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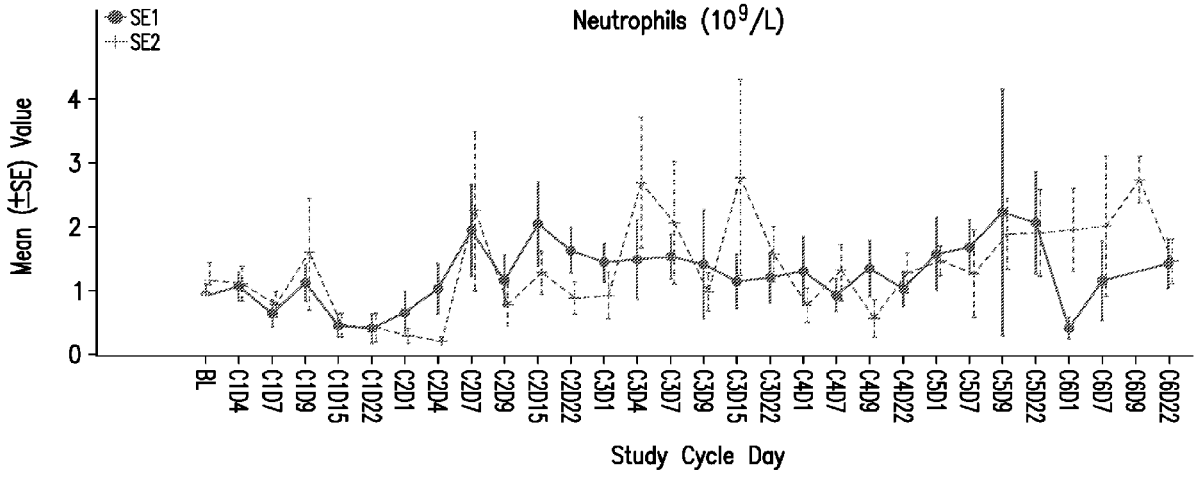

FIG. 1

(57) Abstract: The invention described herein relates to therapeutic dosing regimens comprising administering venetoclax in combination with azacitidine and a CYP3A inhibitor for treating myelodysplastic syndromes (MDS).

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VENETOCLAX DOSING REGIMENS FOR USE IN TREATING MYELODYSPLASTIC SYNDROMES IN COMBINATION WITH A CYP3A INHIBITOR AND AZACITIDINE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 63/201,743, filed May 11, 2021, the disclosure of which is incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

[0002] This invention relates to methods for treating myelodysplastic syndromes (MDS) in a human subject comprising administering to the subject venetoclax in combination with azacitidine, where the subject is also receiving a CYP3A inhibitor.

BACKGROUND OF THE INVENTION

[0003] Myelodysplastic Syndromes (MDS) represent a heterogeneous group of clonal hematopoietic stem cell disorders with significant morbidity and high mortality. These syndromes are characterized by ineffective hematopoiesis that manifest clinically as cytopenias and a variable rate of transformation to acute myeloid leukemia (secondary or sAML). Although about one-third of all MDS patients later develop AML, MDS are not considered to be an early form of AML. The primary reason for death in MDS patients is not because of AML transformation, but due to consequences of bone marrow failure, and in particular neutropenia leading to infections, including septic shock, or thrombocytopenia leading to bleeding.

[0004] Approximately half (45%) of MDS patients present with higher-risk MDS risk (International Prognostic Scoring System (IPSS) overall score > 1.5) and have a median survival less than one year with best supportive care. The only curative treatment for higher-risk MDS is an allogeneic stem cell or bone marrow transplantation. However, not all patients are eligible for this intensive treatment approach. If bone marrow transplantation is not possible, patients are typically treated with hypomethylating agents such as azacitidine. Currently, azacitidine is the only drug shown to prolong survival in treatment-naïve higher-risk MDS, however, overall outcomes need to be improved.

[0005] Venetoclax is an oral small molecule inhibitor of B-cell lymphoma 2 (BCL-2) that rapidly induces multiple hallmarks of apoptotic cell death. Venetoclax is being investigated in

clinical oncology studies as a monotherapy and in combination with a variety of compounds for the treatment of a number of hematologic malignancies, including chronic lymphocytic leukemia (CLL) and acute myeloid leukemia (AML). However, the dosing regimen used in the first clinical trial of venetoclax in MDS produced deleterious side effects in certain patients. For example, two subjects developed fatal sepsis in the setting of severe neutropenia. Thus, there exists in the art a need for dosing regimen for MDS patients experiencing certain side effects. In addition, venetoclax may be dosed with CYP3A inhibitors. Therefore, there is a need in the art for dosing regimens for MDS with venetoclax and azacitidine when co-dosed with strong or moderate CYP3A inhibitors.

BRIEF SUMMARY OF THE INVENTION

[0006] The present disclosure relates to methods for treating myelodysplastic syndromes in a human subject, and in some aspects, more specifically treatment-naïve higher-risk myelodysplastic syndromes.

[0007] In certain embodiments, a method for treating myelodysplastic syndromes in a human subject is provided, comprising administering to the human subject a daily dose of 200 mg, 100 mg, 70 mg, or 50 mg of venetoclax for 14 days in a 28 day dosing cycle, a daily dose of 75 mg/m^2 of azacitidine for 7 days in a 28 day dosing cycle, and a CYP3A inhibitor. In certain aspects, the myelodysplastic syndromes are treatment-naïve higher-risk myelodysplastic syndromes.

[0008] In certain embodiments, the daily dose of venetoclax is 200 mg and the CYP3A inhibitor is a moderate CYP3A inhibitor. In other embodiments, the daily dose of venetoclax is 100 mg and the CYP3A inhibitor is a strong CYP3A inhibitor. In yet other embodiments, the daily dose of venetoclax is 70 mg and the CYP3A inhibitor is posaconazole.

[0009] In certain embodiments, a method for treating myelodysplastic syndromes in a human subject is provided. The method comprises administering to the human subject a daily dose of venetoclax for 14 days in a 28 day dosing cycle, a daily dose of 75 mg/m^2 of azacitidine for 7 days in a 28 day dosing cycle, and a CYP3A inhibitor; wherein the daily dose of venetoclax is: 200 mg when administered in combination with a moderate CYP3A inhibitor, 100 mg when administered in combination with a strong CYP3A inhibitor other than posaconazole, and 70 mg when administered in combination with posaconazole.

[0010] In certain embodiments, a method for treating myelodysplastic syndromes in a human subject is provided, wherein the myelodysplastic syndromes are treatment-naïve higher-risk myelodysplastic syndromes. The method comprises administering to the human subject a daily dose of venetoclax for 14 days in a 28 day dosing cycle, a daily dose of 75 mg/m^2 of azacitidine for 7 days in a 28 day dosing cycle, and a CYP3A inhibitor; wherein the daily dose of venetoclax is: 200 mg when administered in combination with a moderate CYP3A inhibitor, and 50 mg when administered in combination with a strong CYP3A inhibitor.

[0011] In certain embodiments, a method for treating myelodysplastic syndromes in a human subject is provided, wherein the myelodysplastic syndromes are treatment-naïve higher-risk myelodysplastic syndromes. The method comprises administering to the human subject a daily dose of venetoclax for 14 days in a 28 day dosing cycle, a daily dose of 75 mg/m^2 of azacitidine for 7 days in a 28 day dosing cycle, and a CYP3A inhibitor; wherein the daily dose of venetoclax is: 200 mg when administered in combination with a moderate CYP3A inhibitor, and 100 mg when administered in combination with a strong CYP3A inhibitor.

BRIEF DESCRIPTION OF THE FIGURES

[0012] **FIG. 1** is a plot of the mean value of the absolute neutrophil count versus study day cycle. The number of observations is shown in Table 11.

[0013] **FIG. 2** is a plot of the mean value of the platelet count versus study day cycle. The number of observations is shown in Table 11.

[0014] **FIGs. 3A-3F** are bar graphs of hematologic toxicity showing the number of patients with worsening common terminology criteria grade over baseline per cycle. **FIG. 3A** is anemia. **FIG. 3B** is febrile neutropenia. **FIG. 3C** is leukopenia. **FIG. 3D** is neutropenia. **FIG. 3E** is thrombocytopenia. **FIG. 3F** is infections.

[0015] **FIGs. 4A-4C** are bar graphs of gastrointestinal toxicity showing the number of patients with worsening common terminology criteria grade over baseline per cycle. **FIG. 4A** is diarrhea. **FIG. 4B** is vomiting. **FIG. 4C** is nausea.

DETAILED DESCRIPTION OF THE INVENTION

[0016] This present disclosure relates to methods for treating treatment-naïve higher-risk myelodysplastic syndromes (MDS) in a human subject comprising administering to the subject

venetoclax in combination with azacitidine.

[0017] Although venetoclax has been administered to patients with AML who had a prior history of MDS (sAML), herein is the first disclosure evaluating venetoclax in combination with azacitidine in subjects with MDS, more specifically, in those subjects with treatment-naïve higher-risk MDS, in which the dosing regimen is modified to account for subjects who are also receiving a strong or moderate CYP3A inhibitor. Apart from the specific dosing modifications disclosed herein who are receiving a strong or moderate CYP3A inhibitor while being dosed with venetoclax, other significant differences between dosing venetoclax in combination with azacitidine for MDS versus AML include reducing the duration of venetoclax dosing from 28 to 14 days in the 28 day cycle for MDS, as well the lack of any dosing ramp up for subjects with MDS.

[0018] In certain embodiments, a method for treating myelodysplastic syndromes in a human subject is provided. The method comprises administering to the human subject a daily dose of 200 mg, 100 mg, 70 mg, or 50 mg of venetoclax for 14 days in a 28 day dosing cycle, a daily dose of 75 mg/m^2 of azacitidine for 7 days in a 28 day dosing cycle, and a CYP3A inhibitor.

[0019] "Venetoclax" is 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-*N*-({3nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1*H*-pyrrolo[2,3-*b*]pyridin5-yloxy)benzamide. Venetoclax is a selective Bcl-2 inhibitor approved for adult patients with CLL and adult patients with newly diagnosed AML who are 75 years or older, or who are ineligible for intensive induction chemotherapy.

