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(54) **Title:** METHODS FOR TREATING ACUTE MYELOID LEUKEMIA AND RELATED CONDITIONS

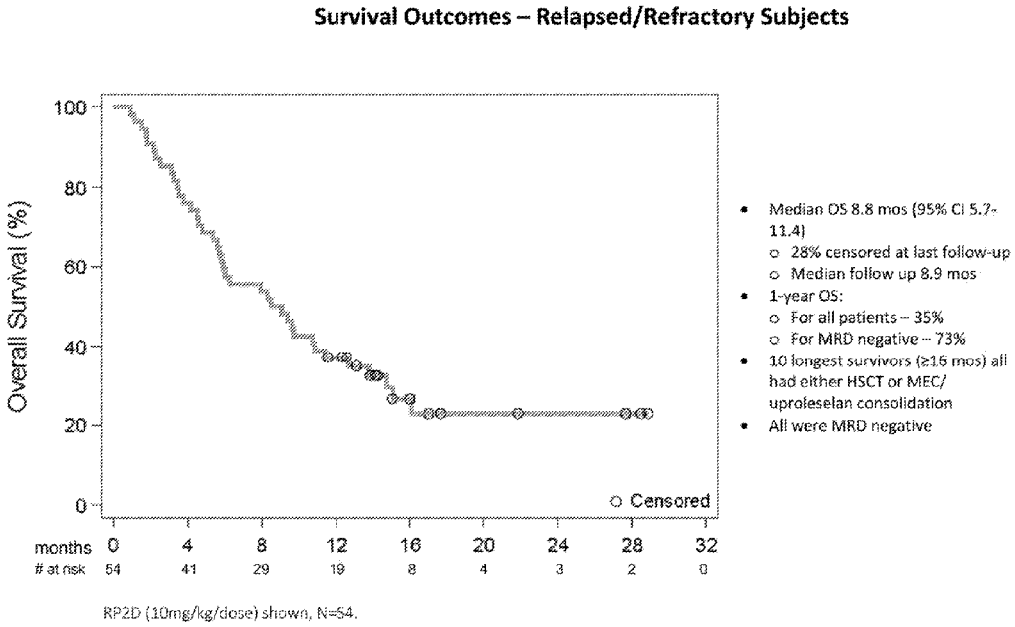


FIG. 15

(57) **Abstract:** Methods for treating or inhibiting cancer and/or one or more related conditions by administering to a subject in need thereof an effective amount of a compound of Formula (I) a prodrug thereof or a pharmaceutically acceptable salt of any of the foregoing. For example, methods for treating AML, MDS, neutropenia, and/or mucositis comprising administering a pharmaceutical composition comprising a compound of Formula (I) are described.

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METHODS FOR TREATING ACUTE MYELOID LEUKEMIA AND RELATED CONDITIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 62/638,569, filed March 5, 2018, the contents of which are hereby incorporated by reference.

BACKGROUND

[0002] The present disclosure relates to methods for treating or inhibiting cancer and/or one or more related conditions comprising administering to a subject in need thereof an effective amount of at least one compound of Formula (I), prodrug thereof, and/or pharmaceutically acceptable salt of any of the foregoing.

[0003] The present disclosure provides methods for treating patients with cancers, including drug-resistant cancers, cancers with a high likelihood of relapse, cancers with accelerated disease progression, and/or cancers with reduced survival.

[0004] A number of cancers are highly treatable when treated before the cancer has moved beyond the primary site. However, often once the cancer has spread beyond the primary site, the treatment options are limited, and the survival statistics decline dramatically. For example, when colorectal cancer is detected at a local stage (i.e., confined to the colon or rectum), over 90% of those diagnosed survive more than five years. Conversely, when colorectal cancer has spread to distant sites (i.e., metastasized from the primary site to distant sites), the five-year survival rate of those diagnosed drops dramatically to only 11%.

[0005] The four most common hematological cancers are acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), and acute myelogenous leukemia (AML). Leukemias and other cancers of the blood, bone

marrow, and lymphatic system affect 10 times more adults than children. AML is the most common leukemia in adults.

[0006] AML results when bone marrow begins making blasts instead of mature white blood cells. The immature blasts are unable to fight infections. AML is the most common acute leukemia, and it progresses rapidly. Left untreated, AML may lead to death in weeks or months.

[0007] Current treatments for AML include chemotherapy, including targeted chemotherapies, radiation therapy, and autologous stem cell transplantation or allogeneic stem cell transplantation. The side effects of each of these treatments are well documented. Typically, a newly diagnosed AML patient will be treated with an induction chemotherapy regimen to attempt to put the cancer in remission. Remission does not cure the patient; it merely means the disease can no longer be detected. Remission, however, is most often a temporary measure as most AML patients in remission eventually relapse. Post-remission therapies include consolidation chemotherapy (typically three to five courses of intensive chemotherapy for leukemias with good prognoses), allogenic stem cell transplantation (for higher risk leukemias *and* with a matched donor), and autologous stem cell transplant (when possible based on the patients underlying condition, and when a matched donor is not available). Very few medications are available to treat relapsing AML, such as the highly toxic arsenic trioxide, which only works in AML patients with the acute promylocytic leukemia subtype of AML. In persons with relapsing AML, the only potential cure is stem cell transplant. When stem cell transplant is not possible, immunotherapy may be attempted to extend remission as long as possible. With such limited treatment options, palliative care is often the only treatment available for relapsing AML patients. Therefore, there is a need for additional therapeutics for treating (including preventing) AML.

[0008] Myelodysplastic syndrome ("MDS") refers to a diverse group of hematopoietic stem cell ("HSC") disorders. MDS is characterized by a cellular marrow with impaired morphology and maturation (dysmyelopoiesis), peripheral blood cytopenias, and a risk of progression to acute leukemia resulting from ineffective blood cell production. (See The Merck Manual. 1999. 17:953; List, et al. The Myelodysplastic Syndromes: Biology and Implications for Management. J. Clin. Oncol. 1990. 8:1424.)

[0009] The common trait shared by MDS HSC disorders is the presence of dysplastic changes in one or more of the hematopoietic lineages, for example, dysplastic changes in the myeloid, erythroid, or megakaryocytic series. These changes result in cytopenia in one or more of the lineages. Patients afflicted with MDS may develop complications related to anemia, neutropenia (infections), and/or thrombocytopenia (bleeding). From about 10% to about 70% of patients with MDS develop acute leukemia. In the early stages of MDS, the main cause of cytopenia is increased programmed cell death (apoptosis). As the disease progresses and converts into leukemia, a proliferation of leukemic cells overwhelms the healthy marrow. The disease course differs, with some cases behaving as an indolent disease and others behaving aggressively with very short clinical courses that convert into acute forms of leukemia. The majority of people with higher risk MDS eventually experience bone marrow failure. Up to 50% of MDS patients succumb to complications, such as infection or bleeding, before progressing to AML.

[0010] The initial HSC injury can be from causes such as, but not limited to, cytotoxic chemotherapy, radiation, viral infection, chemical exposure, and genetic predisposition. Alkylating chemotherapy or radiation therapy can cause MDS, which nearly always progresses to AML in these subjects.

[0011] MDS is primarily a disease of elderly people, with the median onset in the seventh decade of life. The median age of these patients is 65 years, with ages ranging from the early

third decade of life to as old as 80 years or older. However, the syndrome may occur in any age group, including the pediatric population. Patients who survive malignancy treatment with alkylating agents, with or without radiotherapy, have a high incidence of developing MDS or secondary acute leukemia. About 60–70% of patients do not have an obvious exposure or cause for MDS and are classified as primary MDS patients.

[0012] Currently U.S. Food and Drug Administration-approved drugs for the treatment of MDS are not curative, and their effect on survival is limited. They include the hypomethylating agents ("HMA") (such as azacitidine and decitabine), and lenalidomide for treating MDS with isolated del(5q). To date, allogenic stem cell transplantation ("ASCT") remains the only treatment option for possible cure. However, ASCT is painful for both the donor and the recipient because of the involvement of invasive procedures. ASCT can cause severe and even fatal complications to the recipient, particularly when Graft Versus Host Disease ("GVHD") occurs. Therefore, the risk of GVHD restricts the use of bone marrow transplantation to patients with otherwise fatal diseases. Further, as most patients are elderly and often only a few young MDS patients will have a matched donor, the use of bone marrow transplantation is limited. Accordingly, there is a need for additional therapeutics for treating MDS.

[0013] Neutropenia is a frequent complication of chemotherapy and occurs when myelosuppressive chemotherapeutic treatment reduces absolute neutrophil counts. One of the side effects of chemotherapy is myeloablative bone marrow toxicity. Bone marrow fills the inside of some bones such as the sternum, hip, femur, and humerus. Cells in the bone marrow are susceptible to the effects of chemotherapy due to their rapid rate of division. Chemotherapeutic agents prevent bone marrow stem cells from forming new blood cells. With time, after exposure to a chemotherapeutic agent, counts of the blood cells will fall at various rates, depending upon the particular type of cell as their average life spans differ.

Low white blood cell count (e.g. neutropenia), for example, makes an individual more susceptible to infection.

[0014] Neutropenia predisposes cancer patients to potentially life-threatening infection, particularly from Gram-negative bacilli, Gram-positive cocci, and fungi. Risk of infection and mortality increases with the degree and duration of the neutropenic episode and the presence of fever.

[0015] Neutropenia requiring hospitalization is particularly common in patients with hematologic tumors. It is estimated to affect 1 in 23 patients diagnosed with such malignancies and 1 in 10 patients treated with chemotherapy. (See Cagglano V., et al. Incidence, Cost, and Mortality of Neutropenia Hospitalization Associated with Chemotherapy. Cancer. 2005. 103(9):1916.)

[0016] Neutropenia can compromise optimal cancer management by causing chemotherapy dose reduction, delay, or even discontinuation. These dose modifications often are implemented during the first cycles of chemotherapy because neutropenic events often occur early during the course of chemotherapy. Treatment response frequently depends on the delivery of standard chemotherapy doses, and modifications in dosing may threaten complete response rates and reduce survival. Thus, caregivers may face a challenge in maintaining adequate chemotherapeutic doses while managing neutropenic complications. Accordingly, there is a need for additional therapeutics for treating (including preventing) neutropenia.

[0017] Mucositis is a common and debilitating adverse event that often arises as a complication of antineoplastic therapy, such as chemotherapy and/or radiation therapy. The goal of such cancer therapies is to kill rapidly-dividing cancer cells; unfortunately, other cells may be killed by the treatments as well, including epithelial cells of the mucous membranes, which can lead to mucositis.

[0018] Mucositis is a serious and often very painful disorder involving inflammation and ulceration of the mucous membranes, such as those of the gastrointestinal tract, the oral and oropharyngeal cavities including the esophagus, as well as the bladder, ear, nasal, optical, vaginal, and rectal mucosa.

[0019] Severe mucositis especially concurrent with the cytopenic period can increase the risk of infection and death, prolong hospitalization, and impact quality of life. (See Niscola P., et al. Mucositis in Patients with Hematologic Malignancies: An Overview. Haematologica. 2007. 92:222.)

[0020] While the overall frequency of mucositis, as well as its severity, depends on factors including, for example, the treatment regimen and on the treatment modality, it is believed that approximately half of all cancer patients undergoing therapy suffer some degree of mucositis. Mucositis is believed to occur, for example, in virtually all patients treated with radiation therapy for head and neck tumors, all patients receiving radiation along the GI tract, and approximately 40% of those subjected to radiation therapy and/or chemotherapy for tumors in other locations (e.g., leukemias or lymphomas). It is also is believed to be highly prevalent in patients treated with high dose chemotherapy and/or irradiation for the purpose of myeloablation, such as in preparation for stem cell or bone marrow transplantation.

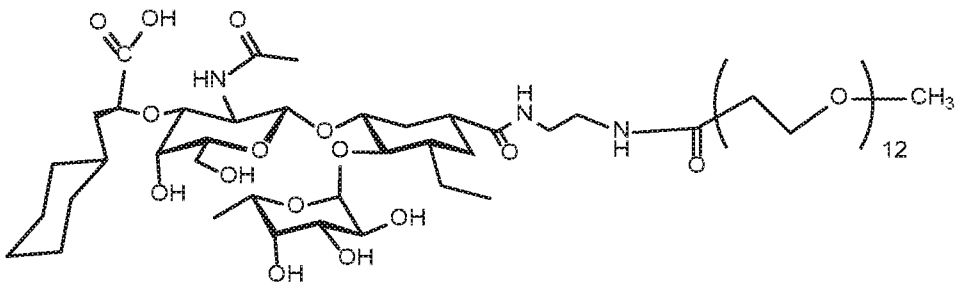
[0021] Mucositis can adversely impact the quality of life of cancer patients. Patients may experience pain, erythema, and/or deep, diffuse ulcers than can cause difficulty speaking, eating, and swallowing. Patients may also experience nausea and/or gastro-enteritis. Severe mucositis can lead to the need for parenteral nutrition or hospitalization or to disruptions in cancer treatment, alterations in treatment dosages, and/or shifting to different modes of treatment.

[0022] Mucositis may also be accompanied by a severe risk of fever and infection, as it can lead to a breach in the otherwise protective linings of the oral mucosa and gastrointestinal

tract. The alimentary canal and gastrointestinal tract are colonized by a vast array of microorganisms, and mucosal lesions can provide a portal of entry for bacteria.

[0023] Current therapy for mucositis is largely palliative, including administration of antibiotics, antifungals, or anti-inflammatory agents combined with topical treatments containing compounds that modulate wound-healing and prevent infection. There is only a single medication approved for the treatment of mucositis—palifermin. It is approved for use, however, only in a limited subset of patients. Therefore, there is a need for additional therapeutics for treating (including preventing) mucositis.

[0024] The present application discloses methods for treating AML, MDS, neutropenia, and/or mucositis comprising administering to a subject in need thereof an effective amount of a compound of Formula (I) and compositions comprising the same.



(I)

[0025] In some embodiments, a method is provided for treating AML, MDS, neutropenia, and/or mucositis comprising administering to a subject in need thereof an effective amount of a compound of Formula (I).

[0026] In some embodiments, a compound of Formula (I) is administered as a fixed daily dose. In some embodiments, a method is provided for treating AML, MDS, neutropenia, or mucositis comprising administering to a subject in need thereof a fixed dose of 200 mg to 4000 mg per day, 800 mg to 3200 mg per day, or 1000 mg to 2000 mg per day of a compound of Formula (I). In some embodiments, a method is provided for treating AML,

MDS, neutropenia, or mucositis comprising administering to a subject in need thereof a fixed dose of 1600 mg per day of a compound of Formula (I).

[0027] In some embodiments, a compound of Formula (I) is administered as a weight-based daily dose. In some embodiments, a method is provided for treating AML, MDS, neutropenia, or mucositis comprising administering to a subject in need thereof 1 mg/kg to 100 mg/kg per day, 5 mg/kg to 80 mg/kg per day, or 10 mg/kg to 40 mg/kg per day of a compound of Formula (I). In some embodiments, a method is provided for treating AML, MDS, neutropenia, or mucositis comprising administering to a subject in need thereof 20 mg/kg per day of a compound of Formula (I).

[0028] In some embodiments, the daily dose (fixed or weight-based) of a compound of Formula (I) is administered as a single dose. In some embodiments, the daily dose of a compound of Formula (I) is administered in separate doses over the day. In some embodiments, the daily dose of a compound of Formula (I) is administered twice daily (i.e. BID). In some embodiments, the daily dose of a compound of Formula (I) is administered in two doses with about 12 hours between each dose. In some embodiments, the subject receives two doses of 800 mg each of a compound of Formula (I) per day. In some embodiments, the two doses per day of 800 mg each of a compound of Formula (I) are administered about 12 hours apart. For example, a fixed daily dose of 1600 mg may be administered over the day as two separate doses of 800 mg each, with the two 800 mg doses being administered about 12 hours apart. As another example, a weight-based daily dose of 20 mg/kg per day may be administered over the day as two separate doses of 10 mg/kg each, with the two 10 mg/kg doses being administered about 12 hours apart.

[0029] A compound of Formula (I) may be administered in a variety of methods, as described herein. For example, a compound of Formula (I) may be administered intravenously or subcutaneously.

[0030] In some embodiments, a compound of Formula (I) is administered to a subject that is receiving, has received, or will receive chemotherapy and/or radiotherapy, as described herein. For example, a compound of Formula (I) may be administered to a subject that is receiving, has received, or will receive two or more chemotherapeutic agents, such as mitoxantrone, etoposide, and cytarabine or fludarabine, cytarabine, and idarubicin. As another example, a compound of Formula (I) may be administered to a subject that is receiving, has received, or will receive velafermin, palifermin, thalidomide, and/or a thalidomide derivative.

[0031] In some embodiments, a compound of Formula (I) is administered to a subject that is receiving, has received, or will receive MMP inhibitors, inflammatory cytokine inhibitors, mast cell inhibitors, NSAIDs, NO inhibitors, MDM2 inhibitors, or antimicrobial compounds.

[0032] In some embodiments, where the subject has AML, the administration of the compound of Formula (I) extends the number of days the subject is in remission, reduces the number of days until remission, inhibits the metastasis of AML cells, and/or improves survival.

[0033] In some embodiments, where the subject has MDS, the administration of the compound of Formula (I) slows the progression of MDS, prevents the progression of MDS to leukemia, and/or improves survival.

[0034] In some embodiments, where the subject has neutropenia, the administration of the compound of Formula (I) reduces the number of days the subject is afflicted with neutropenia or reduces the severity of the neutropenia.

[0035] In some embodiments, where the subject has mucositis, the administration of the compound of Formula (I) reduces the number of days the subject is afflicted with mucositis or reduces the severity of the mucositis.

[0036] In some embodiments, a compound of Formula (I) is administered as a prodrug of Formula (I) or a pharmaceutically acceptable salt of any of the foregoing.

[0037] In some embodiments, the compound of Formula (I), prodrug of Formula (I), or pharmaceutically acceptable salt of any of the foregoing is administered in combination with a pharmaceutically acceptable carrier or diluent.

BRIEF DESCRIPTION OF THE DRAWINGS

[0038] Figure 1A illustrates the effect of a compound of Formula (I) on small intestine weight (a measure of inflammation) in mice, after 5-FU chemotherapy. Figure 1B illustrates that 5-FU induced intestinal erosion, villous loss, and macrophage infiltration was attenuated treatment with a compound of Formula (I).

[0039] Figure 2 illustrates the effect of a compound of Formula (I), on macrophage infiltration of the intestine in mice, after radiation therapy.

[0040] Figures 3A-3B illustrate the efficacy of cytarabine in E-selectin knockout mice as compared to wild-type mice (Figure 3A), and in wild-type mice when combined with a compound of Formula (I) as compared to cytarabine ("AraC") treatment alone (Figure 3B).

[0041] Figure 4 illustrates circulating leukemic cell burden in mice engrafted with human AML blasts when treated with 5 mg/kg of a compound of Formula (I), cytarabine, and daunorubicin ("DNR") as compared to treatment with cytarabine and DNR.

[0042] Figure 5 illustrates survival of mice engrafted with human AML blasts when treated with a compound of Formula (I) (10 mg/kg and 40 mg/kg BID (i.e. 20 mg/kg and 80 mg/kg per day)), cytarabine, and DNR as compared to treatment with cytarabine and DNR.

[0043] Figure 6 illustrates survival of mice bearing the human AML cell line, U937, when given no treatment, as compared to mice treated with cytarabine and DNR, and a

compound of Formula (I) (40 mg/kg BID (i.e., 80 mg/kg per day) for 9 days), cytarabine and DNR.

[0044] Figure 7 illustrates survival of mice bearing MLL-AF9-induced AML leukemia when given no treatment, as compared to mice treated with cytarabine and doxorubicin ("DOX"), and mice treated with a compound of Formula (I) (40 mg/kg BID (i.e., 80 mg/kg per day) for 10 days), cytarabine, and DOX.

[0045] Figure 8 illustrates adhesion of KG1 cells treated with 5-azacytidine to E-selectin-coated wells compared to KG1 cells treated with a compound of Formula (I) and 5-azacytidine, providing a graph quantifying the fluorescence demonstrated in the control cells, 5-azacytidine treated cells, and cells treated with 5-azacytidine and a compound of Formula (I) .

[0046] Figure 9 illustrates survival of KG1 AML model mice when given no treatment, as comparted to mice treated with a compound of Formula (I) (40 mg/kg per day for 14 days), 5-azacytidine, or a compound of Formula (I) and 5-azacytidine.

[0047] Figures 10A-10B illustrate E-selectin ligand binding (Figure 10A) or $sLe^{a/x}$ binding (Figure 10B) to AML blasts in newly diagnosed older patients (aged 60 years or older) and relapsed/refractory (R/R) leukemia patients.

[0048] Figure 11 illustrates plasma soluble E-selectin levels across an 8-day treatment period in human subjects treated with various levels of a compound of Formula (I), and MEC chemotherapy. Subjects were divided into three cohorts for the eight-day study. On day 1, subjects received a single dose of a compound of Formula (I), days 2-6 each comprised MEC treatment combined with two doses of a compound of Formula (I), and days 7-8 each comprised two doses of a compound of Formula (I). Cohort 1 received doses of 5 mg/kg of a compound of Formula (I) (i.e. 5 mg/kg on day 1; 5 mg/kg BID (10 mg/kg per day) on days 2-8), cohort 2 received 10 mg/kg doses of a compound of Formula (I) (i.e. 10 mg/kg on day 1;

10 mg/kg BID (20 mg/kg per day) on days 2-8), and cohort 3 received 20 mg/kg doses of a compound of Formula (I) (i.e. 20 mg/kg on day 1; 20 mg/kg BID (400 mg/kg per day) on days 2-8). The decrease from baseline to Day 8 was highly significant ($P<0.0001$) with no dose response.

[0049] Figures 12A-12D illustrate metrics quantifying exposure-response to a compound of Formula (I), during treatment across clinical response categories. Figure 12A plots the fraction of dosing interval greater than the IC_{50} of a compound of Formula (I) against four categories of efficacy response (CR = complete remission; CRi = complete remission with incomplete count recovery; MLFS = morphologic leukemia-free state; PD = persistent disease). Figure 12B plots the fraction of dosing interval greater than the IC_{90} of a compound of Formula (I) against the four categories of efficacy response. Figure 12C plots Cmax (μg/ml) of a compound of Formula (I) against the four categories of efficacy response. Figure 12D plots area under the curve ("AUC") of a compound of Formula (I) against the four categories of efficacy response. Box and whisker plots to illustrate the minimum, 25th percentile, median, 75th percentile, and maximum exposure metric in each category.

