(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 March 2018 (22.03.2018)

W!P O ¦ PCT

(10) International Publication Number
WO 2018/053190 Al

(51) International Patent Classification:
A61K 31/4985 (2006.01) *A61P 37/08* (2006.01)
A61K 31/5377 (2006.01) *A61P 7/06* (2006.01)
A61P 35/00 (2006.01) *A61P 29/00* (2006.01)
A61P 55/02 (2006.01)

(21) International Application Number:
PCT/US20 17/05 1649

(22) International Filing Date:
14 September 2017 (14.09.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/394,573 14 September 2016 (14.09.2016) US
62/416,047 0 1 November 201 6 (01 .11.2016) US
62/429,209 02 December 20 16 (02 .12 .20 16) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available):* AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available):* ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(Hi))*

Published:
— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2018/053190 A1

(54) Title: SYK INHIBITORS

(57) Abstract: The application provides methods of treating or reducing thrombocytopenia, leukopenia, anemia, or neutropenia in a patient in need thereof, comprising the step of administering an effective amount of a compound selected from Compounds 1-6, disclosed herein.

SYK INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit under 35 U.S.C. § 119(e) of United States Provisional Application Nos. 62/394,573, filed September 14, 2016, 62/416,047, filed November 1, 2016; and 62/429,209, filed December 2, 2016, which are hereby incorporated by reference in their entirety.

FIELD

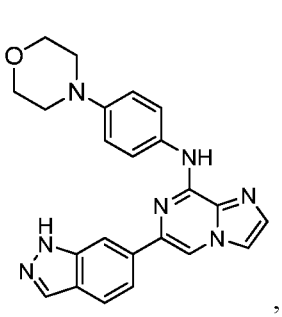
[0002] The present disclosure relates to methods of treatment of diseases and disorders using compounds and compositions that inhibit Spleen Tyrosine Kinase (SYK) activity.

BACKGROUND

[0003] Protein kinases, the largest family of human enzymes, encompass well over 500 proteins. Spleen Tyrosine Kinase (SYK) is a member of the family of tyrosine kinases, and is a regulator of early B-cell development as well as mature B-cell activation, signaling, and survival. SYK has roles in immunoreceptor- and integrin-mediated signaling in a variety of cell types, including B-cells, macrophages, monocytes, mast cells, eosinophils, basophils, neutrophils, dendritic cells, T-cells, natural killer cells, platelets, and osteoclasts. The inhibition of Syk activity can be useful for the treatment cancers and inflammatory diseases. U.S. Patents 8,455,493, 8,440,667, 9,376,441, 9,416,111, 9,353,066 and 9,376,418 disclose SYK inhibitors. Several SYK inhibitors are in advanced stages of clinical trials. Fostamatinib is a SYK inhibitor currently undergoing phase III clinical trials for chronic immune thrombocytopenic purpura (chronic ITP). (NCT02076412; Clinicaltrials.gov). Fostamatinib, however, has adverse side effects including hypertension, neutropenia and transaminitis. (Nijjar J.S., et al., *Rheumatology* 2013, 1556-1562).

SUMMARY

[0004] Some embodiments provide methods for treating or reducing thrombocytopenia, leukopenia, anemia, or neutropenia in a patient in need thereof, comprising the step of administering an effective amount of a compound selected from:



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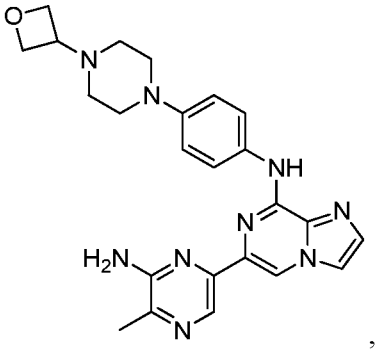

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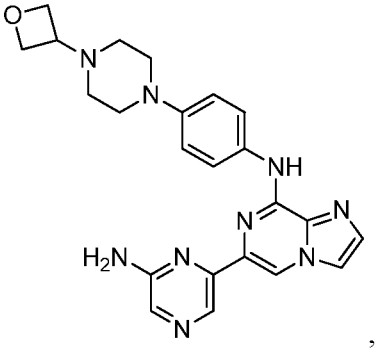
Compound- 1 Compound-2



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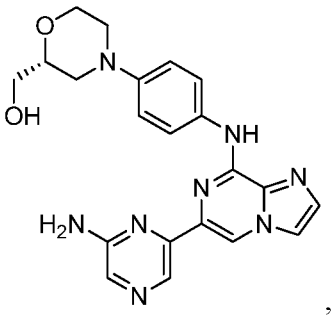

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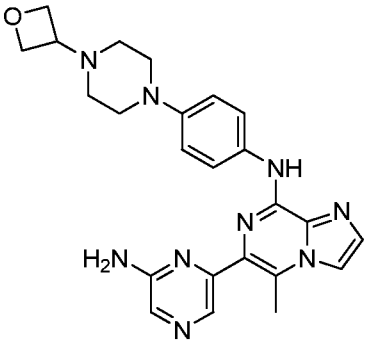
Compound-3 Compound-4



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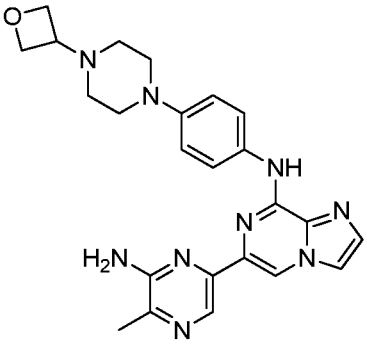

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Compound-5 Compound-6

or a pharmaceutically acceptable salt, ester or derivative thereof. Some embodiments provide methods of treatment for anemia, thrombocytopenia, leukopenia or neutropenia wherein said patient is not undergoing chemotherapy.

[0005] Some embodiments provide methods for treating a disease or condition selected from the group consisting of an inflammatory disorder, an allergic disorder, an autoimmune disease, and a cancer in a subject in need thereof, the method comprising administering to the human in need thereof a therapeutically effective amount of a

compound selected from Compounds 1-6, or a pharmaceutically acceptable salt, ester or derivative thereof, wherein said subject is additionally undergoing proton pump inhibitor therapy; and, wherein said compound selected from Compounds 1-6 is administered at a daily dosage of about 25% to about 75% higher than the daily dosage recommended for a subject not undergoing proton pump inhibitor therapy.

[0006] Some embodiments provide methods for treating a proliferative disease or disorder in a subject in need thereof, comprising the step of administering a therapeutically effective amount of a compound selected from Compounds 1-6, or a pharmaceutically acceptable salt thereof, to said subject, wherein said subject has one or more abnormal core-binding karyotypes selected fromt(8;21)(q22;q22), inv(16)(pl3.1q22) and t(16;16)(pl3.1;q22); or wherein said subject has one or more chromosomal abnormalities selected from the deletion of 5, 5q, 7, 7q, 17p, inv(3)(q21;q26) and t(3;3)(q21;q26); or wherein said subject has a llq23 rearrangement of MLL gene.

[0007] Some embodiments provide methods for treating a proliferative disease or disorder in a subject in need thereof, comprising the step of administering a therapeutically effective amount of a compound selected from Compounds 1-6, or a pharmaceutically acceptable salt thereof, to said subject, wherein said subject has mixed lineage leukaemia gene-partial tandem duplications (MLL-PTD). MLL-PTD confer a worse prognosis with shortened overall and event free survival in childhood and adult AML. (Basecke J., et al, *British Journal of Hematology,* 2006, 135(4):).

[0008] Some embodiments provide methods for treating a proliferative disease or disorder in a subject in need thereof, comprising the step of administering a therapeutically effective amount of a compound selected from Compounds 1-6, or a pharmaceutically acceptable salt thereof, to said subject, wherein said subject has or expresses a mixed lineage leukemia (MLL) fusion protein, a BCR-ABL fusion protein, FLT3 internal tandem duplications, NPM1 mutation, IDH1 mutation, IDH2 mutation, a deleted or mutated p53, high or elevated levels of meningioma 1, and/or high or levels of lactate dehydrogenase. MLL fusion partners can vary and more than 51 fusion partners have been identified. MLL/AF9 often results in AML while MLL/AF4 oftent results in B-lineage ALL. (Basecke J. et al, *supra.).* Some embodiments provide methods for identifying abnormal MLL fusion protein expression in a patient followed by the

administration of a compound selected from Compounds 1-6, or a pharmaceutically acceptable salt thereof to a patient in need thereof.

[0009] Homeobox (HOX) proteins are homeo-domain DNA binding transcription factors that play an important role in regulation of hematopoiesis (Sitwala, *Int. J. Clin. Exp. Pathol.* 2008, Mar 30; l(6):461-74). Myeloid Ecotropic Viral Integration Site 1 (MEISl) is a co-factor of Homeobox A9 (HOXA9) that recruits additional DNA binding proteins to HOXA9 binding sites in order to maintain the Mixed Lineage Leukemia (MLL) stem cell transcriptional program (Collins, *Curr. Opin. Hematol.* 2016, Jul; 23(4):354-61). Overexpression of these two proteins in hematopoietic stem cells (HSCs) results in a rapid and fatal leukemia when transduced HSCs are transplanted in mice (Thorsteinsdottir, *EMBOJ.* 2001, Feb 1; 20(3):350-61). A subset of acute lymphoid leukemia (ALL), pro-B-acute lymphocytic leukemia (pro-B ALL), myelodysplastic syndrome (MDS) and T-ALL patients can be characterized by tumor cells collected from bone marrow showing high co-expression of HOXA9 and MEISl that are associated with increased SYK protein levels. Some embodiments provide a method for treating patients with ALL, pro-B ALL, MDS, AML, MDS and T-ALL where HOXA9 and MEISl are overexpressed by the administration of a therapeutically effective amount of a SYK inhibitor selected from Compounds 1-6, or a pharmaceutically acceptable salt, ester or derivative thereof.

[0010] Some embodiments provide methods for treating a proliferative disease or disorder in a subject in need thereof, comprising the step of administering a therapeutically effective amount of a compound selected from Compounds 1-6, or a pharmaceutically acceptable salt thereof, to said subject, wherein said subject is administered one or more anti-cancer agents selected from the group consisting of AMG-330, anti-miR155, AntiJL-l+, CD117-MTX aptamer, CD47mAb, CD-98mAb, GO-203c, hBF4-mAb, LAIRl-mAb, IL-IRAP-mAb, MG006, miR-150, MRX-6313, MSK-777, SP-2065, SPM-2, SIRPaFc, TTT-3002, MLL/Menin inhibitor, AML-IL2/CD80, 4G8SDIEM, AG-221, AG-120, AKN-028, ALT 801, Anti-CD44 mAb, ASP-2215, AT-109, AT-406, AT-9283, AZ-1208, BGB-324, BI 836858, BMS-936564, BP-100-01, Carbozatinib, CB-839, CART-CD 123, CART-CD33, CPI-613, CPI-0610, CSL-362, CWP-232291, Dacogen, Dinacilib, DC/AML fusion, Elesclomol, EPZ-5676, GSK2879552, IGN 523, INNO-305, Iomab-B, KX-2391, LeY, LOR-253, MK-8242,

MGD006, Oxi-4503, PF-449913, Plerixafor, PRI-724, Rebistanib, Rigosertib, RO-5503781, PF-04449913, SG-2000, SL-401, SGN-CD33a, TCN-P, Tiecycline, Triciribine, Vismodegib, Zosuquidar, Actimab-A, AEG 35156, Belinostat, Bl 811283, Bismab-A, Birinapant, BL-8040, CC-486, CNDO-109, Crenolanib, Deformolus, DFP-10917, Flavopiridol, GVAX, KB-004, KPT-330, Lestartinib, Lirilumab, LO-02040, LY209314, MK8776, Omacetaxine, Pacritinib, Panobinostat, PD-616, Pdilizumab, PR-104, Pracinostat, PLX-3397, R-l 15777, Ribovarin, Selumetinib, SGI-110, Sorafenib, Tresosulfan, Temodar, Tosedostat, Vorinostat, WT-1, Arsenix trioxide, Clofarabine, Decitabine, Laromustine, Tipfarnib, Palbocyclib, Quizartinib and Mylotarg.

DESCRIPTION OF THE FIGURES

[0011] FIG. **1**: Neutrophil counts in patients receiving chemotherapy and 200 or 400 mg twice daily dose of entospletinib (ENTO or Compound-1). The figure shows daily levels for individual patients and neutrophil recovery through induction treatment.