[0020] Azacitidine is 4-amino-1-β-D-ribofuranosyl-s-triazin-2(1H)-one. Azacitidine is supplied in a sterile form for reconstitution as a suspension for subcutaneous injection or reconstitution as a solution with further dilution for intravenous infusion.

[0021] Strong and moderate CYP3A inhibitors are drugs that increase the AUC of sensitive index substrates of the CYP3A metabolic pathway ≥5-fold and ≥2 to <5-fold, respectively.

[0022] Examples of strong CYP3A inhibitors include boceprevir, clarithromycin, cobicistat, danoprevir/ritonavir, elvitegravir/ritonavir, idelalisib, indinavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir, nefazodone, nelfinavir, paritaprevir/ritonavir combinations, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir,

troleandomycin, and voriconazole.

[0023] Examples of moderate CYP3A inhibitors include aprepitant, cimetidine, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, isavuconazole, fluvoxamine, imatinib, tofisopam, and verapamil.

[0024] Posaconazole is available as concentrated solution to be diluted before intravenous administration, delayed-release tablet, or suspension for oral administration.

[0025] The term "AE" as used herein refers to adverse event.

[0026] The term "AML" as used herein refers to acute myeloid leukemia.

[0027] The term "ANC" as used herein refers to absolute neutrophil count.

[0028] The term "CLL" as used herein refers to chronic lymphocytic leukemia.

[0029] The term "CML" as used herein refers to chronic myeloid leukemia.

[0030] The term "CMML" as used herein refers to chronic myelomonocytic leukemia.

[0031] The term "CR" as used herein refers to complete remission.

[0032] The term "CTC" as used herein refers to common terminology criteria.

[0033] The term "ECOG" as used herein refers to Eastern Cooperative Oncology Group.

[0034] The term "G-CSF" as used herein refers to granulocyte colony-stimulating factor.

[0035] The term "HRQoL" as used herein refers to health-related quality of life.

[0036] The term "HMAs" as used herein refers to hypomethylating agents.

[0037] The term "HR-MDS" as used herein refers to higher risk myelodysplastic syndromes.

[0038] The term "IPSS" as used herein refers to International Prognostic Scoring System.

[0039] The term "IPSS-R" as used herein refers to Revised International Prognostic Scoring System.

[0040] The term "JMML" as used herein refers to juvenile myelomonocytic leukemia.

[0041] The term "mCR" as used herein refers to marrow complete remission.

[0042] The term "MDS" as used herein refers to myelodysplastic syndromes.

[0043] The term "MPN" as used herein refers to myeloproliferative neoplasm.

[0044] The term "OS" as used herein refers to overall survival.

[0045] The term "PR" as used herein refers to partial remission.

[0046] The term "RAEB" as used herein refers to refractory anemia with excess blasts.

[0047] The term "sAML" as used herein refers to secondary acute myeloid leukemia.

[0048] The term "SE1" as used herein refers to Safety Expansion Cohort 1.

[0049] The term "SE2" as used herein refers to Safety Expansion Cohort 2.

[0050] The term "TEAE" as used herein refers to treatment-emergent adverse events.

[0051] The term "tMDS" as used herein refers to treatment-related or therapy-related myelodysplastic syndromes.

[0052] In certain embodiments, a method for treating myelodysplastic syndromes in a human subject is provided, wherein the myelodysplastic syndromes are treatment-naïve higher-risk myelodysplastic syndromes. The method comprises administering to the human subject a daily dose of 200 mg, 100 mg, 70 mg, or 50 mg of venetoclax for 14 days in a 28 day dosing cycle, a daily dose of 75 mg/m^2 of azacitidine for 7 days in a 28 day dosing cycle, and a CYP3A inhibitor.

[0053] In certain embodiments, a method for treating myelodysplastic syndromes in a human subject is provided, wherein the myelodysplastic syndromes are treatment-naïve higher-risk myelodysplastic syndromes. The method comprises administering to the human subject a daily dose of 200 mg of venetoclax for 14 days in a 28 day dosing cycle, a daily dose of 75 mg/m^2 of azacitidine for 7 days in a 28 day dosing cycle, and a moderate CYP3A inhibitor. In certain aspects, the moderate CYP3A inhibitor is selected from the group consisting of aprepitant, cimetidine, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, isavuconazole, fluvoxamine, imatinib, tofisopam, and verapamil.

[0054] In certain embodiments, a method for treating myelodysplastic syndromes in a human subject is provided, wherein the myelodysplastic syndromes are treatment-naïve higher-risk myelodysplastic syndromes. The method comprises administering to the human subject a daily dose of 200 mg of venetoclax for 14 days in a 28 day dosing cycle, a daily dose of 75 mg/m^2 of azacitidine for 7 days in a 28 day dosing cycle, and a moderate CYP3A inhibitor; wherein the moderate CYP3A inhibitor is selected from the group consisting of aprepitant, cimetidine, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, isavuconazole, fluvoxamine, imatinib, tofisopam, and verapamil; and wherein the venetoclax is administered on each of days 1-14 of the dosing cycle.

[0055] In certain embodiments, a method for treating myelodysplastic syndromes in a human subject is provided, wherein the myelodysplastic syndromes are treatment-naïve higher-risk myelodysplastic syndromes. The method comprises administering to the human subject a

daily dose of 200 mg of venetoclax for 14 days in a 28 day dosing cycle, a daily dose of 75 mg/m^2 of azacitidine for 7 days in a 28 day dosing cycle, and a moderate CYP3A inhibitor; wherein the moderate CYP3A inhibitor is selected from the group consisting of aprepitant, cimetidine, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, isavuconazole, fluvoxamine, imatinib, tofisopam, and verapamil; wherein the venetoclax is administered on each of days 1-14 of the dosing cycle; and wherein the 7 days of the daily dose of azacitidine is during a first 9 days of the 28 day dosing cycle. In some aspects, the azacitidine is administered intravenously. In some aspects, the azacitidine is administered subcutaneously.

[0056] In certain embodiments, a method for treating myelodysplastic syndromes in a human subject is provided, wherein the myelodysplastic syndromes are treatment-naïve higher-risk myelodysplastic syndromes. The method comprises administering to the human subject a daily dose of 100 mg of venetoclax for 14 days in a 28 day dosing cycle, a daily dose of 75 mg/m^2 of azacitidine for 7 days in a 28 day dosing cycle, and a strong CYP3A inhibitor. In some aspects, the strong CYP3A inhibitor is selected from the group consisting of boceprevir, clarithromycin, cobicistat, danoprevir/ritonavir combinations, elvitegravir/ritonavir combinations, idelalisib, indinavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir combinations, nefazodone, nelfinavir, paritaprevir/ritonavir combinations, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir combinations, troleandomycin, and voriconazole. In some aspects, the daily dose of venetoclax is 100 mg. In some aspects, the daily dose of venetoclax is 50 mg.

[0057] In certain embodiments, a method for treating myelodysplastic syndromes in a human subject is provided, wherein the myelodysplastic syndromes are treatment-naïve higher-risk myelodysplastic syndromes. The method comprises administering to the human subject a daily dose of 100 mg of venetoclax for 14 days in a 28 day dosing cycle, a daily dose of 75 mg/m^2 of azacitidine for 7 days in a 28 day dosing cycle, and a strong CYP3A inhibitor; wherein the strong CYP3A inhibitor is selected from the group consisting of boceprevir, clarithromycin, cobicistat, danoprevir/ritonavir combinations, elvitegravir/ritonavir combinations, idelalisib, indinavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir combinations, nefazodone, nelfinavir, paritaprevir/ritonavir combinations, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir combinations, troleandomycin, and voriconazole; and wherein

the venetoclax is administered on each of days 1-14 of the dosing cycle.

[0058] In certain embodiments, a method for treating myelodysplastic syndromes in a human subject is provided, wherein the myelodysplastic syndromes are treatment-naïve higher-risk myelodysplastic syndromes. The method comprises administering to the human subject a daily dose of 100 mg of venetoclax for 14 days in a 28 day dosing cycle, a daily dose of 75 mg/m^2 of azacitidine for 7 days in a 28 day dosing cycle, and a strong CYP3A inhibitor; wherein the strong CYP3A inhibitor is selected from the group consisting of boceprevir, clarithromycin, cobicistat, danoprevir/ritonavir combinations, elvitegravir/ritonavir combinations, idelalisib, indinavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir combinations, nefazodone, nelfinavir, paritaprevir/ritonavir combinations, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir combinations, troleandomycin, and voriconazole; wherein the venetoclax is administered on each of days 1-14 of the dosing cycle; and wherein the days of the daily dose of azacitidine is during a first 9 days of the 28 day dosing cycle. In some aspects, the azacitidine is administered intravenously. In some aspects, the azacitidine is administered subcutaneously.

[0059] In certain embodiments, a method for treating myelodysplastic syndromes in a human subject is provided, wherein the myelodysplastic syndromes are treatment-naïve higher-risk myelodysplastic syndromes. The method comprises administering to the human subject a daily dose of 50 mg of venetoclax for 14 days in a 28 day dosing cycle, a daily dose of 75 mg/m^2 of azacitidine for 7 days in a 28 day dosing cycle, and a strong CYP3A inhibitor; wherein the strong CYP3A inhibitor is selected from the group consisting of boceprevir, clarithromycin, cobicistat, danoprevir/ritonavir combinations, elvitegravir/ritonavir combinations, idelalisib, indinavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir combinations, nefazodone, nelfinavir, paritaprevir/ritonavir combinations, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir combinations, troleandomycin, and voriconazole; wherein the venetoclax is administered on each of days 1-14 of the dosing cycle, In some aspects, the days of the daily dose of azacitidine is during a first 9 days of the 28 day dosing cycle. In some aspects, the azacitidine is administered intravenously. In some aspects, the azacitidine is administered subcutaneously.