[0050] Figures 13A-13D illustrate adverse events ("AEs") plotted against exposure to a compound of Formula (I) during treatment. Percentile rankings (left graphs) and normalized values (right graphs) of each subject's calculated AUC, cumulative AUC, and Cmax are reported. AEs identified for E-R analyses were: neutropenia (Figures 13A and 13B), thrombocytopenia (Figure 13C and 13D), febrile neutropenia (Figures 13E and 13F), infection (Figures 13G and 13H), mucositis (Figures 13I and 13J), and anemia (Figures 13K and 13L). If a subject experienced the event twice, they are shown twice in the figures, as indicted by "Replicate IDs." The number of subjects who did not have evaluable PK data is annotated as "No PK," and those subjects' data are not shown in the graphs.

[0051] Figures 14A-14B illustrate select induction and consolidation treatment protocols. During induction subjects receive chemotherapy, either MEC or FAI, for five consecutive days and a compound of Formula (I) for eight consecutive days. Treatment with a compound of Formula (I) is initiated one day prior to initiating chemotherapy (Figure 14A). During consolidation patients receive consolidation chemotherapy, HiDAC, IDAC option 1, IDAC option 2, or MEC. Treatment with a compound of Formula (I) is initiated one day prior to initiating consolidation chemotherapy with a single dose of a compound of Formula (1). Then Formula (1) is administered twice daily on chemotherapy days and twice daily for two days following the last dose of chemotherapy (Figure 14B).

[0052] Figure 15 illustrates the survival outcomes of 54 relapsed/refractory (R/R) AML subjects administered the RP2D dose of 10 mg/kg/dose of a compound Formula (1) according to the protocol described in Example 21.

[0053] Figures 16A-16B illustrate the survival outcomes of 25 newly diagnosed older AML subjects (aged 60 years or older) administered the RP2D dose of 10 mg/kg/dose of a compound Formula (1) according to the protocol described in Example 22. Figure 16A illustrates the event-free survival rates, and Figure 16B illustrates the overall survival rates.

[0054] The terms "a," "an," and "the" refer to "one or more" when used in this application, including the claims. Thus, for example, reference to "a cell" includes one cell or a plurality of cells, and so forth.

[0055] The term "E-selectin antagonist" includes inhibitors of E-selectin only, as well as inhibitors of E-selectin and either P-selectin or L-selectin, and inhibitors of E-selectin, P-selectin, and L-selectin.

[0056] The terms "patient," "subject," "individual," and the like are used interchangeably herein, and refer to any animal, or cells thereof whether in vitro or in situ, amenable to the methods described herein. In some embodiments, the patient, subject or individual is a

human. In some embodiments, the patient, subject or individual is in need of treatment includes those who already have the disease, condition, or disorder as well as those prone to have or at risk of developing the disease, condition, or disorder, and those in which the disease, condition, or disorder is to be prevented.

[0057] The term "prodrug" includes compounds that may be converted, for example, under physiological conditions or by solvolysis, to a biologically active compound described herein. Thus, the term "prodrug" includes metabolic precursors of compounds described herein that are pharmaceutically acceptable. A discussion of prodrugs can be found, for example, in Higuchi, T., et al., "Pro-drugs as Novel Delivery Systems," A.C.S. Symposium Series, Vol. 14, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987. The term "prodrug" also includes covalently bonded carriers that release the active compound(s) as described herein *in vivo* when such prodrug is administered to a subject.

[0058] The term "pharmaceutically acceptable salt" includes both acid and base addition salts. Non-limiting examples of pharmaceutically acceptable acid addition salts include chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, methane sulfonates, formates, tartrates, maleates, citrates, benzoates, salicylates, and ascorbates. Non-limiting examples of pharmaceutically acceptable base addition salts include sodium, potassium, lithium, ammonium (substituted and unsubstituted), calcium, magnesium, iron, zinc, copper, manganese, and aluminum salts. Pharmaceutically acceptable salts may, for example, be obtained using standard procedures well known in the field of pharmaceuticals.

[0059] The term "therapy" refers to "treating" or "treatment" of a disease or condition including preventing or inhibiting the disease (slowing or arresting its development), providing relief from the symptoms or side-effects of the disease (including palliative treatment), and relieving the disease (causing regression of the disease). "Therapy,"

"treating," or "treatment" may also refer to prophylactic treatment, which includes preventing or delaying the onset of the disease or condition from occurring in a subject that may be predisposed to the disease but does not yet experience or exhibit symptoms of the disease. "Therapy," "treating," or "treatment" can also refer to prolonging survival when compared to expected survival if a subject were not receiving treatment. It is not necessary for the "treatment" to show effectiveness in 100% of the patients treated, rather, the term "treatment" is intended to mean that a statistically significant proportion of patients can be treated effectively, in such a way that the symptoms and clinical signs show at least an improvement. The person skilled in the art can easily establish whether the proportion is statistically significant using various statistical methods (e.g. confidence intervals, determination of them P value, Student's t-test, Mann-Whitney test etc.). Confidence intervals have a confidence of at least 90%, at least 95%, at least 97%, at least 98%, or at least 99%. The P values are 0.1, 0.05, 0.01, 0.005, or 0.0001.

[0060] In some embodiments, the methods described herein provide at least one a compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient described herein in an amount sufficient to result in at least one desired therapeutic and/or prophylactic benefit. Therapeutic or prophylactic benefit includes, for example, an improved clinical outcome in either therapeutic treatment or prophylactic/preventative measures, wherein the object is to prevent or slow or retard (lessen) an undesired physiological change or disorder, or to prevent or slow or retard the expansion or severity of such disorder. As discussed herein, beneficial or desired clinical results from treating a subject include, but are not limited to, abatement, lessening, or alleviation of symptoms that result from or are associated with the disease, condition, or disorder to be treated; decreased occurrence of symptoms; improved quality of life; longer disease-free status (i.e., decreasing the likelihood or the propensity that a subject will present symptoms on the basis of which a

diagnosis of a disease is made); diminishment of extent of disease; stabilized (i.e., not worsening) state of disease; delay or slowing of disease progression; amelioration or palliation of the disease state; and remission (whether partial or total), whether detectable or undetectable; or overall survival.

[0061] An "effective amount" or "therapeutically effective" amount refers to an amount of a compound of the present disclosure or a composition comprising at least one such compound that, when administered to a subject, either as a single dose or as part of a series of doses, is effective to produce at least one therapeutic effect.

[0062] Compounds of Formula (I) may, for example, be synthesized according to methods disclosed in U.S. Patent No. 9,109,002, which is hereby incorporated by reference.

[0063] The present disclosure includes within its scope all the possible geometric isomers, e.g. Z and E isomers (*cis* and *trans* isomers), of the compounds as well as all the possible optical isomers, e.g. diastereomers and enantiomers, of the compounds. Furthermore, the present disclosure includes in its scope both the individual isomers and any mixtures thereof, e.g. racemic mixtures. The individual isomers may be obtained using the corresponding isomeric forms of the starting material or they may be separated after the preparation of the end compound according to conventional separation methods. For the separation of optical isomers, e.g. enantiomers, from the mixture thereof conventional resolution methods, e.g. fractional crystallization, may be used.

[0064] Compounds described herein may exist as polymorphs, which are also included by the present disclosure. In addition, some of the compounds may form hydrates with water or solvates with other solvents. Such hydrates and solvates are similarly included within the scope of compounds and compositions described herein.

[0065] Recently E-selectin-mediated interactions have been identified as targets for treating certain cancers. Not all cancer cells are alike. Even within a group of related cancer

cells (e.g., a multiple myeloma cell line or prostate cancer tumor), gene expression and cell surface epitopes vary. Certain cancer cells, referred to as cancer stem cells, can establish new tumors, and the presence of higher numbers of these stem cells in a patient are associated with poorer prognoses. These cancer stem cells may also exhibit the more aggressive cancer traits such as drug resistance, accelerated disease progression, shorter survival, and higher incidence of relapse. Therefore, there is a need for treatments that will target cancer stem cells.

[0066] Cancer stem cells have been found to express cell surface carbohydrates that can bind to E-selectin. Cancer cells that can bind to E-selectin are capable of resisting certain standard treatments for cancer, such as chemotherapy, and are correlated with drug-resistance, accelerated disease progression, shorter survival, and higher incidence of relapse. It is thought that cancer cells expressing the carbohydrate epitope that binds E-selectin are able to survive chemotherapy treatment because they are also able to bind to E-selectin expressed on the vascular endothelium in protective niches in bone marrow. Thus, for example, when bound to the E-selectin in the protective niches of bone marrow, these cancer cells are able to survive cancer treatments such as chemotherapy. This is further evidence of the need for treatments that target cancer cells that bind to E-selectin.

[0067] E-selectin is an adhesion molecule expressed on the vascular endothelium that recognizes and binds to carbohydrate structures on the surfaces of cells in the bloodstream facilitating extravasation from the circulation. The carbohydrate ligands that bind E-selectin were first identified as tumor markers and the binding of E-selectin is thought to play a role in tumor metastasis and resistance to chemotherapy. E-selectin binds a trisaccharide domain common to both the carbohydrate structures sialyl Le^a (sLe^a) and sialyl Le^x (sLe^x) that is the epitope on tumor cells recognized by E-selectin.

[0068] A growing body of literature has reported that E-selectin-mediated interactions may play a role in AML, and the expression of E-selectin or its binding epitope (sialyl $Le^{a/x}$) may predict the clinical course and patient outcomes in AML (see Aref, S., et al. L and E Selectins in Acute Myeloid Leukemia: Expression, Clinical Relevance and Relation to Patient outcome. Hematology. 2002. 7(2):83-87). Soluble E-selectin (sE-selectin) may be shed from the cell membrane and detected by enzyme-linked immunosorbent assay (ELISA) in the peripheral blood. AML is associated with increased vessel density, and sE-selectin release by activated/proliferating endothelial cells in the bone marrow may contribute to increased E-selectin levels in patients with untreated AML (see Glenjen, N., et al., Serum Levels of Angiogenin, Basic Fibroblast Growth Factor and Endostatin in Patients Receiving Intensive Chemotherapy for Acute Myelogenous Leukemia. Intl. J. Cancer. 2002. 101(1):86). Soluble E-selectin levels are increased in the serum of patients with newly diagnosed AML compared with that in the serum of healthy subjects (see Horacek, J., et al., Biochip Array Technology and Evaluation of Serum Levels of Multiple Cytokines and Adhesion Molecules in Patients with Newly Diagnosed Acute Myeloid Leukemia. Experimental Oncology. 2014. 36(1):50). sE-selectin levels have also been correlated with the extramedullary infiltration of AML cells ($P<0.001$) and predict the occurrence of relapse of AML ($P=0.01$). Elevated sE-selectin levels at diagnosis of AML predicted low survival ($P<0.001$), and decreases in sE-selectin levels correlated with durable remission of AML (see Glenjen (2002) and Horacek (2014)). Therefore, there is a need for therapeutics for AML directed to the E-selectin mediated pathways.

[0069] E-selectin expression is transient in the normal vasculature during an inflammatory response but constitutive in the bone marrow ("BM"), generally resulting in sequestration of AML cells that express E-selectin or its binding epitope (sialyl $Le^{a/x}$) (i.e.,

AML blasts) in the bone marrow. Adhesion of AML-blasts to E-selectin initiates up-regulation of pathways critical to leukemia progression.

[0070] E-selectin is unique among vascular adhesion molecules in being able to directly activate the NF-κB pathway. Upstream blockade of E-selectin has been shown to inhibit NF-κB activation, suggesting that adhesion to E-selectin activates pro-survival NF-κB signaling in AML cells leading to enhanced chemoresistance (see Winkler, I.G., et al. Vascular E-selectin Protects Leukemia Cells from Chemotherapy by Directly Activating Pro-survival NF-kB Signaling - Therapeutic Blockade of E-selectin dampens NK-kB Activation. Blood. 2016. 128:2823). Collectively, these results suggest that E-selectin is a key vascular niche component in the bone marrow mediating resistance to chemotherapy. Therefore, there is a need for therapeutics for preventing the E-selectin mediated activation of the NF-κB pathway.

[0071] Chemotherapeutic agents can be ineffective at accessing and killing cancerous cells in the bone marrow, thereby reducing the treatment's overall effectiveness at eliminating the tumor. One explanation for the inability to completely eliminate the tumor may be attributed to the role of E-selectin interactions with AML blasts. AML blasts bound to E-selectin are resistant to the effects of chemotherapy (cell-adhesion mediated drug resistance, or CAMDR) *in vitro*, which is hypothesized to be a source of relapse *in vivo* (see Pezeshkian B., et al. Leukemia Mediated Endothelial Cell Activation Modulates Leukemia Cell Susceptibility to Chemotherapy Through a Positive Feedback Loop Mechanism. PLoS One. 2013. 8:e60823). E-selectin inhibition is hypothesized to disrupt the adhesion of AML cells in bone marrow and can mobilize AML blasts out of the bone marrow into the blood stream. These effects of E-selectin inhibition are proposed to result in greater susceptibility of AML cells to cytotoxic chemotherapy. In particular, it is thought that by blocking or otherwise inhibiting E-selectin, E-selectin is unable to bind to the cell surface carbohydrate.

Without being able to bind to E-selectin, the cancer stem cells are unable to hide in protective niches in bone marrow and unable escape chemotherapy treatment. Therefore, there is a need for additional therapeutics for treating AML, particularly for treatments that target the AML blasts that bind to E-selectin.

[0072] As disclosed above, the present application is drawn to uses of a compound of Formula (I) or a pharmaceutical composition comprising the same for treating (including preventing) metastasis of cancer cells (also called tumor cells herein) in an individual (e.g., a subject, a patient) with AML, MDS, neutropenia, and/or mucositis by administering the compound or composition to the individual. In some embodiments, a compound of Formula (I) is used for treating (including preventing) metastasis of AML in a subject in need thereof. In some embodiments, AML is inhibited from infiltrating bone. Without wishing to be bound by theory, by inhibiting tumor cells from metastasizing to the bone marrow or to other protective niches in the body, the tumor cells may be inhibited from sequestration and protection from exposure to chemotherapy or radiotherapy. A subject in need of such treatment includes subjects who have been diagnosed with AML and/or subjects with an increased risk of developing AML.

[0073] In some embodiments of the methods described herein, the subject in need of treatment described herein is a human or non-human animal. A subject in need of treatment may exhibit symptoms of AML, MDS, neutropenia, and/or mucositis or may be at risk of developing AML, MDS, neutropenia, and/or mucositis. Non-human animals that may be treated include mammals, for example, non-human primates (e.g., monkey, chimpanzee, gorilla, and the like), rodents (e.g., rats, mice, gerbils, hamsters, ferrets, rabbits), lagomorphs, swine (e.g., pig, miniature pig), equine, canine, feline, bovine, and other domestic, farm, and zoo animals.

[0074] One or a combination of diagnostic methods, including physical examination, assessment and monitoring of clinical symptoms, and performance of analytical tests and methods described herein, may be used to monitor the health status of the subject and to assess likelihood of responding to treatment.

[0075] A suitable subject in need of treatment of AML, MDS, neutropenia, and/or mucositis may express a highly active E-selectin as determined by the genetic polymorphism for E-selectin of S128R (Alessandro R., et al., Role of S128R Polymorphism of E-selectin in Colon Metastasis Formation. Intl. J. Cancer. 2007. 121:528). In addition, subjects may be identified based on elevated expression of the E-selectin binding ligands (sialyl Le^a and sialyl Le^x) as determined by antibodies directed against cancer-associated antigens CA-19-9 (Zheng C.X., et al. The Prognostic Value of Preoperative Serum Levels of CEA, CA19-9 and CA 72-4 in Patients with Colorectal Cancer. World J. Gastroenterol. 2001. 7:431), CD65, and FH-6. Antibody HECA-452 which recognizes similar carbohydrate ligands of E-selectin may also be used in a diagnostic assay to select the cancer patient population most likely to respond to this treatment. Subjects in need of the disclosed treatment also may be identified by elevated E-selectin ligand expression on AML blasts as determined by flow cytometry utilizing fluorescently labelled recombinant human E-selectin linked to the Fc domain of IgG.

[0076] In some embodiments, a compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient is administered in conjunction with (i.e., as an adjunct therapy, which is also called adjunctive therapy) chemotherapy or radiation or both.

Accordingly, a subject who has AML, MDS, neutropenia, and/or mucositis or who is at risk of developing AML, MDS, neutropenia, and/or mucositis may be administered a compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient in combination with at least one additional anti-cancer agent. In some embodiments, the at

least one additional anti-cancer agent is chosen from chemotherapy agents, radiotherapeutic agents, inhibitors of phosphoinositide-3 kinase (PI3K), and inhibitors of VEGF. In some embodiments, the inhibitors of PI3K include a compound named by Exelixis as "XL499." In some embodiments, the VEGF inhibitors include a compound called "cabo" (previously known as XL184).

[0077] In some embodiments, the chemotherapy or radiation therapy is the primary therapy for treating AML or MDS. The chemotherapy and radiotherapy that may be administered depend upon several factors including the type of cancer or dysplasia, location of the tumor(s), stage of the cancer or dysplasia, age and gender and general health status of the subject. A compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient may be administered prior to, concurrently with, or subsequent to the primary chemotherapy or radiation treatment. In some embodiments, the compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient is/are administered with one or more cycles of chemotherapy or radiotherapy when multiple cycles of the chemotherapy or radiotherapy are administered to a subject for the treatment of a cancer. In the methods disclosed herein, the compound of Formula (I) may function independent of or in coordination with the anti-cancer agent, e.g., by enhancing effectiveness of the anti-cancer agent or vice versa. In some embodiments, the compound of Formula (I) enhances the efficacy of the chemotherapeutic agent(s) or radiotherapy.

[0078] In addition, serious and potentially life-threatening chemotherapy-induced neutropenia and mucositis are associated with E-selectin up-regulation, and inhibition or genetic ablation of E-selectin protects against these deleterious side effects (Winkler IG, Barbier V, Nutt HL, et al. Administration Of E-Selectin Antagonist GMI-1271 Improves Survival After High-Dose Chemotherapy By Alleviating Mucositis and Accelerating Neutrophil Recovery (Poster). 55th ASH Annual Meeting and Exposition; 2013; New

Orleans, LA). For example, E-selectin plays an important role in chemotherapy-induced mucositis through the regulation of macrophage trafficking to the site of injury in the gut lining. Chemotherapy causes initial cell damage, and through a series of inflammatory and adhesion-molecule-mediated stages, the damage is propagated with resulting loss of mucosal integrity. E-selectin knockout mice are protected against chemotherapy-induced mucositis using 5-fluorouracil (5-FU). Similar results were demonstrated where mice administered a glycomimetic E-selectin inhibitor with 5-FU had enhanced neutrophil recovery (see Winkler, I.G., et al. Vascular Niche E-selectin Regulates Hematopoietic Stem Cell Dormancy, Self Renewal and Chemoresistance. Nature medicine. 2012. 18(11):1651), less mucositis and improved weight loss as compared with mice treated with 5-FU alone (see Winkler, I.G., et al. Administration of E-Selectin Antagonist GMI-1271 Improves Survival After High-Dose Chemotherapy by Alleviating Mucositis and Accelerating Neutrophil Recovery. Blood. 2013. 122(21):2266). Furthermore, E-selectin was up-regulated in the intestines following chemotherapy or radiation damage. Both genetic deletion of E-selectin and pharmacologic inhibition using glycomimetic E-selectin antagonist effectively blocked secondary migration of inflammatory F4/80+ Ly-6C+ macrophages to intestines of mice following chemotherapy or irradiation.

[0079] A compound of Formula (I) is useful in methods of the present invention as it relates to reducing a myeloablative bone marrow toxicity of chemotherapy, e.g., to treat neutropenia associated with chemotherapy treatments of AML or MDS patients. In some embodiments, an individual who is in need of reducing a myeloablative bone marrow toxicity of chemotherapy is administered a compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient in an amount effective for the reducing myeloablative bone marrow toxicity. As used herein, the term "reducing" (including variations such as "reduction") includes partial and total reduction of at least one (i.e., one or

more) myeloablative bone marrow toxicity of chemotherapy; and also includes partial and total prevention of at least one such toxicity (e.g., by administration of a compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient prior to, simultaneous with, or shortly after, initiation of chemotherapy). For example, a compound of Formula (I) may not prevent neutropenia, but may promote a more rapid and sustained recovery of neutrophils after chemotherapy.

[0080] In some embodiments, methods are provided for treating or preventing neutropenia in a subject with AML or MDS who is treated with or will be treated with a chemotherapeutic drug(s) or radioactive therapy comprising administering a compound of Formula (I) and, optionally, at least one pharmaceutically acceptable ingredient. In some embodiments, the subject has received, is receiving, or will receive both chemotherapy and radiation therapy. Also, provided herein are methods for reducing chemosensitivity or radiosensitivity of HSCs to the chemotherapeutic drug(s) or radioactive therapy, respectively, in a subject. Because repeated cycles of chemotherapy and radiotherapy often diminish the ability of HSCs to recover and replenish bone marrow, a compound of Formula (I), a prodrug thereof, or a pharmaceutically acceptable salt of any of the foregoing may be used in subjects who will receive more than one cycle of chemotherapy or radiotherapy or a combination of both chemotherapy and radiotherapy. A compound of Formula (I) and, optionally, at least one pharmaceutically acceptable ingredient, may therefore be administered with any one or more of each of the cycles of chemotherapy or radiotherapy (or combination) administered to the subject. Also provided herein is a method for inhibiting adhesion of AML tumor cells or MDS cells that express a ligand of E-selectin to an endothelial cell expressing E-selectin on its cell surface, which method comprises contacting the endothelial cell with a compound of Formula (I) as described herein, thereby permitting the compound to interact with E-selectin on the endothelial cell surface and inhibiting binding of the AML tumor cell or MDS cell to

the endothelial cell. Without wishing to be bound by theory, inhibiting adhesion of tumor or MDS cells to endothelial cells may reduce in a significant manner, the capability of the tumor or MDS cells to extravasate into other organs, blood vessels, lymph, or bone marrow and thereby reduce, decrease, or inhibit, or slow the progression of the cancer, including reducing, decreasing, inhibiting, or slowing metastasis.

