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

[0013a] The present disclosure refers to use of a telomerase inhibitor in the manufacture of a medicament for alleviating at least one symptom resulting from myelodysplastic syndrome in an individual, wherein the telomerase inhibitor is imetelstat or a pharmaceutically acceptable salt thereof.

[0014] The 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 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 example, 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 examples, 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 examples the myeloproliferative neoplasms are, for example, Essential Thrombocythemia (ET), Polycythemia Vera (PV), Myelofibrosis (MF), and Acute Myelogenous Leukemia (AML). In some examples of any of the examples herein, the telomerase inhibitor comprises an oligonucleotide. In some examples, the oligonucleotide is complementary to the RNA component of telomerase. In some examples, the oligonucleotide is 10-20 base pairs in length. In some examples, the oligonucleotide comprises the sequence TAGGGTTAGACAA. In some examples of any of the examples herein, the oligonucleotide comprises at least one N3'→ P5' thiophosphoramidate internucleoside linkage. In some examples of any of the examples herein, oligonucleotide comprises N3'→ P5' thiophosphoramidate internucleoside linkages. In some examples of any of the examples herein, the oligonucleotide further comprises a lipid moiety linked to the 5' and/or 3' end of the oligonucleotide. In some examples of any of the examples herein, the lipid moiety is linked to the 5' and/or 3' end of the oligonucleotide via a linker. In some examples, the linker is a glycerol or aminoglycerol linker. In some examples of any of the examples herein, the lipid moiety is a palmitoyl (C16) moiety. In

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

[0016] Accordingly, in one example, 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 examples, 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 examples of any of the examples herein, the telomerase inhibitor comprises an oligonucleotide. In some examples, the oligonucleotide is complementary to the RNA component of telomerase. In some examples, the oligonucleotide is 10-20 base pairs in length. In some examples, the oligonucleotide comprises the sequence TAGGGTTAGACAA. In some examples of any of the examples herein, the oligonucleotide comprises at least one N3'→ P5' thiophosphoramidate internucleoside linkage. In some examples of any of the examples herein, oligonucleotide comprises N3'→ P5' thiophosphoramidate internucleoside linkages. In some examples of any of the examples herein, the oligonucleotide further comprises a lipid moiety linked to the 5' and/or 3' end of the oligonucleotide. In some examples of any of the examples herein, the lipid moiety is linked to the 5' and/or 3' end of the oligonucleotide via a linker. In some examples, the linker is a glycerol or aminoglycerol linker. In some examples of any of the examples herein, the lipid moiety is a palmitoyl (C16) moiety. In some examples of any of the examples herein, the telomerase inhibitor is imetelstat. In some examples of any of the examples herein, the telomerase inhibitor is administered with a pharmaceutically acceptable excipient. In some examples of any of the examples herein, the telomerase inhibitor is formulated for oral, intravenous, subcutaneous, intramuscular, topical, intraperitoneal, intranasal, inhalation, or intraocular administration. In some examples of any of the examples 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 examples of any of the examples herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 9.3 mg/kg. In some examples of any of the examples herein, the effective amount of a telomerase inhibitor is 9.5 mg/kg to 11.7 mg/kg. In some examples herein, the effective amount of a telomerase inhibitor is 6.5 mg/kg to 11.7 mg/kg. In some examples herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 11.7 mg/kg. In some examples herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 9.4 mg/kg. In some examples of any of the examples herein, administration of the telomerase inhibitor does not inhibit cytokine-dependent megakaryocyte growth. In some examples of any of the examples herein, the individual carries a V617F gain of function mutation in the Janus kinase 2 (JAK2) gene. In some examples, administration of the telomerase inhibitor decreases the percentage of JAK2 V617F allelic burden in the individual. In some examples of any of the examples herein,

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

[0017] In another example, 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 examples the myeloproliferative neoplasms are, for example, Essential Thrombocythemia (ET), Polycythemia Vera (PV), Myelofibrosis (MF), and Acute Myelogenous Leukemia (AML). In some examples,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 examples, 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 examples of any of the example herein, the individual does not experience a thromboembolic event. In some examples of any of the example 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 examples of any of the example 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 examples, the individual is resistant or intolerant to a prior non-telomerase inhibitor-based therapy. In some examples, 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 examples, 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 examples, 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 examples of any of the examples herein, the