[0060] In certain embodiments, a method for treating myelodysplastic syndromes in a human subject is provided, wherein the myelodysplastic syndromes are treatment-naïve higher-

risk myelodysplastic syndromes. The method comprises administering to the human subject a daily dose of 70 mg of venetoclax for 14 days in a 28 day dosing cycle, a daily dose of 75 mg/m^2 of azacitidine for 7 days in a 28 day dosing cycle, and posaconazole.

[0061] In certain embodiments, a method for treating myelodysplastic syndromes in a human subject is provided, wherein the myelodysplastic syndromes are treatment-naïve higher-risk myelodysplastic syndromes. The method comprises administering to the human subject a daily dose of 70 mg of venetoclax for 14 days in a 28 day dosing cycle, a daily dose of 75 mg/m^2 of azacitidine for 7 days in a 28 day dosing cycle, and posaconazole; and wherein the venetoclax is administered on each of days 1-14 of the dosing cycle.

[0062] In certain embodiments, a method for treating myelodysplastic syndromes in a human subject is provided, wherein the myelodysplastic syndromes are treatment-naïve higher-risk myelodysplastic syndromes. The method comprises administering to the human subject a daily dose of 70 mg of venetoclax for 14 days in a 28 day dosing cycle, a daily dose of 75 mg/m^2 of azacitidine for 7 days in a 28 day dosing cycle, and posaconazole; wherein the venetoclax is administered on each of days 1-14 of the dosing cycle; and wherein the 7 days the daily dose of azacitidine is during a first 9 days of the 28 day dosing cycle. In some aspects, the azacitidine is administered intravenously. In some aspects, the azacitidine is administered subcutaneously.

[0063] In certain embodiments, a method for treating myelodysplastic syndromes in a human subject is provided, wherein the myelodysplastic syndromes are treatment-naïve higher-risk myelodysplastic syndromes. The method comprises administering to the human subject a daily dose of 100 mg of venetoclax for 14 days in a 28 day dosing cycle, a daily dose of 75 mg/m^2 of azacitidine for 7 days in a 28 day dosing cycle, and posaconazole.

[0064] In certain embodiments, a method for treating myelodysplastic syndromes in a human subject is provided, wherein the myelodysplastic syndromes are treatment-naïve higher-risk myelodysplastic syndromes. The method comprises administering to the human subject a daily dose of 100 mg of venetoclax for 14 days in a 28 day dosing cycle, a daily dose of 75 mg/m^2 of azacitidine for 7 days in a 28 day dosing cycle, and posaconazole; and wherein the venetoclax is administered on each of days 1-14 of the dosing cycle.

[0065] In certain embodiments, a method for treating myelodysplastic syndromes in a human subject is provided, wherein the myelodysplastic syndromes are treatment-naïve higher-risk myelodysplastic syndromes. The method comprises administering to the human subject a

daily dose of 100 mg of venetoclax for 14 days in a 28 day dosing cycle, a daily dose of 75 mg/m^2 of azacitidine for 7 days in a 28 day dosing cycle, and posaconazole; wherein the venetoclax is administered on each of days 1-14 of the dosing cycle; and wherein the 7 days the daily dose of azacitidine is during a first 9 days of the 28 day dosing cycle. In some aspects, the azacitidine is administered intravenously. In some aspects, the azacitidine is administered subcutaneously.

[0066] In certain embodiments, a method for treating myelodysplastic syndromes in a human subject is provided. The method comprises administering to the human subject a daily dose of venetoclax for 14 days in a 28 day dosing cycle, a daily dose of 75 mg/m^2 of azacitidine for 7 days in a 28 day dosing cycle, and a CYP3A inhibitor; wherein the daily dose of venetoclax is: 200 mg when administered in combination with a moderate CYP3A inhibitor, 100 mg when administered in combination with a strong CYP3A inhibitor other than posaconazole, and 70 mg when administered in combination with posaconazole. In some aspects, the myelodysplastic syndromes are treatment-naïve higher-risk myelodysplastic syndromes.

[0067] In certain embodiments, a method for treating myelodysplastic syndromes in a human subject is provided, the myelodysplastic syndromes are treatment-naïve higher-risk myelodysplastic syndromes. The method comprises administering to the human subject a daily dose of venetoclax for 14 days in a 28 day dosing cycle, a daily dose of 75 mg/m^2 of azacitidine for 7 days in a 28 day dosing cycle, and a CYP3A inhibitor; wherein the daily dose of venetoclax is: 200 mg when administered in combination with a moderate CYP3A inhibitor, 100 mg when administered in combination with a strong CYP3A inhibitor other than posaconazole, and 70 mg when administered in combination with posaconazole; wherein the moderate CYP3A inhibitor is selected from the group consisting of aprepitant, cimetidine, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, isavuconazole, fluvoxamine, imatinib, tofisopam, and verapamil; and wherein the strong CYP3A inhibitor is selected from the group consisting of boceprevir, clarithromycin, cobicistat, danoprevir/ritonavir combinations, elvitegravir/ritonavir combinations, idelalisib, indinavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir combinations, nefazodone, nelfinavir, paritaprevir/ritonavir combinations, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir combinations, troleandomycin, and voriconazole. In some aspects, the venetoclax is administered on each of days 1-14 of the dosing cycle. In other aspects, the 7 days

the daily dose of azacitidine is during a first 9 days of the 28 day dosing cycle. In some aspects, the azacitidine is administered intravenously. In some aspects, the azacitidine is administered subcutaneously.

[0068] In certain embodiments, a method for treating myelodysplastic syndromes in a human subject is provided. The method comprises administering to the human subject a daily dose of venetoclax for 14 days in a 28 day dosing cycle, a daily dose of 75 mg/m^2 of azacitidine for 7 days in a 28 day dosing cycle, and a CYP3A inhibitor; wherein the daily dose of venetoclax is: 200 mg when administered in combination with a moderate CYP3A inhibitor, and 50 mg, or 70 mg, or 100 mg when administered in combination with a strong CYP3A inhibitor. In some aspects, the myelodysplastic syndromes are treatment-naïve higher-risk myelodysplastic syndromes.

[0069] In certain embodiments, a method for treating myelodysplastic syndromes in a human subject is provided, wherein the myelodysplastic syndromes are treatment-naïve higher-risk myelodysplastic syndromes. The method comprises administering to the human subject a daily dose of venetoclax for 14 days in a 28 day dosing cycle, a daily dose of 75 mg/m^2 of azacitidine for 7 days in a 28 day dosing cycle, and a CYP3A inhibitor; wherein the daily dose of venetoclax is: 200 mg when administered in combination with a moderate CYP3A inhibitor, and 50 mg when administered in combination with a strong CYP3A inhibitor.

[0070] In certain embodiments, a method for treating myelodysplastic syndromes in a human subject is provided, wherein the myelodysplastic syndromes are treatment-naïve higher-risk myelodysplastic syndromes. The method comprises administering to the human subject a daily dose of venetoclax for 14 days in a 28 day dosing cycle, a daily dose of 75 mg/m^2 of azacitidine for 7 days in a 28 day dosing cycle, and a CYP3A inhibitor; wherein the daily dose of venetoclax is: 200 mg when administered in combination with a moderate CYP3A inhibitor, and 50 mg when administered in combination with a strong CYP3A inhibitor; wherein the moderate CYP3A inhibitor is selected from the group consisting of aprepitant, cimetidine, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, isavuconazole, fluvoxamine, imatinib, tofisopam, and verapamil; and wherein the strong CYP3A inhibitor is selected from the group consisting of boceprevir, clarithromycin, cobicistat, danoprevir/ritonavir combinations, elvitegravir/ritonavir combinations, idelalisib, indinavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir combinations, nefazodone, nelfinavir,

paritaprevir/ritonavir combinations, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir combinations, troleandomycin, and voriconazole. In some aspects, the venetoclax is administered on each of days 1-14 of the dosing cycle. In other aspects, the 7 days the daily dose of azacitidine is during a first 9 days of the 28 day dosing cycle. In some aspects, the azacitidine is administered intravenously. In some aspects, the azacitidine is administered subcutaneously.

[0071] In certain embodiments, a method for treating myelodysplastic syndromes in a human subject is provided, wherein the myelodysplastic syndromes are treatment-naïve higher-risk myelodysplastic syndromes. The method comprises administering to the human subject a daily dose of venetoclax for 14 days in a 28 day dosing cycle, a daily dose of 75 mg/m^2 of azacitidine for 7 days in a 28 day dosing cycle, and a CYP3A inhibitor; wherein the daily dose of venetoclax is: 200 mg when administered in combination with a moderate CYP3A inhibitor, and 100 mg when administered in combination with a strong CYP3A inhibitor.

[0072] In certain embodiments, a method for treating myelodysplastic syndromes in a human subject is provided, wherein the myelodysplastic syndromes are treatment-naïve higher-risk myelodysplastic syndromes. The method comprises administering to the human subject a daily dose of venetoclax for 14 days in a 28 day dosing cycle, a daily dose of 75 mg/m^2 of azacitidine for 7 days in a 28 day dosing cycle, and a CYP3A inhibitor; wherein the daily dose of venetoclax is: 200 mg when administered in combination with a moderate CYP3A inhibitor, and 70 mg, or 100 mg when administered in combination with a strong CYP3A inhibitor; wherein the moderate CYP3A inhibitor is selected from the group consisting of aprepitant, cimetidine, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, isavuconazole, fluvoxamine, imatinib, tofisopam, and verapamil; and wherein the strong CYP3A inhibitor is selected from the group consisting of boceprevir, clarithromycin, cobicistat, danoprevir/ritonavir combinations, elvitegravir/ritonavir combinations, idelalisib, indinavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir combinations, nefazodone, nelfinavir, paritaprevir/ritonavir combinations, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir combinations, troleandomycin, and voriconazole. In some aspects, the venetoclax is administered on each of days 1-14 of the dosing cycle. In other aspects, the 7 days the daily dose of azacitidine is during a first 9 days of the 28 day dosing cycle. In some aspects, the azacitidine is administered intravenously. In some aspects, the

azacitidine is administered subcutaneously.

EXAMPLES

[0073] In order that the invention described herein may be more fully understood, the following examples are set forth.