[0012] FIG. **2**: Platelet counts in patients receiving chemotherapy and 200 or 400 mg doses of entospletinib (ENTO or Compound-1). The figure shows daily levels for individual patients and platelet recovery through induction treatment.

[0013] FIG. **3**: Platelet recovery during the entospletinib (ENTO or Compound-1) monotherapy lead-in window.

[0014] FIG. **4**: Scatter Plot of MEIS1 and a HOXA10 Expression in Leukemia Subtypes. Leukemia subtypes with high co-expression of HOXA10 and MEIS1 are boxed in red. Healthy bone marrow is boxed in blue. Data source: Microarray Innovations in Leukemia (MILE) study (GSE13159, PMID: 18573112 and 20406941).

[0015] FIG. **5**: HOXA10 and HOXA9 RNA Expression is Highly Correlated in AML. Data Source: The Cancer Genome Atlas (TCGA), RNAseq data, release 2016_01_28.

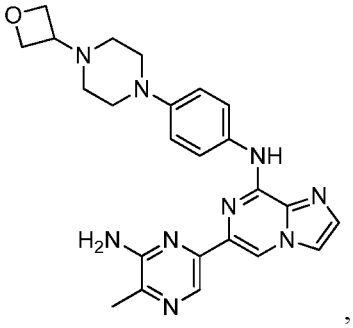
[0016] FIG. **6**: Expression of HOXA9 and MEIS1 RNA in Cancer Types from TCGA. MEIS1 and HOXA9 RNA levels were plotted for cancers in the TCGA. Blue lines in each panel represent the linear regression line. The red box signifies the high HOXA9 and MEIS1 population in AML. Data Source: TCGA, RNAseq data, release 2016_01_28.

[0017] FIG. 7: Expression of HOXA9 and MEIS 1 RNA in Tumor and Normal from Bladder, Breast Invasive Carcinoma, Prostate and Uterine Cancers from TCGA Data. Data Source: TCGA, RNAseq data, release 2016_01_28.

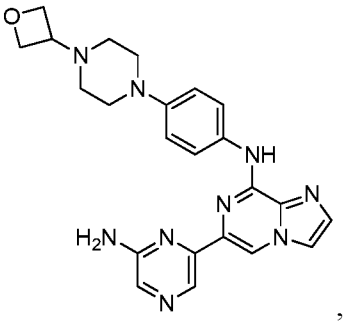
DETAILED DESCRIPTION

[0018] Some embodiments provide methods for treating or reducing thrombocytopenia, leukopenia, anemia, or neutropenia in a patient in need thereof, comprising the step of administering an effective amount of a compound selected from:

Compound- 1



Compound-2



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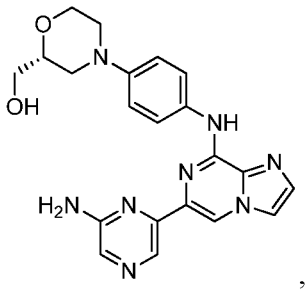
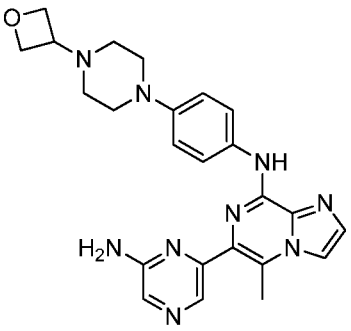


Compound-4



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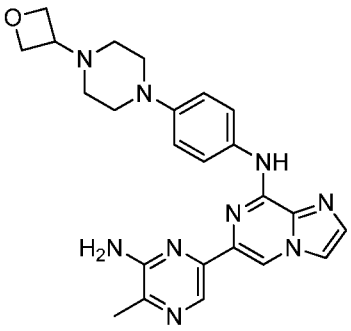


Compound-5 Compound-6

or a pharmaceutically acceptable salt, ester or derivative thereof. Some embodiments provide methods of treatment for anemia, thrombocytopenia, leukopenia or neutropenia wherein said patient is not undergoing chemotherapy.

[0019] Without being bound to a mechanism or theory, the disclosure herein provides methods to increase neutrophil and platelet levels in patients in need thereof. It is the expectation that the compounds herein will be useful in the treatment of, for example, conditions that cause or exacerbate neutropenia, anemia, leukopenia and thrombocytopenia.

[0020] Some embodiments provide methods for treating anemia comprising the step of administering a therapeutically effective amount of a compound selected from Compounds 1-6 to a subject in need thereof. In some embodiments, anemia is selected from the group consisting of hemolytic anemia, microangiopathic hemolytic anemia, hypersplenism, dyserythropoietic anemia, spherocytosis, sideroblastic anemia, autoimmune hemolytic anemia, sickle cell anemia, thalassemia, Glucose-6-phosphate dehydrogenase (G6PD)-deficient anemia, pernicious anemia, aplastic anemia, anemia caused by liver disease or renal disease, and anemia caused by the deficiency of one or more vitamins or nutrients. Some embodiments provide a method of treatment where anemia is caused by deficiency of one or more nutrients or vitamins, for example, a vitamin B12, B2, B6, C, Al, D, **E** or K, iron, folic acid, zinc, copper, calcium or protein.

[0021] Some embodiments provide methods for treating thrombocytopenia comprising the step of administering a therapeutically effective amount of a compound selected from Compounds 1-6 to a subject in need thereof. In some embodiments, thrombocytopenia is selected from idiopathic thrombocytopenia, alcohol-induced thrombocytopenia, drug-induced immune thrombocytopenia, thrombotic thrombocytopenic purpura, transfusion-induced thrombocytopenia, primary thrombocythemia, disseminated intravascular coagulation, hypersplenism, hemolytic uremic syndrome, paroxysmal nocturnal hemoglobinuria and immune thrombocytopenia. In some embodiments, thrombocytopenia is due to low production of platelets in bone marrow, while in some embodiments, it is due to increased breakdown of platelets in the bloodstream, spleen or liver, or due to hemodilution.

[0022] Some embodiments provide methods for treating neutropenia comprising the step of administering a therapeutically effective amount of a compound selected from

Compounds **1-6** to a subject in need thereof. In some embodiments, neutropenia is selected from primary neutropenia, acute neutropenia, severe chronic neutropenia, severe congenital neutropenia (Kostmann's syndrome), severe infantile genetic agranulocytosis, benign neutropenia, cyclic neutropenia, chronic idiopathic neutropenia, secondary neutropenia, syndrome associated neutropenia, and immune-mediated neutropenia.

[0023] Some embodiments provide methods for treating neutropenia comprising the step of administering a therapeutically effective amount of a compound selected from Compounds **1-6** to a subject in need thereof, wherein neutropenia is caused or associated with radiation, alcoholism, allergic disorders, aplastic anemia, autoimmune disease, myelodysplasia, myelofibrosis, dysgammaglobulinemia, paroxysmal nocturnal hemoglobinuria, vitamin B12 deficiency, folate deficiency, viral infection, bacterial infection, spleen disorder, hemodialysis or transplantation, myeloma, lymphoma, metastatic solid tumors which infiltrate and replace the bone marrow, toxins, bone marrow failure, Schwachman-Diamond syndrome, cartilage-hair hypoplasia, dyskeratosis congenita, glycogen storage disease type IB, splenomegaly, or intrinsic defects in myeloid cells.

[0024] Some embodiments provide methods for treating leukopenia comprising the step of administering a therapeutically effective amount of a compound selected from Compounds **1-6** to a subject in need thereof. In some embodiments, leukopenia is caused or associated with one or more diseases or disorders selected from aplastic anemia, autoimmune diseases, chemotherapy, radiation, hyperthyroidism, rheumatoid arthritis, liver disorders, spleen disorders, congenital disorders, viral infections, bacterial infections and parasitic infections. In some embodiments, leukopenia is caused or associated with parasitic infection, for example, infection selected from Acanthamoeba keratitism, amoebiasis, ascariasis, babesiosis, balantidiasis, baylisascariasis, Chagas disease, clonorchiasis, cochliomyia, cryptosporidiosis, diphyllobothriasis, dracunculiasis, echinococcosis, elephantiasis, enterobiasis, fascioliasis, fasciolopsiasis, filariasis, giardiasis, gnathostomiasis, hymenolepiasis, isosporiasis, Katayama fever, leishmaniasis, Lyme disease, malaria, metagonimiasis, myiasis, onchocerciasis, pediculosis, scabies, schistosomiasis, sleeping sickness, strongyloidiasis, taeniasis, toxocariasis, toxoplasmosis, trichinosis, and trichuriasis. In some embodiments, leukopenia is caused by or associated with viral infection, for example, infection selected from HCV, HIV, influenza, Ebola virus, Marburg virus, flavivirus, Venezuelean equine encephalitis,

Chikungunya virus, and West Nile virus. In some embodiments, fiavivirus is selected from the group consisting of Absettarov, Alfuy, Apoi, Aroa, Bagaza, Banzi, Bouboui, Bussuquara, Cacipacore, Carey Island, Dakar bat, Dengue 1, Dengue 2, Dengue 3, Dengue 4, Edge Hill, Entebbe bat, Gadgets Gully, Hanzalova, Hypr, Ilheus, Israel turkey meningoencephalitis, Japanese encephalitis, Jugra, Jutiapa, Kadam, Karshi, Kedougou, Kokobera, Koutango, Kumlinge, Kunjin, Kyasanur Forest disease, Langat, Louping ill, Meaban, Modoc, Montana myotis leukoencephalitis, Murray valley encephalitis, Naranjal, Negishi, Ntaya, Omsk hemorrhagic fever, Phnom-Penh bat, Powassan, Rio Bravo, Rocio, royal farm, Russian spring-summer encephalitis, Saboya, St. Louis encephalitis, Sal Vieja, San Perlita, Saumarez Reef, Sepik, Sokuluk, Spondweni, Stratford, Tembusu, Tyuleniy, Uganda S, Usutu, Wesselsbron, west Nile, Yaounde, yellow fever, and Zika. In some embodiments, leukopenia is caused or associated with bacterial infection, for example, infection resulting from Acidobacteria, Actinobacteria, Aquificae, Bacteroidetes, Caldiserica, Chlamydiae, Chlorobi, Chloroflexi, Chrysiogenetes, Cyanobacteria, Deferribacteres, Deinococcus-Thermus, Dictyoglomi, Elusimicrobia, Fibrobacteres, Firmicutes, Fusobacteria, Gemmatimonadetes, Lentisphaerae, Nitrospira, Planctomycetes, Proteobacteria, Spirochaetes, Synergistetes, Tenericutes, Firmicutes, Thermodesulfobacteria, Thermomicrobia, Thermotogae, or Verrucomicrobia.

[0025] Some embodiments provide methods for treating a disease or condition selected from the group consisting of an inflammatory disorder, an allergic disorder, an autoimmune disease, and a cancer in a subject in need thereof, the method comprising administering to the human in need thereof a therapeutically effective amount of a compound selected from Compounds 1-6, or a pharmaceutically acceptable salt, ester or derivative thereof, wherein said subject is additionally undergoing proton pump inhibitor therapy; and, wherein said compound selected from Compounds 1-6 is administered at an increased daily dosage compared to the daily dosage recommended for a subject not undergoing proton pump inhibitor therapy. In some embodiments, proton pump inhibitor is selected selected from omeprazole, hydroxy omeprazole, esomeprazole, tenatoprazole, lansoprazole, pantoprazole, rabeprazole, dontoprazole, habeprazole, perprazole, ransoprazole, pariprazole, leminoprazole, tenatoprazole, S-tenatoprazole-Na, and dexlansoprazole. For example, a patient undergoing proton pump therapy is administered a daily dosage of a compound selected from Compounds 1-6 that is increased by

between 25-75% of the recommended daily dosage. In one embodiment, the daily dosage of compound 1 is increased by about 200%, 100%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30% or 25%. For example, a daily dosage of recommendation of about 800 mg of compound- 1 can be increased by about 200%, 100%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30% or 25% for patient undergoing proton pump inhibitor therapy. For example, the increased dosage can be about 2400 mg or 1600 mg or 1400 mg or about 1360 mg or about 1320 mg or about 1280 mg or about 1240 mg or about 1200 mg or about 1160 mg or about 1140 mg or about 1100 mg or about 1060 mg or about 1020 mg or about 980 mg or about 940 mg or about 900 mg. In one embodiment, the application provides methods for treating a proliferative disease or disorder in a subject in need thereof, comprising the step of administering a therapeutically effective amount of a compound selected from Compounds 1-6, or a pharmaceutically acceptable salt thereof, to said subject, wherein said subject has one or more abnormal core-binding karyotypes selected from t(8;21)(q22;q22), inv(16)(pl3.1q22) and t(16;16)(pl3.1;q22); or wherein said subject has one or more chromosomal abnormalities selected from the deletion of 5, 5q, 7, 7q, 17p, inv(3)(q21;q26) and t(3;3)(q21;q26); or wherein said subject has a 1lq23 rearrangement of MLL gene.