telomerase inhibitor comprises an oligonucleotide. In some examples, the oligonucleotide is complementary to the RNA component of telomerase. In some examples, the oligonucleotide is 10-20 base pairs in length. In some examples, the oligonucleotide comprises the sequence TAGGGTTAGACAA. In some examples of any of the examples herein, the oligonucleotide comprises at least one N3'→ P5' thiophosphoramidate internucleoside linkage. In some examples of any of the examples herein, oligonucleotide comprises N3'→ P5' thiophosphoramidate internucleoside linkages. In some examples of any of the examples herein, the oligonucleotide further comprises a lipid moiety linked to the 5' and/or 3' end of the oligonucleotide. In some examples of any of the examples herein, the lipid moiety is linked to the 5' and/or 3' end of the oligonucleotide via a linker. In some examples, the linker is a glycerol or aminoglycerol linker. In some examples of any of the examples herein, the lipid moiety is a palmitoyl (C16) moiety. In some examples of any of the examples herein, the telomerase inhibitor is imetelstat. In some examples of any of the examples herein, the telomerase inhibitor is administered with a pharmaceutically acceptable excipient. In some examples of any of the examples herein, the telomerase inhibitor is formulated for oral, intravenous, subcutaneous, intramuscular, topical, intraperitoneal, intranasal, inhalation, or intraocular administration. In some examples of any of the examples 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 examples of any of the examples herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 9.3 mg/kg. In some examples of any of the examples herein, the effective amount of a telomerase inhibitor is 9.5 mg/kg to 11.7 mg/kg. In some examples herein, the effective amount of a telomerase inhibitor is 6.5 mg/kg to 11.7 mg/kg. In some examples herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 11.7 mg/kg. In some examples herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 9.4 mg/kg. In some examples of any of the examples herein, administration of the telomerase inhibitor does not inhibit cytokine-dependent megakaryocyte growth. In some examples of any of the examples herein, the individual carries a V617F gain of function mutation in the Janus kinase 2 (JAK2) gene. In some examples, administration of the telomerase inhibitor decreases the percentage of JAK2 V617F allelic burden in the individual. In some examples of any of the examples herein, administration of the telomerase inhibitor inhibits cytokine-independent megakaryocyte growth. In some examples of any of the examples herein, administration of the telomerase

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

[0018] In another example, 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 examples, 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 examples, 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 examples of any of the example herein, the individual does not experience a thromboembolic event. In some examples of any of the example 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 examples of any of the example 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 examples, the individual is resistant or intolerant to a prior non- telomerase inhibitor-based therapy. In some examples, the prior non- telomerase inhibitor-based therapy is hydroxyurea, anagrelide, or Interferon α-2B. In some examples of any of the examples herein, the telomerase inhibitor comprises an oligonucleotide. In some examples, the oligonucleotide is complementary to the RNA component of telomerase. In some examples, the oligonucleotide is 10-20 base pairs in length. In some examples, the oligonucleotide comprises the sequence TAGGGTTAGACAA. In some examples of any of the examples herein, the oligonucleotide comprises at least one N3'→ P5' thiophosphoramidate internucleoside linkage. In some examples of any of the examples herein, oligonucleotide comprises N3'→ P5' thiophosphoramidate internucleoside linkages. In some examples of any of the examples herein, the oligonucleotide further comprises a lipid moiety linked to the 5' and/or 3' end of the oligonucleotide. In some examples of any of the examples herein, the lipid moiety is linked to the 5' and/or 3' end of the oligonucleotide via a linker. In some examples, the linker is a glycerol or aminoglycerol linker. In some examples of any of the examples herein, the lipid moiety is a palmitoyl

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

[0019] In another example, 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 examples, the telomerase inhibitor is administered no more than once every two weeks. In other examples, 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

examples of any of the examples herein, the telomerase inhibitor comprises an oligonucleotide. In some examples, the oligonucleotide is complementary to the RNA component of telomerase. In some examples, the oligonucleotide is 10-20 base pairs in length. In some examples, the oligonucleotide comprises the sequence TAGGGTTAGACAA. In some examples of any of the examples herein, the oligonucleotide comprises at least one N3'→ P5' thiophosphoramidate internucleoside linkage. In some examples of any of the examples herein, oligonucleotide comprises N3'→ P5' thiophosphoramidate internucleoside linkages. In some examples of any of the examples herein, the oligonucleotide further comprises a lipid moiety linked to the 5' and/or 3' end of the oligonucleotide. In some examples of any of the examples herein, the lipid moiety is linked to the 5' and/or 3' end of the oligonucleotide via a linker. In some examples, the linker is a glycerol or aminoglycerol linker. In some examples of any of the examples herein, the lipid moiety is a palmitoyl (C16) moiety. In some examples of any of the examples herein, the telomerase inhibitor is imetelstat. In some examples of any of the examples herein, the telomerase inhibitor is administered with a pharmaceutically acceptable excipient. In some examples of any of the examples herein, the telomerase inhibitor is formulated for oral, intravenous, subcutaneous, intramuscular, topical, intraperitoneal, intranasal, inhalation, or intraocular administration. In some examples of any of the examples 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 examples of any of the examples herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 9.3 mg/kg. In some examples of any of the examples herein, the effective amount of a telomerase inhibitor is 9.5 mg/kg to 11.7 mg/kg. In some examples herein, the effective amount of a telomerase inhibitor is 6.5 mg/kg to 11.7 mg/kg. In some examples herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 11.7 mg/kg. In some examples herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 9.4 mg/kg. In some examples of any of the examples herein, administration of the telomerase inhibitor does not inhibit cytokine-dependent megakaryocyte growth. In some examples of any of the examples herein, the individual carries a V617F gain of function mutation in the Janus kinase 2 (JAK2) gene. In some examples, administration of the telomerase inhibitor decreases the percentage of JAK2 V617F allelic burden in the individual. In some examples of any of the examples herein, administration of the telomerase inhibitor inhibits cytokine-independent megakaryocyte growth.