[0081] In some embodiments, the amount of a compound of Formula (I) administered per day (i.e., the daily dosage) is a fixed amount. In some embodiments, the fixed daily dosage is 200 mg to 4000 mg per day. In some embodiments, the fixed daily dosage is 800 mg to 3200 mg per day. In some embodiments, the fixed daily dosage is 1000 mg to 2000 mg per day. In some embodiments, the fixed daily dosage is 1600 mg per day.

[0082] In some embodiments, the daily dosage is based on the weight of the subject to which the dosage is administered (i.e., weight-based). In some embodiments, the weight-based daily dosage is 1 mg/kg to 100 mg/kg per day, 5 mg/kg to 80 mg/kg per day, or 10 mg/kg to 40 mg/kg per day. In some embodiments, the weight-based daily dosage is 20 mg/kg per day.

[0083] The daily dosage (whether fixed or weight-based) may be administered as one dose per day or in multiple doses in a single day. In some embodiments, the daily dosage is equally divided between multiple doses. In some embodiments, the daily dosage is unequally divided between multiple doses. In some embodiments, the fixed daily dosage is 1600 mg, administered as 2 doses, with each dose comprising 800 mg of a compound of Formula (I). In some embodiments, the weight-based daily dosage is 20 mg/kg, administered as 2 doses, with each dose comprising 10 mg/kg of a compound of Formula (I). In some embodiments, the doses are administered about 12 hours apart.

[0084] The minimum dose that is sufficient to provide effective therapy may be used in some embodiments. Subjects may generally be monitored for therapeutic effectiveness using

assays suitable for the disease or condition being treated or prevented, which assays will be familiar to those having ordinary skill in the art and are described herein. The level of a compound that is administered to a subject may be monitored by determining the level of the compound (or a metabolite of the compound) in a biological fluid, for example, in the blood, blood fraction (e.g., serum), and/or in the urine, and/or other biological sample from the subject. Any method practiced in the art to detect the compound, or metabolite thereof, may be used to measure the level of the compound during the course of a therapeutic regimen.

[0085] The daily dosage amount and dose of a compound described herein may depend upon the subject's condition, that is, stage of the disease, severity of symptoms caused by the disease, general health status, as well as age, gender, and weight, and other factors apparent to a person of ordinary skill in the medical art. Similarly, the dose of the therapeutic for treating a disease or disorder may be determined according to parameters understood by a person of ordinary skill in the medical art.

[0086] In pharmaceutical dosage forms, any one or more of the compounds of the present disclosure may be administered in the form of a pharmaceutically acceptable derivative, such as a salt or prodrug, and/or it/they may also be used alone and/or in appropriate association, as well as in combination, with other pharmaceutically active compounds.

[0087] One of ordinary skill in the art would understand the amount of pharmaceutically acceptable derivative, such as a prodrug or pharmaceutically acceptable salt, that is equivalent to the daily dosages and individual doses of a compound of Formula (I) described herein. That is, for example, given the disclosure above of a fixed daily dose of 1600 mg of a compound of Formula (I), one of ordinary skill in the art would understand how to determine an equivalent fixed daily dose of a prodrug of Formula (I) or a pharmaceutically acceptable salt of any of the foregoing.

[0088] Pharmaceutical compositions may be administered in any manner appropriate to the disease or disorder to be treated as determined by persons of ordinary skill in the medical arts. An appropriate dose and a suitable duration and frequency of administration will be determined by such factors as discussed herein, including the condition of the patient, the type and severity of the patient's disease, the particular form of the active ingredient, and the method of administration. In general, an appropriate dose (or effective dose) and treatment regimen provides the pharmaceutical composition in an amount sufficient to provide therapeutic and/or prophylactic benefit (for example, an improved clinical outcome, such as more frequent complete or partial remissions, or longer disease-free and/or overall survival, or a lessening of symptom severity or other benefit as described in detail herein).

[0089] The pharmaceutical compositions described herein may be administered to a subject in need thereof by any of several routes that can effectively deliver an effective amount of the compound. In some embodiments, the pharmaceutical composition is administered parenterally. Non-limiting suitable routes of parenteral administration include subcutaneous, intravenous, intramuscular, intrasternal, intracavernous, intrameatal, and intraurethral injection and/or infusion. In some embodiments, the pharmaceutical composition is administered intravenously (IV). Non-limiting suitable routes of IV administration include via a peripheral line, a central catheter, and a peripherally inserted central line catheter (PICC). In some embodiments, the pharmaceutical composition is administered subcutaneously.

[0090] In some embodiments, the composition comprising a compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient is formulated as a liquid and is administered parenterally. In some embodiments a compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient is formulated as a liquid and is administered intravenously (IV). In some embodiments a

compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient is formulated as a liquid and is administered subcutaneously (subQ). In some embodiments a compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient is formulated as a liquid and is administered intramuscularly (IM). In some embodiments a compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient is formulated as a liquid and is administered by intraosseous infusion.

[0091] The pharmaceutical compositions described herein may be sterile aqueous or sterile non-aqueous solutions, suspensions or emulsions, and may additionally comprise at least one pharmaceutically acceptable excipient or diluent (i.e., a non-toxic material that does not interfere with the activity of the active ingredient). Such compositions may be in the form of a solid, liquid, or gas (aerosol). Alternatively, the compositions described herein may be formulated as a lyophilizate, or compounds described herein may be encapsulated within liposomes using technology known in the art. The pharmaceutical compositions may further comprise at least one additional component, which may be biologically active or inactive. Non-limiting examples of such components include buffers (e.g., neutral buffered saline or phosphate buffered saline), carbohydrates (e.g., glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides, amino acids (e.g., glycine), antioxidants, chelating agents (e.g., EDTA and glutathione), stabilizers, dyes, flavoring agents, suspending agents, and preservatives.

[0092] Any suitable excipient, diluent, or carrier known to those of ordinary skill in the art for use in pharmaceutical compositions may be employed in the compositions described herein. Excipients for therapeutic use are well known, and are described, for example, in Remington: The Science and Practice of Pharmacy (Gennaro, 21st Ed. 2005). In general, the type of excipient or diluent is selected based on the mode of administration, as well as the

chemical composition of the active ingredient(s). Pharmaceutical compositions may be formulated for the particular mode of administration. For parenteral administration, pharmaceutical compositions may further comprise water, saline, alcohols, fats, waxes, and buffers.

[0093] As previously disclosed, the pharmaceutical compositions (e.g., for delivery by injection) may be in the form of a liquid. A liquid pharmaceutical composition may include, for example, at least one the following: a sterile diluent such as water for injection, saline solution, preferably physiological saline, Ringer's solution, isotonic sodium chloride, fixed oils that may serve as the solvent or suspending medium, polyethylene glycols, glycerin, propylene glycol or other solvents; antibacterial agents; antioxidants; chelating agents; buffers and agents for the adjustment of tonicity such as sodium chloride or dextrose. A parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. In some embodiments, the pharmaceutical composition comprises physiological saline. In some embodiments, the pharmaceutical composition is an injectable pharmaceutical composition, and in some embodiments, the injectable pharmaceutical composition is sterile.

[0094] In some embodiments, the effective amount a compound of Formula (I) is administered in conjunction with another treatment.

[0095] In some embodiments, the subject is administered one or more hypomethylating agents such as decitabine, 5-azacitidine, or guadecitabine. In some embodiments, a compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient is administered before, during, and/or after a hypomethylating agent.

[0096] In some embodiments, the subject is administered one or more alkylating agents, such as carboplatin, cisplatin, oxaliplatin, carmustine, lomustine, streptozocin, altretamine, procarbazine, dacarbazine, temozolomide, busulfan, thiotepa, hexamethylmelamine,

mechlorethamine, cyclophosphamide, chlorambucil, melphalan, or ifosfamide. In some embodiments, a compound of Formula (I), a prodrug thereof, or a pharmaceutically acceptable salt of any of the foregoing, and, optionally, at least one additional pharmaceutically acceptable ingredient is administered before, during, and/or after an alkylating agent.

[0097] In some embodiments, the subject is administered one or more plant alkaloids such as vincristine, vinblastine, vinorelbine, paclitaxel, docetaxel, etoposide, tenisopide, irinotecan, or topotecan. In some embodiments, a compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient is administered before, during, and/or after a plant alkaloid.

[0098] In some embodiments, the subject is administered one or more antitumor antibiotics, such as doxorubicin, daunorubicin, epirubicin, mitoxantrone, idarubicin, dactinomycin, plicamycin, mitomycin, or bleomycin. In some embodiments, a compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient is administered before, during, and/or after an antitumor antibiotic.

[0099] In some embodiments, the subject is administered one or more antimetabolites, such as methotrexate, 5-fluorouracil, foxuridine, cytarabine, capecitibine, gemcitabine, 6-mercaptopurine, 6-thioguanine, cladribine, fludarabine, nelarabine, or pentostatin. In some embodiments, a compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient is administered before, during, and/or after an antimetabolite.

[00100] In some embodiments, the subject is administered one or more topoisomerase inhibitors, such as ironotecan, topotecan, amsacrine, etoposide, etoposide phosphate, or teniposide. In some embodiments, a compound of Formula (I) and, optionally, at least one

additional pharmaceutically acceptable ingredient is administered before, during, and/or after a topoisomerase inhibitor.

[00101] In some embodiments, the subject is administered one or more ribonucleotide reductase inhibitors, such as hydroxyurea. In some embodiments, a compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient is administered before, during, and/or after a ribonucleotide reductase inhibitor.

[00102] In some embodiments, the subject is administered one or more adrenocortical steroid inhibitors, such as mitotane. In some embodiments, a compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient is administered before, during, and/or after an adrenocortical steroid inhibitor.

[00103] In some embodiments, the subject is administered one or more enzymes, such as asparaginase or pegaspargase. In some embodiments, a compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient is administered before, during, and/or after an enzyme.

[00104] In some embodiments, the subject is administered one or more antimicrotubule agents, such as estramustine. In some embodiments, a compound of Formula (I) optionally, at least one additional pharmaceutically acceptable ingredient is administered before, during, and/or after an antimicrotubule agent.

[00105] In some embodiments, the subject is administered one or more targeted therapeutic agents, such as midostaruin, gilteritinib, enasidenib, imatininib mesylate, gefitinib, erlotinib, sorafenib, sunitinib, dasatinib, lapatinib, nilotinib, bortezomib, tofacitinib, crizotinib, obatoclax, naviclax, gossypol, apatinib, vemurafenib, dabrafenib, MEK162, temsirolimus, everolimus, rituximab, trastuzumab, alemtuzamab, panitumumab, bevacizumab, idasanutlin ,or ipilimumab. In some embodiments, a compound of Formula (I)

and, optionally, at least one additional pharmaceutically acceptable ingredient is administered before, during, and/or after a targeted therapeutic agent.

[00106] In some embodiments, the subject is administered one or more retinoids, such as bexarotene, isotretinoin, or tretinoin. In some embodiments, a compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient is administered before, during, and/or after a retinoid.

[00107] In some embodiments, the subject is administered one or more chemotherapeutic agents, such as Vyxeos (daunorubicin and cytarabine), Mylotarg (gemtuzamab and ozogamicin), idasanutlin and cytarabine, IA (idarubicin and cytarabine), MEC (mitoxantrone, etoposide, cytarabine), FAI (fludarabine, cytarabine, idarubicin), 7+3 ida (cytarabine, idarubicin), 5+2 ida (cytarabine, idarubicin), 7 +3 dauno (cytarabine, daunorubicin), 5 +2 dauno (cytarabine, daunorubicin), FLAG (fludarabine, cytarabine, G-CSF), FLAG-Ida (fludarabine, cytarabine, idarubicin, G-CSF), FLAG-Mito (mitoxantrone, fludarabine, cytarabine, G-CSF), FLAMSA (fludarabine, cytarabine, amsacrine), FLAMSA-Bu (fludarabine, cytarabine, amsacrine, busulfan), FLAMSA-Mel (fludarabine, cytarabine, amsacrine, melphalan), or TAD (tioguanine, cytarabine, daunorubicin). In some embodiments, the subject is administered two or more chemotherapeutic agents. In some embodiments, when more than one chemotherapeutic agent is used, the chemotherapeutic agents are administered simultaneously with each other or they may be administered sequentially to each other. In some embodiments, the chemotherapeutic agents are given in an alternating fashion (e.g., a first chemotherapeutic agent is administered, then a second chemotherapeutic agent is administered, then the first chemotherapeutic agent is administered). In some embodiments, a compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient is administered before, during, and/or after the administration of one or more chemotherapeutic agents. That is, a compound of Formula

(I), when administered with one or more chemotherapeutic agents, may be administered at any time in relation to the administration of one or more of the chemotherapeutic agents.

[00108] In some embodiments, the subject is administered thalidomide or one or more thalidomide derivatives, such as lenalidomide. In some embodiments, the subject receives thalidomide or a thalidomide derivative and one or more chemotherapeutic agents. In some embodiments, a compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient is administered before, during, and/or after receiving thalidomide or a thalidomide derivative.

[00109] In some embodiments, the subject is administered MEC induction chemotherapy. In some embodiments, a compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient is administered before, during, and/or after the MEC induction chemotherapy. In some embodiments, the cycle of MEC induction chemotherapy lasts for five consecutive days. In some embodiments, a compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient is given one day prior to initiating chemotherapy, each day during chemotherapy, and for two days following the last dose of chemotherapy (see, e.g., Figure 14A). In some embodiments, the MEC induction chemotherapy comprises treatment with IV mitoxantrone, IV etoposide, and IV cytarabine. In some embodiments, the MEC induction chemotherapy comprises treatment with 10 $mg/m^2/d$ IV mitoxantrone, 100 $mg/m^2/d$ IV etoposide, and 1000 $mg/m^2/d$ IV cytarabine.

[00110] In some embodiments, the subject is administered FAI induction chemotherapy. In some embodiments, a compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient is administered before, during, and/or after the FAI induction chemotherapy. In some embodiments, the cycle of FAI induction therapy lasts for five consecutive days. In some embodiments, a compound of Formula (I), a prodrug thereof,

or a pharmaceutically acceptable salt of any of the foregoing, and, optionally, at least one additional pharmaceutically acceptable ingredient is given one day prior to initiating chemotherapy, each day during chemotherapy, and for two days following the last dose of chemotherapy (see, e.g., Figure 14A). In some embodiments, the FAI induction chemotherapy comprises treatment with IV fludarabine, IV cytarabine, and IV idarubicin. In some embodiments, the FAI induction chemotherapy comprises 30 mg/m^2 IV fludarabine and 2 g/m^2 IV cytarabine for the five consecutive days, and 10 mg/m^2 IV idarubicin for the first three consecutive days.

[00111] In some embodiments, chemotherapy treatment continues after the induction cycle.

[00112] In some embodiments, after induction chemotherapy, a subject may receive one or more cycles of reduced-dose MEC consolidation chemotherapy. In some embodiments, the reduced-dose MEC chemotherapy cycle lasts four consecutive days. In some embodiments, a compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient is administered before, during, and/or after the cycle of the reduced-dose chemotherapy. In some embodiments, a compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient is administered one day prior to initiating the reduced-dose cycle of chemotherapy, each day during chemotherapy, and for two days following the last dose of chemotherapy (see, e.g., Figure 14B). In some embodiments, the reduced-dose MEC therapy comprises treatment with IV mitoxantrone and IV etoposide for five consecutive days, and IV cytarabine on days 2-5 of the cycle. In some embodiments, the reduced-dose MEC therapy comprises administration of 10 mg/m^2/d IV mitoxantrone, 100 mg/m^2/d IV etoposide, and 1000 mg/m^2/d IV cytarabine for four consecutive days.

[00113] In some embodiments, after induction chemotherapy, a subject may receive one or more cycles of HiDAC consolidation chemotherapy. In some embodiments, three or four cycles of HiDAC chemotherapy may be administered. In some embodiments, a HiDAC therapy cycle lasts five consecutive days. In some embodiments, a compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient is administered before, during, and/or after the cycle of the HiDAC chemotherapy. In some embodiments, a compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient is administered one day prior to initiating chemotherapy, each day during chemotherapy, and for two days following the last dose of chemotherapy (see, e.g., Figure 14B). In some embodiments, the HiDAC chemotherapy cycle comprises treatment with IV cytarabine about every 3 hours on Days 2, 4, and 6. In some embodiments, the HiDAC chemotherapy cycle comprises treatment with IV cytarabine about every 12 hours on Days 2, 4, and 6. In some embodiments, the HiDAC chemotherapy cycle comprises administration of 3 g/m^2 IV cytarabine about every 3 hours on Days 2, 4, and 6. In some embodiments, the HiDAC chemotherapy cycle comprises administration of 2-3 g/m^2 IV cytarabine about every 12 hours on Days 2, 4, and 6.

[00114] In some embodiments, after induction chemotherapy, a subject may receive one or more cycles of reduced-dose IDAC consolidation chemotherapy. In some embodiments, three cycles of reduced-dose IDAC consolidation chemotherapy may be administered. In some embodiments, the reduced-dose IDAC consolidation therapy cycle lasts five consecutive days. In some embodiments, a compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient is administered before, during, and/or after the cycle of the reduced-dose IDAC consolidation chemotherapy. In some embodiments, a compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient is administered one day prior to initiating the reduced-dose IDAC consolidation

chemotherapy cycle, each day during chemotherapy, and for two days following the last dose of chemotherapy (see, e.g., Figure 14B). In some embodiments, the reduced-dose IDAC consolidation chemotherapy cycle comprises treatment with IV cytarabine for five consecutive days. In some embodiments, the IDAC chemotherapy cycle comprises administration of 1.5 g/m^2/day IV cytarabine for five consecutive days. In some embodiments, the dose of cytarabine may be reduced to 1 g/m^2/day. In some embodiments, the reduced-dose IDAC consolidation chemotherapy cycle comprises treatment with IV cytarabine about every 12 hours on Days 2, 4, and 6 (for a total of 6 doses). In some embodiments, the IDAC chemotherapy cycle comprises administration of 1.5 g/m^2 IV cytarabine about every 12 hours on Days 2, 4, and 6 (for a total of 6 doses). In some embodiments, the dose of cytarabine may be reduced to 1 g/m^2/day for part or all of the cycle.

[00115] In some embodiments, the subject is administered decitabine chemotherapy. In some embodiments, a compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient is administered before, during, and/or after the decitabine chemotherapy cycle. In some embodiments, a cycle of decitabine chemotherapy lasts five consecutive days. In some embodiments, a cycle of decitabine chemotherapy lasts ten consecutive days. In some embodiments, the decitabine chemotherapy treatment comprises treatment with IV decitabine once daily for 5 consecutive days. In some embodiments, the decitabine chemotherapy treatment comprises administering 20 mg/m^2 IV decitabine once daily for 5 consecutive days. In some embodiments, the decitabine chemotherapy treatment comprises treatment with IV decitabine once daily for 10 consecutive days. In some embodiments, the decitabine chemotherapy treatment comprises administering 20 mg/m^2 IV decitabine once daily for 10 consecutive days. In some embodiments, subjects receiving a five-day cycle of decitabine are administered a compound

of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient once the day before the first infusion of decitabine and once each day of chemotherapy. In some embodiments, subjects receiving a ten-day cycle of decitabine are administered a compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient twice the day before the first infusion of decitabine and twice each day of chemotherapy.

[00116] In some embodiments, the subject is administered 7+3 dauno chemotherapy. In some embodiments, a compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient is administered before, during, and/or after the 7+3 dauno chemotherapy cycle. In some embodiments a compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient is given one day prior to initiating chemotherapy, each day during chemotherapy, and for two days following the last dose of chemotherapy. In some embodiments, a cycle of 7+3 dauno chemotherapy lasts seven consecutive days. In some embodiments, the 7+3 duano chemotherapy comprises administering a continuous IV infusion of cytarabine over seven days (168 hours), with IV daunorubicin administered for the first three consecutive days. In some embodiments, the 7+3 dauno chemotherapy comprises administering a continuous IV infusion of 100 $mg/m^2/d$ cytarabine over seven days (168 hours), with 60 $mg/m^2/d$ IV daunorubicin administered for the first three consecutive days. In some embodiments, follow-up cycles of cytarabine and daunorubicin chemotherapy may be administered. In some embodiments, the follow-up cycle comprises administering a continuous IV infusion of cytarabine over five days (120 hours), with IV daunorubicin administered for the first two consecutive days. In some embodiments, the follow-up cycle comprises administering a continuous IV infusion of 100 $mg/m^2/d$ cytarabine over five days (120 hours), with 60 $mg/m^2/d$ IV daunorubicin administered for the first two consecutive days.

[00117] In some embodiments, the subject is administered 7+3 ida chemotherapy. In some embodiments, a compound of Formula (I), a prodrug thereof, or a pharmaceutically acceptable salt of any of the foregoing, and, optionally, at least one additional pharmaceutically acceptable ingredient is administered before, during, and/or after the 7+3 ida chemotherapy cycle. In some embodiments a compound of Formula (I) and, optionally, at least one additional pharmaceutically acceptable ingredient is given one day prior to initiating chemotherapy, each day during chemotherapy, and for two days following the last dose of chemotherapy. In some embodiments, a cycle of 7+3 ida chemotherapy lasts seven consecutive days. In some embodiments, the 7+3 ida chemotherapy comprises administering a continuous IV infusion of 200 $mg/m^2/d$ cytarabine over seven days (168 hours), with 12 $mg/m^2/d$ IV idarubicin administered for the first three consecutive days. In some embodiments, the 7+3 ida chemotherapy comprises administering a continuous IV infusion of cytarabine over seven days (168 hours), with IV idarubicin administered for the first three consecutive days. In some embodiments, follow-up cycles of cytarabine and idarubicin chemotherapy may be administered. In some embodiments, the follow-up cycle comprises administering a continuous IV infusion of 200 $mg/m^2/d$ cytarabine over five days (120 hours), with 12 $mg/m^2/d$ IV idarubicin administered for the first two consecutive days. In some embodiments, the follow-up cycle comprises administering a continuous IV infusion of cytarabine over five days (120 hours), with IV idarubicin administered for the first two consecutive days.