[0026] Cytogenetic data help stratify patients in terms of diagnosis and evaluating prognosis for survival and risk of transformation to AML (U.S. Patent Publication No. 20100009364; Hofmann, W.K., et al, Myelodysplasia syndrome. *Annual Review of Medicine.* 2005, vol. 56, pp. 1-16). Characteristic chromosomal deletions involve chromosome 5 [del(5q), -5], chromosome 11 [del(llq)], chromosome 12 [del(12q)], chromosome 20 [del(20q)], chromosome 7 [del(7q), -7], chromosome 17 [del(17p)], and chromosome 13 [del(13q)]. Other frequent structural and/or numerical chromosomal aberrations include trisomy 8, trisomy 21, and inversion 3(q21q26). Rare reciprocal translocations include t(l; 7)(ql0; plO), t(l; 3)(p36; q21), t(3; 3)(q21; q26), t(6; 9)(p23; q34), and t(5; 12)-fusion between PDGFR^ and TEL(ETV-6), (q33; pl3); t(5; 7)(q33; 11.2). Some embodiments provide methods for treating proliferative diseases including AML and MDS by the administration of a compound selected from Compounds 1-6 or a pharmaceutically acceptable salt thereof to a subject in need thereof.

[0027] Some embodiments provide methods for treating a proliferative disease or disorder in a subject in need thereof, comprising the step of administering a therapeutically effective amount of a compound selected from Compounds 1-6, or a

pharmaceutically acceptable salt thereof, to said subject, wherein said subject has or expresses a mixed lineage leukemia (MLL) fusion protein, a BCR-ABL fusion protein, FLT3 internal tandem duplications, a deleted or mutated p53, high or elevated levels of meningioma 1, and/or high or levels of lactate dehydrogenase.

[0028] Homeobox (HOX) proteins are homeo-domain DNA binding transcription factors that play an important role in regulation of hematopoiesis (Sitwala, *Int. J. Clin. Exp. Pathol.* 2008, Mar 30; l(6):461-74). Myeloid Ecotropic Viral Integration Site 1 (MEISl) is a co-factor of Homeobox A9 (HOXA9) that recruits additional DNA binding proteins to HOXA9 binding sites in order to maintain the Mixed Lineage Leukemia (MLL) stem cell transcriptional program (Collins, *Curr. Opin. Hematol.* 2016, Jul; 23(4):354-61). Over expression of these two proteins in hematopoietic stem cells (HSCs) results in a rapid and fatal leukemia when transduced HSCs are transplanted in mice (Thorsteinsdottir, *EMBOJ.* 2001, Feb 1; 20(3):350-61). A subset of acute lymphoid leukemia (ALL), acute myeloid leukemia (AML), pro-B-acute lymphocytic leukemia (pro-B ALL), myelodysplastic syndrome (MDS) and T-cell acute lymphoblastic leukaemia (T-ALL) patients can be characterized by tumor cells collected from bone marrow showing high co-expression of HOXA9 and MEISl that may be associated with increased SYK protein levels. Increased SYK protein expression can be measured by evaluating pSYK levels. Some embodiments provide a method for treating patients with ALL, pro-B ALL, AML, MDS and T-ALL, where HOXA9 and MEISl are overexpressed, by the administration of a therapeutically effective amount of a SYK inhibitor selected from Compounds 1-6, or a pharmaceutically acceptable salt, ester or derivative thereof.

[0029] Some embodiments provide methods for treating a proliferative disease or disorder in a subject in need thereof, comprising the step of administering a therapeutically effective amount of a compound selected from Compounds 1-6, or a pharmaceutically acceptable salt thereof, to said subject, wherein said subject is administered one or more anti-cancer agents selected from the group consisting of AMG-330, anti-miR155, AntiJL-l+, CD117-MTX aptamer, CD47mAb, CD-98mAb, GO-203c, hBF4-mAb, LAIRl-mAb, IL-IRAP-mAb, MG006, miR-150, MRX-6313, MSK-777, SP-2065, SPM-2, SIRPaFc, TTT-3002, MLL/Menin inhibitor, AML-IL2/CD80, 4G8SDIEM, AG-221, AG-120, AKN-028, ALT 801, Anti-CD44 mAb, ASP-2215, AT-109, AT-406, AT-9283, AZ-1208, BGB-324, BI 836858, BMS-936564, BP-100-01,

Carbozatinib, CB-839, CART-CD 123, CART-CD33, CPI-613, CPI-0610, CSL-362, CWP-232291, Dacogen, Dinacilib, DC/AML fusion, Elesclomol, EPZ-5676, GSK2879552, IGN 523, INNO-305, Iomab-B, KX-2391, LeY, LOR-253, MK-8242, MGD006, Oxi-4503, PF-449913, Plerixafor, PRI-724, Rebistanib, Rigosertib, RO-5503781, PF-04449913, SG-2000, SL-401, SGN-CD33a, TCN-P, Tiecycline, Triciribine, Vismodegib, Zosuquidar, Actimab-A, AEG 35156, Belinostat, Bl 8 11283, Bismab-A, Birinapant, BL-8040, CC-486, CNDO-109, Crenolanib, Deformolus, DFP-10917, Flavopiridol, GVAX, KB-004, KPT-330, Lestartinib, Lirilumab, LO-02040, LY209314, MK8776, Omacetaxine, Pacritinib, Panobinostat, PD-616, Pdilizumab, PR-104, Pracinostat, PLX-3397, R-l 15777, Ribovarin, Selumetinib, SGI-110, Sorafenib, Tresosulfan, Temodar, Tosedostat, Vorinostat, WT-1, Arsenix trioxide, Clofarabine, Decitabine, Laromustine, Tipfarnib and Mylotarg.

[0030] Some embodiments provide methods of treatment for anemia, thrombocytopenia, leukopenia or neutropenia wherein said patient is not undergoing chemotherapy. For example, the subject is treated with a compound selected from Compounds 1-6 while the subject is not undergoing chemotherapy with agents such as DNA damaging agents, antibiotic agents, antimitotic agents, steroids or glucocorticoids. DNA alkylating agents can be selected from, for example, actinomycin, amsacrine, busulfan, carboplatin, chlorambucil, cisplatin, cyclophosphamide, Cytoxan, dactinomycin, daunorubicin, doxorubicin, epirubicin, iphosphamide, melphalan, merchlorethamine, mitomycin, mitoxantrone, nitrosourea, procarbazine, Taxol, Taxotere, teniposide, etoposide and triethylenethiophosphoramide. The antibiotic chemotherapy agents can be selected from dactinomycin (actinomycin D), daunorubicin, doxorubicin (adriamycin), idarubicin, anthracyclines, mitoxantrone, bleomycins, plicamycin (mithramycin) and mitomycin. The antimitotic agents can be selected from vinca alkaloids, a taxane, nocodazole, epothilones, navelbine and epidipodophyllotoxin. Vinca alkaloids can be selected from vinblastine and vincristine, or derivatives thereof. Taxanes can be selected from paclitaxel and docetaxel, or derivatives thereof.

Pharmaceutical Compositions and Modes of Administration

[0031] Compounds provided herein are usually administered in the form of pharmaceutical compositions. Thus, provided herein are also pharmaceutical compositions that contain one or more of the compounds of any of the formulae disclosed herein or a pharmaceutically acceptable salt, isomer, prodrug, or solvate

thereof, and one or more pharmaceutically acceptable vehicles selected from carriers, adjuvants and excipients. Suitable pharmaceutically acceptable vehicles may include, for example, inert solid diluents and fillers, diluents, including sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants. Such compositions are prepared in a manner well known in the pharmaceutical art. *See, e.g.,* Remington's Pharmaceutical Sciences, Mace Publishing Co., Philadelphia, Pa. 17th Ed. (1985); and Modem Pharmaceutics, Marcel Dekker, Inc. 3rd Ed. (G.S. Banker & C.T. Rhodes, Eds.).

[0032] The pharmaceutical compositions may be administered in either single or multiple doses. The pharmaceutical composition may be administered by various methods including, for example, rectal, buccal, intranasal and transdermal routes. In certain embodiments, the pharmaceutical composition may be administered by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, topically, or as an inhalant. In some embodiments, the pharmaceutical composition is administered orally.

[0033] One mode for administration is parenteral, for example, by injection. The forms in which the pharmaceutical compositions described herein may be incorporated for administration by injection include, for example, aqueous or oil suspensions, or emulsions, with sesame oil, com oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles.

[0034] Oral administration may be another route for administration of the compounds described herein. Administration may be via, for example, capsule or enteric coated tablets. In making the pharmaceutical compositions that include at least one compound of any of the formulae described herein or a pharmaceutically acceptable salt, prodrug, or solvate thereof, the active ingredient is usually diluted by an excipient and/or enclosed within such a carrier that can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be in the form of a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, sterile injectable solutions, and sterile

packaged powders. In certain embodiments, the pharmaceutical composition is in the form of tablets.

[0035] As used herein, "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

[0036] Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally include lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl and propylhydroxy-benzoates; sweetening agents; and flavoring agents.

[0037] The compositions that include at least one compound of any of the formulae described herein or a pharmaceutically acceptable salt, isomer, prodrug, or solvate thereof, can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the subject by employing procedures known in the art. Controlled release drug delivery systems for oral administration include osmotic pump systems and dissolution systems containing polymer-coated reservoirs or drug-polymer matrix formulations. Examples of controlled release systems are given in U.S. Patent Nos. 3,845,770, 4,326,525, 4,902,514 and 5,616,345. Another formulation for use in the methods of the present application employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds described herein in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. *See, e.g.,* U.S. Patent Nos. 5,023,252, 4,992,445 and 5,001,139. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

[0038] For preparing solid compositions such as tablets, the principal active ingredient may be mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of any of the above formulae or a pharmaceutically acceptable salt, prodrug, or solvate thereof. When referring to these preformulation compositions as homogeneous, the active ingredient may be dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

[0039] The tablets or pills of the compounds described herein may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action, or to protect from the acid conditions of the stomach. For example, the tablet or pill can include an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer that serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

[0040] Compositions for inhalation or insufflation may include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described supra. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. In other embodiments, compositions in pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be inhaled directly from the nebulizing device or the nebulizing device may be attached to a facemask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices that deliver the formulation in an appropriate manner.

Dosing

[0041] The specific dose level of compounds described herein for any particular subject will depend upon a variety of factors including the activity of the specific

compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease in the subj ect undergoing therapy. For example, a dosage may be expressed as a number of milligrams of a compound of the formula per kilogram of the subject's body weight (mg/kg). Dosages of between about 0.01 and 200 mg/kg may be appropriate. In some embodiments, about 0.01 and 150 mg/kg may be appropriate. In other embodiments a dosage of between 0.05 and 100 mg/kg may be appropriate. Normalizing according to the subject's body weight is particularly useful when adjusting dosages between subjects of widely disparate size, such as occurs when using the drug in both children and adult humans or when converting an effective dosage in a non-human subject such as dog to a dosage suitable for a human subject.

[0042] The daily dosage may also be described as a total amount of a compound of the formulae administered per dose or per day. Daily dosage of a compound may be between about 1 mg and 2,000 mg, between about 1,000 to 2,000 mg/day, between about 1 to 1,000 mg/day, between about 1 to 500 mg/day, between about 100 to 150 mg/day, between about 1 to 100 mg/day, between about 1 to 50 mg/day, between about 50 to 100 mg/day, between about 100 to 125 mg/day, between about 100 to 150 mg/day, between about 100 to 175 mg/day, between about 100 to 200 mg/day, between about 100 to 225 mg/day, between about 100 to 250 mg/day, between about 100 to 350 mg/day, between about 100 to 400 mg/day, between about 100 to 450 mg/day, or between about 100 to 500 mg/day.