[0074] A multicenter, non-randomized Phase 1b study in adults with previously untreated higher-risk MDS, defined as IPSS risk categories of Int-2 or High (IPSS overall score ≥ 1.5) was initiated. The original protocol randomized patients into 1 of 3 treatment groups: venetoclax 800 mg + azacitidine, venetoclax 400 mg + azacitidine, and azacitidine monotherapy. Under the original protocol, venetoclax was administered on Days 1 through 28 of each 28-day-cycle and dosing was initiated according to a ramp-up dosing schedule in Cycle 1. With this dosing schedule, 2 patients developed fatal sepsis in the setting of severe neutropenia, after which the study was placed on partial clinical hold and enrollment was suspended. The partial clinical hold was lifted based on a revised protocol, which ultimately resulted in a lower incidence of infections and leukopenia events.

Study Design

Subject Inclusion Criteria

[0075] Subjects 18 years or older diagnosed with treatment-naïve IPSS intermediate-2 or high-risk myelodysplastic syndromes with ECOG ≤ 2 were enrolled. For this study, inclusion criteria included the following:

1. Subject must be ≥ 18 years of age.
2. Subject must have documented diagnosis of previously untreated *de novo* MDS with:
    a. International Prognostic Scoring System (IPSS) risk categories Intermediate-2 or High (i.e., minimum IPSS score of 1.5) OR Revised IPSS (IPSS-R) categories Intermediate, High or Very High (score of > 3); and
    b. Presence of < 20% bone marrow blasts per bone marrow biopsy/aspirate.
3. Subject must have an Eastern Cooperative Oncology Group (ECOG) performance score of ≤ 2.

[0076] According to the International Prognostic Scoring System, myelodysplastic syndromes patients are grouped into two major risk groups, low risk and higher-risk. Higher-risk myelodysplastic syndromes as used herein are defined as an International Prognostic Scoring System (IPSS) risk categories Int-2 or High (i.e., minimum IPSS score of 1.5) or Revised IPSS (IPSS-R) categories Intermediate, High or Very High (overall score of > 3).

Table 1: International Prognostic Scoring System (IPSS)

	Score				
Category	0	0.5	1.0	1.5	2.0
Bone Marrow Blasts (%)	< 5	5 to 10	-	11 to 20	21 to 30
Karyotype	Normal, Y-, 5q-, 20q-	All other cytogenetic abnormalities	Abnormal chromosome 7 or 3 or more abnormalities		
Cytopenias defined as: • Hemoglobin < 10 g/dL • absolute neutrophil count < 1800/μL • platelet count < 100,000 μL	No cytopenia or cytopenia of 1 cell type	Cytopenia of 2 or 3 cell types			

[0077] Subjects with higher-risk MDS are classified into the Revised International Prognostic Scoring System (IPSS-R) categories of Intermediate, High and Very High. This patient population largely corresponds to IPSS Intermediate risk-2 and High groups and World Health Organization (WHO) histologic subtypes of refractory anemia with excess blasts (RAEB)-1 and RAEB-2. The IPSS-R is now also considered a well-validated assessment tool to identify patients who are commonly considered clinically appropriate to receive active treatment. The Revised International Prognostic Scoring System (IPSS-R) is shown in Table 2 and includes a refined classification of cytogenetic abnormalities, more specific cut-offs for bone marrow blast counts and cytopenias, and is weighted for their severity. The Revised International Prognostic Scoring System risk groups for myelodysplastic syndromes are defined based an overall score. The overall score is calculated as the sum of the blast score, cytogenetics score, hemoglobin score, platelets score, and absolute neutrophil count score.

Table 2: Revised International Prognostic Scoring System (IPSS-R) Criteria and Scoring for MDS

Parameter	Criteria	Score	Risk Groups (Overall Score[1] and Median Survival Time)
Blasts in bone marrow (%)	≤ 2	0	Very Low: Overall Risk Score ≤ 1.5 Median survival time = 8.8 years Low: Overall Risk Score > 1.5 to 3.0 Median survival time = 5.3 years Intermediate: Overall Risk Score > 3.0 to 4.5 Median survival time = 3 years High: Overall Risk Score > 4.5 to 6.0 Median survival time = 1.6 years Very High: Overall Risk Score > 6.0 Median survival time = 0.8 years
	> 2 to < 5	1.0	
	5 to 10	2.0	
	> 10	3.0	
Cytogenics	Very good	0	
	Good	1.0	
	Intermediate	2.0	
	Poor	3.0	
	Very Poor	4.0	
Hemoglobin (g/dL)	≥ 10	0	
	8 to < 10	1.0	
	< 8	1.5	
Platelets (10^9 / L)	≥ 100	0	
	50 to < 100	0.5	
	< 50	1.0	
ANC (10^9 / L)	≥ 0.8	0	
	< 8	0.5	

[1] Overall score is calculated as the blast score + cytogenetics score + hemoglobin score + platelets score + absolute neutrophil count score

[0078] ECOG performance status was assessed using the criteria in Table 3.

Table 3: ECOG performance status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined

	to bed or chair.

Key Exclusion Criteria

1. Subject has received prior therapy for MDS.
2. Subject has received prior therapy with a BH3 mimetic
3. Subject has a diagnosis other than previously untreated de novo MDS, including:
    a. MDS with IPSS risk categories Low or Int-1 (overall IPSS score < 1.5)
    b. Therapy-related MDS (t-MDS)
    c. MDS evolving from a pre-existing myeloproliferative neoplasm (MPN)
    d. MDS/MPN including chronic myelomonocytic leukemia (CMML), atypical chronic myeloid leukemia (CML), juvenile myelomonocytic leukemia (JMML) and unclassifiable MDS/MPN.
4. Subject has received strong or moderate CYP3A inducers within 7 days prior to the first dose of study drug.
5. Subject enrolled in a Dose-Escalation cohort has received strong or moderate CYP3A inhibitors within 3 days prior to the first dose of study drug with the exception of Safety Expansion cohorts.

[0079] Azacitidine 75 mg/m^2 (intravenous or subcutaneous daily) was administered for 7 days and venetoclax was administered at 400 mg for 14 days in each 28 day cycle. In both cohorts, dose modification during Cycle 1 was not recommended. Dose modifications in subsequent cycles were prescribed for adverse events. In Safety Expansion Cohort 1 (SE1), venetoclax was initially reduced for significant neutrophil or platelet toxicity. Dose reductions per protocol were 33% for azacitidine or 50% for venetoclax for 14 days in each cycle. In subsequent cycles, venetoclax duration could be shortened to 9 days of each cycle. In Safety Expansion Cohort 2 (SE2), dose modification guidelines recommended stepwise reductions, first in azacitidine dose (first to 50 mg/m^2, then 36 mg/m^2) and subsequently in venetoclax duration to 7 days of each cycle (venetoclax 400 mg) as shown in Table 4. The impact of each dose modification strategy on safety and efficacy in SE1 versus SE2 was compared. Worsening of treatment-emergent adverse events grades from baseline was analyzed by cycle. Responses were evaluated using IWG 2006 criteria. Analyses included all subject who received ≥1 dose of study

drug.

Table 4: SE2 Dose Modification Guidelines

	Azacitidine	Venetoclax
Planned Dose	75 mg/m^2 x 7 days	400 mg x 14 days
1st Dose Reduction	50 mg/m^2 x 7 days	400 mg x 14 days
2nd Dose Reduction	36 mg/m^2 x 7 days	400 mg x 14 days
3rd Dose Reduction	36 mg/m^2 x 7 days	400 mg x 7 days

[0080] When venetoclax was co-administered with a moderate CYP3A inhibitor or a strong CYP3A inhibitor, the venetoclax dose was reduced as shown in Table 5.

Table 5: Venetoclax Dose Modification A when Co-Administered with CYP3A Inhibitors

Initial Venetoclax dose	Venetoclax Dose if Co-Administered with Moderate CYP3A Inhibitor	Venetoclax Dose if Co-Administered with Strong CYP3A Inhibitor
400 mg	200 mg	50 mg

[0081] After a previous interruption of treatment, delay starting the next cycle, onset of adverse events associated with hematological toxicity, significant reduction of neutrophils, or significant reduction of platelets, a treatment dose reduction may be indicated. Stepwise azacitidine dose modification occurred followed by adjustment of the venetoclax treatment from 14 to 7 days at the last step after all azacitidine dose modification steps have occurred. Venetoclax and azacitidine were resumed on the same day after any delays or interruptions in treatment.

Results

[0082] Baseline characteristics for SE1 and SE2 are shown in Table 6. 22 Subjects in SE1 and 21 subjects in SE2 were compared with median (range) follow-up of 7.5 (1.0–8.9) and 7.9 (1.8–10.1) months, respectively, as shown in Table 7.

Table 6. SE1 and SE2 Baseline Characteristics

n (%)	SE1 n=22	SE2 n=21
Male	15 (68)	13 (62)
Median age, years [range]	70 [55–79]	68 [59–87]
ECOG performance score		
0	7 (32)	11 (52)
1	13 (59)	9 (43)
2	2 (9)	1 (5)
Bone marrow blasts		
≤ 5%	1 (4.5)	2 (9.5)
> 5% to ≤ 10%	7 (32)	6 (29)
> 10% to ≤ 20%	14 (64)	13 (62)
Baseline transfusion dependence		
RBC or platelet	13 (59)	10 (48)
RBC	13 (59)	9 (43)
Platelet	3 (14)	2 (10)
IPSS risk classification		
Intermediate-2	17 (77)	15 (71)
High	5 (23)	6 (29)
IPSS-R risk classification		
Intermediate	5 (23)	3 (14)
High	5 (23)	7 (33)
Very high	12 (54)	11 (52)
Baseline cytopenias (Grade ≥3)		
Neutropenia	14 (64)	14 (67)
Thrombocytopenia	6 (27)	7 (33)
Leukopenia	10 (46)	10 (48)
Anemia	3 (14)	3 (14)

Table 7: Follow-up Time and Dose Administration

	SE1 n=22	SE2 n=21
Median follow-up, months (min, max)	7.5 (1.0, 8.9)	7.9 (1.8, 10.1)
Azacitidine		
Median duration, days	156	184
Cycles, median (range)	4 (1–17)	5 (1–11)
Patients with dose reductions in Azacitidine, n (%):		
0 reductions	16 (73)	14 (67)
1 reduction	5 (23)	5 (24)
2 reductions	0	2 (10)
>2 reductions	1 (4.5)	0

Median days to dose modification	125.5	115
Venetoclax		
Median duration, days	156	184
Median days dosed	56	70
# of reductions in Venetoclax duration*	3 (14)	0
Patients with ≥1 Ven dose amount reduction, n (%)	10 (45)	10 (48)
Median days to duration reduction	52	n/a

*Reductions due to hematologic toxicity

[0083] The summary of adverse events in >20% of subjects is shown in Table 8. A similar frequency of ≥ Grade 3 hematologic treatment-emergent adverse events (approximate %) were reported in SE1 and SE2, respectively, including anemia (14% and 33%), febrile neutropenia (46% and 48%), leukopenia (36% and 19%), neutropenia (55% and 48%) and thrombocytopenia (32% and 38%). Infections (59% and 38%) and leukopenia (36% and 19%) were more frequent in SE1 than SE2.