[00118] Kits comprising unit doses of at least one compound of the present disclosure, for example in injectable doses, are provided. Such kits may include a container comprising the unit dose, an informational package insert describing the use and attendant benefits of the therapeutic in treating the pathological condition of interest, and/or optionally an appliance or device for delivery of the at least one compound or composition comprising the same.

EXAMPLES

EXAMPLE 1

E-SELECTIN ACTIVITY - BINDING ASSAY

[00119] The inhibition assay to screen for and characterize glycomimetic antagonists of E-selectin is a competitive binding assay, which allows the determination of IC_{50} and IC_{90} values. An E-selectin/Ig chimera was immobilized in 96 well microtiter plates by incubation at 37 °C for 2 hours. To reduce nonspecific binding, bovine serum albumin was added to each well and incubated at room temperature for 2 hours. The plate was washed and serial dilutions of the test compounds were added to the wells in the presence of conjugates of biotinylated, sLe^a polyacrylamide with streptavidin/horseradish peroxidase and incubated for 2 hours at room temperature.

[00120] To determine the amount of sLe^a bound to immobilized E-selectin after washing, the peroxidase substrate, 3, 3', 5, 5' tetramethylbenzidine (TMB) was added. After 3 minutes, the enzyme reaction was stopped by the addition of H_3PO_4, and the absorbance of light at a wavelength of 450 nm was determined. The concentration of a compound of Formula (I), required to inhibit binding by 50% was determined and reported as the IC_{50}. The concentration required to inhibit binding by 90% was determined and reported as the IC_{90}. IC_{50} and IC_{90} values: disclosed herein are provided in the following table.

E-Selectin Antagonist Activity

Species	IC_{50}		IC_{90}	
	μM	ng/mL	μM	ng/mL
Mouse	2.45	3250	3.70	4908
Human	2.4	3184	5.68	7535

EXAMPLE 2

5-FU INDUCED MUCOSITIS ASSAY

[00121] Mice (C57bl/6) were treated with 150 mg/kg of 5-fluorouracil (5-FU) intraperitoneal (IP) on days 0 and 10. After the second injection of 5-FU, the mice were treated with a compound of Formula (I) (20 mg/kg in saline, IP, BID (i.e. 40 mg/kg per day)) or saline alone (0.15 M NaCl) for 4 days. Mice were then sacrificed and the small intestines were removed and weighed to determine the degree of inflammation. Figure 1A illustrates that treatment with a compound of Formula (I) protects against chemotherapy induced gastrointestinal mucositis as measured by intestinal weight. Figure 1B illustrates that intestinal erosion, villous loss, and macrophage infiltration after administration of chemotherapy were ameliorated by concurrent administration of a compound of Formula (I).

[00122] The results show an amelioration of chemotherapy-induced intestinal mucositis in mice treated with a compound of Formula (I).

EXAMPLE 3

RADIATION INDUCED MUCOSITIS ASSAY

[00123] Mice (C57bl/6) were subjected to whole body irradiation (8.0 Gy) and immediately afterwards treated with a compound of Formula (I) (20 mg/kg in saline, IP, BID (i.e. 40 mg/kg per day)) or saline alone (0.15 M NaCl) for 6 days. The small intestine was removed at day 6 and digested to release cells. The number of $CD11b^{+}F4/80^{+}$ macrophages from the small intestine was determined by flow cytometry (Figure 2).

[00124] The results show treatment with a compound of Formula (I), decreased migration of inflammatory macrophages to the intestines of mice subjected to whole body radiation.

EXAMPLE 4

EFFICACY OF A COMPOUND OF FORMULA (I) COMPARED TO GENETIC ABLATION OF E-SELECTIN

[00125] In addition to promoting the adherence of tumor cells to the endothelium, E-selectin-mediated interactions may promote leukemic stem cell ("LSC") survival following chemotherapy. Wild-type or E-selectin knock-out mice were transplanted with MLL-AF9 leukemic cells and following engraftment, treated with high dose cytarabine (2 doses of 900 mg/kg at a 12-hour interval (1800 mg/kg total)). Bone-marrow cells were harvested 24 hours after treatment and the surviving functional LSCs were quantified by limiting dilution transplantation assays in irradiated wild-type syngeneic recipients. The proportion of recipients who developed leukemia was used to calculate the number of surviving LSC by Poisson's distribution. The data demonstrated that although the absence of E-selectin had no effect on total LSC numbers per femur, the absence of E-selectin increased the sensitivity of LSC to cytarabine treatment by 20-fold (Figure 3A).

[00126] These results suggest that E-selectin is a key vascular niche component in the bone marrow mediating LSC chemoresistance.

[00127] Wild-type mice were transplanted with MLL-AF9 leukemic cells and following engraftment, treated with high dose cytarabine (2 doses of 900 mg/kg at a 12-hour interval (1800 mg/kg total)) alone or in combination with a compound of Formula (I). Bone-marrow cells were harvested 24 hours after treatment and the surviving functional LSCs were quantified by limiting dilution transplantation assays in irradiated wild-type syngeneic recipients. The proportion of recipients who developed leukemia was used to calculate the number of surviving LSC by Poisson's distribution. The data demonstrated that inhibition of E-selectin by a compound of Formula (I) increased the sensitivity of LSC to cytarabine treatment by approximately 20-fold (Figure 3B).

[00128] These results suggest that inhibition of E-selectin by a compound of Formula (I) increases the efficacy of cytarabine by decreasing LSC chemoresistance.

EXAMPLE 5

IMPACT OF A COMPOUND OF FORMULA (I) ON MICE ENGRAFTED WITH HUMAN AML BLASTS AND TREATED WITH CYTARABINE AND DNR

[00129] The impact of a compound of Formula (I) on survival was evaluated in NOD-SCID mice in an orthotopic model of human AML in combination with cytarabine and DNR. A series of dose-response assessments of a compound of Formula (I) ranging from 5 mg/kg to 80 mg/kg BID (i.e., 10 mg/kg to 160 mg/kg per day) for 10 days, demonstrated 5 mg/kg BID (i.e., 10 mg/kg per day) of a compound of Formula (I) was biologically active with a marked enhancement of tumor cell chemosensitivity as determined by circulating leukemic cells (Figure 4). However, greater doses were required to exert a therapeutic (survival) benefit in combination with cytarabine and DNR suggesting a threshold for effect.

[00130] 10 mg/kg per day was identified as the minimally active murine dose that augmented cytarabine and DNR survival benefits. The data summarized in Figure 5 shows a Kaplan-Meier survival plot in this tumor model following treatment with cytarabine and DNR alone, or in combination with 10 mg/kg and 40 mg/kg of a compound of Formula (I) administered BID. Mice treated with 40 mg/kg of a compound of Formula (I) also had fewer numbers of AML blasts than mice treated with cytarabine and DNR alone. In animals treated with a compound of Formula (I) and chemotherapy, the number of blasts was significantly lower in the combined compartments of the spleen and bone marrow.

[00131] These results suggest that a compound of Formula (I) when given in combination with cytarabine and DNR chemotherapy enhances tumor cell chemosensitivity, and survival in an orthotopic model of human AML.

EXAMPLE 6

COMPOUND OF FORMULA (I) IN COMBINATION WITH CYTARABINE AND DNR EXTENDS THE SURVIVAL OF MICE BEARING THE HUMAN AML CELL LINE, U937

[00132] A compound of Formula (I) in combination with cytarabine/DNR chemotherapy was evaluated in the systemic U-937 AML NOD/SCID mouse survival model.

[00133] The U937 cell line was chosen because the cells express the E-selectin ligand and react with antibody HECA-452. After engraftment, mice were randomized into 4 groups (n=10/group) and treatment was initiated. The groups included a saline control group; a group administered the compound of Formula (I) at 40 mg/kg BID (i.e., 80 mg/kg per day) for 9 days, a group administered cytarabine at 300 mg/kg QD (i.e., 300 mg/kg per day) for 3 days and a single dose of DNR at 3 mg/kg; and a group administered the combined regimen of the compound of Formula (I) and chemotherapy (cytarabine and DNR).

[00134] The combined cytarabine/DNR/compound of Formula (I) regimen resulted in a median survival time ("MST") of greater than 120 days with five animals surviving to the end of the study. This was a significant outcome compared to the control group and to monotherapy with a compound of Formula (I) ($P<0.001$, Figure 6). Administration of a compound of Formula (I) alone does not extend survival beyond saline control. More importantly, the comparison of survival for the combined cytarabine/DNR/ compound of Formula (I) regimen to the cytarabine/DNR regimen reached statistical significance ($P=0.0341$, Figure 6).

[00135] These results suggest that survival is enhanced in a murine model of human AML when a compound of Formula (I) is administered in combination with cytarabine and DNR chemotherapy.

EXAMPLE 7

COMPOUND OF FORMULA (I) IN COMBINATION WITH CYTARABINE AND DOX EXTENDS THE SURVIVAL OF MICE BEARING THE MLL-AF9-INDUCED AML LEUKEMIA

[00136] The impact of a compound of Formula (I) when administered adjunctively with cytarabine/DOX chemotherapy was evaluated in the syngeneic MLL-AF9 induced AML leukemia model.

[00137] Bone marrow from mice bearing MLL-AF9-inducted leukemia was harvested and enriched for kit+ cells and frozen in aliquots for subsequent transplant. Recipient mice were then injected with $3x10^4$ leukemic cells 2 days after conditioning (Study day 0). Six days after leukemic injection, mice were randomized into 3 groups (n=8/group): a group administered a compound of Formula (I) at 40 mg/kg BID (i.e. 80 mg/kg per day) for 10 days, a group administered cytarabine/DOX (cytarabine at 100 mg/kg QD for 5 days, DOX at 1 mg/kg QD for 2 days), and a group administered a combined regimen of cytarabine/DOX/compound of Formula (I).

[00138] All treated mice progressed with tumor. Administration of a compound of Formula (I) adjunctively with cytarabine/DOX chemotherapy resulted in a MST of 41 days corresponding to a 64% increased lifespan. This was a significant outcome compared to monotherapy with a compound of Formula (I) (P=0.0009) and chemotherapy alone (30% increased lifespan, P=0.0054, Figure 7).

[00139] These results suggest that survival is enhanced in a murine model of human AML when a compound of Formula (I) is given in combination with cytarabine and DOX chemotherapy.

EXAMPLE 8

EFFECTS OF A COMPOUND OF FORMULA (I) ON RESPONSE TO 5-AZACYTIDINE IN SYSTEMIC KG1 AML MODEL

[00140] Data utilizing flow cytometry demonstrated that treatment of the human AML cell line KG1 with a non-cytotoxic concentration of 5-azacytidine (100 nM) lead to a 38% increase in cell binding of E-selectin-PE conjugate to cells. Further *in vitro* studies showed that treatment of KG1 cells with 5-azacytidine resulted in a 57% increase in static adhesion to E-selectin coated plates (compared to control treated KG1 cells, $P<0.05$, Figure 8). These findings indicate that hypomethylating agents, including 5-azacytidine, may increase the adhesion of leukemic blasts in the bone marrow and therefore hinder the intended anti-leukemic effect. This could explain a source of chemoresistance, and potential for relapse, in patients treated with hypomethylating agents. Importantly, therefore, the addition of a compound of Formula (I) post-binding of KG1 cells led to an approximate 90% uncoupling of adhesion, demonstrating that the effect could be reversed with the E-selectin antagonist.

[00141] The potential relevance of these *in vitro* observations was assessed in NSG female mice with pre-existing disseminated KG1 cells and treated with a compound of Formula (I) (40 mg/kg, IP, QD for 14 days), 5-azacytidine (5 mg/kg, IP, administered on days 7, 10, 13, 16, and 19 (5 doses total)), or the combination of both compounds. Under the conditions of the assay, the median survival time of mice treated with saline alone or a compound of Formula (I) was 69.5 and 69 days, respectively (Figure 9). Administration of a compound of Formula (I) with 5-azacytidine increased median survival time beyond that obtained with 5-azacytidine treatment alone (>104 days versus 88 days; $P=0.014$, Figure 9).

[00142] Collectively, these data suggest that a compound of Formula (I) does in fact attenuate the binding of AML cells by inhibiting E-selectin, complementing the antitumor activity of 5-azacytidine, and significantly improving survival above chemotherapy alone.

EXAMPLE 9

E-SELECTIN LIGAND AND $sLe^{a/x}$ BINDING BY AML BLASTS IN NEWLY DIAGNOSED OLDER PATIENTS (AGED 60 YEARS OR OLDER) AND RELAPSED/REFRACTORY LEUKEMIA PATIENTS

[00143] Binding of E-selectin-Ig chimeric protein (n=51 patients) or the HECA-452 antibody (n=43 patients) to AML blasts and CD34+CD38-CD123+ LSCs from older patients (aged 60 years or older) with newly diagnosed AML or relapsed/refractory (R/R) AML was assessed by flow cytometry (Figures 10A-10B). The HECA-452 antibody recognizes an E-selectin carbohydrate ligand shared by sLe^a and sLe^x, which is present in P-selectin glycoprotein ligand-1 and CD44 as the glycoforms known as Cutaneous Lymphocyte-associated Antigen and Hematopoietic Cell E-selectin/L-selectin ligand, respectively. Binding in this analysis was defined as >10% of positive cells in each patient sample. AML blasts from 76% of the patients bound E-selectin-Ig chimeric protein (mean 33.6 ± 27.4% positive cells). Mean binding of E-selectin-Ig chimeric protein by the LSC fraction from the same patients was 41.6 ± 32.5%. The percentages of AML blasts and LSCs positive for HECA-452 (expression of $sLe^{a/x}$) were 56.3 ± 33.9% and 63.4 ± 34.1%, respectively.

[00144] A comparison between newly diagnosed older patients and R/R patient blasts demonstrated the mean fluorescence intensities of E-selectin-Ig chimeric protein and HECA-452 binding were both higher in R/R patients than in newly diagnosed older patients (P=0.0024 and 0.00087, respectively, Figures 10A-10B).

[00145] These results suggest that an increased density of the E-selectin ligand expressed on the surface of AML blasts is associated with relapse.

EXAMPLE 10

PHARMACOKINETICS OF WEIGHT-BASED DOSES

[00146] Three cohorts of 6-7 human subjects with acute myeloid leukemia (AML) each received a total of 15 infusions of 5, 10, or 20 mg/kg/dose over 8 days with a nominal

infusion duration of 20 minutes. The first dose of a compound of Formula (I), was administered 24 hours ± 1 hour prior to the first dose of MEC (mitoxantrone, etoposide, and cytarabine) induction chemotherapy as a sentinel dose to evaluate the effect of the compound of Formula (I) alone, and then every 12 hours ± 1 hour on chemotherapy days, starting 2 hours prior to chemotherapy. Hence, the interval between the first and second doses of compound of Formula (I) was approximately 24 hours. MEC chemotherapy was administered on Days 2-6. Samples were obtained pre-dose, on Day 1, Day 3, Day 8, Day 9, and Day 10 (where Day 1 refers to the first day of dosing with a compound of Formula (I)).

Metric	Dose (mg/kg/dose)	N	Mean	SD	Median	Min	Max
Cmax (µg/ml)	5	6	38.48	14.18	36.30	22.47	62.41
	10	7	79.62	17.95	76.21	56.94	110.29
	20	6	166.72	43.03	152.72	129.13	249.42
AUC (µg/ml • days)	5	6	5.21	1.51	4.83	3.36	7.35
	10	7	9.63	4.24	9.63	5.55	17.96
	20	6	20.43	9.23	19.33	10.40	36.34
Fx of Time > IC_{50}	5	6	0.490	0.105	0.459	0.369	0.671
	10	7	0.582	0.205	0.571	0.381	1.000
	20	6	0.776	0.227	0.803	0.442	1.000
Fx of Time > IC_{90}	5	6	0.222	0.090	0.210	0.096	0.357
	10	7	0.404	0.233	0.377	0.217	0.907
	20	6	0.612	0.255	0.577	0.302	1.000

* Values are determined for the period starting at dose 13 and ending at dose 15. To determine AUC for the entire 15-dose period, multiply these values by 7.5.

[00147] These results show that increased weight-based daily doses of up to 40 mg/kg (i.e. 20 mg/kg per dose) are associated with an increase in Cmax, AUC, and the fraction of the dosing period in which Cp was greater than each of IC_{50} and IC_{90}.

EXAMPLE 11

PHARMACOKINETICS OF FIXED DOSES

[00148] Simulations were performed to evaluate systemic exposure (area-under-the-curve ("AUC") and maximal plasma concentration ("Cmax")) of a compound of Formula (I) and the fraction of the dosing interval in which the Cp of the compound of Formula (I) was higher

than the human E-selectin IC_{50} (3184 ng/ml) or IC_{90} (7535 ng/ml) for fixed doses of 400 mg per dose, 800 mg per dose, and 1600 mg per dose. Simulations were based on the *post hoc* parameters for each subject in Example 10, their creatinine clearance, and a fixed dose matched to the nominal dose. Subjects assigned to the 5, 10, and 20 mg/kg per dose groups (i.e., 10, 20, and 40 mg/kg per day) were assigned to the 400, 800, and 1600 mg per dose groups (i.e., 800, 1600, and 3200 mg/kg per day), respectively.

[00149] For all simulations, the dosing regimen was fifteen doses infused over 20 minutes at intervals of 12 hours; samples were simulated at intervals of 20 minutes over 7.5 days. For each simulated subject, Cmax was determined by inspection of the data; AUC for the final day in which two doses were administered (doses 13 and 14) was determined using linear trapezoids. The fraction of each interval in which Cp exceeded each of IC_{50} and IC_{90} was determined for that same time period. All calculations were performed with R.

Metric	Dose (mg/dose)	N	Mean	SD	Median	Min	Max
Cmax (µg/ml)	400	6	42.09	8.54	40.39	33.05	55.91
	800	7	71.22	14.45	64.72	54.95	93.27
	1600	6	161.42	42.03	167.09	103.39	224.96
AUC (µg/ml • days)*	400	6	5.76	0.75	5.63	4.95	6.89
	800	7	8.52	3.51	7.41	5.85	15.90
	1600	6	19.85	8.75	19.93	8.68	32.77
Fx of Time > IC_{50}	400	6	0.526	0.052	0.501	0.489	0.616
	800	7	0.559	0.204	0.501	0.395	1.000
	1600	6	0.771	0.236	0.788	0.413	1.000
Fx of Time > IC_{90}	400	6	0.258	0.041	0.241	0.219	0.318
	800	7	0.371	0.211	0.285	0.231	0.837
	1600	6	0.610	0.266	0.570	0.272	1.000

* Values are determined for the period starting at dose 13 and ending at dose 15. To determine AUC for the entire 15-dose period, multiply these values by 7.5.

[00150] These results show that increased fixed doses up to 3200 mg per day (i.e. 1600 mg per dose BID) are associated with an increase in Cmax, AUC, and the fraction of the dosing period in which Cp was greater than each of IC_{50} and IC_{90}.

EXAMPLE 12

PLASMA SOLUBLE E-SELECTIN CONCENTRATION-TIME CURVE

[00151] Plasma sE-selectin was quantified using a commercially available sandwich format ELISA assay, in which a monoclonal antibody specific for sE-selectin has been pre-coated onto a microplate (Human sE-Selectin Platinum ELISA kit, eBioscience, cat. no. BMS205). Standards, samples and controls were pipetted into the wells of the microplate where they bind to the antibodies coated on the microplate. After a wash step, an HRP-conjugated anti-human sE-selectin antibody was added to the wells to bind the sE-selectin captured by the first antibody. After washing the plate wells to remove unbound HRP-conjugated anti-human sE-selectin antibody, a substrate solution reactive with HRP is added to the wells. Colored product formed in proportion to the amount of human sE-selectin present in the sample or standard. The color-producing reaction was stopped by addition of acid and absorbance of each well was measured at 450 nm. Six human serum samples from healthy donors served as the quality control samples. In addition, two control lyophilized plasma samples (high and low) included with the assay kit were also added to each run.

[00152] Plasma soluble E-selectin levels decreased over the treatment period in all dose groups. This response was seen both in mean levels and Area-Under-Effect-Curve ("AUEC"). Decrease from baseline to Day 8 (at the end of 6 days of treatment with a compound of Formula (I), given concurrently with MEC chemotherapy) was highly significant ($P<0.0001$) with no dose response. Figure 11 illustrates decreasing mean levels of plasma soluble E-selectin over the treatment period in all dose groups, where doses were BID (i.e., the 5, 10, and 20 mg/kg "Per Dose" amounts of a compound of Formula (I) correspond to dosages of 10, 20, and 40 mg/kg per day, respectively).

		AUEC (hrxng/mL)			Percent Change from Day 1	
Per Dose (mg/kg)	**Subject**	**Day 1**	**Day 3**	**Day 8**	**Day 3**	**Day 8**
5	IE0010001	563.47	494.30	440.68	-12.28	-21.79
	US0020001	1,605.18	1,445.26	728.47	-9.96	-54.62
	US0030001	339.27	275.71	156.25	-18.74	-53.95
	US0050002	328.40	332.11	161.11	1.13	-50.94
10	US0030003	230.35	185.98	158.91	-19.26	-31.01
	US0040001	338.36	313.04	168.71	-7.48	-50.14
	US0040003	707.63	981.09	218.03	38.64	-69.19
	US0060001	325.19	298.31	25.51	-8.26	-92.15
	US0060003	269.90	202.99	103.74	-24.79	-61.57
20	US0060004	2,206.19	1,743.61	956.57	-20.97	-56.64
	US0060005	750.41	632.82	294.47	-15.67	-60.76
	US0060006	202.19	163.18	31.49	-19.30	-84.43

[00153] These results show that levels of sE-selectin decreased across all tested doses of the compound of Formula (I).