[0043] When administered orally, the total daily dosage for a human subj ect may be between 1 mg and 1,000 mg/day, between about 1 to 100 mg/day, between about 1 to 50 mg/day, between about 50 to 100 mg/day, between 50 to 300 mg/day, between 50 to 200 mg/day, between 75 to 200 mg/day, between 75 to 150 mg/day, between 100 to 200 mg/day, between about 200 to 300 mg/day, between about 300 to 400 mg/day, between about 400 to 500 mg/day, between about 100 to 150 mg/day, between about 150 to 200 mg/day, between about 200 to 250 mg/day, between about 75 to 150 mg/day, or between about 150 to 300 mg/day.

[0044] The compounds of the present application or the compositions thereof may be administered once, twice, three, or four times daily, using any suitable mode described above.

Example

[0045] Methods: In this phase lb/2 study (NCT02343939), patients age 18 to 70 years with previously untreated AML, preserved organ function, and ECOG ≤ 2 were eligible to receive dose escalated entospletinib (ENTO or Compound-1) for 14 days as monotherapy (days -14 to 0) followed by combination with daunorubicin 60 mg/m2/d, cycle 1 day 1 to 3, and cytarabine 100 mg/m2/d, cycle 1 day 1 to 7. All patients received entospletinib (ENTO or Compound-1) monotherapy for up to 14 days prior to starting induction. Chemotherapy could be initiated after 5 days of monotherapy (and entospletinib continued for 4+ weeks) in patients with leukemia-related complications necessitating chemotherapy. Patients enrolled to dose level (DL) 0 and DL 1 received entospletinib 200 mg po BID and 400 mg po BID, respectively. Patients with residual disease two weeks after chemotherapy received a second induction cycle identical to the first. Entospletinib was continued without interruption until remission was assessed at count recovery.

[0046] Results: Twelve patients enrolled with a median age of 54 (range, 18-69) years. Patients were in the following European LeukemiaNet genetic risk groups: favorable (n=l), intermediate I (n=3), intermediate II (n=2), and adverse (n=4), respectively. Three patients were not evaluable for dose limiting toxicity (DLT) assessment and were replaced (due to detection of CNS disease requiring non-study therapy (n=l), and withdrawal of consent unrelated to drug toxicity (n=2)). Single-agent entospletinib during the window period was well tolerated; toxicities after combination with intensive chemotherapy were common and typical. Among three patients treated at 200 mg BID, no DLT was observed. Of three patients treated at 400 mg BID, a patient with documented fungal pneumonia developed grade 3 pneumonitis that was possibly related to entospletinib. Although this did not meet DLT criteria, DL 1 was expanded with 3 additional patients, none of whom experienced DLT. Overall, the most common non hematologic adverse events (inclusive of intensive chemotherapy periods) were febrile neutropenia, nausea, and diarrhea. Based on this clinical experience and compiled pharmacokinetic data demonstrating lack of benefit to further dose escalation, 400 mg BID was selected as the recommended phase 2 dose. Responses were seen at both levels. Among the 3 patients treated at 200 mg BID, two required a second induction but each achieved a complete remission (CR) (3/3; 100%). Of the 6 patients treated at 400 mg BID, none required a second induction and the CR rate was also 100%. Remarkably, an

18 year old male with 1lq23-rearranged AML achieved morphologic and cytogenetic CR after only the 14 day entospletinib monotherapy window (prior to chemotherapy). Another patient with 1lq23-rearranged AML had significant platelet response during the window period (this patient refused disease evaluation by marrow aspiration prior to chemotherapy).

[0047] A neutrophil recovery plot for all enrolled subjects in the above study is provided in Figure 1. During the entospletinib monotherapy lead-in period, absolute neutrophil counts (ANC) remained largely stable. All three of the evaluable subjects at the entospletinib 400 mg dose level who were under the severe neutropenia cutoff of 200/μL ANC at baseline recovered to above 200/μL during treatment. Severe neutropenia in these subjects was short lived, with a median (Ql, Q3) time to recovery of 8 (8, 14) days; individual values were 8, 8, and 14 days. The only evaluable subject with severe neutropenia at baseline at the entospletinib 200 mg dose level also recovered during treatment (recovery time of 66 days). Among the five subjects (treated at both entospletinib dose levels) who did not have severe neutropenia at baseline and had at least one post-baseline ANC assessment, none experienced severe neutropenia at any time during induction treatment; however, two of the five subjects, both treated at the entospletinib 400 mg dose level, did experience severe neutropenia during the entospletinib monotherapy lead-in period, which recovered to above 200/μL by the end of the first induction cycle in both subjects (Figure 1).

[0048] A plot of platelet counts through induction treatment for all enrolled subjects in the above study is provided in Figure 2. During the two week entospletinib monotherapy window, platelet count remained stable, or in some cases, improved from baseline. One subject received platelet transfusions at the entospletinib 200 mg dose level and no transfusions were required at the entospletinib 400 mg dose level. During induction treatment, the mean number of transfusions required per subject was 4.1 during Cycle 1 and 5.5 during Cycle 2. Across the monotherapy lead-in and induction treatment cycles, the mean number of platelet transfusions required per subject was 8.7 at the ENTO 200 mg dose level, 4.1 at the entospletinib 400 mg dose level, and 5.5 overall (Figure 3).

[0049] Throughout this specification, various patents, patent applications and other types of publications (e.g., journal articles) are referenced. The disclosure of all patents,

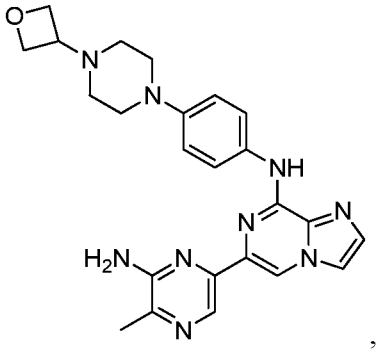
patent applications, and publications cited herein are hereby incorporated by reference in their entirety for all purposes.

CLAIMS

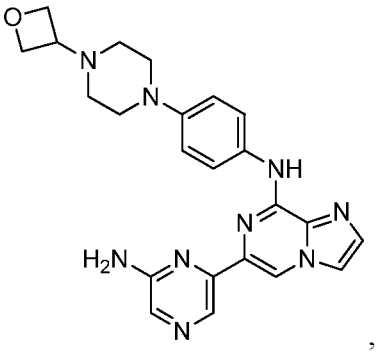
What is claimed is:

1. A method of treating or reducing thrombocytopenia, leukopenia, anemia, or neutropenia in a patient in need thereof, comprising the step of administering an effective amount of a compound selected from:

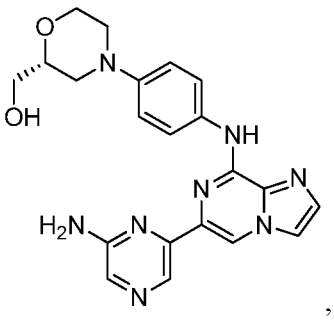
Compound- 1



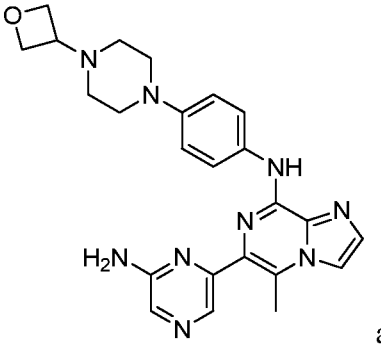
Compound-2



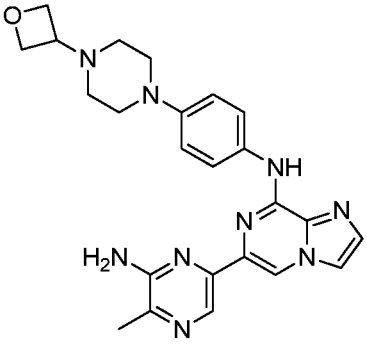
Compound-3



Compound-4



and



Compound-5 Compound-6

or a pharmaceutically acceptable salt thereof.

2. The method according to claim 1 wherein said anemia is selected from the group consisting of hemolytic anemia, microangiopathic hemolytic anemia, hypersplenism, dyserythropoietic anemia, spherocytosis, sideroblastic anemia, autoimmune hemolytic anemia, sickle cell anemia, thalassemia, Glucose-6-phosphate dehydrogenase (G6PD)-deficient anemia, pernicious anemia, aplastic anemia, anemia caused by liver disease or renal disease, and anemia caused by the deficiency of one or more vitamins or nutrients.

3. The method according to claim 2 wherein said vitamin or nutrient is selected from the group consisting of vitamin B12, B2, B6, C, Al, D, E or K, iron, folic acid, zinc, copper, calcium and protein.

4. The method according to claim 1 wherein said thrombocytopenia is selected from idiopathic thrombocytopenia, alcohol-induced thrombocytopenia, drug-induced immune thrombocytopenia, thrombotic thrombocytopenic purpura, transfusion-induced thrombocytopenia, primary thrombocythemia, disseminated intravascular coagulation, hypersplenism, hemolytic uremic syndrome, paroxysmal nocturnal hemoglobinuria and immune thrombocytopenia.

5. The method according to claim 4 wherein said drug-induced immune thrombocytopenia is associated with the administration of heparin.

6. The method according to claim 1 wherein the thrombocytopenia is due to low production of platelets in the bone marrow.

7. The method according to claim 1 wherein the thrombocytopenia is due to increased breakdown of platelets in the bloodstream, spleen or liver.

8. The method according to claim 1 wherein the thrombocytopenia is due to hemodilution in a patient receiving blood transfusion.

9. The method according to claim 1 wherein neutropenia is selected from the group consisting of primary neutropenia, acute neutropenia, severe chronic neutropenia, severe congenital neutropenia (Kostmann's syndrome), severe infantile genetic agranulocytosis, benign neutropenia, cyclic neutropenia, chronic idiopathic neutropenia, secondary neutropenia, syndrome associated neutropenia, and immune-mediated neutropenia.

10. The method according to claim 1 or claim 9 wherein said neutropenia is caused or associated with radiation, alcoholism, allergic disorders, aplastic anemia, autoimmune disease, myelodysplasia, myelofibrosis, dysgammaglobulinemia, paroxysmal nocturnal

hemoglobinuria, vitamin $_{B12}$ deficiency, folate deficiency, viral infection, bacterial infection, spleen disorder, hemodialysis or transplantation, myeloma, lymphoma, metastatic solid tumors which infiltrate and replace the bone marrow, toxins, bone marrow failure, Schwachman-Diamond syndrome, cartilage-hair hypoplasia, dyskeratosis congenita, glycogen storage disease type IB, splenomegaly, or intrinsic defects in myeloid cells.

11. The method according to claim 1 wherein said leukopenia is caused or associated with one or more diseases or disorders selected from aplastic anemia, autoimmune diseases, chemotherapy, radiation, hyperthyroidism, rheumatoid arthritis, liver disorders, spleen disorders, congenital disorders, viral infections, bacterial infections and parasitic infections.

12. The method according to claim 11 wherein said parasitic infection is selected from the group consisting of Acanthamoeba keratitism, amoebiasis, ascariasis, babesiosis, balantidiasis, baylisascariasis, Chagas disease, clonorchiasis, cochliomyia, cryptosporidiosis, diphyllobothriasis, dracunculiasis, echinococcosis, elephantiasis, enterobiasis, fascioliasis, fasciolopsiasis, filariasis, giardiasis, gnathostomiasis, hymenolepiasis, isosporiasis, Katayama fever, leishmaniasis, Lyme disease, malaria, metagonimiasis, myiasis, onchocerciasis, pediculosis, scabies, schistosomiasis, sleeping sickness, strongyloidiasis, taeniasis, toxocariasis, toxoplasmosis, trichinosis, and trichuriasis.

13. The method according to claim 11 wherein said viral infection is selected from the group consisting of HCV, HIV, influenza, Ebola virus, Marburg virus, flavivirus, Venezuelean equine encephalitis, Chikungunya virus, and West Nile virus.