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

[0020] Accordingly, in one example, 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 examples, 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 examples of any of the examples herein, the telomerase inhibitor comprises an oligonucleotide. In some examples, the oligonucleotide is complementary to the RNA component of telomerase. In some examples, the oligonucleotide is 10-20 base pairs in length. In some examples, the oligonucleotide comprises the sequence TAGGGTTAGACAA. In some examples of any of the examples herein, the oligonucleotide comprises at least one N3'→ P5' thiophosphoramidate internucleoside linkage. In some examples of any of the examples herein, oligonucleotide comprises N3'→ P5' thiophosphoramidate internucleoside linkages. In some examples of any of the examples herein, the oligonucleotide further comprises a lipid moiety linked to the 5' and/or 3' end of the oligonucleotide. In some examples of any of the examples herein, the lipid moiety is linked to the 5' and/or 3' end of the oligonucleotide via a linker. In some examples, the linker is a glycerol or aminoglycerol linker. In some examples of any of the examples herein, the lipid moiety is a palmitoyl (C16) moiety. In some examples of any of the examples herein, the telomerase inhibitor is imetelstat. In some examples of any of the examples herein, the telomerase inhibitor is administered with a pharmaceutically acceptable excipient. In some examples of any of the examples herein, the telomerase inhibitor is formulated for oral, intravenous, subcutaneous, intramuscular, topical, intraperitoneal, intranasal, inhalation, or intraocular administration. In some examples of any of the examples 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 examples of any of the examples herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 9.3 mg/kg. In some examples of any of the examples herein, the effective amount of a telomerase inhibitor is 9.5 mg/kg to 11.7 mg/kg. In some examples herein, the effective amount of a telomerase inhibitor is 6.5 mg/kg to 11.7 mg/kg. In some examples herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 11.7 mg/kg. In some examples herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 9.4 mg/kg. In some examples of any of the examples herein, administration of the telomerase inhibitor inhibits erythroid growth. In some examples of any of the examples herein, administration of the telomerase inhibitor inhibits CFU-erythroid. . In some examples of any of the examples herein, the individual carries a V617F gain of function mutation in the Janus kinase 2 (JAK2) gene. In some examples, administration of the telomerase inhibitor decreases the percentage of JAK2 V617F allelic burden in the individual. In some examples, the individual is resistant or intolerant to a prior non- telomerase inhibitor-based therapy. In some examples, the individual is a human.

[0021] Accordingly, in one example, 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 examples, 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 examples of any of the examples herein, the telomerase inhibitor comprises an oligonucleotide. In some examples, the oligonucleotide is complementary to the RNA component of telomerase. In some examples, the oligonucleotide is 10-20 base pairs in length. In some examples, the oligonucleotide comprises the sequence TAGGGTTAGACAA. In some examples of any of the examples herein, the oligonucleotide comprises at least one N3'→ P5' thiophosphoramidate internucleoside linkage. In some examples of any of the examples herein, oligonucleotide comprises N3'→ P5' thiophosphoramidate internucleoside linkages. In some examples of any of the examples herein, the oligonucleotide further comprises a lipid moiety linked to the 5' and/or 3' end of the oligonucleotide. In some examples of any of the examples herein, the lipid moiety is linked to the 5' and/or