EXAMPLE 13

CLINICAL OUTCOMES – RELAPSED/RECOVERY SUBJECTS "PHASE 1"

[00154] Three cohorts of 6-7 human subjects with relapsed/refractory type acute myeloid leukemia (AML) each received a total of 15 infusions of 5, 10, or 20 mg/kg/dose of the compound of Formula (I), administered as the sodium salt, over 8 days with a nominal infusion duration of 20 minutes. The nominal infusion duration of 20 minutes was constant across cohorts (e.g., a slower infusion rate was used for the administration of the 5 mg/kg/dose arm than for the 10 mg/kg/dose arm). The formulation for the infusion solution was as follows:

Component	Target Concentration
Compound of Formula (I)	50 mg/mL
NaCl	6.0 mg/mL
10 mM TRIS buffer solution	1.2 mg/mL
Water for injection	Quantity sufficient to volume

[00155] The first dose of a compound of Formula (I) was administered 24 hours ± 1 hour prior to the first dose of MEC (mitoxantrone, etoposide, and cytarabine) induction chemotherapy as a sentinel dose to evaluate the effect of the compound of Formula (I) alone (i.e., a single dose of 5, 10, or 20 mg/kg the day before the first chemotherapy day). The compound of Formula (I) was then administered every 12 hours ± 1 hour on chemotherapy days, starting 2 hours prior to chemotherapy (i.e., 10, 20, or 40 mg/kg per day on chemotherapy days). Hence, the interval between the first and second dose of the compound of Formula (I) was approximately 24 hours. MEC chemotherapy was administered on Days 2-6.

[00156] The clinical outcome for each subject was assessed at the time of count recovery following completion of induction chemotherapy. Subjects were assigned to one of four response groups: complete remission ("CR"); complete remission with incomplete count recovery ("CRi"); morphologic leukemia-free state ("MLFS"); persistent disease ("PD"). Complete remission was defined as bone marrow blasts < 5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; ANC $\geq 1.0 \times 10^9$/L and platelets $\geq 100{,}000 \times 10^9$/L. Complete remission with incomplete recovery was defined as: all CR criteria except for residual neutropenia ($<1.0 \times 10^9$/L) or thrombocytopenia ($<100{,}000 \times 10^9$/L). Morphologic leukemia-free state was defined as: bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required. Persistent disease was defined as: bone marrow blasts > 5%.

Outcome, Reported as n (%)	5 mg/kg/ dose	10 mg/kg/ dose	20 mg/kg/ dose	Total
N Completing Induction Period	6	7	6	19
Response				
CR + CRi	**3 (50)**	**5 (71)**	**1 (17)**	**9 (47)**
Complete Remission (CR)	2 (33)	5 (71)	1 (17)	8 (42)
CR with incomplete recovery (CRi)	1 (17)	0	0	1 (5)
CR + CRi + MLFS + PR	**4 (67)**	**5 (71)**	**1 (17)**	**10 (53)**
Morphologic Leukemia-Free State (MLFS)	1 (17)	0	0	1 (5)
Persistent Disease	**2 (33)**	**2 (29)**	**5 (83)**	**9 (47)**

AML Subgroup	CR Rate n (%)
N Completing Induction Period	19
Primary Refractory	4/7 (57%)
Relapsed	5/12 (20%)
Relapsed <6 months	1/5 (20%)
Relapsed 6-12 months	1/4 (25%)
Relapsed >12 months	3/3 (100%)
Age <60 years	7/14 (50%)
Age ≥60 years	2/5 (60%)
Cytogenetics	
Favorable risk	0
Intermediate risk	5/7 (71%)
Unfavorable risk	4/12 (33%)
FLT3-ITD mutated	1/2 (50%)
Extramedullary disease	1/1 (100%)

[00157] These results demonstrate a response rate of almost 50% (CR/CRi) after a single course of induction treatment with MEC and a compound of Formula (I). This rate is higher than expected response rate, given the high-risk cytogenetic and other disease features of the study population, when compared to historical controls of similar populations treated with MEC (see Feldman, et al. Phase III randomized multicenter study of a humanized anti-CD33 monoclonal antibody, lintuzumab, in combination with chemotherapy, versus chemotherapy alone in patients with refractory or first-relapsed acute myeloid leukemia. J. Clin. Oncol. 2005 Jun 20;23(18):4110-6; Greenberg, et al. Mitoxantrone, etoposide, and cytarabine with or without valspodar in patients with relapsed or refractory acute myeloid leukemia and high-

risk myelodysplastic syndrome: a phase III trial (E2995). J. Clin. Oncol. 2004 Mar 15;22(6):1078-86.)

EXAMPLE 14

EXPOSURE-RESPONSE ANALYSIS FOR EFFICACY

[00158] To generate exposure metrics for the analyses in Example 14 and Example 15, a Pop-PK analysis, based on sampling of plasma concentrations (Cp) of the compound of Formula (I) during induction treatment, was conducted to identify an appropriate PK model, key covariates of the model, and to generate post hoc population PK metrics for all patients sampled for PK. The Pop-PK analysis comprised 59 subjects, 46 subjects diagnosed with relapsed/refractory (R/R) AML who were administered a compound of Formula (I) with MEC chemotherapy and 13 older subjects (aged 60 years or older) with newly diagnosed AML who were administered a compound of Formula (I) with 7+3 chemotherapy. Pop-PK modeling identified a three compartment model with renal function as the only significant covariate.

[00159] For Example 14, Exposure-Response ("E-R") analysis evaluating efficacy measures against PK metrics was conducted using clinical response efficacy data from the 46 R/R AML subjects. R/R AML subjects were administered MEC chemotherapy and 5, 10, and 20 mg/kg of a compound of Formula (I) BID (i.e. 10, 20, and 40 mg/kg per day).

[00160] Exposure metrics were generated using the Pop-PK model described above. For each subject the Cp profile for during a single dosing interval at steady state, was examined to determine the fraction of the dosing interval during which Cp was above IC_{50} (3.184 µg/mL) (Figure 12A) and IC_{90} (7.535 µg/mL) (Figure 12B), the Cmax (Figure 12C), and AUC (determined using linear trapezoids) (Figure 12D) during that interval.

[00161] Using clinical measures of efficacy described in Example 13 each subject was assigned to one of five clinical response categories: CR, CRi, MLFS, PD, and death. These

were plotted against the measures of exposure and evaluated for trends suggestive of exposure response. Figures 12A-12D plot exposure individual metrics against each category of efficacy response. In addition, box and whisker plots to illustrate the minimum, 25th percentile, median, 75th percentile and maximum exposure metric in each category were added to the graphics. Inspection of Figures 12A-12D reveals significant overlap in all exposure-response metrics relating to remission for those subjects attaining CR and those with PD.

EXAMPLE 15

EXPOSURE-RESPONSE ANALYSIS FOR ADVERSE EVENTS

[00162] For Example 15, Exposure-Response ("E-R") analysis evaluating adverse events against PK metrics was conducted. The sample population for Example 15 included 53 subjects with relapsed/refractory (R/R) AML and 25 older subjects (aged 60 years or older) with newly diagnosed AML. R/R AML subjects were administered MEC chemotherapy and 5, 10, and 20 mg/kg of a compound of Formula (I) BID (i.e., 10, 20, and 40 mg/kg per day). The older subjects (aged 60 years or older) with newly diagnosed AML were administered 7+3 chemotherapy and 10 mg/kg of a compound of Formula (I) BID (i.e., 20 mg/kg per day).

[00163] Exposure metrics for the adverse events ("AE") analysis were generated using the same Pop-PK model described in Example 14. For each subject, the Cp profile during each 24-hour interval (midnight to midnight) was examined to determine Cmax and AUC (determined using linear trapezoids) during that interval. Cumulative AUC was determined through each study day. For each metric / day combination, percentile rankings and normalized values were determined. For example, the median of Day 6 AUC values was determined, and normalized values were obtained by dividing each value by the median. In addition, these Day 6 AUC values were ranked, and then multiplied by 100% divided by the number of values to obtain a percentile value.

[00164] Adverse events ("AEs") were classified according the Common Terminology Criteria for Adverse Events ("CTCAE"). CTCAE AEs identified for E-R analyses were: neutropenia (Figures 13A and 13B), thrombocytopenia (Figure 13C and 13D), febrile neutropenia (Figures 13E and 13F), infection (Figures 13G and 13H), mucositis (Figures 13I and 13J), and anemia (Figures 13K and 13L). These events were categorized by CTCAE grade (3, 4, or 5), and by onset of dosing, either on or after the first day of dosing.

[00165] For each event, the study day (referenced to the first day of dosing) was identified. For an event occurring during dosing (typically, the first 8 days of Cycle 1), the corresponding percentile and normalized values (described above) were identified. If the event occurred after dosing (e.g., Day 15), concurrent exposure would be negligible; therefore, the following exposure metrics were applied:

a. Cmax: The highest Cmax attained at any time during treatment

b. AUC, Cumulative AUC: Cumulative values

[00166] Inspection of Figures 13A-F reveals no strong tendency toward increased AEs, nor increased severity of AEs with exposure as measured by AUC, cumulative AUC over the treatment cycle, or Cmax. Thus, the range of exposures presents a low safety risk to AML subjects administered a compound of Formula (I) with cytotoxic chemotherapy.

EXAMPLE 16

MEC AND FAI INDUCTION CHEMOTHERAPY PROTOCOLS

[00167] Subjects receive induction chemotherapy, either MEC or FAI, for 5 consecutive days. A compound of Formula (I) is given one day prior to initiating chemotherapy, each day during chemotherapy, and for two days following the last dose of chemotherapy (Figure 14A). Subjects receiving MEC induction chemotherapy are treated with mitoxantrone 10 mg/m^2/d IV over 15 to 20 minutes, etoposide 100 mg/m^2/d IV over 60 minutes, and cytarabine 1000 mg/m^2/d IV over 60 minutes for five consecutive days. Subjects receiving

FAI induction chemotherapy are treated with fludarabine 30 mg/m^2 IV over 30 minutes for five consecutive days, cytarabine 2 g/m^2 IV over 4 hours for five consecutive days, and idarubicin 10 mg/m^2 IV for the first three consecutive days.

EXAMPLE 17

MEC, HiDAC, AND IDAC CONSOLIDATION CHEMOTHERAPY PROTOCOLS

[00168] Subjects achieving remission following induction chemotherapy receive additional consolidation chemotherapy. Subjects receive reduced dose MEC, high-dose cytarabine (HiDAC), or intermediate-dose cytarabine (IDAC) consolidation chemotherapy. A compound of Formula (I) is given one day prior to initiating chemotherapy, each day during chemotherapy, and for two days following the last dose of chemotherapy (Figure 14B). Reduced-dose MEC therapy consists of mitoxantrone 10 mg/m^2/d IV over 15 to 20 minutes, etoposide 100 mg/m^2/d IV over 60 minutes, and cytarabine 1000 mg/m^2/d IV over 60 minutes on Days 2-5 for one cycle. HiDAC may be given as either of two regimens, for example, at the treating physician's discretion and in accordance with the NCCN guidelines, consisting of: cytarabine 3 g/m^2 IV every 3 hours on Days 2, 4 and 6 for up to 3-4 cycles, or cytarabine 2-3 g/m^2 IV every 12 hours on Days 2, 4 and 6 for up to 3-4 cycles. IDAC may be given as either of two regimens at the treating physician's discretion and in accordance with the NCCN guidelines consisting of: cytarabine 1.5 g/m^2/day IV for 5 days for up to 3 cycles (the dose of cytarabine may be reduced to 1 g/m^2/day at the treating physician's discretion), or cytarabine 1.5 g/m^2 IV over 3 hours every 12 hours on Days 2, 4, and 6 (total 6 doses) for up to 3 cycles (the dose of cytarabine may be reduced to 1 g/m^2/day at the treating physician's discretion).

EXAMPLE 18

DECITABINE CHEMOTHERAPY PROTOCOLS

[00169] Subjects receive decitabine 20 mg/m^2 IV once daily for either 5 consecutive days or 10 consecutive days. Subjects receiving decitabine for 5 days are administered a compound of Formula (I), once per day prior to infusion of decitabine each day of chemotherapy. Subjects receiving decitabine for 10 days are administered a compound of Formula (I) twice per day each day of chemotherapy with one dose given prior to infusion of decitabine.

EXAMPLE 19

7+3 DAUNO CHEMOTHERAPY PROTOCOL

[00170] A compound of Formula (I) is given one day prior to initiating chemotherapy, each day during chemotherapy, and for two days following the last dose of chemotherapy. Subjects receive a continuous IV infusion of cytarabine 100 mg/m^2/d over seven days (168 hours), and daunorubicin 60 mg/m^2/d IV for the first three consecutive days. On follow-up cycles, subjects may receive a continuous IV infusion of cytarabine 100 mg/m^2/d over five days (120 hours), and daunorubicin 60 mg/m^2/d IV for the first two consecutive days.

EXAMPLE 20

7+3 IDA CHEMOTHERAPY PROTOCOL

[00171] A compound of Formula (I) is given one day prior to initiating chemotherapy, each day during chemotherapy, and for two days following the last dose of chemotherapy. Subjects receive a continuous IV infusion of cytarabine 100 mg/m^2/d over seven days (168 hours), and idarubicin 12 mg/m^2/d IV for the first three consecutive days. On follow-up cycles, subjects may receive a continuous IV infusion of cytarabine 100 mg/m^2/d over five days (120 hours), and idarubicin 12 mg/m^2/d IV for the first two consecutive days.

EXAMPLE 21

CLINICAL OUTCOMES – RELAPSED/REFRACTORY SUBJECTS "PHASE 2"

[00172] In this Phase 2 study related to the Phase 1 study described above (see Example 13), 47 additional subjects were administered the RP2D dose of 10 mg/kg/dose. The data of the 19 subjects in the 10 mg/kg/dose arm of the Phase 1 study was added to the data of these 47 additional subjects, resulting in data for 66 human subjects being considered in the Phase 2 study.

[00173] In detail, consistent with the Phase 1 study protocols, a total of 66 human subjects with relapsed/refractory (R/R) acute myeloid leukemia (AML) were selected for this study (i.e., the 19 subjects from the 10 mg/kg/dose arm of the Phase 1 study plus 47 additional subjects).

[00174] Whether as part of the Phase 1 study (for 19 of the subjects) or as an additional subject for the Phase 2 study, each subject received a total of 15 infusions of the RP2D dose of 10 mg/kg/dose of the compound of Formula (I), administered as the sodium salt, over 8 days with a nominal infusion duration of 20 minutes (either as part of the Phase 1 study for 19 subjects or as a new Phase 2). The formulation for the infusion solution was as follows:

Component	**Target Concentration**
Compound of Formula (I)	50 mg/mL
NaCl	6.0 mg/mL
10 mM TRIS buffer solution	1.2 mg/mL
Water for injection	Quantity sufficient to volume

[00175] The first dose of a compound of Formula (I) was administered 24 hours ± 1 hour prior to the first dose of MEC (mitoxantrone, etoposide, and cytarabine) induction chemotherapy as a sentinel dose to evaluate the effect of the compound of Formula (I) alone (i.e., a single dose of 10 mg/kg the day before the first chemotherapy day). The compound of Formula (I) was then administered every 12 hours ± 1 hour on chemotherapy days, starting 2 hours prior to chemotherapy (i.e., 20 mg/kg per day on chemotherapy days). Hence, the

interval between the first and second dose of the compound of Formula (I) was approximately 24 hours. MEC chemotherapy was administered on Days 2-6.

[00176] The clinical outcome for each subject was assessed at the time of count recovery following completion of induction chemotherapy. Subjects were assigned to one of four response groups: complete remission ("CR"); complete remission with incomplete count recovery ("CRi"); morphologic leukemia-free state ("MLFS"); persistent disease ("PD"). Complete remission was defined as bone marrow blasts < 5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; ANC $\geq 1.0 \times 10^9$/L and platelets $\geq 100{,}000 \times 10^9$/L. Complete remission with incomplete recovery was defined as: all CR criteria except for residual neutropenia ($<1.0 \times 10^9$/L) or thrombocytopenia ($<100{,}000 \times 10^9$/L). Morphologic leukemia-free state was defined as: bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required. Persistent disease was defined as: bone marrow blasts > 5%.

[00177] Outcomes shown below provide data for Phase 1 (Example 13, all cohorts combined), Phase 2, and Total (Phase 1 and Phase 2) subject populations.

Outcome, reported as n (%)	Phase 1	Phase 2	Total	RP2D
N Completing Induction Period	**19**	**47**	**66**	**54**
Response				
CR + CRi	**9 (47)**	**17 (36)**	**26 (39)**	**22 (41)**
Complete Remission (CR)	8 (42)	14 (30)	22 (33)	19 (35)
CR with incomplete recovery (CRi)	1 (5)	3 (6)	4 (6)	3 (6)
CR + CRi + MLFS + PR	**10 (53)**	**22 (47)**	**32 (48)**	**27 (50)**
Morphologic Leukemia-Free State (MLFS)	1 (5)	3 (6)	4 (6)	3 (6)
Partial Remission (PR)	0	2 (4)	2 (3)	2 (4)
Persistent Disease	**9 (47)**	**25 (53)**	**34 (52)**	**27 (50)**
All-Cause Mortality 30 days	0	1 (2)	1 (2)	1 (2)
All-Cause Mortality 60 days	2 (11)	4 (9)	6 (9)	5 (9)
Proceeded to HSCT	6 (32)	11 (23)	17 (26)	16 (30)

Subgroup	CR/CRi Rate n (%) of sub-group			
	Phase 1	Phase 2	Total	RP2D
N Completing Induction Period	**19**	**47**	**66**	**54**
Primary Refractory	4/7 (57)	4/15 (27)	8/22 (36)	5/17 (29)
Relapsed	5/12 (42)	14/32 (44)	19/44 (43)	18/37 (49)
Relapsed <6 months	1/5 (20)	5/17 (29)	6/22 (27)	6/19 (32)
Relapsed 6-<12 months	1/4 (25)	3/7 (43)	4/11 (36)	3/7 (43)
Relapsed ≥12-<24 months	0	3/4 (75)	3/4 (75)	3/4 (75)
Relapsed ≥24 months	3/3 (100)	3/4 (75)	6/7 (86)	6/7 (86)
Age <60 years	7/14 (50)	8/21 (38)	15/35 (43)	13/28 (46)
Age ≥60 years	2/5 (40)	10/26 (38)	12/31 (39)	10/26 (38)
Cytogenetics (SWOG)				
Favorable risk	0	1/1 (100)	1/1 (100)	1/1 (100)
e	5/7 (71)	7/17 (41)	12/24 (50)	10/20 (50)
Unfavorable risk	4/12 (33)	9/27 (33)	13/39 (33)	11/31 (35)
Cytogenetics (ELN)				
Favorable risk	2/2 (100)	2/5 (40)	4/7 (57)	4/7 (57)
Intermediate risk	2/2 (100)	5/9 (56)	7/11 (64)	6/10 (60)
Adverse risk	3/11 (27)	5/22 (23)	8/33 (24)	6/25 (24)
Extramedullary disease	1/1 (100)	1/1 (100)	2/2 (100)	2/2 (100)
FLT3-ITD mutated	0	2/3 (66)	2/3 (66)	2/3 (66)
TP53 mutation or monosomy 17 [del (17p)]	0/1 (0)	1/3 (33)	1/4 (25)	1/3 (33)

[00178] These results demonstrate a response rate of over 40% (CR/CRi) after a single course of induction treatment with MEC and a compound of Formula (I). This rate is higher than expected response rate, given the high-risk cytogenetic and other disease features of the study population, when compared to historical controls of similar populations treated with MEC (see Feldman 2005; Greenberg 2004).

[00179] Adverse event data is provided below, showing the numbers and percentages for Grade 3/4 adverse events for several types of adverse events, and showing the numbers and percentages of both Grade 1/2 and 3/4 oral mucositis events.

Grade 3/4 Adverse Events Event Type	Total N=66	RP2D N=54
Cardiac	6 (9)	5 (9)
Colitis	2 (3)	1 (2)
GI	7 (11)	4 (7)
Hepatic	3 (5)	3 (6)
Infectious	50 (76)	39 (72)
Bacteraemia	8 (12)	8 (15)
Febrile neutropenia	31 (47)	27 (50)
Sepsis	12 (18)	8 (15)
Oral Mucositis Events		
Grades 1/2	14 (21)	9 (17)
Grades 3/4	2 (3)	1 (2)

[00180] The severe oral mucositis rate was 2-3% in this trial group. The expected rate was >20% (see Feldman 2005).

[00181] Survival data for these subjects is illustrated in Figure 15. The median overall survival of the subjects was 8.8 months, with a 95% confidence interval of 5.7-11.4 months. The one-year survival rate for all subjects was 35%, and the one-year survival rate for MRD negative subjects was 73%.

EXAMPLE 22

CLINICAL OUTCOMES – NEWLY DIAGNOSED OLDER SUBJECTS

[00182] In this study, 25 human subjects who were newly diagnosed at age 60 or older with acute myeloid leukemia (AML) were selected for this study. Subjects were not disqualified for prior treatment or diagnosis for MDS or CMML.

[00183] Each subject received a total of 19 infusions of 10 mg/kg/dose of the compound of Formula (I), administered as the sodium salt, over 10 days with a nominal infusion duration of 20 minutes. The formulation for the infusion solution was as follows:

Component	**Target Concentration**
Compound of Formula (I)	50 mg/mL
NaCl	6.0 mg/mL
10 mM TRIS buffer solution	1.2 mg/mL
Water for injection	Quantity sufficient to volume

[00184] The first dose of a compound of Formula (I) was administered 24 hours ± 1 hour prior to the first dose of 7+3 (cytarabine and idarubicin) chemotherapy as a sentinel dose to evaluate the effect of the compound of Formula (I) alone (i.e., a single dose of 10 mg/kg the day before the first chemotherapy day). The compound of Formula (I) was then administered every 12 hours ± 1 hour on chemotherapy days (i.e., 20 mg/kg per day on chemotherapy days) and for two days following the last dose of chemotherapy. Hence, the interval between the first and second dose of the compound of Formula (I) was approximately 24 hours. 7+3 (cytarabine and idarubicin) chemotherapy was administered on Days 2-8 comprising a

continuous IV infusion of cytarabine 100 mg/m^2/d over seven days (168 hours, from days 2-8), and idarubicin 12 mg/m^2/d IV for the first three consecutive days (36 hours, from days 2-4).