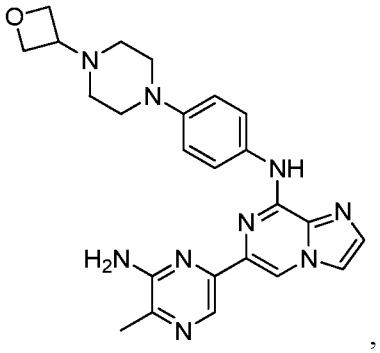
14. The method according to claim 13 wherein said flavivirus is selected from the group consisting of Absettarov, Alfuy, Apoi, Aroa, Bagaza, Banzi, Bouboui, Bussuquara, Cacipacore, Carey Island, Dakar bat, Dengue 1, Dengue 2, Dengue 3, Dengue 4, Edge Hill, Entebbe bat, Gadgets Gully, Hanzalova, Hypr, Ilheus, Israel turkey meningoencephalitis, Japanese encephalitis, Jugra, Jutiapa, Kadam, Karshi, Kedougou, Kokobera, Koutango, Kumlinge, Kunjin, Kyasanur Forest disease, Langat, Louping ill, Meaban, Modoc, Montana myotis leukoencephalitis, Murray valley encephalitis, Naranjal, Negishi, Ntaya, Omsk hemorrhagic fever, Phnom-Penh bat, Powassan, Rio Bravo, Rocio, royal farm, Russian spring-summer encephalitis, Saboya, St. Louis

encephalitis, Sal Vieja, San Perlita, Saumarez Reef, Sepik, Sokuluk, Spondweni, Stratford, Tembusu, Tyuleniy, Uganda S, Usutu, Wesselsbron, west Nile, Yaounde, yellow fever, and Zika.

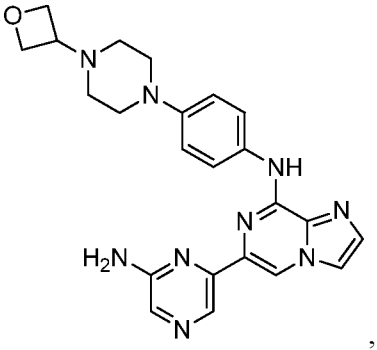
15. The method according to claim 11 wherein said bacterial infection results from a bacteria of the phyla selected from Acidobacteria, Actinobacteria, Aquificae. Bacteroidetes, Caldiserica, Chlamydiae, Chlorobi, Chloroflexi, Chrysiogenetes, Cyanobacteria, Deferribacteres, Deinococcus-Thermus, Dictyoglomi, Elusimicrobia, Fibrobacteres, Firmicutes, Fusobacteria, Gemmatimonadetes, Lentisphaerae, Nitrospira, Planctomycetes, Proteobacteria, Spirochaetes, Synergistetes, Tenericutes, Firmicutes, Thermodesulfobacteria, Thermomicrobia, Thermotogae, and Verrucomicrobia.

16. A method for treating in a human a disease or condition selected from the group consisting of an inflammatory disorder, an allergic disorder, an autoimmune disease, and a cancer in a subject in need thereof, the method comprising administering to the human in need thereof, a therapeutically effective amount of a compound selected from Compounds 1-6:

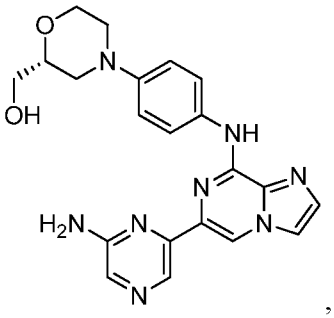
Compound-1



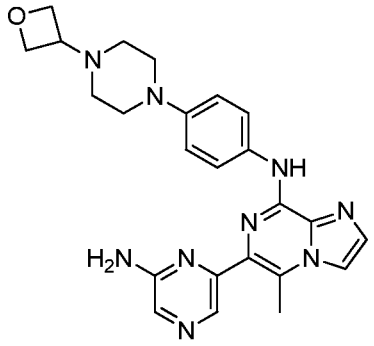
Compound-2



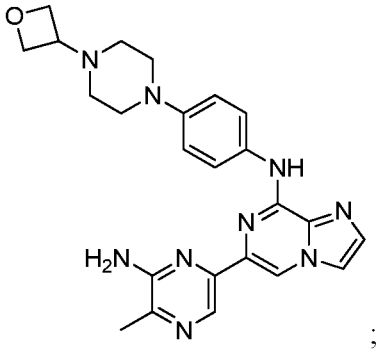
Compound-3



Compound-4



and



;

Compound-5 Compound-6

or a pharmaceutically acceptable salt thereof;

wherein said subject is additionally undergoing proton pump inhibitor therapy; and,

wherein said compound selected from Compounds 1-6 is administered at an increased daily dosage of about 25% to about 75% of a daily dosage recommended for a subject not undergoing proton pump inhibitor therapy.

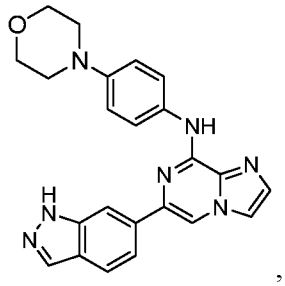
17. The method according to claim 16 wherein said proton pump inhibitor is selected from omeprazole, hydroxy omeprazole, esomeprazole, tenatoprazole, lansoprazole, pantoprazole, rabeprazole, dontoprazole, habeprazole, perprazole, ransoprazole, pariprazole, leminoprazole, tenatoprazole, S-tenatoprazole-Na, and dexlansoprazole.

18. The method according to claim 16 wherein said compound selected from Compounds 1-6 is administered to said subject undergoing proton pump inhibitor therapy at a daily dosage of between about 250 mg to about 1600 mg; and wherein said recommended daily dosage for a subject not undergoing proton pump inhibitor therapy is between about 200 mg to about 800 mg.

19. The method according to any of claims 16-18 wherein said patient is diagnosed with a disease or disorder selected from acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), myelodysplastic syndrome (MDS), myeloproliferative disease (MPD), chronic myeloid leukemia (CML), multiple myeloma (MM), non-Hodgkin's lymphoma (NHL), mantle cell lymphoma (MCL), follicular lymphoma, Waldestrom's macroglobulinemia (WM), T-cell lymphoma, B-cell lymphoma, diffuse large B-cell lymphoma (DLBCL), pancreatic cancer, bladder cancer, colorectal cancer, breast cancer, prostate cancer, renal cancer, hepatocellular cancer, lung cancer, ovarian cancer, cervical

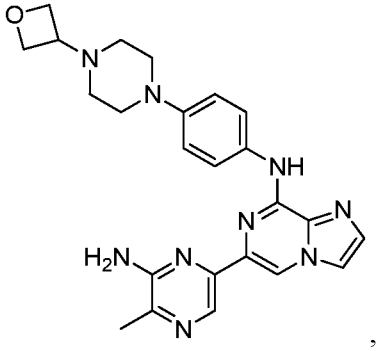
cancer, gastric cancer, esophageal cancer, head and neck cancer, melanoma, neuroendocrine cancer, CNS cancer, brain cancer, bone cancer, soft tissue sarcoma, non-small cell lung cancer, small-cell lung cancer and colon cancer.

20. A method of treating a proliferative disease or disorder in a subject in need thereof, comprising the step of administering a therapeutically effective amount of a compound selected from Compounds 1-6, or a pharmaceutically acceptable salt thereof, to said subject;



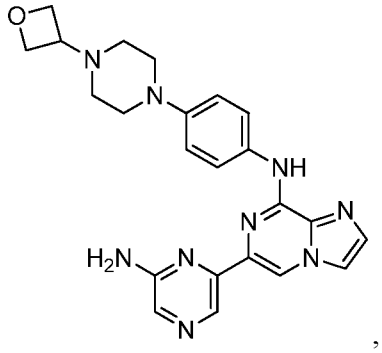
,

Compound-1



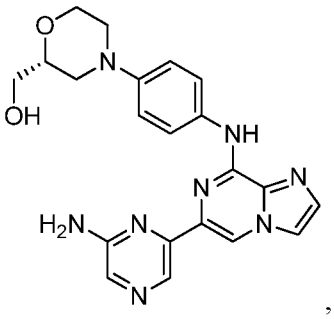
,

Compound-2



,

Compound-3



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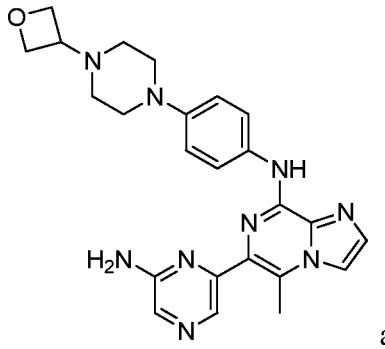
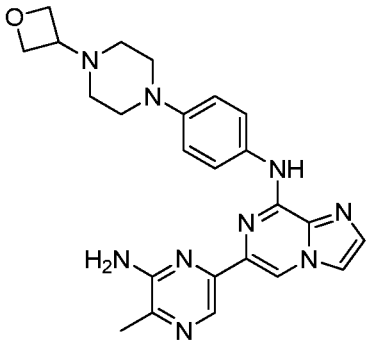
Compound-4



and



;

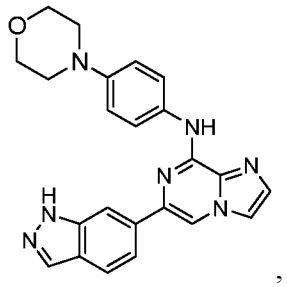
Compound-5 Compound-6

wherein said subject has one or more abnormal core-binding karyotypes selected from t(8;21)(q22;q22), inv(16)(pl3. 1q22) and t(1 6;16)(pl 3.1;q22); or wherein said subject has one or more chromosomal abnormalities selected from the deletion of 5, 5q, 7, 7q, 17p, inv(3)(q21;q26) and t(3;3)(q21;q26); or wherein said subject has a 11q23 rearrangement of MLL gene.

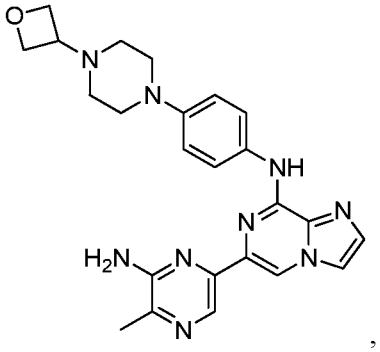
21. The method according to claim 20 wherein said subject has two more of said abnormalities.

22. The method according to claim 20 wherein said subject has three or more of said abnormalities.

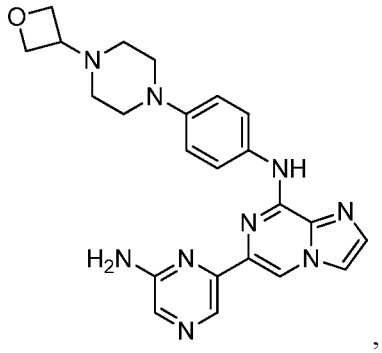
23. A method of treating a proliferative disease or disorder in a subject in need thereof, comprising the step of administering a therapeutically effective amount of a compound selected from Compounds 1-6, or a pharmaceutically acceptable salt thereof, to said subject;



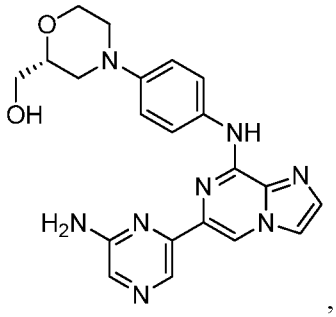
Compound- 1



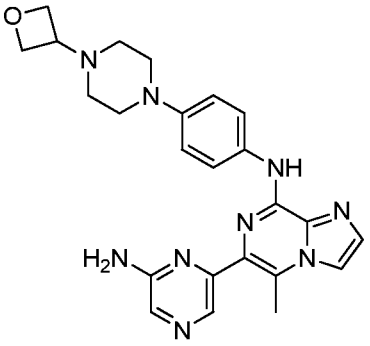
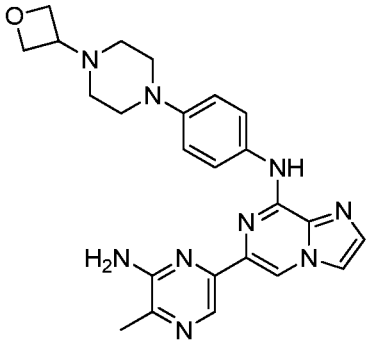
Compound-2



Compound-3



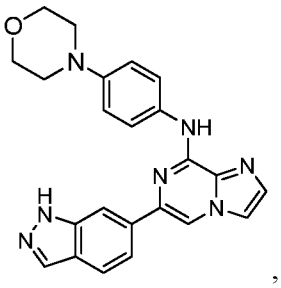
Compound-4


and

;

Compound-5 Compound-6

wherein said subject has or expresses a mixed lineage leukemia (MLL) fusion protein, a BCR-ABL fusion protein, FLT3 intemal tandem duplications, a deleted or mutated p53, high or elevated levels of meningioma 1, and/or high levels of lactate dehydrogenase.