Table 8: Summary of Adverse Events

n (%)	**SE1 n=22**	**SE2 n=21**
Any Adverse Event		
Infections	13 (59)	8 (38)
Neutropenia	12 (55)	10 (48)
Febrile neutropenia	10 (46)	10 (48)
Thrombocytopenia	8 (36)	10 (48)
Leukopenia	8 (36)	4 (19)
Anemia	3 (14)	10 (48)
Nausea	7 (32)	13 (62)
Constipation	8 (36)	9 (43)
Vomiting	8 (36)	11 (52)
Diarrhea	6 (27)	12 (57)
Grade ≥ 3 Adverse Events		
Neutropenia	12 (55)	10 (48)
Febrile neutropenia	10 (46)	10 (48)
Infections	9 (41)	4 (19)
Leukopenia	8 (36)	4 (19)
Thrombocytopenia	7 (32)	8 (38)
Anemia	3 (14)	7 (33)
Serious Adverse Events[a]		
Febrile neutropenia	8 (36)	9 (43)
Infections	8 (36)	3 (14)

GI disorders	3 (13)	3 (14)

[a] Includes death, life-threatening, requiring hospitalization or surgical intervention, persistent/significant disability.

[b] SE1: abdominal pain, diverticular perforation, and gastroesophageal reflux disease; SE2: nausea, pancreatitis, vomiting, and gastrointestinal hemorrhage

[0084] Worsening of treatment-emergent adverse events grades from baseline was analyzed by cycle. As shown in **FIGs. 3A-3F** and **FIGs. 4A-4C**, adverse event progression remains low after the first few cycles, such as cycles 1 and 2. **FIGs. 3A-3F** are hematologic toxicity showing the number of patients with worsening common terminology criteria grade over baseline per cycle. **FIGs. 4A-4C** are gastrointestinal toxicity showing the number of patients with worsening common terminology criteria grade over baseline per cycle.

[0085] Response rates were identical for SE1 and SE2 as shown in Table 9: 86% of subjects in both SE1 and SE2 had complete remission (CR) or marrow complete remission (mCR). For subjects with mCR, hematologic improvement occurred in 50% of SE1 and 46% of SE2 subjects.

Table 9: Response Rates

n (%)	**SE1 n=22**	**SE2 n=21**
Overall Response Rate (CR+mCR+PR)	86.30%	85.7%
Best Response		
Complete remission	7 (32)	5 (24)
Marrow complete remission	12 (55)	13 (62)
+ hematologic improvement	6 (50)	6 (46)
– hematologic improvement	6 (50)	7 (54)
Partial remission	0	0
Stable disease	2 (9)	2 (10)
Progressive disease	0	0
Not evaluable	1 (5)	1 (5)
Time on study, median months [min, max]	7.5 [1.0, 8.9]	7.9 [1.8, 10.1]

[0086] The summary of cycle delays is shown in Table 10. Cycle delays were comparable between SE1 and SE2, with a slightly longer duration for SE1 in early cycles.

Table 10: Summary of Cycle Delays

	SE1 n=22		SE2 n=21	
Venetoclax dose delay by end of each cycle	**n (%)**	**Median # days (range)**	**n (%)**	**Median # days (range)**
Cycle 2	14 (63)	7.5 (1-21)	13 (62)	8 (5-21)
Cycle 3	12 (55)	14 (3-28)	10 (48)	8.5 (1-48)
Cycle 4	8 (36)	17 (1-54)	6 (28)	9 (6-43)
Cycle 5	7 (32)	14 (3-28)	9 (43)	14 (1-97)
Cycle 6	7 (32)	7 (1-21)	5 (24)	14 (6-91)

[0087] The mean value of absolute neutrophil count and platelet count is shown in **FIGs. 1** and **2**, respectively. The number of count observations per study cycle day for both absolute neutrophil count and platelet count is shown in Table 11.

Table 11: Number of Count Observations per Study Cycle Day

	Absolute Neutrophil Count Observations		Platelet Count Observations	
Study Cycle Day	**SE1**	**SE2**	**SE1**	**SE2**
Baseline	22	21	19	19
C1D4	16	19	15	18
C1D7	11	13	9	12
C1D9	9	8	8	7
C1D15	20	20	20	17
C1D22	20	18	19	16
C2D1	8	12	8	12
C2D4	5	6	5	6
C2D7	9	12	9	11
C2D9	7	6	7	6
C2D15	17	17	17	16
C2D22	19	16	20	17
C3D1	15	14	15	13
C3D4	3	3	3	3
C3D7	9	10	8	10
C3D9	4	4	4	4
C3D15	13	16	12	16
C3D22	11	13	11	12
C4D1	15	11	15	12
C4D7	11	5	10	5
C4D9	3	5	3	5
C4D22	13	11	13	12
C5D1	8	5	8	6

C5D7	6	6	6	6
C5D9	2	2	2	2
C5D22	13	12	13	12
C6D1	4	8	4	7
C6D7	7	5	7	5
C6D9	0	2	0	2
C6D22	10	9	10	9

[0088] 86% of patients in both SE1 and SE2 had complete remission or marrow complete remission.

[0089] Venetoclax dose modifications in patients receiving moderate or strong CYP3A inhibitors were used in subsequent clinical studies as shown in Table 12 and Table 13.

Table 12. Venetoclax Dose Modification B when Co-Administered with CYP3A Inhibitors

Initial Venetoclax dose	**Venetoclax Dose if Co-Administered with Moderate CYP3A Inhibitor**	**Venetoclax Dose if Co-Administered with Strong CYP3A Inhibitor**	**Venetoclax Dose if Co-Administered with Posaconzaloe**
400 mg	200 mg	100 mg	70 mg

Table 13. Venetoclax Dose Modification C when Co-Administered with CYP3A Inhibitors

Initial Venetoclax dose	**Venetoclax Dose if Co-Administered with Moderate CYP3A Inhibitor**	**Venetoclax Dose if Co-Administered with Strong CYP3A Inhibitor**
400 mg	200 mg	100 mg

[0090] It is understood that the foregoing detailed description and accompanying examples are merely illustrative and are not to be taken as limitations upon the scope of the invention, which is defined solely by the appended claims and their equivalents. Various changes and modifications to the disclosed embodiments will be apparent to those skilled in the art. Such changes and modifications, including those relating to the methods of use of the invention, may be made without departing from the spirit and scope thereof. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

WE CLAIM:

1. A method for treating myelodysplastic syndromes in a human subject, comprising administering to the human subject a daily dose of 200 mg, 100 mg, 70 mg, or 50 mg of venetoclax for 14 days in a 28 day dosing cycle, a daily dose of 75 mg/m^2 of azacitidine for 7 days in a 28 day dosing cycle, and a CYP3A inhibitor.
2. The method of claim 1, wherein the myelodysplastic syndromes are treatment-naïve higher-risk myelodysplastic syndromes.
3. The method of claim 1 or 2, wherein the daily dose of venetoclax is 200 mg; and wherein the CYP3A inhibitor is a moderate CYP3A inhibitor.
4. The method of claim 3, wherein the moderate CYP3A inhibitor is selected from the group consisting of aprepitant, cimetidine, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, isavuconazole, fluvoxamine, imatinib, tofisopam, and verapamil.
5. The method of claim 1 or 2, wherein the daily dose of venetoclax is 100 mg; and wherein the CYP3A inhibitor is a strong CYP3A inhibitor.
6. The method of claim 5, wherein the strong CYP3A inhibitor is selected from the group consisting of boceprevir, clarithromycin, cobicistat, danoprevir/ritonavir combinations, elvitegravir/ritonavir combinations, idelalisib, indinavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir combinations, nefazodone, nelfinavir, paritaprevir/ritonavir combinations, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir combinations, troleandomycin, and voriconazole.
7. The method of claim 1-6, wherein the daily dose of venetoclax is 100 mg.
8. The method of claim 1-6, wherein the daily dose of venetoclax is 50 mg.
9. The method of claim 1 or 2, wherein the daily dose of venetoclax is 70 mg; and wherein the CYP3A inhibitor is posaconazole.
10. The method of claim 1 or 2, wherein the daily dose of venetoclax is 100 mg; and wherein the CYP3A inhibitor is posaconazole.
11. A method for treating myelodysplastic syndromes in a human subject, comprising administering to the human subject a daily dose of venetoclax for 14 days in a 28 day dosing cycle, a daily dose of 75 mg/m^2 of azacitidine for 7 days in a 28 day dosing cycle, and a CYP3A inhibitor;

wherein the daily dose of venetoclax is:

a. 200 mg when administered in combination with a moderate CYP3A inhibitor,

b. 100 mg when administered in combination with a strong CYP3A inhibitor other than posaconazole, and

c. 70 mg when administered in combination with posaconazole.

12. The method of claim 11, wherein the myelodysplastic syndromes are treatment-naïve higher-risk myelodysplastic syndromes.