[00185] The clinical outcome for each subject was assessed at the time of count recovery following completion of induction chemotherapy. Subjects were assigned to one of four response groups: complete remission ("CR"); complete remission with incomplete count recovery ("CRi"); morphologic leukemia-free state ("MLFS"); persistent disease ("PD"). Complete remission was defined as bone marrow blasts < 5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; ANC ≥ 1.0 x 10^9/L and platelets ≥ 100,000 x 10^9/L. Complete remission with incomplete recovery was defined as: all CR criteria except for residual neutropenia (<1.0 x 10^9/L) or thrombocytopenia (<100,000 x 10^9/L). Morphologic leukemia-free state was defined as: bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required. Persistent disease was defined as: bone marrow blasts > 5%.

Outcome	n (%)
N Completing Induction Period	**25**
N Receiving Re-Induction (5+2)	**8 (32)**
Response	
CR + CRi	**18 (72)**
Complete Remission (CR)	13 (52)
CR with incomplete recovery (CRi)	5 (20)
CR + CRi + MLFS	**20 (80)**
Morphologic Leukemia-Free State (MLFS)	2 (8)
Death Before Response Assessment	**2 (8)**
Persistent Disease	**3 (12)**
Proceeded to HSCT	**11 (44)**
All-Cause Mortality 30 days	2 (8)
All-Cause Mortality 60 days	3 (12)

AML Subgroup	CR/CRi Rate n (%) of sub-group
N Completing Induction Period	**25**
de novo	9/12 (75)
Secondary AML	8/13 (62)
Cytogenetics (SWOG)	
Favorable risk	1/1 (100)
Intermediate risk	11/16 (69)
Unfavorable risk	5/8 (63)

Cytogenetics (ELN)	
Favorable risk	3/3 (100)
Intermediate risk	4/7 (57)
Unfavorable risk	8/12 (67)
FLT3-ITD mutated	1/1 (100)
TP53 or monosomy 17 [del (17p)]	1/2 (50)

[00186] These results demonstrate a response rate of 72% (CR/CRi) after a single course of induction treatment with 7+3 (cytarabine and idarubicin) chemotherapy and a compound of Formula (I). This rate is higher than expected response rate, given the high-risk cytogenetic and other disease features of the study population, when compared to historical controls of similar populations treated with 7+3 (cytarabine and idarubicin) chemotherapy (see Burnett et al. The impact of dose escalation and resistance modulation in older patients with acute myeloid leukaemia and high-risk myelodysplastic syndrome: the results of the LRF AML14 trial. British J. Haematology, 2009. 145:218-332; Lancet, et al. Phase 2 trial of CPX-351, a fixed 5:1 molar ratio of cytarabine/daunorubicin, vs cytarabine/ daunorubicin in older adults with untreated AML. Blood. 2014. 123(21):3239-3246).

[00187] Adverse event data is provided below, showing the numbers and percentages for Grade 3/4 adverse events for several types of adverse events, and showing the numbers and percentages of both Grade 1/2 and 3/4 oral mucositis events.

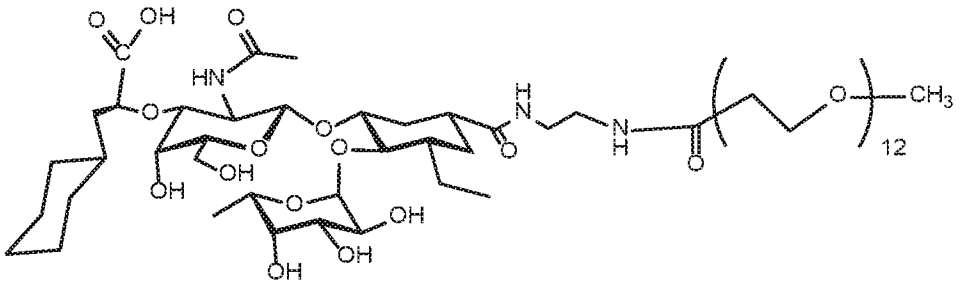
Grade 3/4 Adverse Events Event Type	**Total N=25**
Colitis	**3 (12)**
Respiratory	**7 (28)**
Infectious	**19 (76)**
Febrile neutropenia	17 (68)
Sepsis	4 (16)
Pneumonia	3 (12)
Oral Mucositis Events	
Grades 1/2	5 (20)
Grades 3/4	0

[00188] The severe oral mucositis rate was 0% in this trial group. The expected rate was approximately 5-10%.

[00189] Figure 16A illustrates the event-free survival data, and Figure 16B illustrates the overall survival data for these subjects. The median event-free survival is 9.2 months with a 95% confidence interval of 3-12.6 months. The median overall survival is 12.6 months with a 95% confidence interval of lower range of 9.9 months (upper end of 95% confidence interval was not achieved). The one-year overall survival rate for all subjects was 52%, and the one-year survival rate for MRD negative subjects was 60%.

What is claimed is:

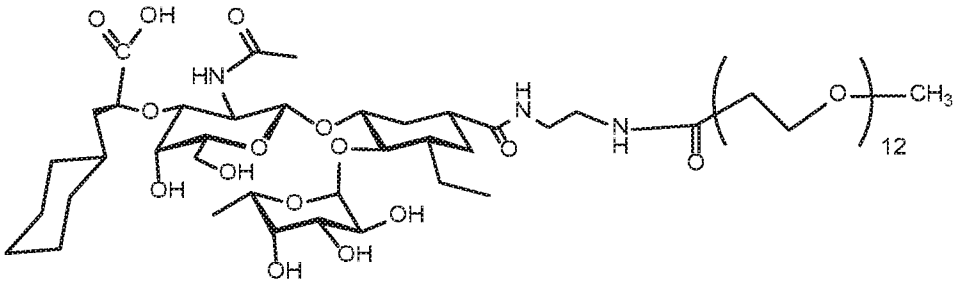
1. A method for treating AML, MDS, neutropenia, or mucositis comprising administering to a subject in need thereof a fixed dose of 200 mg to 4000 mg per day of a compound of Formula (I):



(I).

2. The method of claim 1, wherein 1600 mg per day of the compound of Formula (I) is administered.

3. A method for treating AML, MDS, neutropenia, or mucositis comprising administering to a subject in need thereof 1 mg/kg to 100 mg/kg per day of a compound of Formula (I):



(I)

4. The method of claim 3, wherein 20 mg/kg per day of the compound of Formula (I) administered.

5. The method of any of the preceding claims, wherein the compound of Formula (I) is administered twice daily.

6. The method according to any of the preceding claims, wherein the compound of Formula (I) is administered intravenously.

7. The method according to any one of claims 1-5, wherein the compound of Formula (I) is administered subcutaneously.

8. The method according to any of the preceding claims, wherein the subject is receiving, has received, or will receive chemotherapy and/or radiotherapy.

9. The method according to claim 8, wherein the subject is receiving, has received, or will receive two or more chemotherapeutic agents.

10. The method according to claim 8, wherein the chemotherapy comprises administration of mitoxantrone, etoposide, and cytarabine.

11. The method according to claim 8, wherein the chemotherapy comprises administration of fludarabine, cytarabine, and idarubicin.

12. The method according to claim 8, wherein the chemotherapy comprises administration of velafermin and/or palifermin.

13. The method according to claim 8, further comprising administering at least one additional compound chosen from MMP inhibitors, inflammatory cytokine inhibitors, mast cell inhibitors, NSAIDs, NO inhibitors, MDM2 inhibitors, and antimicrobial compounds.

14. The method according to claim 8, further comprising administering thalidomide or a thalidomide derivative.

15. The method according to any one of claims 1-8, wherein the subject has AML.

16. The method according to claim 15, wherein the administration of the compound of Formula (I) extends the number of days the subject is in remission, reduces the number of days until remission, inhibits the metastasis of AML cells, or improves survival.

17. The method according to any one of claims 1-8, wherein the subject has MDS.

18. The method according to claim 17, wherein the administration of the compound of Formula (I) slows the progression of MDS, prevents the progression of MDS to leukemia, or improves survival.

19. The method according to any one of claims 1-8, wherein the subject has neutropenia.

20. The method according to claim 19, wherein the administration of the compound of Formula (I) reduces the number of days the subject is afflicted with neutropenia or reduces the severity of neutropenia.

21. The method according to any one of claims 1-8, wherein the subject has mucositis.

22. The method according to claim 21, wherein the administration of the compound of Formula (I) reduces the number of days the subject is afflicted with mucositis or reduces the severity of the mucositis.

23. The method according to any one of claims 1-22 wherein the compound of Formula (I) is administered as a prodrug of Formula (I) or a pharmaceutically acceptable salt of any of the foregoing.

24. The method according to any one of claims 1-23 wherein the compound of Formula (I), prodrug of Formula (I), or pharmaceutically acceptable salt of any of the foregoing is administered in combination with a pharmaceutically acceptable carrier or diluent.

Compound of Formula (I) Protects Against Chemotherapy Induced Gastrointestinal Mucositis

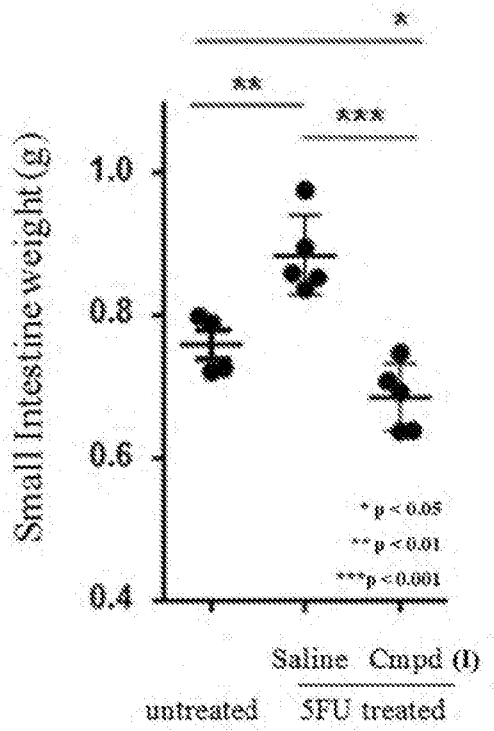


FIG. 1A

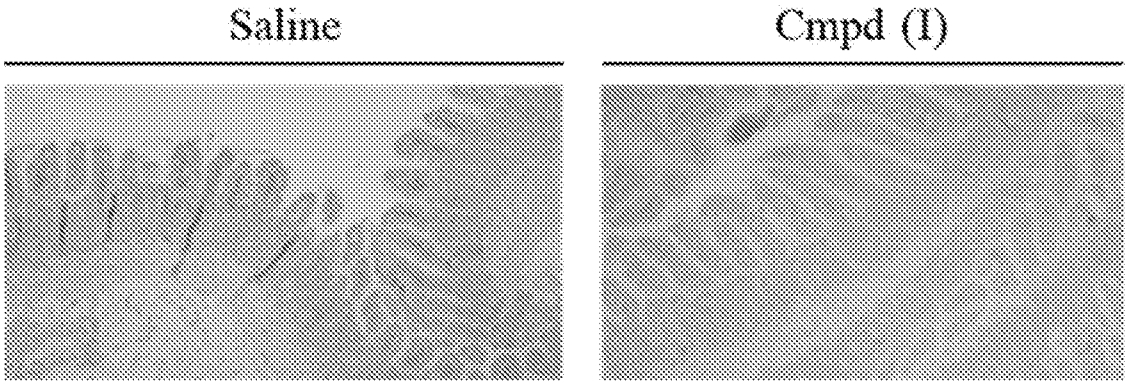


FIG. 1B

Compound of Formula (I) Inhibits Migration of Inflammatory Macrophages to the Intestine after Radiation Therapy

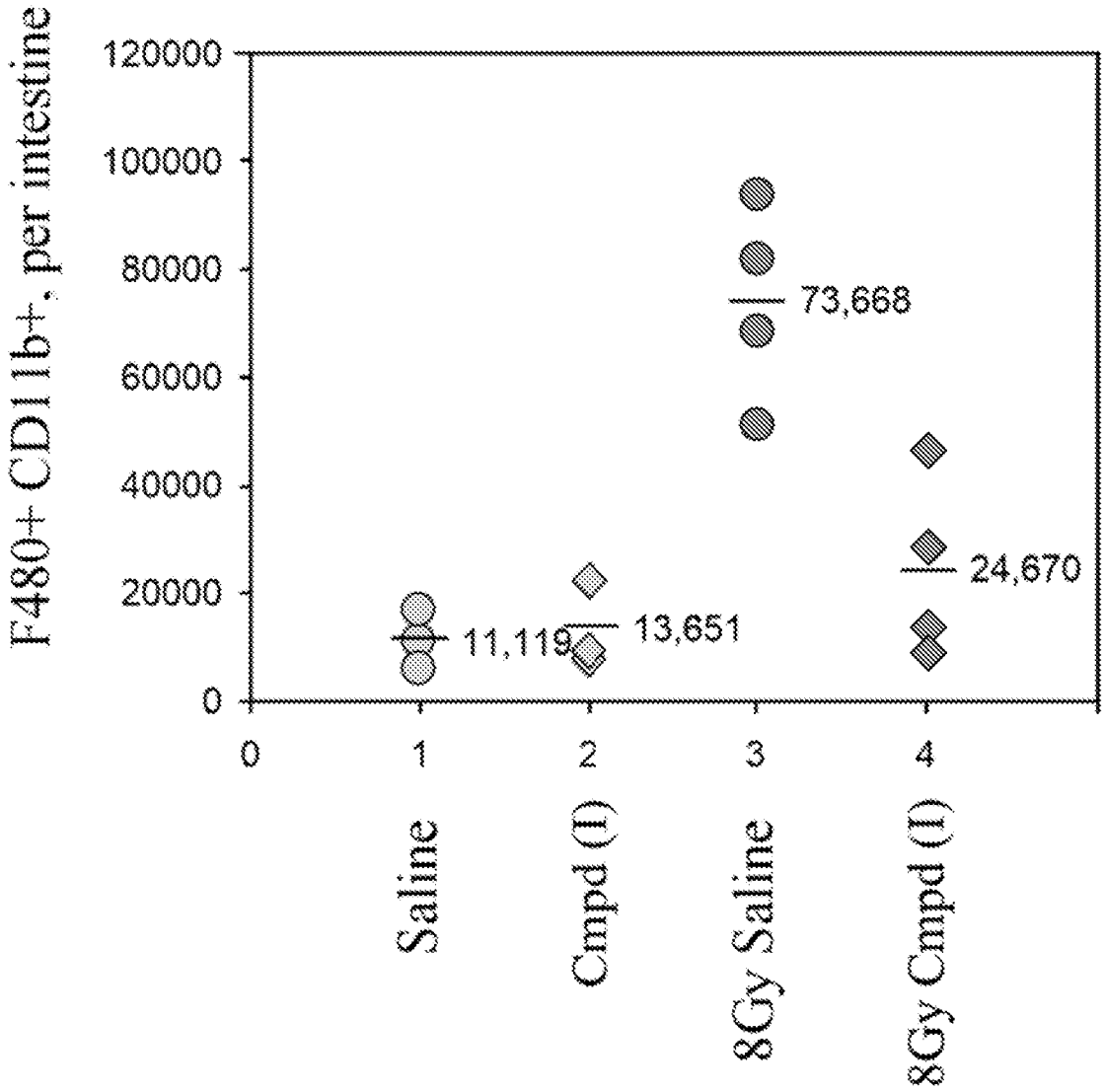


FIG. 2

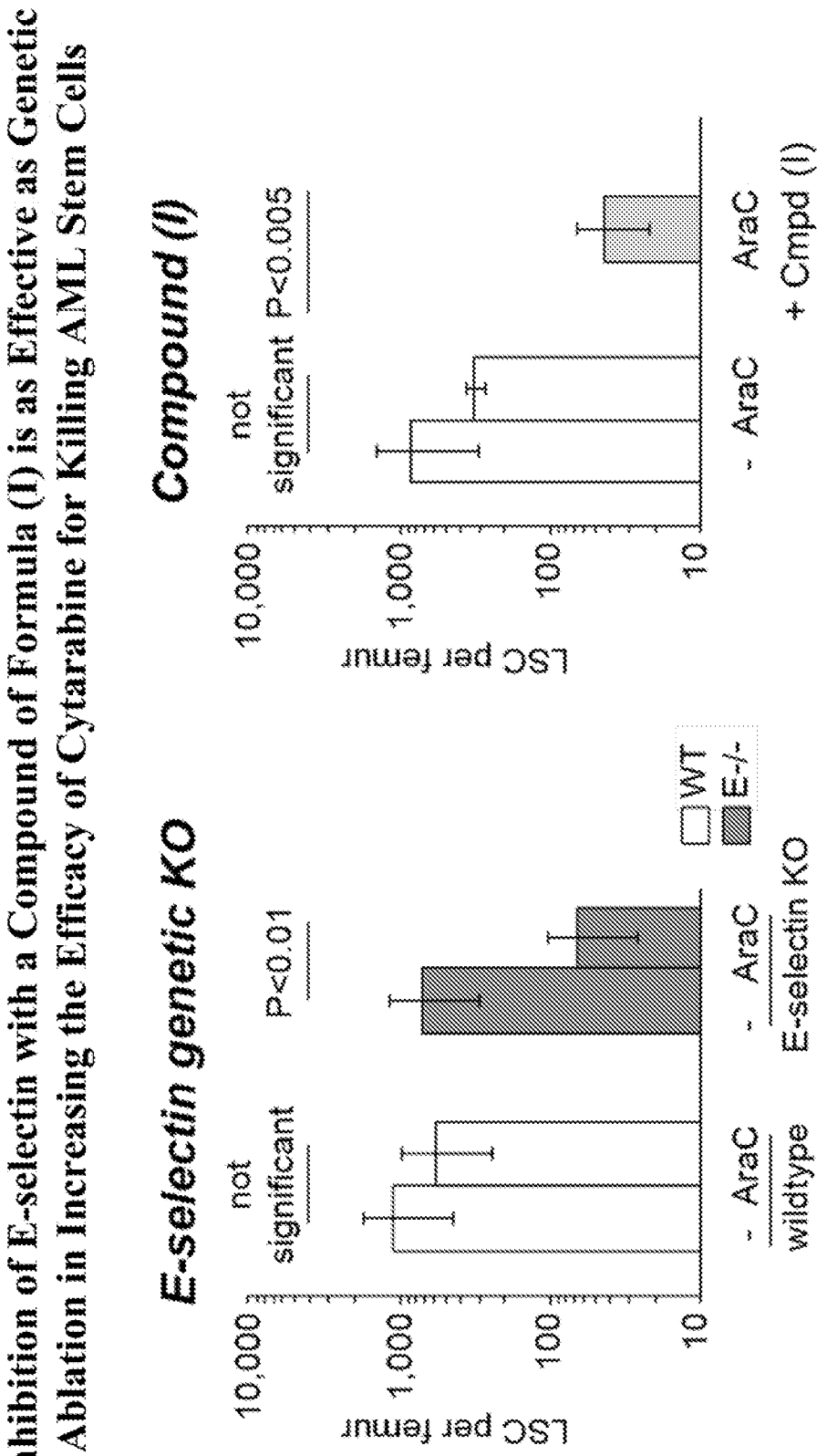

Inhibition of E-selectin with a Compound of Formula (I) is as Effective as Genetic Ablation in Increasing the Efficacy of Cytarabine for Killing AML Stem Cells
E-selectin genetic KO
not significant
P<0.01
LSC per femur
10,000
1,000
100
10
WT
E-/-
- AraC
- AraC
wildtype
E-selectin KO
Compound (I)
not significant
P<0.005
- AraC
AraC
+ Cmpd (I)

FIG. 3A

FIG. 3B

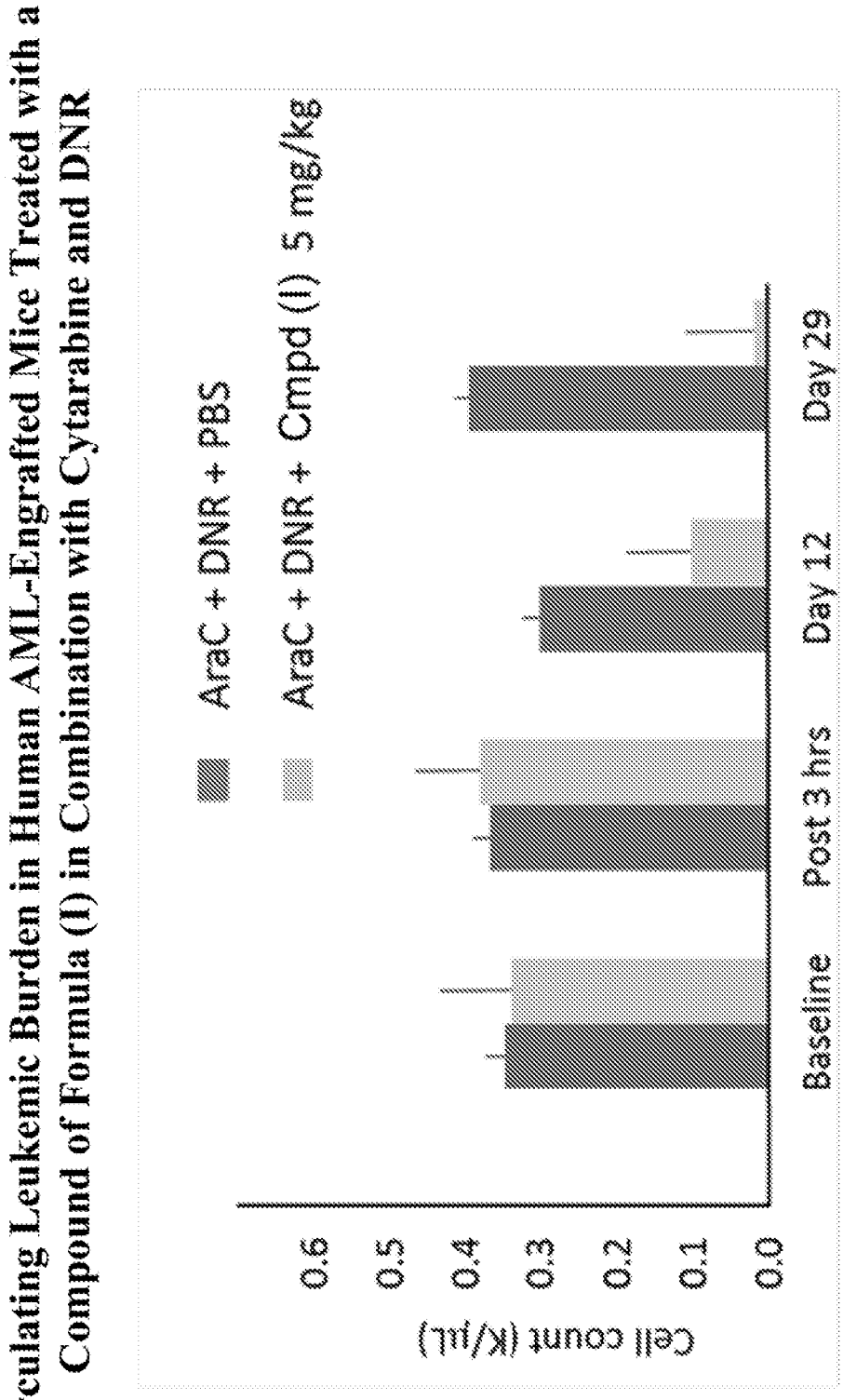
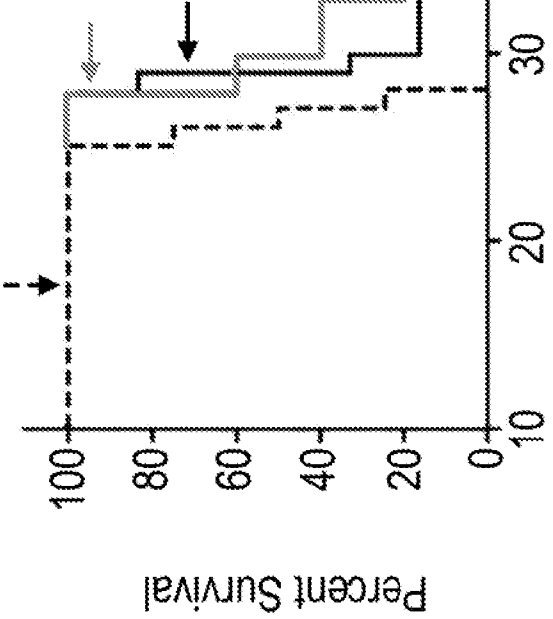