24. A method of treating a proliferative disease or disorder in a subject in need thereof, comprising the step of administering a therapeutically effective amount of a compound selected from Compounds 1-6, or a pharmaceutically acceptable salt thereof, to said subject;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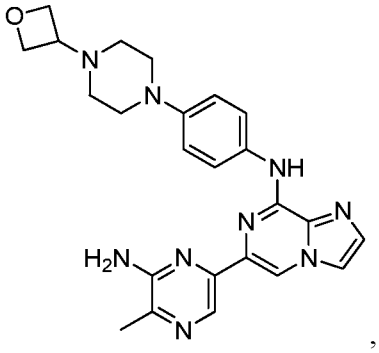
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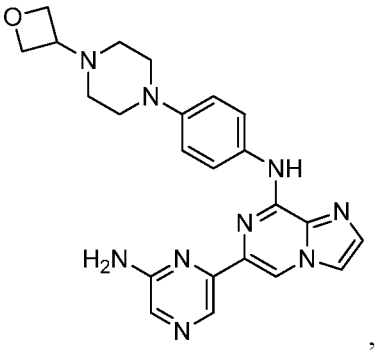
Compound-1 Compound-2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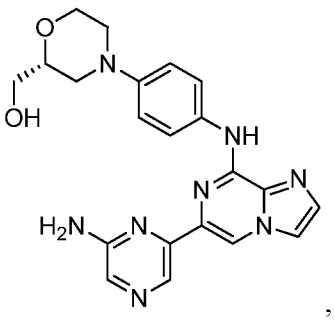
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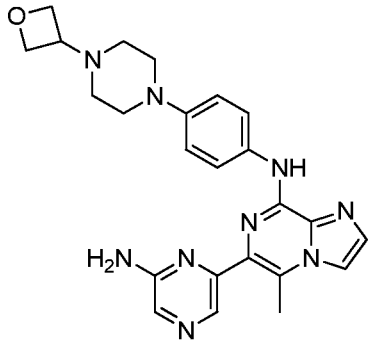
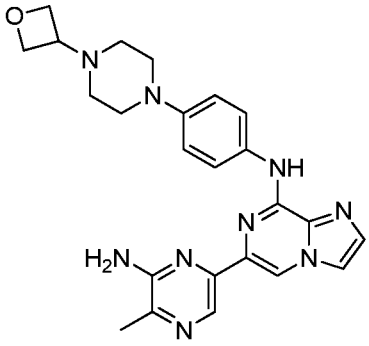
Compound-3 Compound-4



and



;

Compound-5 Compound-6

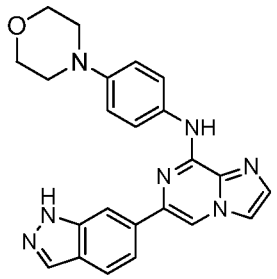
wherein said subject is administered one or more anti-cancer agents selected from the group consisting of AMG-330, anti-miR155, AntiJL-l+, CD117-MTX aptamer, CD47mAb, CD-98mAb, GO-203c, hBF4-mAb, LAIRl-mAb, IL-IRAP-mAb, MG006, miR-150, MRX-6313, MSK-777, SP-2065, SPM-2, SIRPaFc, TTT-3002, MLL/Menin inhibitor, AML-IL2/CD80, 4G8SDIEM, AG-221, AG-120, AKN-028, ALT 801, Anti-CD44 mAb, ASP-2215, AT-109, AT-406, AT-9283, AZ-1208, BGB-324, BI 836858, BMS-936564, BP-100-01, Carbozatinib, CB-839, CART-CD 123, CART-CD33, CPI-613, CPI-0610, CSL-362, CWP-232291, Dacogen, Dinacilib, DC/AML fusion, Elesclomol, EPZ-5676, GSK2879552, IGN 523, INNO-305, Iomab-B, KX-2391, LeY, LOR-253, MK-8242, MGD006, Oxi-4503, PF-449913, Plerixafor, PRI-724, Rebistanib, Rigosertib, RO-5503781, PF-04449913, SG-2000, SL-401, SGN-CD33a, TCN-P, Tiecycline, Triciribine, Vismodegib, Zosuquidar, Actimab-A, AEG 35156, Belinostat, B1811283, Bismab-A, Birinapant, BL-8040, CC-486, CNDO-109, Crenolanib, Deformolus, DFP-10917, Flavopiridol, GVAX, KB-004, KPT-330, Lestartinib, Lirilumab, LO-02040, LY209314, MK8776, Omacetaxine, Pacritinib, Panobinostat, PD-616, Pdilizumab, PR-104, Pracinostat, PLX-3397, R-l 15777, Ribovarin, Selumetinib, SGI-110, Sorafenib, Tresosulfan, Temodar, Tosedostat, Vorinostat, WT-1, Arsenix trioxide, Clofarabine, Decitabine, Laromustine, Tipfamib, Palbocyclib, Quizartinib and Mylotarg.

25. The method according to any of claims 17-24 wherein said proliferative disease or disorder is selected from acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), myelodysplastic syndrome (MDS), myeloproliferative disease (MPD), chronic myeloid leukemia (CML), multiple myeloma (MM), non-Hodgkin's lymphoma (NHL), mantle cell lymphoma (MCL), follicular lymphoma, Waldestrom's macroglobulinemia (WM),

T-cell lymphoma, B-cell lymphoma, diffuse large B-cell lymphoma (DLBCL), pancreatic cancer, bladder cancer, colorectal cancer, breast cancer, prostate cancer, renal cancer, hepatocellular cancer, lung cancer, ovarian cancer, cervical cancer, gastric cancer, esophageal cancer, head and neck cancer, melanoma, neuroendocrine cancer, CNS cancer, brain cancer, bone cancer, soft tissue sarcoma, non-small cell lung cancer, small-cell lung cancer and colon cancer.

26. The method according to claim 25 wherein said disease or disorder is selected from AML, DLBCL, ALL and MDS.

27. The method according to any of the above claims wherein said compound is a bis-mesylate salt of Compound-1:



Compound-1,

or a hydrate thereof.

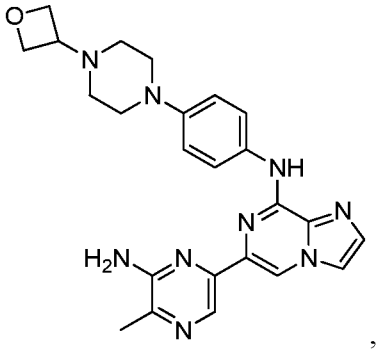
28. The method according to any of the above claims wherein said disease or disorder is AML.

29. The method according to any of the above claims wherein said subject is not undergoing chemotherapy.

30. The method according to claim 29 wherein said chemotherapy is selected from DNA damaging agents, antibiotic agents, antimitotic agents, steroids glucocorticoids.

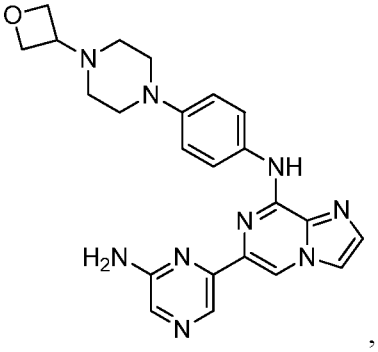
31. A method of treating a patient suffering from ALL, pro-B ALL, AML, MDS or T-ALL associated with the overexpression of HOXA9 and MEISl, comprising the step determining the level of HOXA9 and MEISl in said patient, followed by the step of administering a therapeutically effective amount of a compound selected from Compounds 1-6, or a pharmaceutically acceptable salt thereof, to said patient;

,



,

Compound-1 Compound-2



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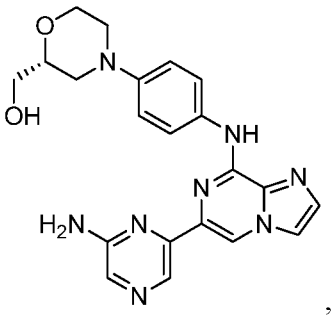
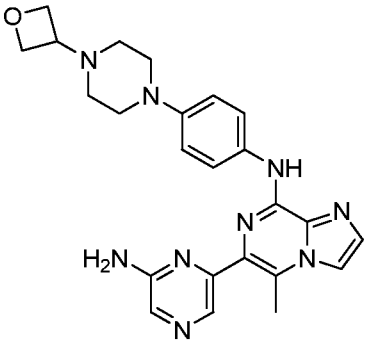
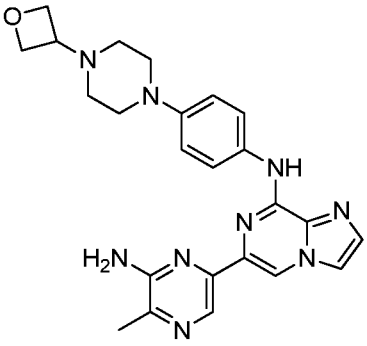


,

Compound-3 Compound-4



and



;

Compound-5 Compound-6

wherein HOXA9 and MEISl are overexpressed in said patient.

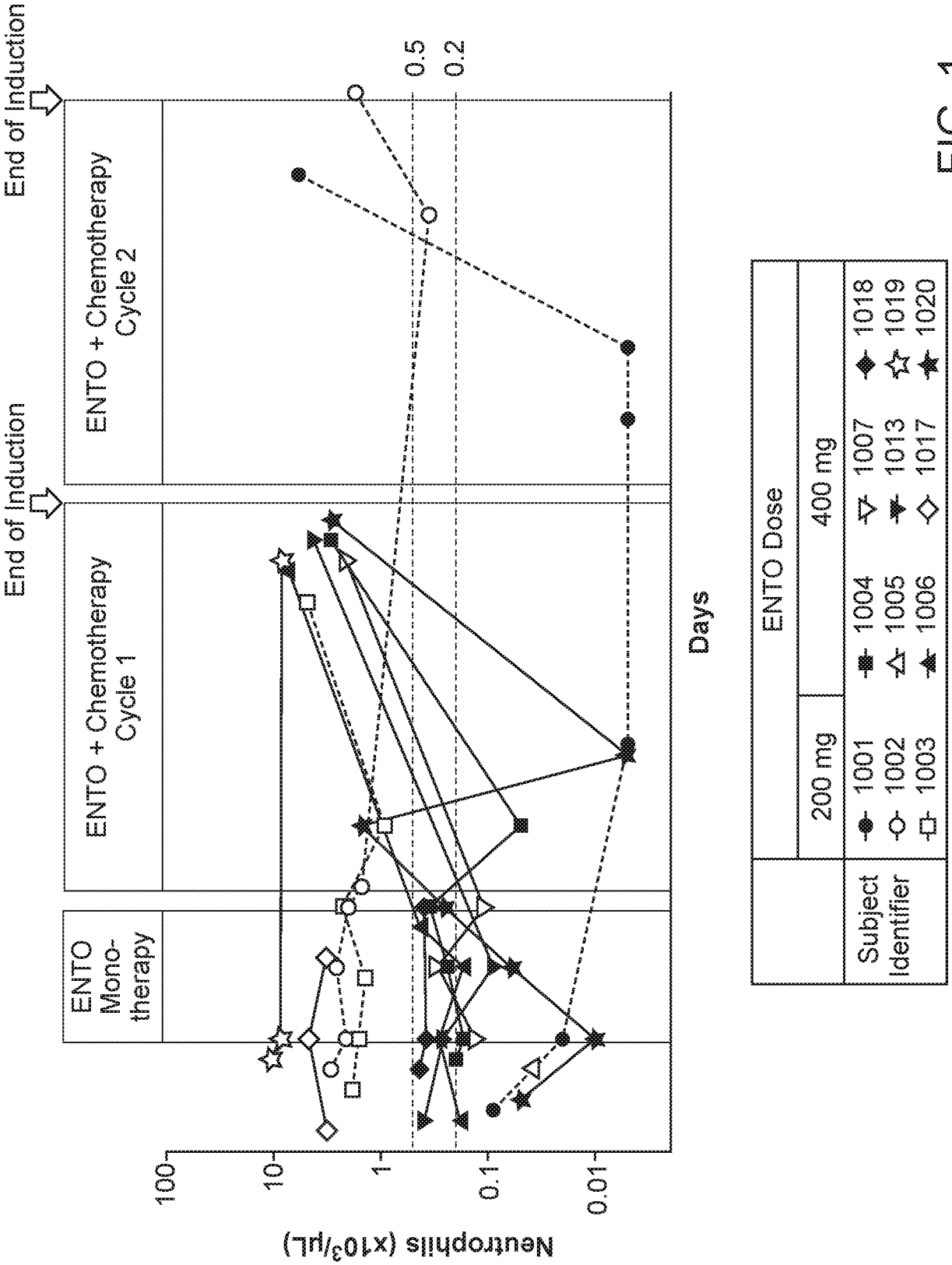

End of Induction
End of Induction
ENTO Mono-therapy
ENTO + Chemotherapy Cycle 1
ENTO + Chemotherapy Cycle 2
0.5
0.2
100
10
1
0.1
0.01
Neutrophils (x10³/μL)
Days
ENTO Dose
200 mg
400 mg
Subject Identifier
1001
1002
1003
1004
1005
1006
1007
1013
1017
1018
1019
1020