13. The method of claim 11 or 12, wherein the moderate CYP3A inhibitor is selected from the group consisting of aprepitant, cimetidine, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, isavuconazole, fluvoxamine, imatinib, tofisopam, and verapamil; and

wherein the strong CYP3A inhibitor is selected from the group consisting of boceprevir, clarithromycin, cobicistat, danoprevir/ritonavir combinations, elvitegravir/ritonavir combinations, idelalisib, indinavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir combinations, nefazodone, nelfinavir, paritaprevir/ritonavir combinations, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir combinations, troleandomycin, and voriconazole.

14. The method of claim 11-13, wherein the venetoclax is administered on each of days 1-14 of the dosing cycle.

15. The method of claim 11-14, wherein the 7 days the daily dose of azacitidine is during a first 9 days of the 28 day dosing cycle.

16. The method of claim 11-15, wherein the azacitidine is administered intravenously.

17. The method of claim 11-15, wherein the azacitidine is administered subcutaneously.

18. A method for treating myelodysplastic syndromes in a human subject, comprising administering to the human subject a daily dose of venetoclax for 14 days in a 28 day dosing cycle, a daily dose of 75 mg/m^2 of azacitidine for 7 days in a 28 day dosing cycle, and a CYP3A inhibitor;

wherein the daily dose of venetoclax is:

a. 200 mg when administered in combination with a moderate CYP3A inhibitor, and

b. 50 mg, or 70 mg, or 100 mg when administered in combination with a strong CYP3A inhibitor.

19. The method of claim 18, wherein the myelodysplastic syndromes are treatment-naïve higher-risk myelodysplastic syndromes.

20. The method of claim 18 or 19, wherein the daily dose of venetoclax is:

a. 200 mg when administered in combination with a moderate CYP3A inhibitor, and

b. 50 mg when administered in combination with a strong CYP3A inhibitor.

21. The method of claim 20, wherein the moderate CYP3A inhibitor is selected from the group consisting of aprepitant, cimetidine, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, isavuconazole, fluvoxamine, imatinib, tofisopam, and verapamil; and

wherein the strong CYP3A inhibitor is selected from the group consisting of boceprevir, clarithromycin, cobicistat, danoprevir/ritonavir combinations, elvitegravir/ritonavir combinations, idelalisib, indinavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir combinations, nefazodone, nelfinavir, paritaprevir/ritonavir combinations, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir combinations, troleandomycin, and voriconazole.

22. The method of claim 18 or 19, wherein the daily dose of venetoclax is:

a. 200 mg when administered in combination with a moderate CYP3A inhibitor, and

b. 100 mg when administered in combination with a strong CYP3A inhibitor.

23. The method of claim 22, wherein the moderate CYP3A inhibitor is selected from the group consisting of aprepitant, cimetidine, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, isavuconazole, fluvoxamine, imatinib, tofisopam, and verapamil; and

wherein the strong CYP3A inhibitor is selected from the group consisting of boceprevir, clarithromycin, cobicistat, danoprevir/ritonavir combinations, elvitegravir/ritonavir combinations, idelalisib, indinavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir combinations, nefazodone, nelfinavir,

paritaprevir/ritonavir combinations, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir combinations, troleandomycin, and voriconazole.

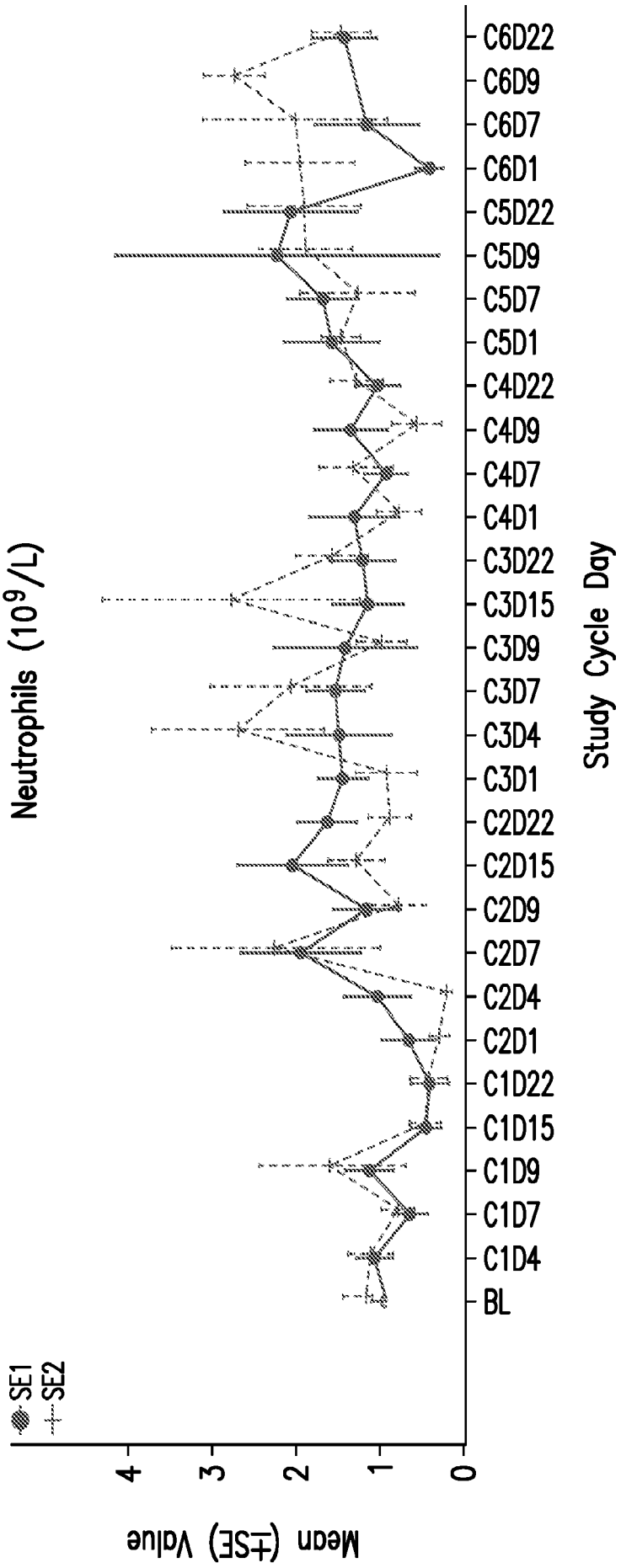
Neutrophils (10^9/L)
Study Cycle Day
Mean (±SE) Value
SE1
SE2
C6D22
C6D9
C6D7
C6D1
C5D22
C5D9
C5D7
C5D1
C4D22
C4D9
C4D7
C4D1
C3D22
C3D15
C3D9
C3D7
C3D4
C3D1
C2D22
C2D15
C2D9
C2D7
C2D4
C2D1
C1D22
C1D15
C1D9
C1D7
C1D4
BL
0
1
2
3
4

FIG. 1

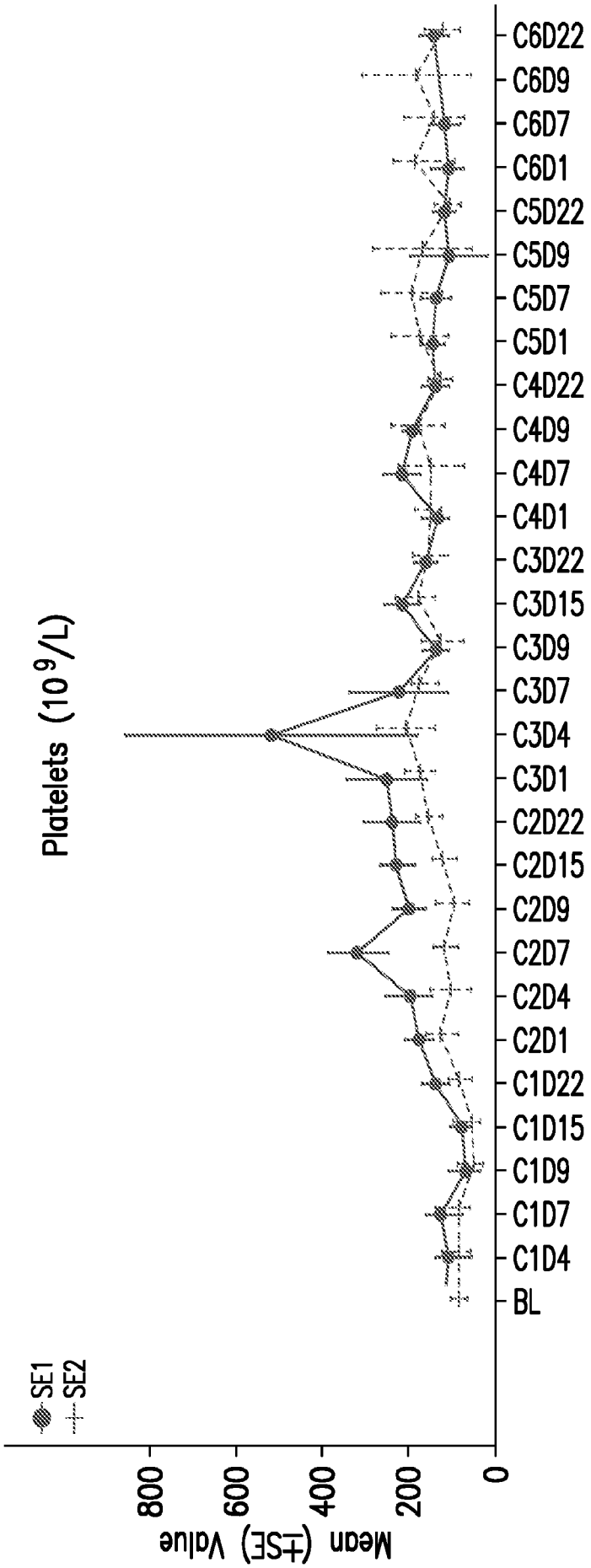
Platelets (10^9/L)
Mean (±SE) Value
0
200
400
600
800
SE1
SE2
Study Cycle Day
BL
C1D4
C1D7
C1D9
C1D15
C1D22
C2D1
C2D4
C2D7
C2D9
C2D15
C2D22
C3D1
C3D4
C3D7
C3D9
C3D15
C3D22
C4D1
C4D7
C4D9
C4D22
C5D1
C5D7
C5D9
C5D22
C6D1
C6D7
C6D9
C6D22