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

[0022] In another example 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 example, 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 example, 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 example, 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 examples, the telomerase inhibitor is administered no more than once every two weeks. In other examples, 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 examples of any of the examples herein, the telomerase inhibitor comprises an oligonucleotide. In some examples, the oligonucleotide is complementary to the RNA component of telomerase. In some examples, the oligonucleotide is 10-20 base pairs in length. In some examples, the oligonucleotide comprises the sequence TAGGGTTAGACAA. In some examples of any of the examples herein, the oligonucleotide comprises at least one N3'→ P5' thiophosphoramidate internucleoside linkage. In some examples of any of the examples herein, oligonucleotide comprises N3'→ P5' thiophosphoramidate internucleoside linkages. In some examples of any of the examples herein, the oligonucleotide further comprises a lipid moiety linked to the 5' and/or 3' end of the oligonucleotide. In some examples of any of the examples herein, the lipid moiety is linked to the 5' and/or 3' end of the oligonucleotide via a linker. In some examples, the linker is a glycerol or aminoglycerol linker. In some examples of any of the examples herein, the lipid moiety is a palmitoyl (C16) moiety. In some examples of any of the examples herein, the telomerase inhibitor is imetelstat. In some examples of any of the examples herein, the telomerase inhibitor is administered with a pharmaceutically acceptable excipient. In some examples of any of the examples herein, the telomerase inhibitor is formulated for oral, intravenous, subcutaneous, intramuscular, topical, intraperitoneal, intranasal, inhalation, or intraocular

administration. In some examples of any of the examples 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 examples of any of the examples herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 9.3 mg/kg. In some examples of any of the examples herein, the effective amount of a telomerase inhibitor is 9.5 mg/kg to 11.7 mg/kg. In some examples herein, the effective amount of a telomerase inhibitor is 6.5 mg/kg to 11.7 mg/kg. In some examples herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 11.7 mg/kg. In some examples herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 9.4 mg/kg.

[0023] Accordingly, in one example, 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 examples, 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 examples of any of the examples herein, the telomerase inhibitor comprises an oligonucleotide. In some examples, the oligonucleotide is complementary to the RNA component of telomerase. In some examples, the oligonucleotide is 10-20 base pairs in length. In some examples, the oligonucleotide comprises the sequence TAGGGTTAGACAA. In some examples of any of the examples herein, the oligonucleotide comprises at least one N3'→ P5' thiophosphoramidate internucleoside linkage. In some examples of any of the examples herein, oligonucleotide comprises N3'→ P5' thiophosphoramidate internucleoside linkages. In some examples of any of the examples herein, the oligonucleotide further comprises a lipid moiety linked to the 5' and/or 3' end of the oligonucleotide. In some examples of any of the examples herein, the lipid moiety is linked to the 5' and/or 3' end of the oligonucleotide via a linker. In some examples, the linker is a glycerol or aminoglycerol linker. In some examples of any of the examples herein, the lipid moiety is a palmitoyl (C16) moiety. In some examples of any of the examples herein, the telomerase inhibitor is imetelstat. In some examples of any of the examples herein, the telomerase inhibitor is administered with a pharmaceutically acceptable excipient. In some examples of any of the examples herein, the telomerase

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

[0024] Accordingly, in one example, 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 examples, the symptoms comprise shortness of breath, fatigue, weakness, fainting, nosebleeds, bruising, bleeding from mouth or gums, bloody stool, petechiae, or stroke. In some examples of any of the examples herein, the telomerase inhibitor comprises an oligonucleotide. In some examples, the oligonucleotide is complementary to the RNA component of telomerase. In

some examples, the oligonucleotide is 10-20 base pairs in length. In some examples, the oligonucleotide comprises the sequence TAGGGTTAGACAA. In some examples of any of the examples herein, the oligonucleotide comprises at least one N3'→ P5' thiophosphoramidate internucleoside linkage. In some examples of any of the examples herein, oligonucleotide comprises N3'→ P5' thiophosphoramidate internucleoside linkages. In some examples of any of the examples herein, the oligonucleotide further comprises a lipid moiety linked to the 5' and/or 3' end of the oligonucleotide. In some examples of any of the examples herein, the lipid moiety is linked to the 5' and/or 3' end of the oligonucleotide via a linker. In some examples, the linker is a glycerol or aminoglycerol linker. In some examples of any of the examples herein, the lipid moiety is a palmitoyl (C16) moiety. In some examples of any of the examples herein, the telomerase inhibitor is imetelstat. In some examples of any of the examples herein, the telomerase inhibitor is administered with a pharmaceutically acceptable excipient. In some examples of any of the examples herein, the telomerase inhibitor is formulated for oral, intravenous, subcutaneous, intramuscular, topical, intraperitoneal, intranasal, inhalation, or intraocular administration. In some examples of any of the examples 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 examples of any of the examples herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 9.3 mg/kg. In some examples of any of the examples herein, the effective amount of a telomerase inhibitor is 9.5 mg/kg to 11.7 mg/kg. In some examples herein, the effective amount of a telomerase inhibitor is 6.5 mg/kg to 11.7 mg/kg. In some examples herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 11.7 mg/kg. In some examples herein, the effective amount of a telomerase inhibitor is 7.5 mg/kg to 9.4 mg/kg. In some examples of any of the examples herein, administration of the telomerase inhibitor inhibits cytokine-independent megakaryocyte growth. In some examples, the individual is resistant or intolerant to a prior non- telomerase inhibitor-based therapy. In some examples, the individual is a human.