Circulating Leukemic Burden in Human AML-Engrafted Mice Treated with a Compound of Formula (I) in Combination with Cytarabine and DNR
AraC + DNR + PBS
AraC + DNR + Cmpd (I) 5 mg/kg
Cell count (K/μL)
0.0
0.1
0.2
0.3
0.4
0.5
0.6
Baseline
Post 3 hrs
Day 12
Day 29

FIG. 4

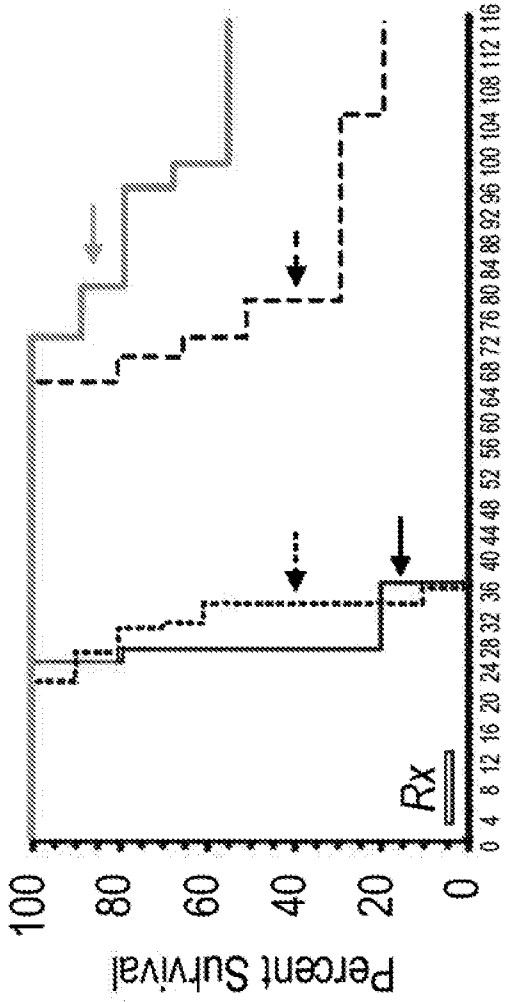
Compound of Formula (I) in combination with Cytarabine and DNR Extends Survival of Mice Engrafted with Human AML Blasts



	Treatment	Regimen	MST (Days)	% Survival (day 40)	Log-rank P value
	AraC/DNR	100 mg/kg IP x 3d + 1.5 mg/kg IV x 1d	26.5	0	--
	AraC/DNR + Cmpd (I)	As above + 40 mg/kg IP bid x 10 d	30	0	0.0143
	AraC/DNR + Cmpd (I)	As above + 10 mg/kg IP bid x 10 d	29	0	0.0031

FIG. 5

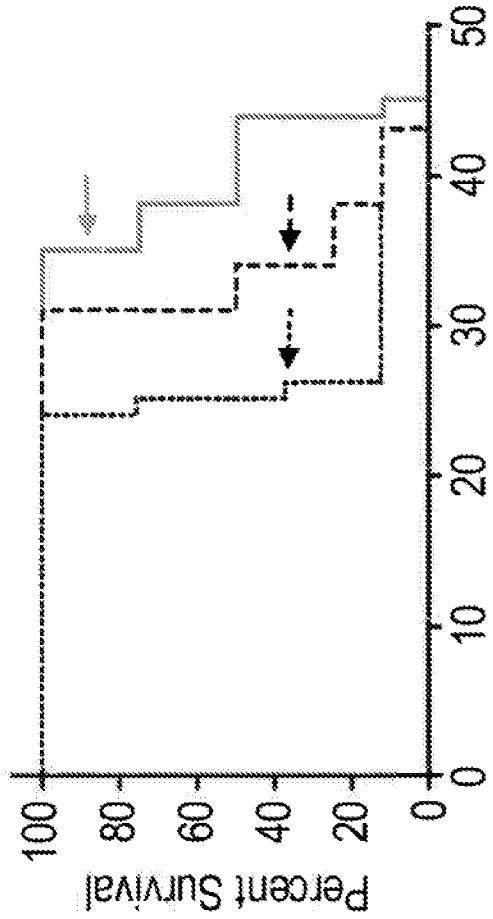
Compound of Formula (I) in combination with Cytarabine and DNR Extends Survival of Mice Bearing the Human AML Cell Line, U937



	Treatment	Regimen	MST (Days)	% Survival (day 45)	Log-rank vs. control	Wilcoxon vs. chemo
	PBS	0.2 mL IP bid x 9d	33	0	--	--
	Cmpd (I)	40 mg/kg IP bid x 9d	26	0	0.2736	--
	AraC/DNR	300 mg/kg IP x 3d + 3 mg/kg IV x 1d	71	20	<0.0001	--
	AraC/DNR + Cmpd (I)	As above	>120	55	<0.0001	0.0341

FIG. 6

Compound of Formula (I) in combination with Cytarabine and DOX Extends the Survival of Mice Bearing the MLL-AF9-Induced AML Leukemia



	Treatment	Regimen	MST (Days)	% Survival (day 45)	Log-rank P value	
					vs. control	vs. chemo
	none		25	0	--	--
	AraC/Dox	100 mg/kg IV x 5d + 1 mg/kg IV x 3d	32.5	0	0.0127	--
	AraC/Dox + Cmpd (I)	As above + 40 mg/kg IP bid x 10 d	41	0	0.0009	0.0054

FIG. 7

Compound of Formula (I) Uncouples the Increased Adhesion of 5-Azacytidine-treated KG1 cells to E-Selectin

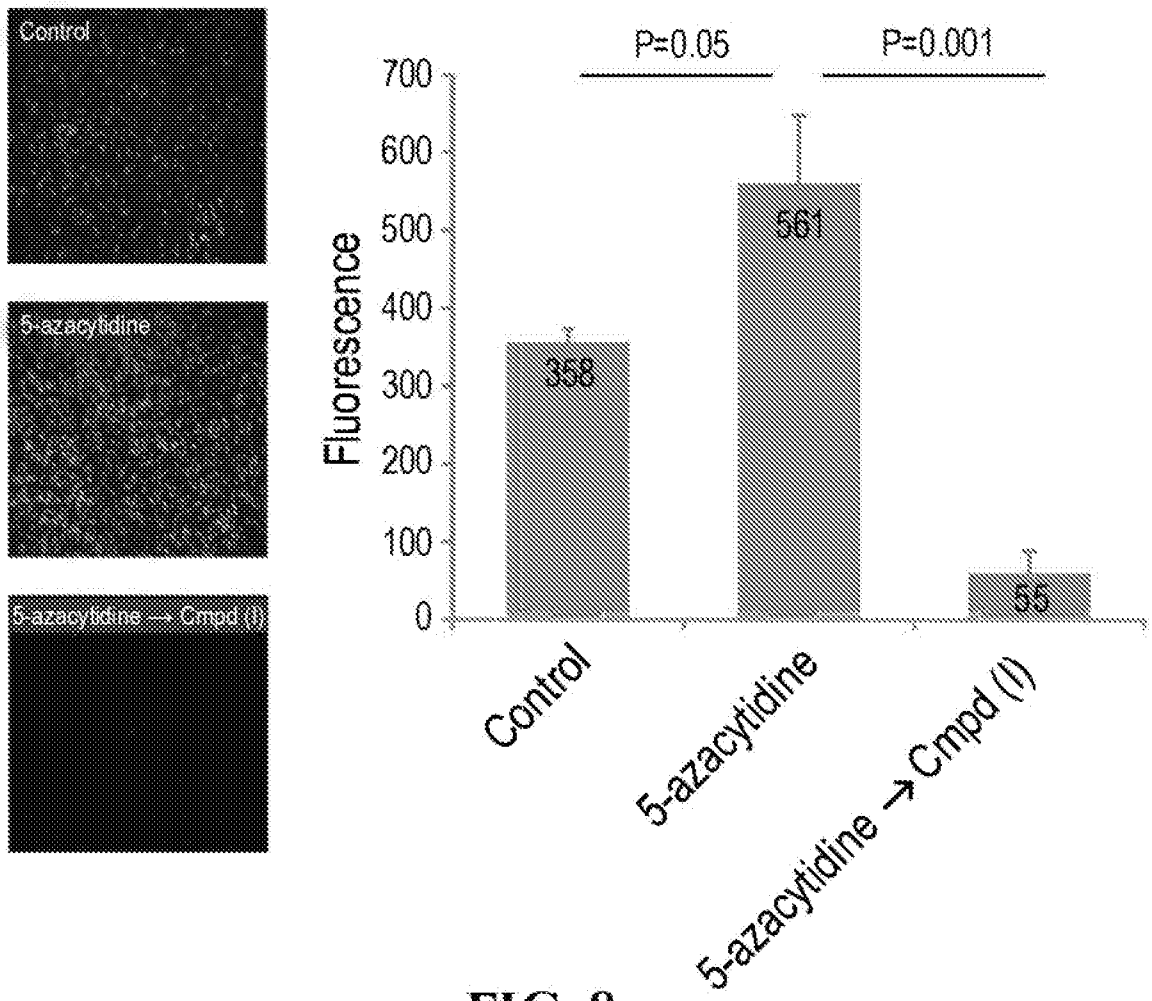


FIG. 8

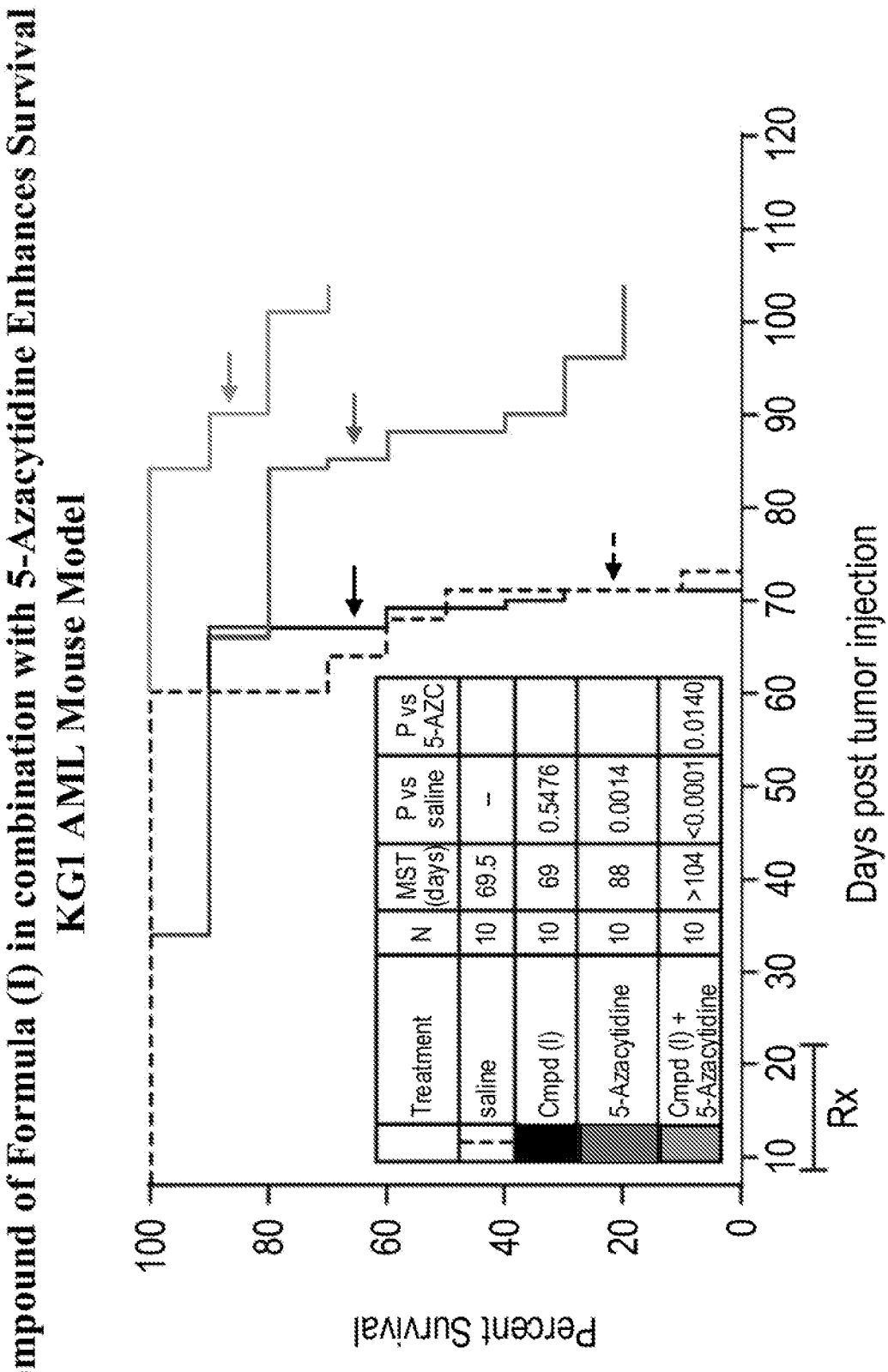

Compound of Formula (I) in combination with 5-Azacytidine Enhances Survival
KG1 AML Mouse Model
Percent Survival
Days post tumor injection
Rx
Treatment
N
MST (days)
P vs saline
P vs 5-AZC
saline
10
69.5
--
Cmpd (I)
10
69
0.5476
5-Azacytidine
10
88
0.0014
Cmpd (I) + 5-Azacytidine
10
>104
<0.0001
0.0140

FIG. 9

E-selectin Ligand Binding by AML Blasts in Newly Diagnosed and Relapsed Leukemia Patients

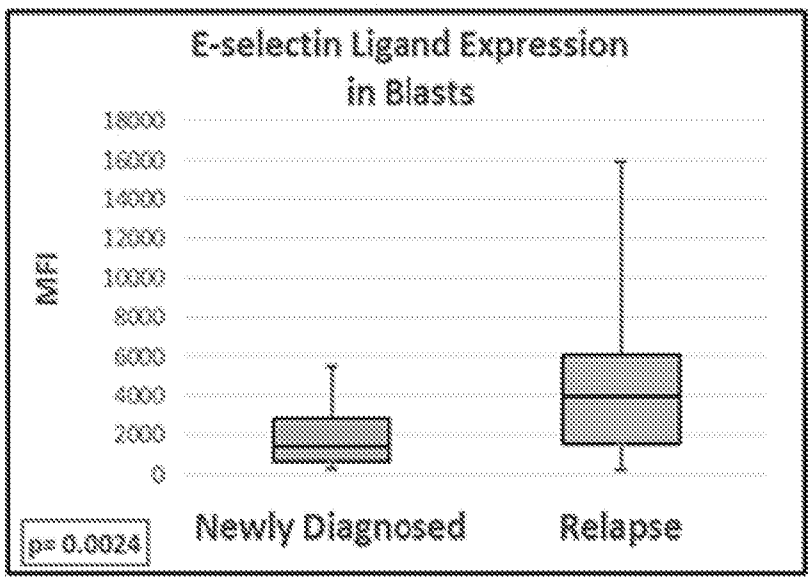


FIG. 10A

$sLe^{a/x}$ Binding by AML Blasts in Newly Diagnosed and Relapsed Leukemia Patients

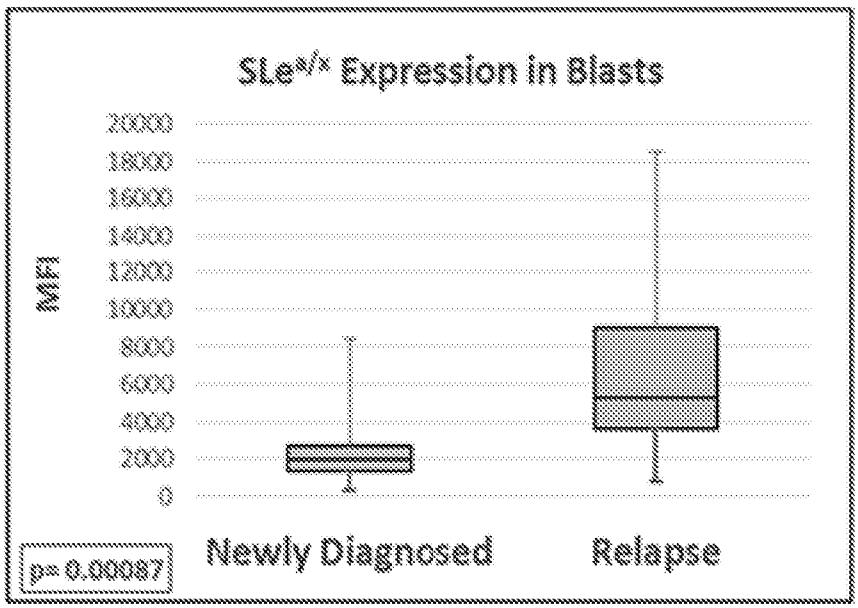


FIG. 10B

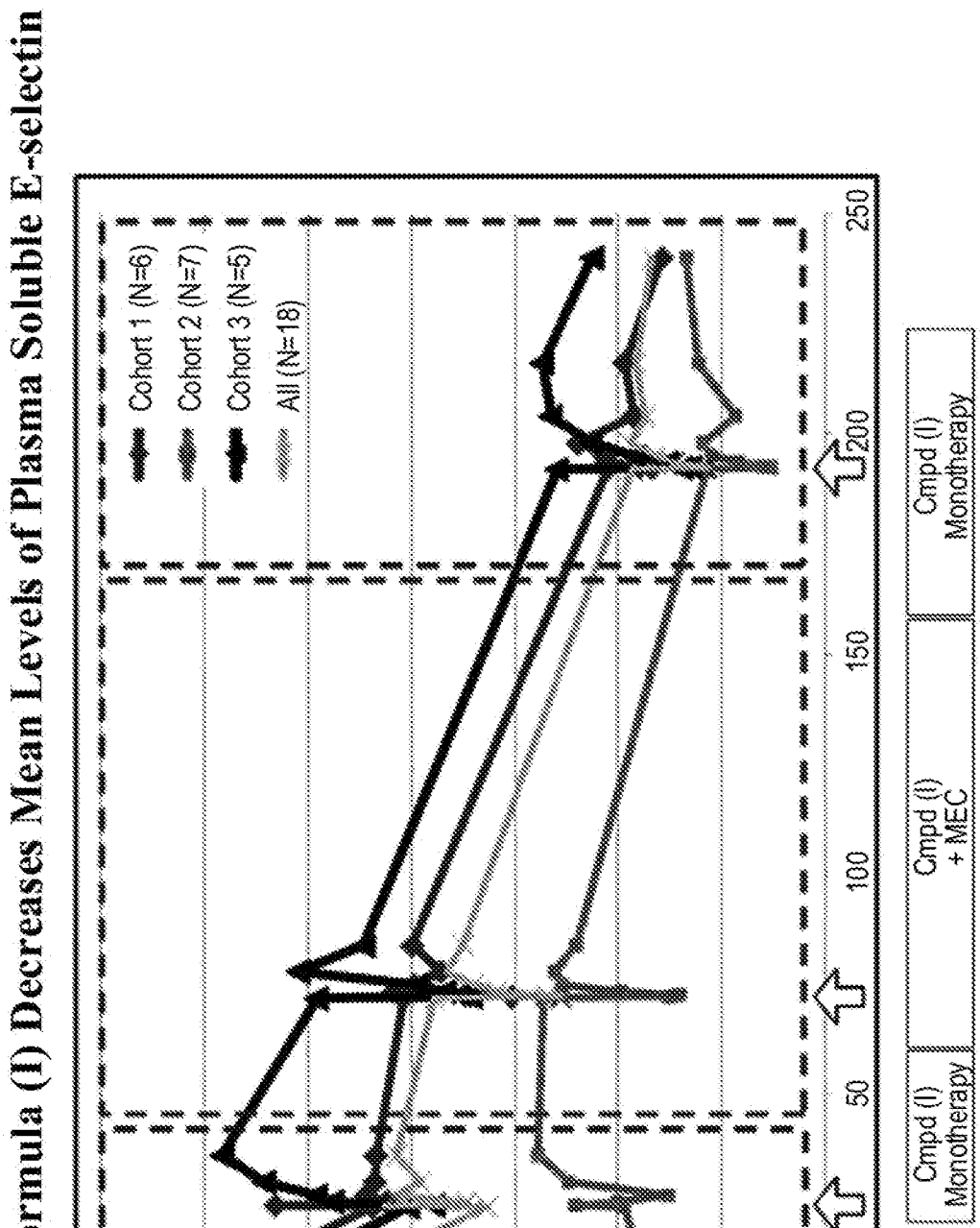

Compound of Formula (I) Decreases Mean Levels of Plasma Soluble E-selectin
sE-Selectin Levels in Plasma (ng/mL)
70
60
50
40
30
20
10
0
Cohort 1 (N=6)
Cohort 2 (N=7)
Cohort 3 (N=5)
All (N=18)
0
50
100
150
200
250
Time (Hours)
Cmpd (I) Monotherapy
Cmpd (I) + MEC
Cmpd (I) Monotherapy