FIG. 2

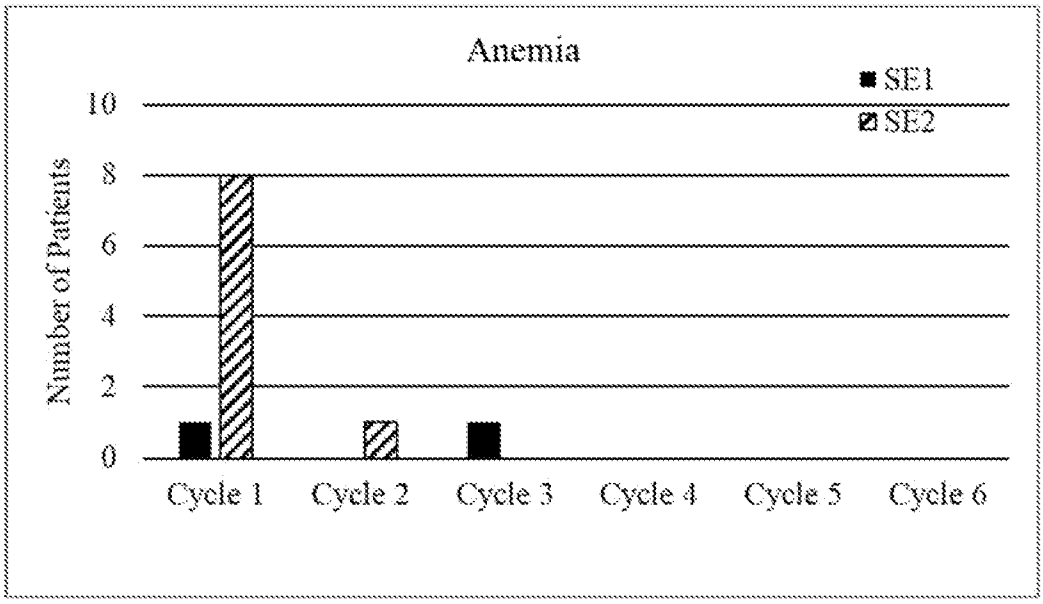
Anemia
SE1
SE2
Number of Patients
10
8
6
4
2
0
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Cycle 6

FIG. 3A

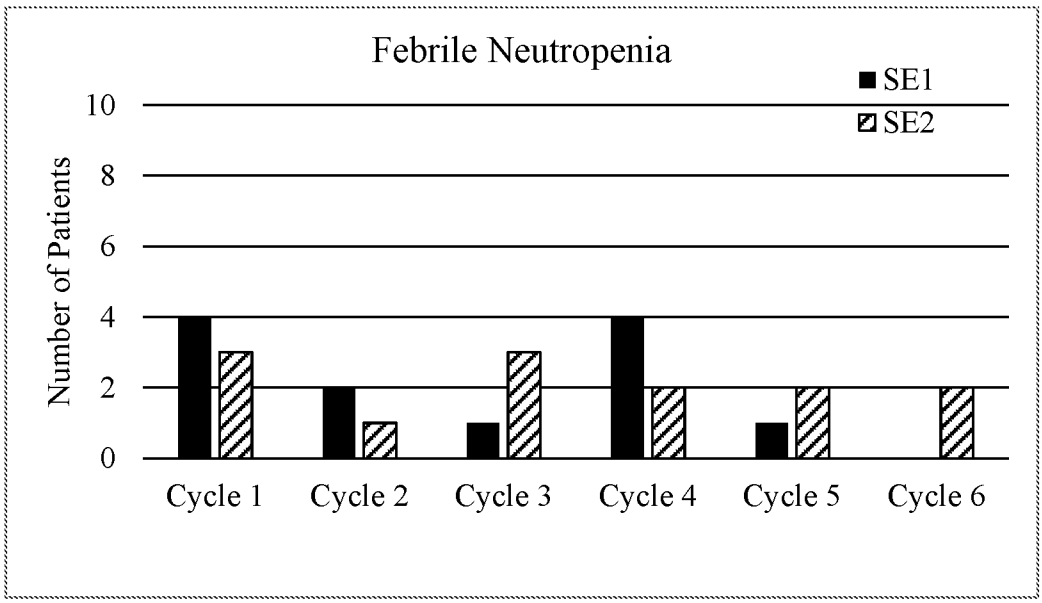
Febrile Neutropenia
SE1
SE2
Number of Patients
10
8
6
4
2
0
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Cycle 6

FIG. 3B

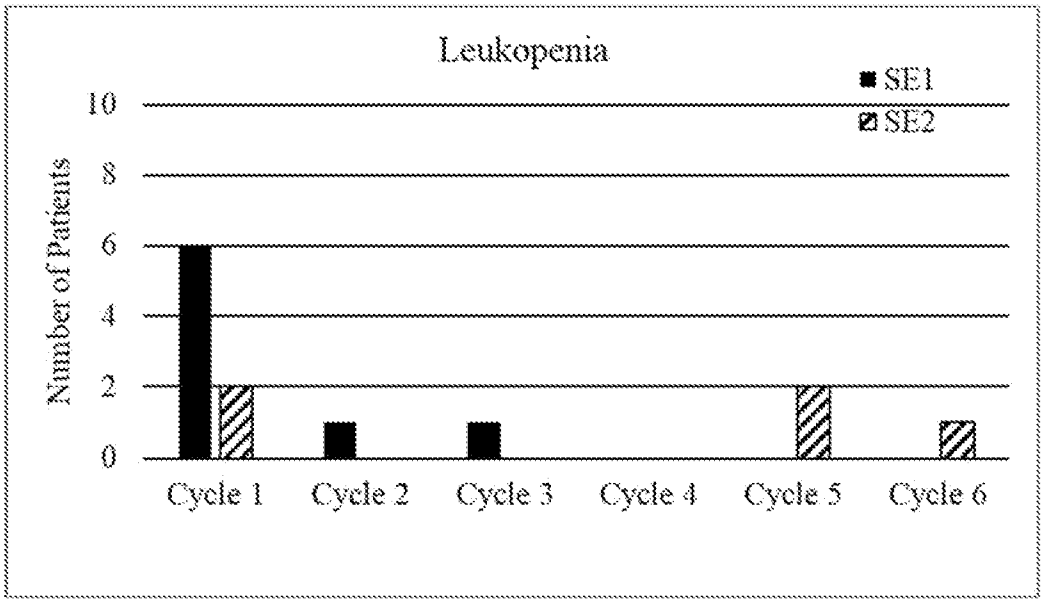
Leukopenia
SE1
SE2
Number of Patients
10
8
6
4
2
0
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Cycle 6

FIG. 3C

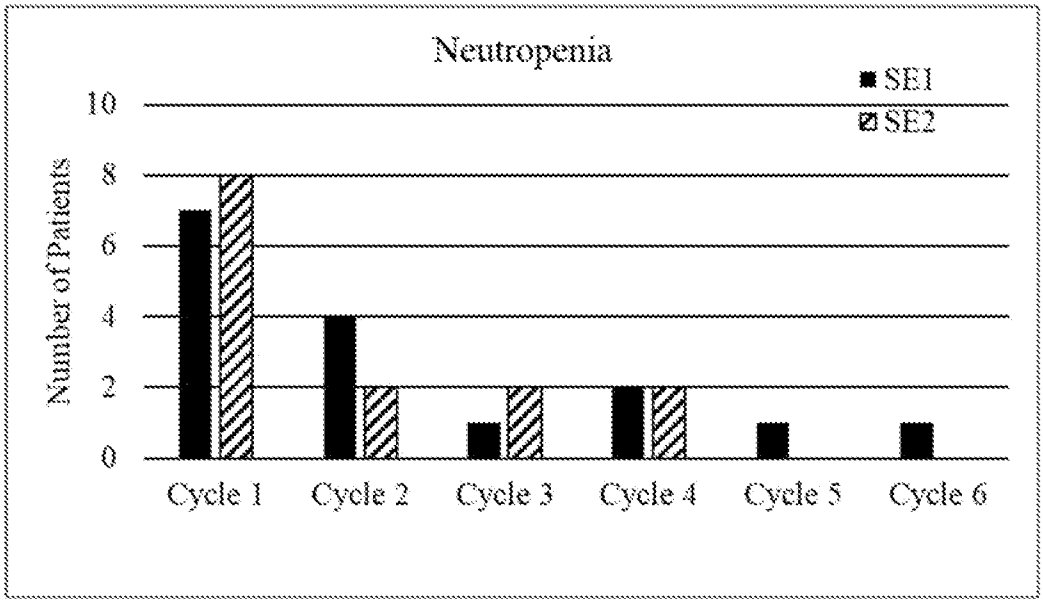
Neutropenia
SE1
SE2
Number of Patients
10
8
6
4
2
0
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Cycle 6