FIG. 1

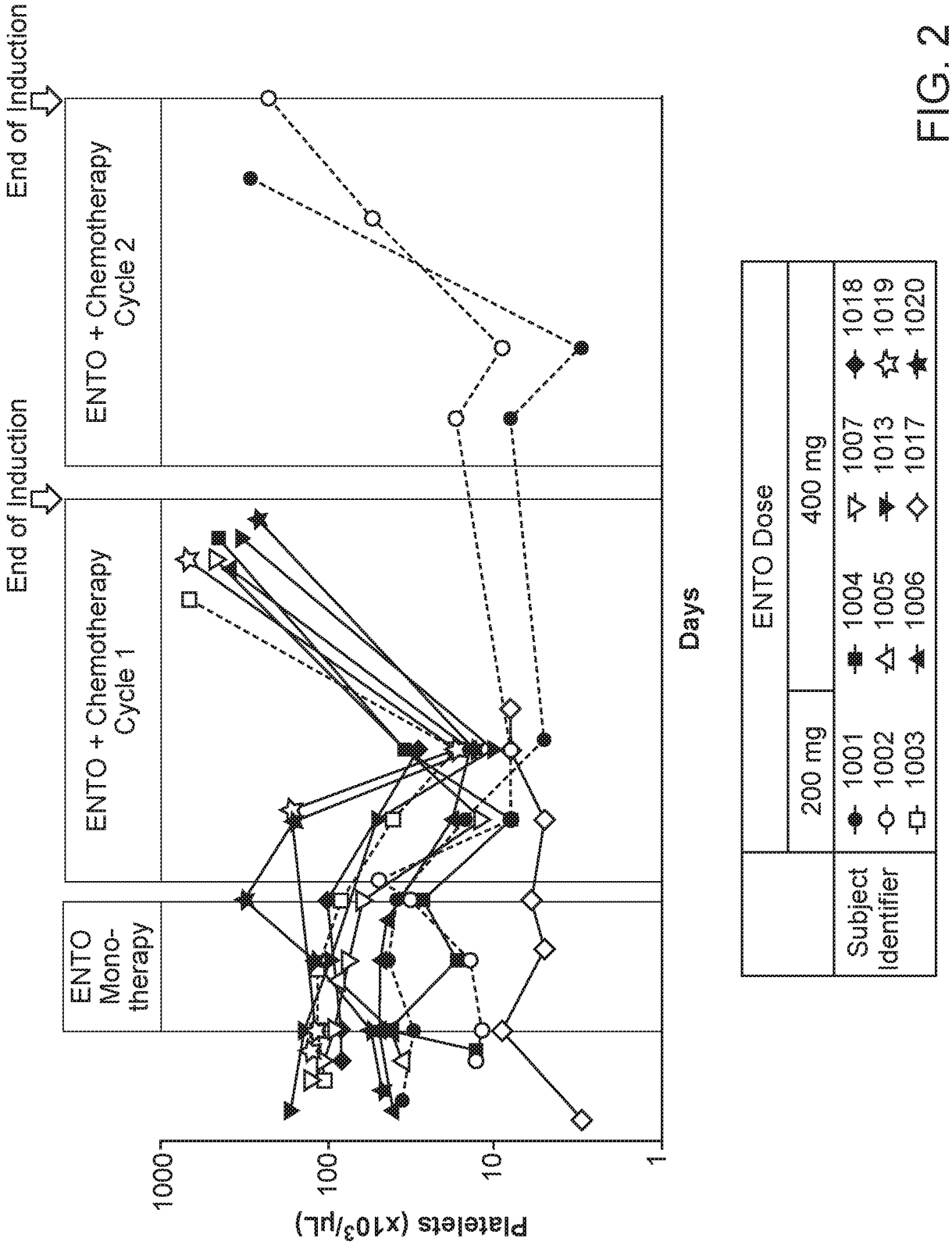

ENTO Mono-therapy
ENTO + Chemotherapy Cycle 1
ENTO + Chemotherapy Cycle 2
End of Induction
End of Induction
End of Induction
Days
Platelets (x10³/μL)
1000
100
10
1
ENTO Dose
200 mg
400 mg
Subject Identifier
1001
1002
1003
1004
1005
1006
1007
1013
1017
1018
1019
1020

FIG. 2

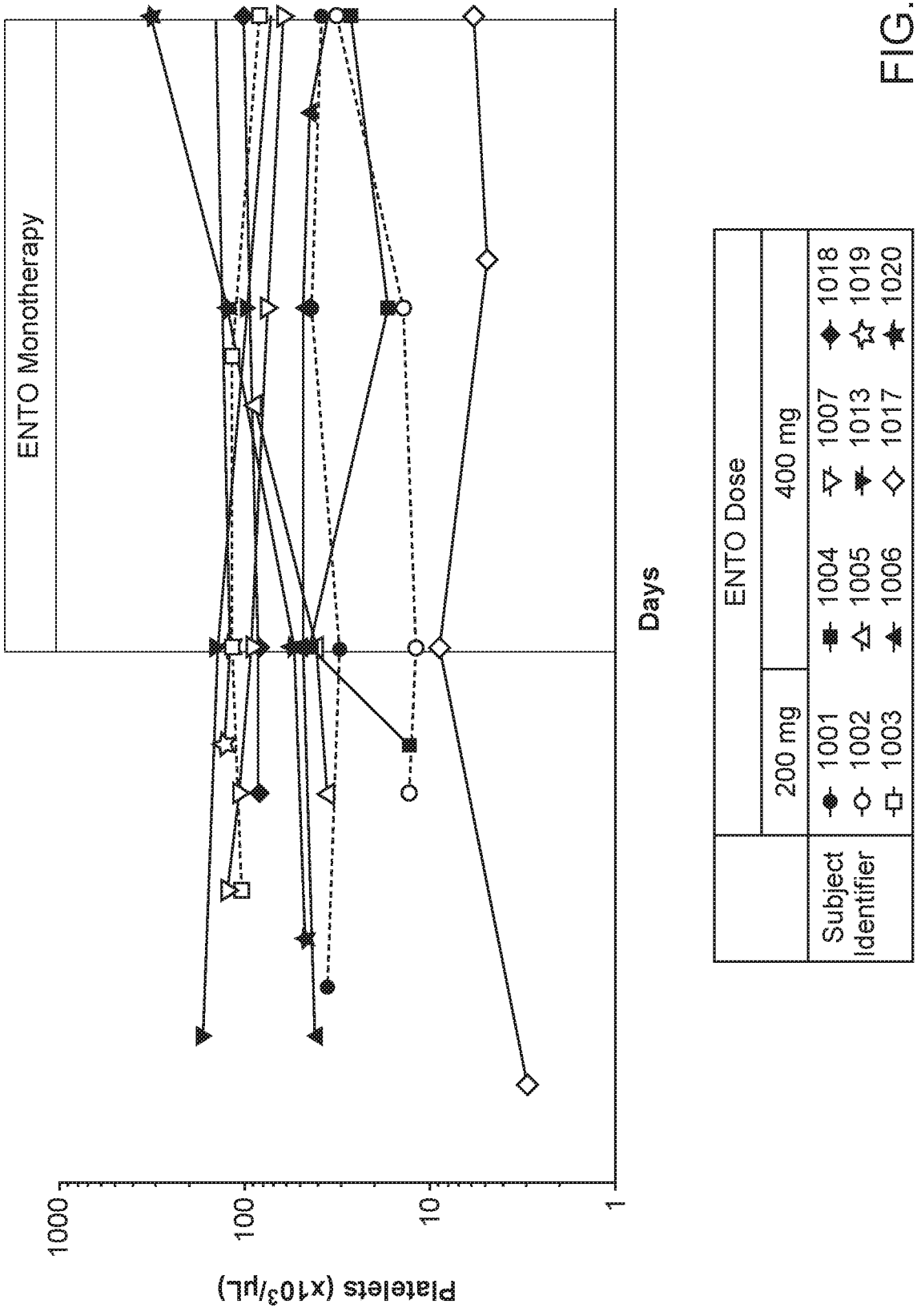

ENTO Monotherapy
Platelets (x10³/μL)
1000
100
10
1
Days
ENTO Dose
200 mg
400 mg
Subject Identifier
1001
1002
1003
1004
1005
1006
1007
1013
1017
1018
1019
1020

FIG. 3

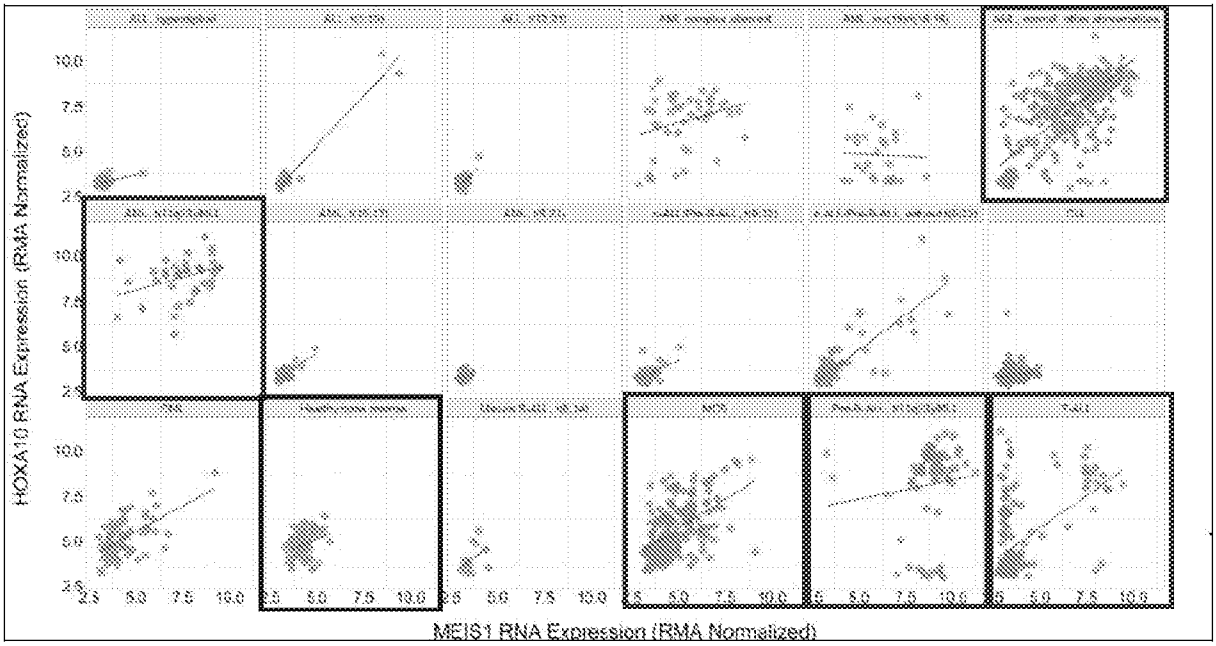

HOXA10 RNA Expression (RMA Normalized)
MEIS1 RNA Expression (RMA Normalized)