DESCRIPTION OF THE DRAWINGS

[0025] Figures 1A and 1B depict Imetelstat effect on megakaryocyte growth and differentiation.

Claims

What is claimed is:

1. Use of a telomerase inhibitor in the manufacture of a medicament for alleviating at least one symptom resulting from myelodysplastic syndrome in an individual, wherein the telomerase inhibitor is imetelstat or a pharmaceutically acceptable salt thereof.

2. The use of claim 1, wherein the at least one symptom comprises shortness of breath, fatigue, weakness, fainting, nosebleeds, bruising, bleeding from mouth or gums, bloody stool, petechiae or stroke.

3. The use 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).

4. The use of claim 3, wherein the myelodysplastic syndrome (MDS) is chronic myelomonocytic leukemia (CMML).

5. The use of claim 1, wherein neoplastic progenitor cell proliferation is reduced by the inhibitor in an individual diagnosed with or suspected of having myelodysplastic syndrome.

6. The use of claim 5, 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.

7. The use of claim 1, wherein bone marrow fibrosis is reduced by the telomerase inhibitor in an individual diagnosed with or suspected of having myelodysplastic syndrome.

8. The use of claim 1, wherein the individual has anemia and requires blood transfusions.

9. The use of any one of claims 1 to 8, wherein the individual carries a V617F gain of function mutation in the Janus kinase 2 (JAK2) gene and the percentage of JAK2 V617F allelic burden is decreased by the telomerase inhibitor in the individual.

10. The use of any one of claims 1 to 9, wherein the individual is resistant or intolerant to a prior non-telomerase inhibitor-based therapy.

11. The use of any one of claims 1 to 10, wherein the medicament is to be used with a pharmaceutically acceptable excipient.

12. The use of any one of claims 1 to 10, wherein the medicament is formulated for oral, intravenous, subcutaneous, intramuscular, topical, intraperitoneal, intranasal, inhalation, or intraocular administration.

13. The use of any one of claims 1 to 10, wherein one or more neoplastic progenitor cells is to be contacted with the telomerase inhibitor.

14. The use of any one of claims 1 to 10, wherein the effective amount of a telomerase inhibitor is 3.5 mg/kg to 11.7 mg/kg.

15. The use of any one of claims 1 to 10, wherein the effective amount of a telomerase inhibitor is 5 mg/kg to 11.7 mg/kg.

16. The use of any one of claims 1 to 10, wherein the effective amount of a telomerase inhibitor is 6.5 mg/kg to 11.7 mg/kg.

17. The use of any one of claims 1 to 10, wherein the effective amount of a telomerase inhibitor is 7.5 mg/kg to 9.4 mg/kg.

18. The use of any one of claims 1 to 10, wherein the effective amount of a telomerase inhibitor is 9.5 mg/kg to 11.7 mg/kg.

19. The use of any one of claims 1 to 10, wherein the telomerase inhibitor does not inhibit cytokine-dependent megakaryocyte growth.

20. The use of any one of claims 1 to 10, wherein the telomerase inhibitor inhibits cytokine-independent megakaryocyte growth.

21. The use of any one of claims 1 to 10, wherein the telomerase inhibitor inhibits CFU-Mega.

22. The use of claim 21, wherein inhibition of CFU-Mega is independent of reduction in JAK2 allelic burden.

23. The use of any one of claims 1 to 10, wherein the telomerase inhibitor is imetelstat sodium.

24. The use of claim 23, wherein the effective amount of a telomerase inhibitor is 3.5 mg/kg to 11.7 mg/kg.

25. The use of claim 23, wherein the effective amount of a telomerase inhibitor is 5 mg/kg to 11.7 mg/kg.

26. The use of claim 23, wherein the effective amount of a telomerase inhibitor is 6.5 mg/kg to 11.7 mg/kg.

27. The use of claim 23, wherein the effective amount of a telomerase inhibitor is 7.5 mg/kg to 9.4 mg/kg.

28. The use of claim 23, wherein the effective amount of a telomerase inhibitor is 9.5 mg/kg to 11.7 mg/kg.