FIG. 3D

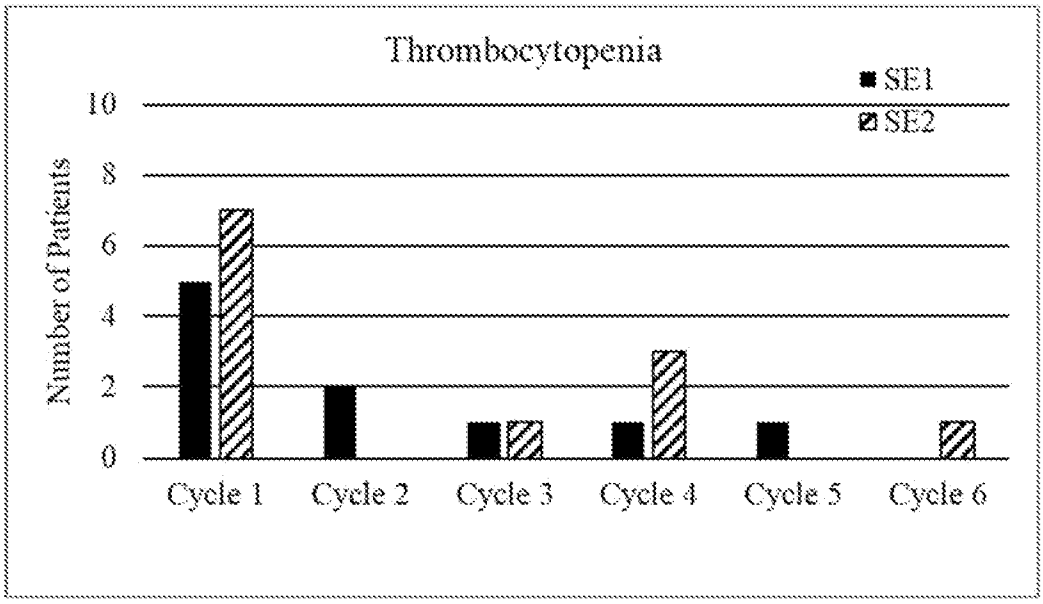
Thrombocytopenia
SE1
SE2
Number of Patients
10
8
6
4
2
0
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Cycle 6

FIG. 3E

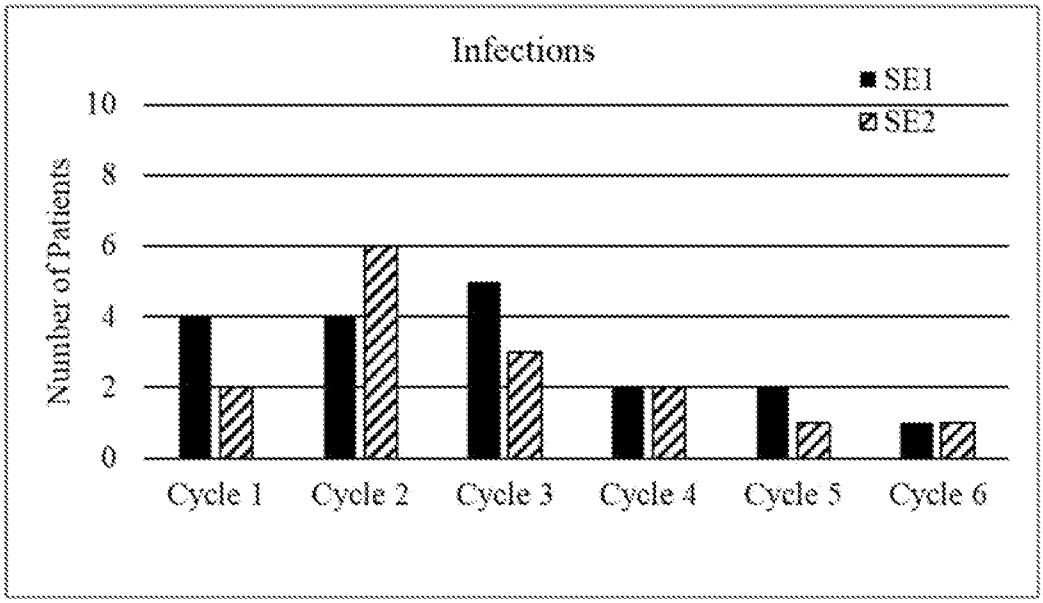
Infections
SE1
SE2
Number of Patients
10
8
6
4
2
0
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Cycle 6

FIG. 3F

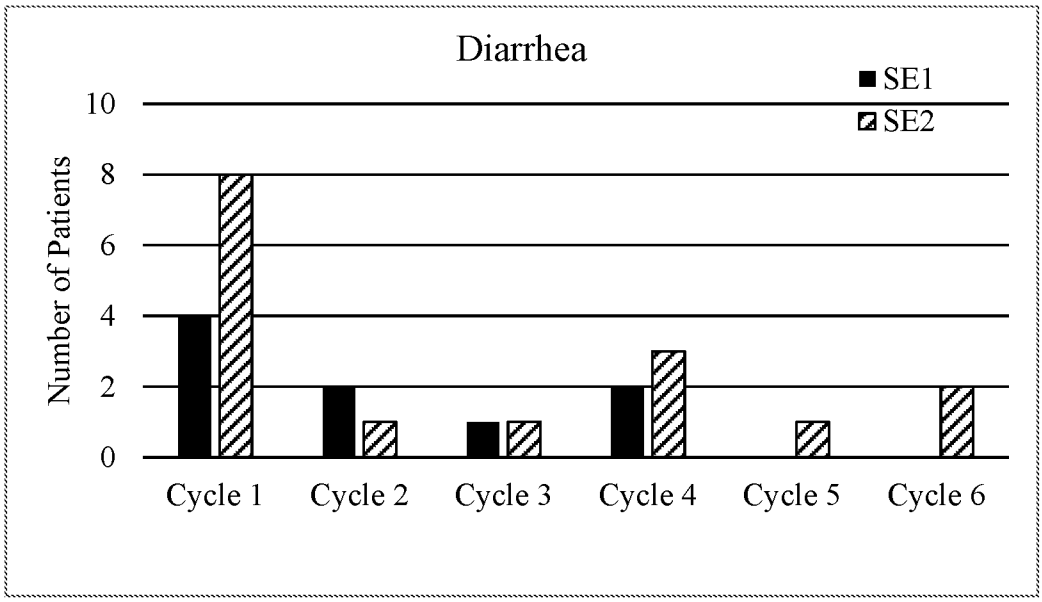
Diarrhea
SE1
SE2
Number of Patients
10
8
6
4
2
0
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Cycle 6

FIG. 4A

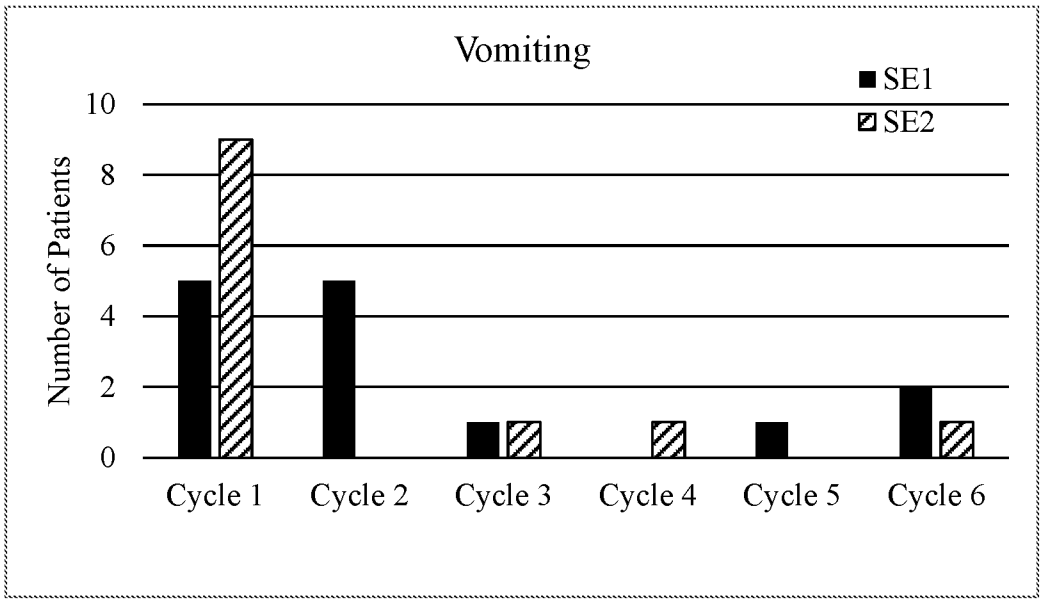
Vomiting
SE1
SE2
Number of Patients
10
8
6
4
2
0
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Cycle 6

FIG. 4B

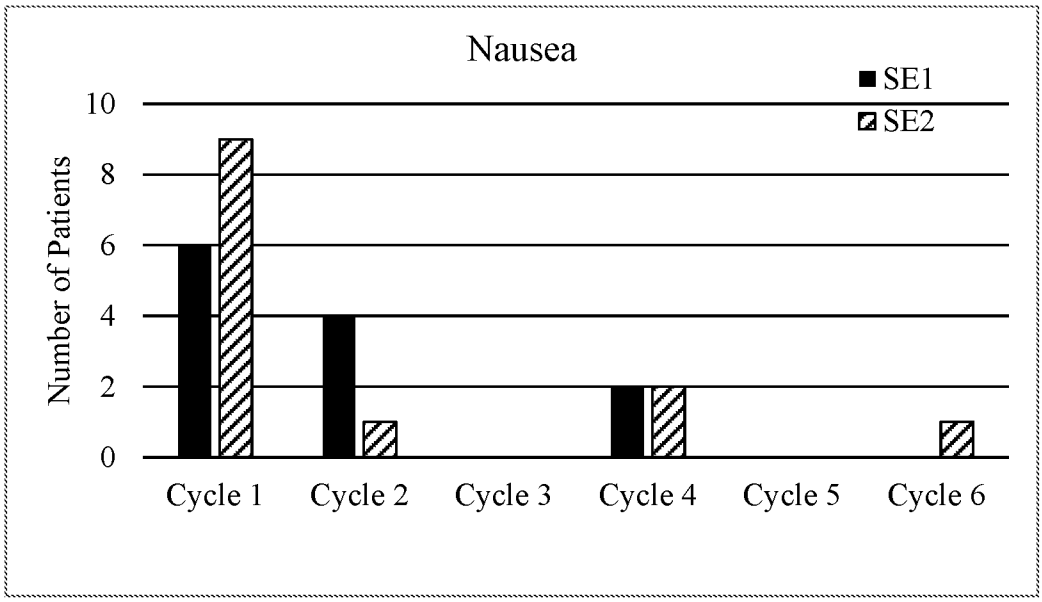
Nausea
SE1
SE2
Number of Patients
10
8
6
4
2
0
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 5
Cycle 6

FIG. 4C