Fig. 4

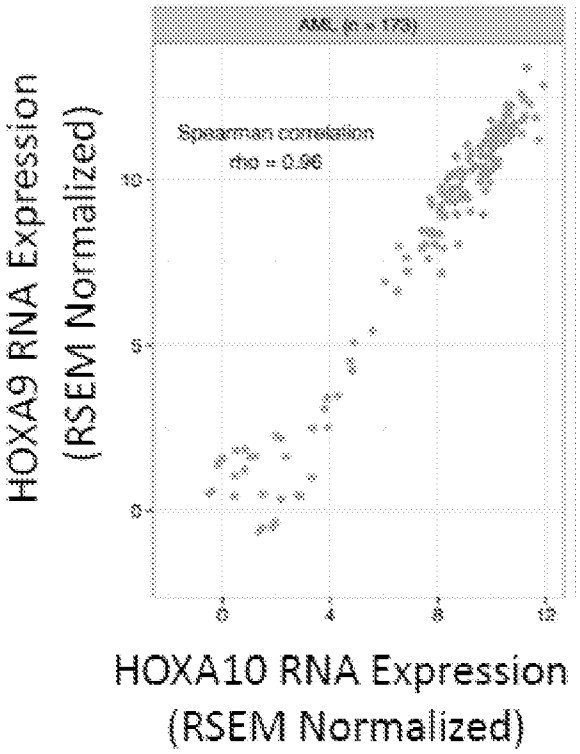

HOXA9 RNA Expression
(RSEM Normalized)
Spearman correlation
HOXA10 RNA Expression
(RSEM Normalized)

Fig. 5

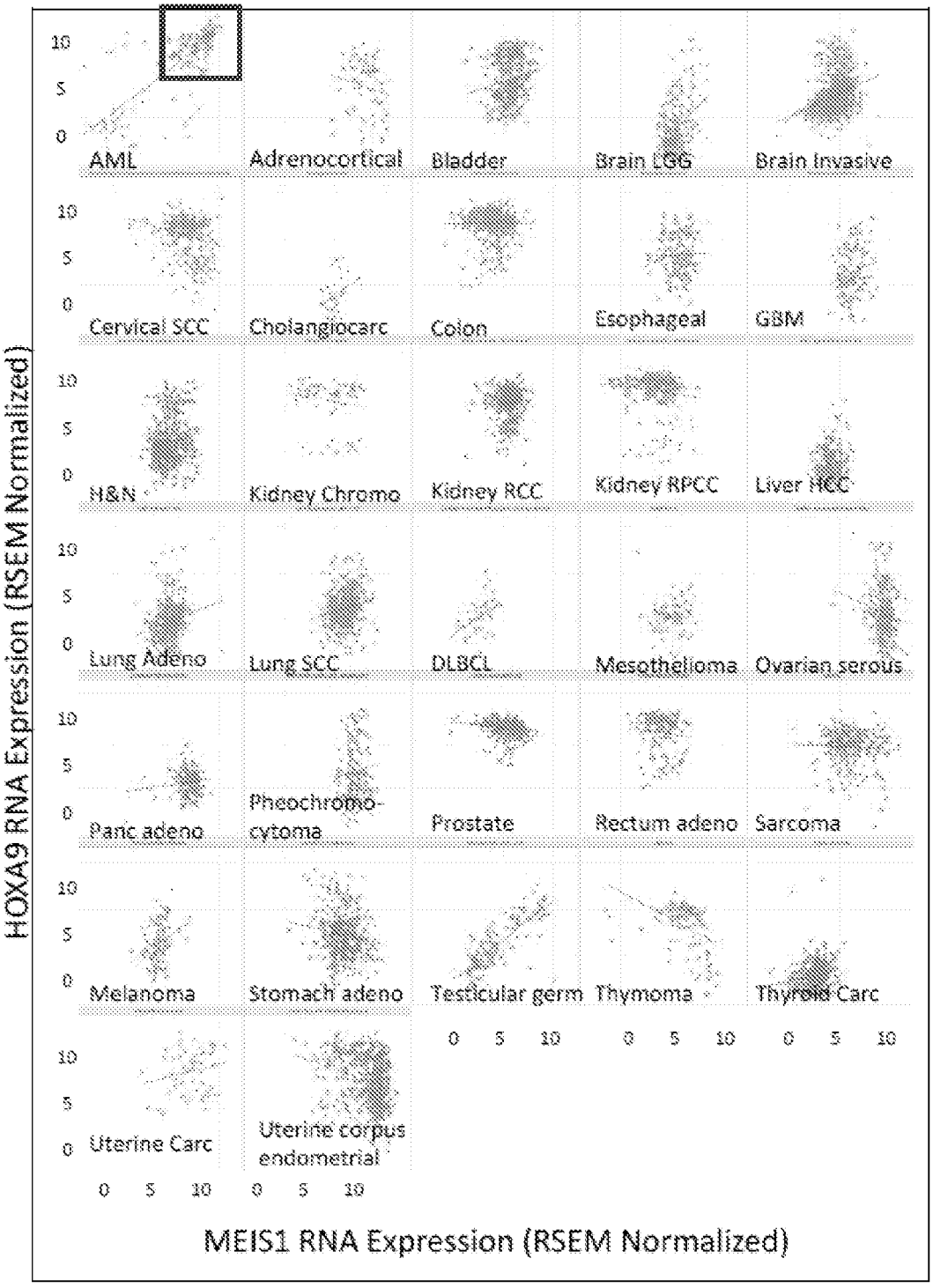

HOXA9 RNA Expression (RSEM Normalized)
MEIS1 RNA Expression (RSEM Normalized)
AML
Adrenocortical
Bladder
Brain LGG
Brain Invasive
Cervical SCC
Cholangiocarc
Colon
Esophageal
GBM
H&N
Kidney Chromo
Kidney RCC
Kidney RPCC
Liver HCC
Lung Adeno
Lung SCC
DLBCL
Mesothelioma
Ovarian serous
Panc adeno
Pheochromo-cytoma
Prostate
Rectum adeno
Sarcoma
Melanoma
Stomach adeno
Testicular germ
Thymoma
Thyroid Carc
Uterine Carc
Uterine corpus endometrial
0
5
10

Fig. 6

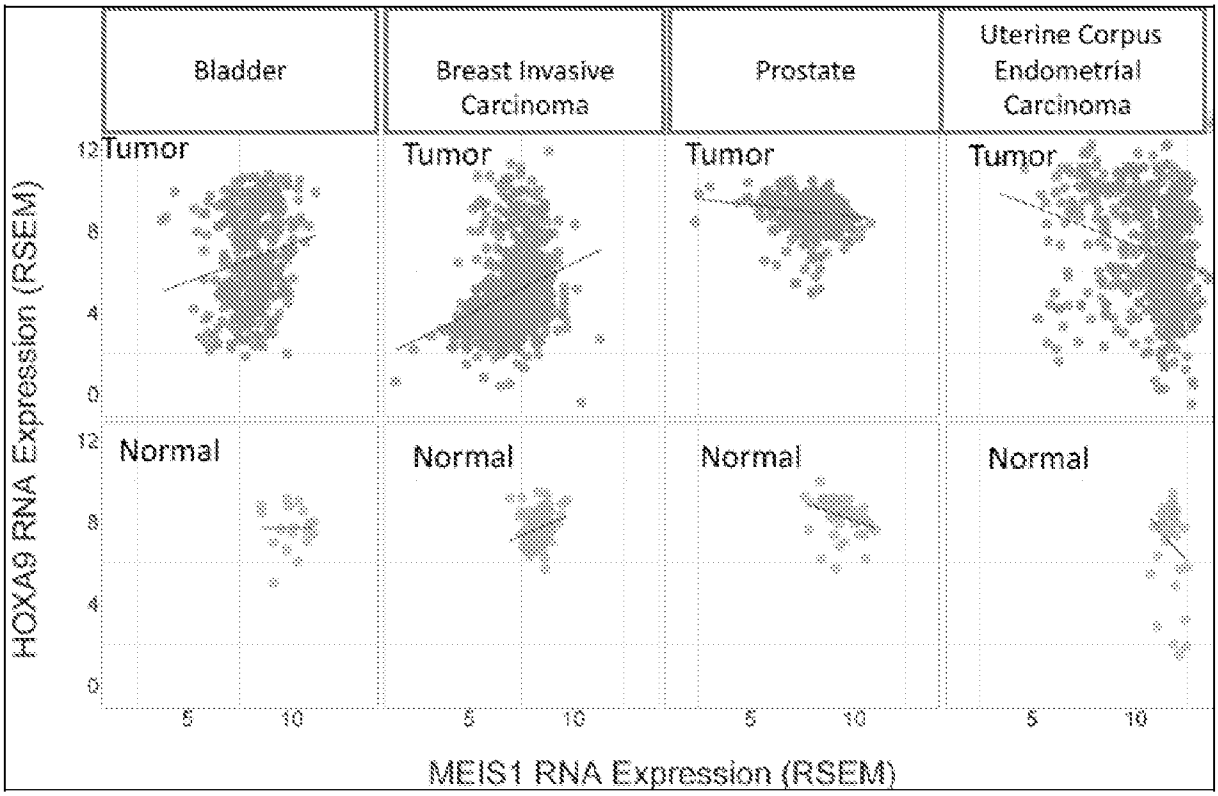

Bladder
Breast Invasive Carcinoma
Prostate
Uterine Corpus Endometrial Carcinoma
Tumor
Normal
HOXA9 RNA Expression (RSEM)
MEIS1 RNA Expression (RSEM)
0
4
8
12
5
10

Fig. 7

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/051649

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4985 A61K31/5377
ADD. A61P35/00 A61P35/02 A61P37/08 A61P7/06 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal , BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2015/100217 A1 (GILEAD SCIENCES INC [US]) 2 July 2015 (2015-07-02) claims 1, 18-19; compounds of examples 1-4; p. 72, l. 2, p. 72, l. 14-15; p. 73, first paragr.	1-15, 27-30
Y	US 2015/150881 A1 (DI PAOLO JULIE [US] ET AL) 4 June 2015 (2015-06-04) claims; [0018]; [0064-0065]; [0076]	1-15, 27-30
X	US 2012/220582 A1 (MITCHELL SCOTT A [US] ET AL) 30 August 2012 (2012-08-30)	1,2,4
Y	claim 1; [0964]	1-15, 27-30

-/- .

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" documentwhich may throw doubts on priority claim(s) orwhich is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 November 2017	30/01/2018

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Dahse, Thomas

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2016/010809 Al (GILEAD SCIENCES INC [US]) 21 January 2016 (2016-01-21)	1,2,4
Y	claims 1, 10; compounds on p. 128, 131, 134, 136, 138, 144	1-15, 27-30
Y	US 2015/038504 Al (CASTEEL MELISSA JEAN [US] ET AL) 5 February 2015 (2015-02-05) [0002] ; claims 52, 59-63	1-15, 27-30
Y	Sharman ET AL: "Phase 2 Trial of Entospleti nib (GS-9973), a Selecti ve SYK Inhi bitor, in Follicular Lymphoma (FL) ¦ Blood Journal ", Blood 2014; 124: 4419, 1 January 2014 (2014-01-01) , XP055426011, Retri eved from the Internet: URL: http: //www. bloodjournal .org/content/124/21/4419? sso-checked=true [retri eved on 2017-11-16] title, abstract	1-15, 27-30
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Y	Crow ET AL: "Inhi bition of Immune Thrombocytopeni c Purpura (ITP) by an Oral ly Bioavai labl e Inhi bitor of Syk Kinase Acti vity. ¦ Blood Journal ", blood 2005 106 2165, 1 January 2005 (2005-01-01) , XP055426026, Retri eved from the Internet: URL: http: //www. bloodjournal .org/content/106/11/2165? sso-checked=true [retri eved on 2017-11-16] title, abstract	1-15, 27-30
Y	W0 2011/014515 Al (IRM LLC [US] ; CHE JIANWEI [US] ; CHEN BEI [US] ; DING QIANG [US] ; HA0 XU) 3 February 2011 (2011-02-03) [000180] to [000184] [000137] , claims 36-37	1-15, 27-30

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, P	CHANG HUA-CHING ET AL: "Spleen tyrosine kinase mediates the actions of EPO and GM-CSF and coordinates with TGF-[beta] in erythropoiesis", BIOCHIMICA ET BIOPHYSICA ACTA. MOLECULAR CELL RESEARCH, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 1864, no. 4, 25 January 2017 (2017-01-25), pages 687-696, XP029929637, ISSN: 0167-4889, DOI: 10.1016/J.BBAMCR.2017.01.014 title, abstract ----	1-15, 27-30

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/051649

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-15 (completely) ; 27-30(partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: l-15 (completely) ; 27-30(partially)

   directed to a method of treating or reducing thrombocytopenia, leukopenia, anemia or neutropenia in a patient in need thereof

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2. claims: 16-24, 27-30(all partially)

   directed to a method of treating an inflammatory disorder, allergic disorder, autoimmune disease in a patient

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3. claims: 25, 26, 31(completely) ; 16-24, 27-30(partially)

   directed to a method of treating cancer or any other proliferative disease other than those covered by invention II.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2017/051649

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2017/051649

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