim 1 wherein the myelodysplastic syndrome is selected from the group consisting of refractory anemia, refractory anemia with excess blasts, refractory cytopenia with multilineage dysplasia, refractory cytopenia with unilineage dysplasia, and chronic myelomonocytic leukemia (CMML).
8. The use of a telomerase inhibitor according to claim 7 wherein the myelodysplastic syndrome (MDS) is chronic myelomonocytic leukemia (CMML).

9. Use of a telomerase inhibitor for the manufacture of a medicament for reducing neoplastic progenitor cell proliferation in an individual diagnosed with or suspected of having a myeloproliferative neoplasm or myelodysplastic syndrome.

10. The use of a telomerase inhibitor according to claim 9 wherein the myeloproliferative neoplasm is selected from the group consisting of Essential Thrombocythemia (ET), Polycythemia vera (PV), ChronicMyelogenous Leukemia (CML), myelofibrosis (MF), chronic neutrophilic leukemia, chronic eosinophilic leukemia and acute myelogenous leukemia (AML).

11. The use of a telomerase inhibitor according to claim 10 wherein the myeloproliferative neoplasm (MPN) is Essential Thrombocythemia (ET) or Polycythemia vera (PV).

12. The use of a telomerase inhibitor according to claim 10 wherein the myeloproliferative neoplasm (MPN) is myelofibrosis (MF).

13. The use of a telomerase inhibitor according to claim 10 wherein the myeloproliferative neoplasm (MPN) is acute myelogenous leukemia (AML).

14. The use of a telomerase inhibitor according to claim 9 wherein the myelodysplastic syndrome is selected from the group consisting of refractory anemia, refractory anemia with excess blasts, refractory cytopenia with multilineage dysplasia, refractory cytopenia with unilineage dysplasia, and chronic myelomonocytic leukemia (CMML).

15. The use of a telomerase inhibitor according to claim 11, wherein reduced neoplastic progenitor cell proliferation results in platelet counts of less than about 600 x 10^3 / μL in the blood of the individual

16. The use of a telomerase inhibitor according to claim 9, wherein the individual is resistant or intolerant to a prior non- telomerase inhibitor-based therapy.

17. Use of a telomerase inhibitor for the manufacture of a medicament for maintaining blood platelet counts of between less than about 400 x 10^3 / μL in the blood of an individual diagnosed with or suspected of having essential thrombocythemia.

18. The use of a telomerase inhibitor according to claim 17, wherein the telomerase inhibitor is used no more than once every two weeks.

19. Use of a telomerase inhibitor for the manufacture of a medicament for reducing bone marrow fibrosis in an individual diagnosed with or suspected of having a myeloproliferative neoplasm or myelodysplastic syndrome.

20. The use of a telomerase inhibitor according to any one of claims 1, 9, 17 and 19, wherein the telomerase inhibitor comprises an oligonucleotide.

21. The use of a telomerase inhibitor according to claim 20, wherein the oligonucleotide is complementary to the RNA component of telomerase.

22. The use of a telomerase inhibitor according to claim 21, wherein the oligonucleotide is 10-20 base pairs in length.

23. The telomerase inhibitor of claim 22, wherein the oligonucleotide comprises the sequence TAGGGTTAGACAA.

24. The use of a telomerase inhibitor according to claim 20, wherein the oligonucleotide comprises at least one N3'→ P5' thiophosphoramidate internucleoside linkage.

25. The use of a telomerase inhibitor according to claim 24, wherein the oligonucleotide comprises N3'→ P5' thiophosphoramidate internucleoside linkages.

26. The use of a telomerase inhibitor according to claim 20, wherein the oligonucleotide further comprises a lipid moiety linked to the 5' and/or 3' end of the oligonucleotide.

27. The use of a telomerase inhibitor according to claim 26, wherein the lipid moiety is linked to the 5' and/or 3' end of the oligonucleotide via a linker.

28. The use of a telomerase inhibitor according to claim 27, wherein the linker is a glycerol or aminoglycerol linker.

29. The use of a telomerase inhibitor according to claim 27, wherein the lipid moiety is a palmitoyl (C16) moiety.

30. The use of a telomerase inhibitor according to any one of claims 1, 9, 17 and 19, wherein the telomerase inhibitor is imetelstat.

31. The use of a telomerase inhibitor according to any one of claims 1, 9, 17 and 19, wherein the telomerase inhibitor is used with a pharmaceutically acceptable excipient.

32. The use of a telomerase inhibitor according to any one of claims 1, 9, 17 and 19, wherein the telomerase inhibitor is formulated for oral, intravenous, subcutaneous, intramuscular, topical, intraperitoneal, intranasal, inhalation, or intraocular administration.

33. The use of a telomerase inhibitor according to claim 9, wherein use of the therapeutically effective amount of the telomerase inhibitor comprises contacting one or more neoplastic progenitor cells with the telomerase inhibitor.

34. The use of a telomerase inhibitor according to claim 30, wherein the effective amount of a telomerase inhibitor is 7.5 mg/kg to 9.3 mg/kg.

35. The use of a telomerase inhibitor according to claim 30, wherein the effective amount of a telomerase inhibitor is 9.5 mg/kg to 11.7 mg/kg.

36. The use of a telomerase inhibitor according to any one of claims 1, 9, 17 and 19, wherein use of the telomerase inhibitor does not inhibit cytokine-dependent megakaryocyte growth.

37. The use of a telomerase inhibitor according to any one of claims 1, 9, 17 and 19, wherein the individual carries a V617F gain of function mutation in the Janus kinase 2 (JAK2) gene.

38. The use of a telomerase inhibitor according to claim 37, wherein use of the telomerase inhibitor decreases the percentage of JAK2 V617F allelic burden in the individual.

39. The use of a telomerase inhibitor according to any one of claims 1, 9, 17 and 19, wherein use of the telomerase inhibitor inhibits cytokine-independent megakaryocyte growth.

40. The use of a telomerase inhibitor according to any one of claims 1, 9, 17 and 19, wherein use of the telomerase inhibitor inhibits CFU-mega.

41. The use of a telomerase inhibitor according to claim 40, wherein inhibition of CFU-Mega is independent of reduction in JAK2 allelic burden.

42. The use of a telomerase inhibitor according to any one of claims 1, 9, 17 and 19, wherein the telomerase inhibitor is imetelstat sodium.

43. The use of a telomerase inhibitor according to claim 42, wherein the effective amount of a telomerase inhibitor is 7.5 mg/kg to 9.3 mg/kg.

44. The use of a telomerase inhibitor according to claim 42, wherein the effective amount of a telomerase inhibitor is 9.5 mg/kg to 11.7 mg/kg.