FIG. 11

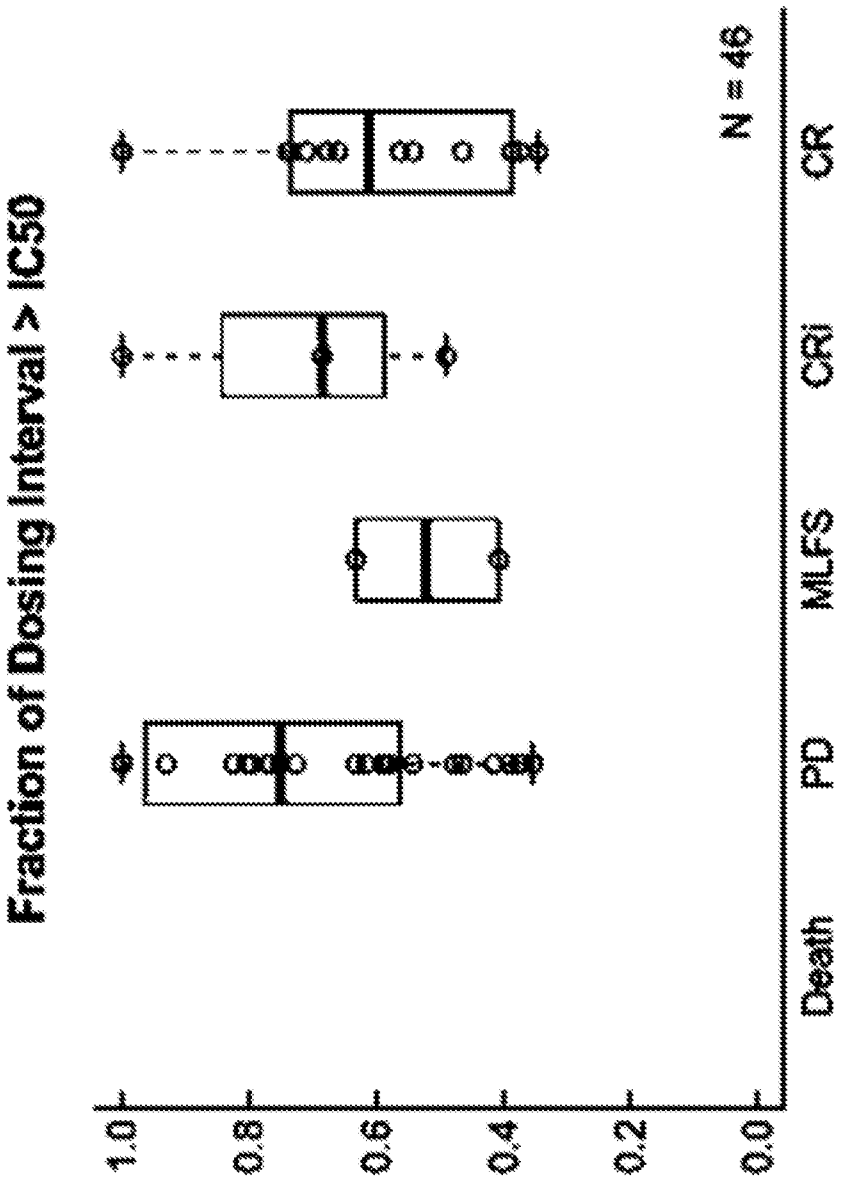

Fraction of Dosing Interval > IC50
1.0
0.8
0.6
0.4
0.2
0.0
N = 46
Death
PD
MLFS
CRi
CR

FIG. 12A

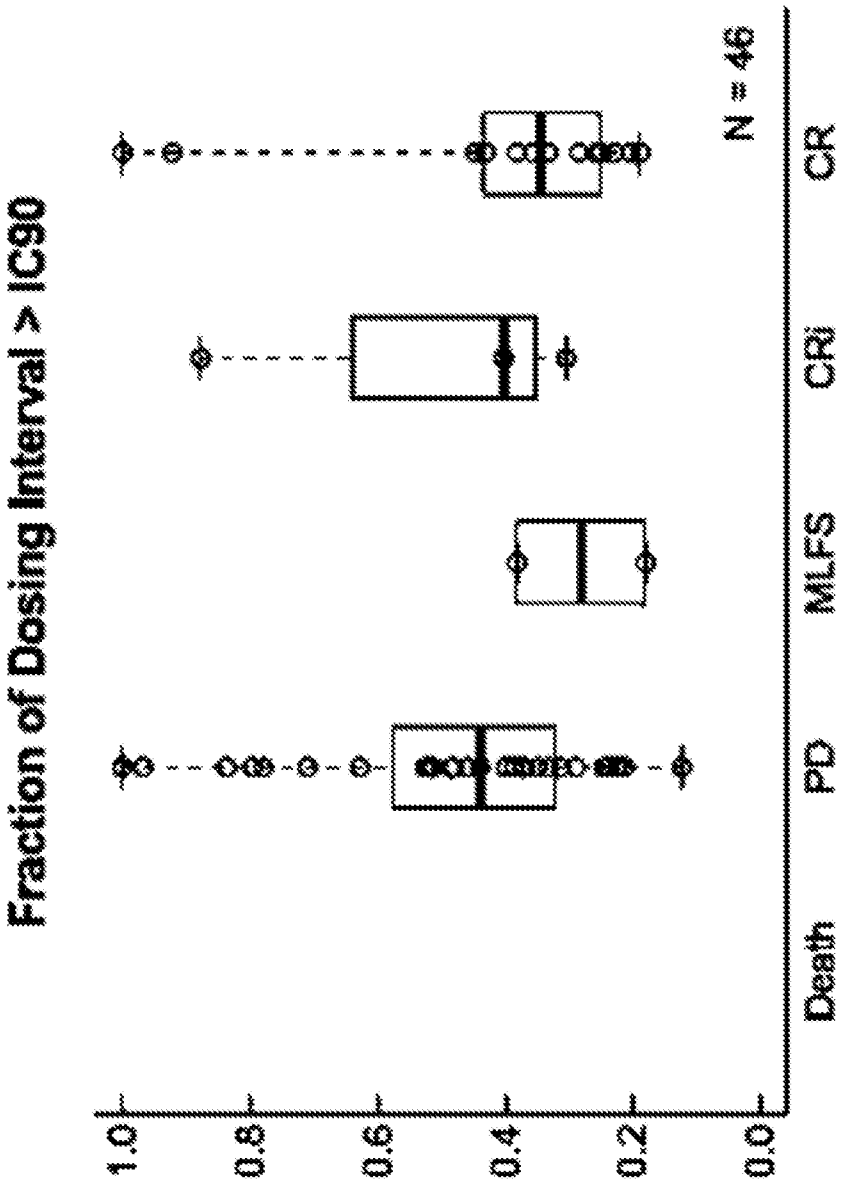

Fraction of Dosing Interval > IC90
1.0
0.8
0.6
0.4
0.2
0.0
Death
PD
MLFS
CRi
CR
N = 46

FIG. 12B

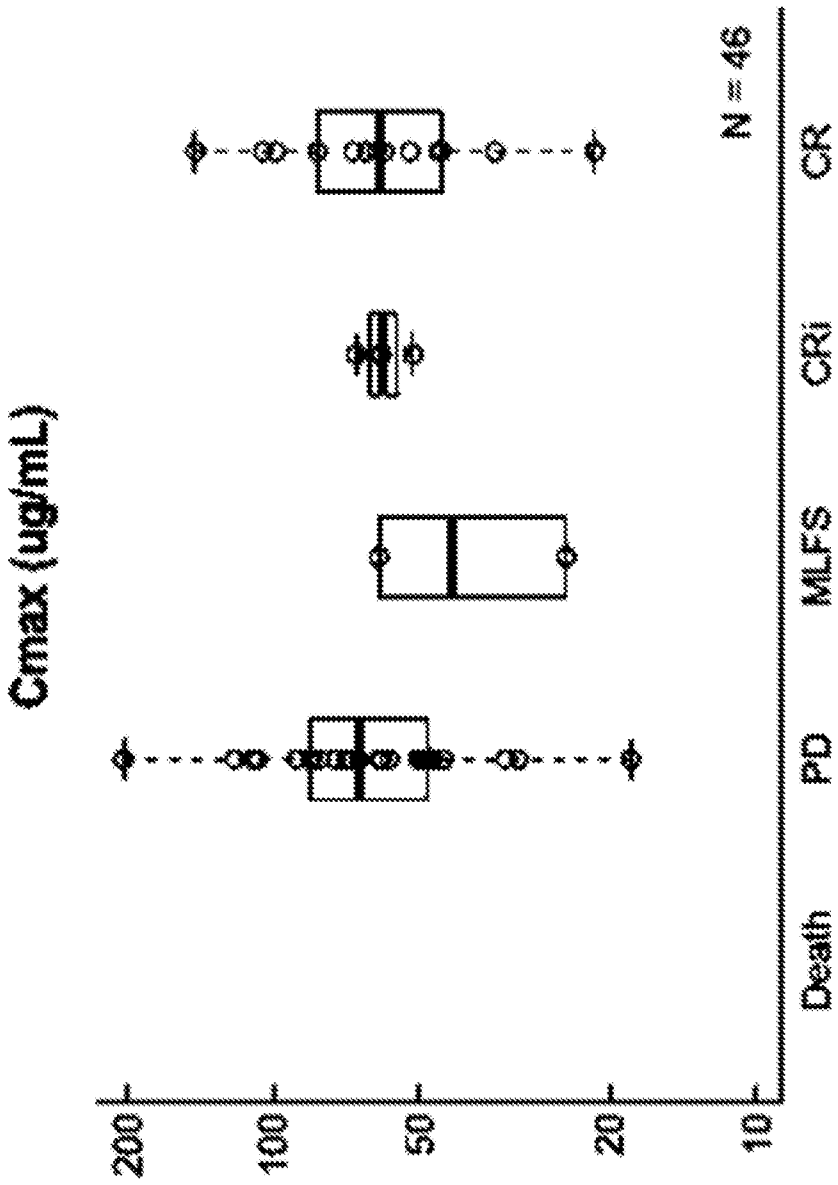


FIG. 12C

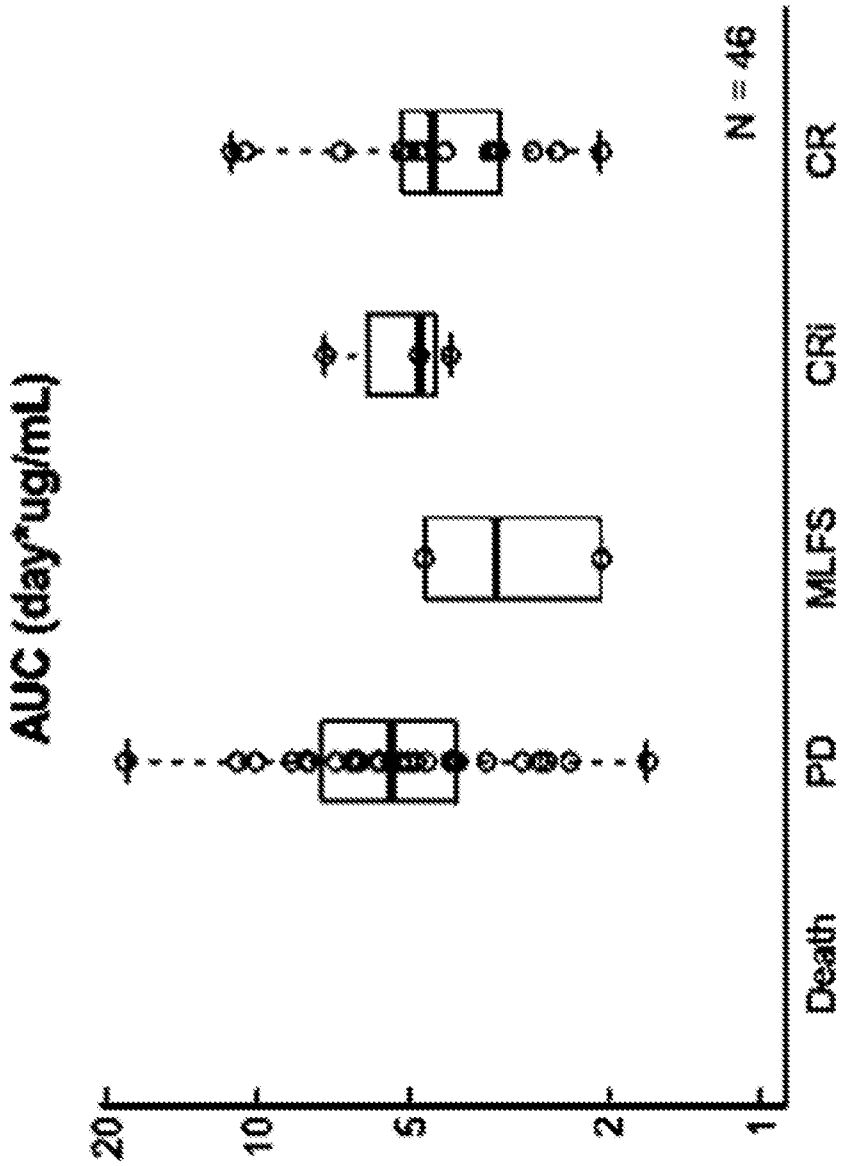


FIG. 12D

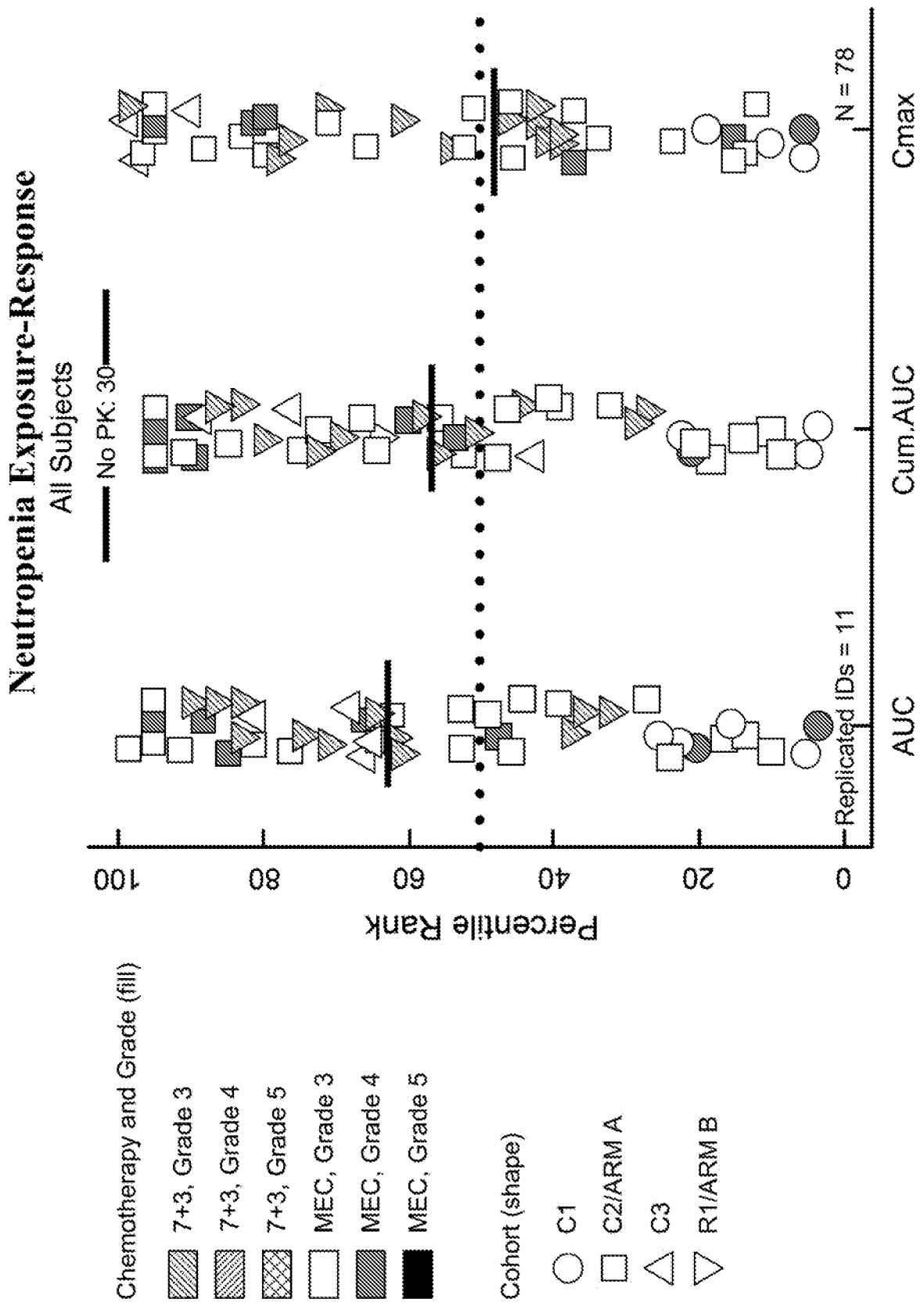

Neutropenia Exposure-Response
All Subjects
No PK: 30
Percentile Rank
0
20
40
60
80
100
Replicated IDs = 11
AUC
Cum.AUC
Cmax
N = 78
Chemotherapy and Grade (fill)
7+3, Grade 3
7+3, Grade 4
7+3, Grade 5
MEC, Grade 3
MEC, Grade 4
MEC, Grade 5
Cohort (shape)
C1
C2/ARM A
C3
R1/ARM B

FIG. 13A

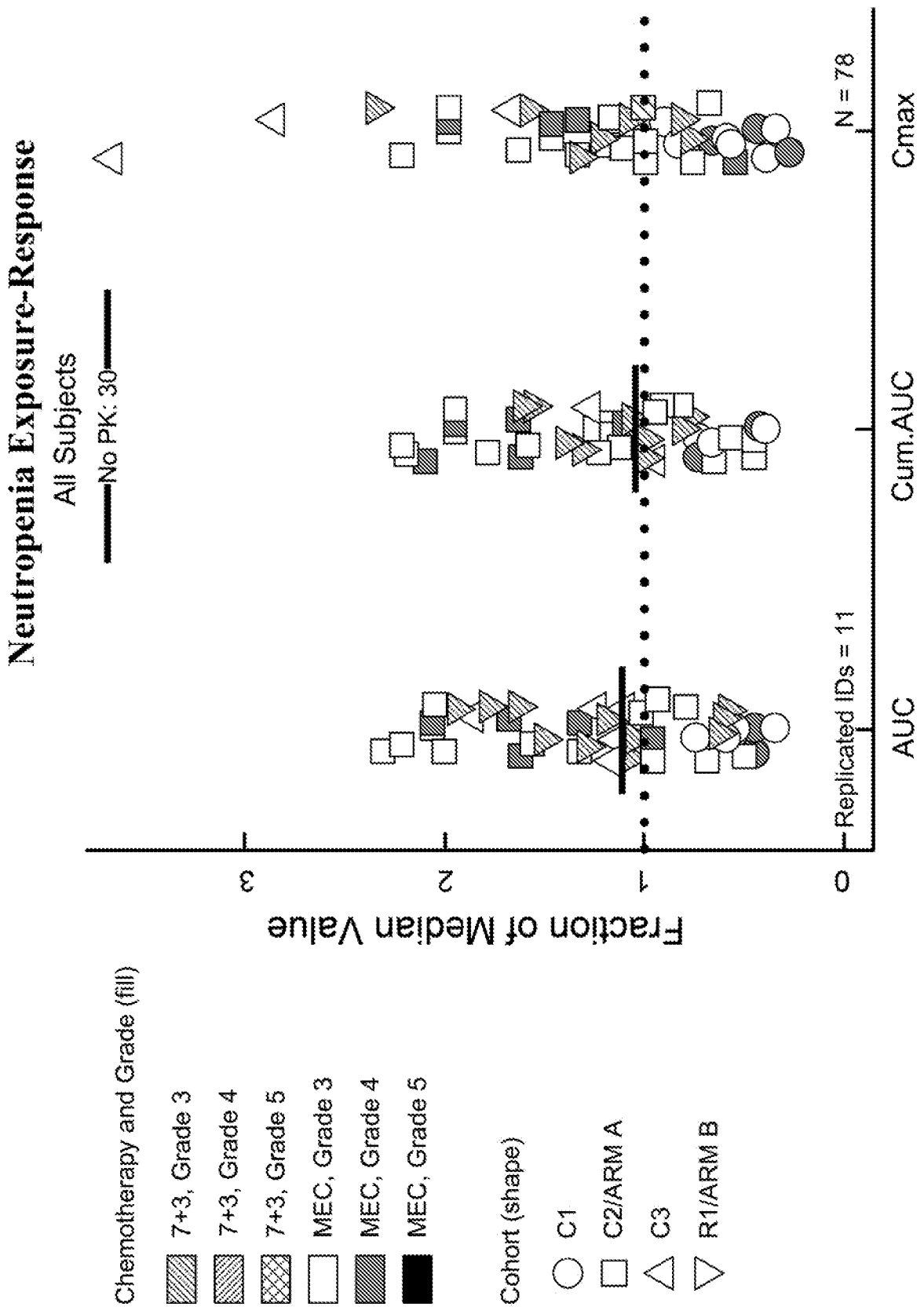

Neutropenia Exposure-Response
All Subjects
No PK: 30
Fraction of Median Value
0
1
2
3
Replicated IDs = 11
AUC
Cum.AUC
Cmax
N = 78
Chemotherapy and Grade (fill)
7+3, Grade 3
7+3, Grade 4
7+3, Grade 5
MEC, Grade 3
MEC, Grade 4
MEC, Grade 5
Cohort (shape)
C1
C2/ARM A
C3
R1/ARM B

FIG. 13B

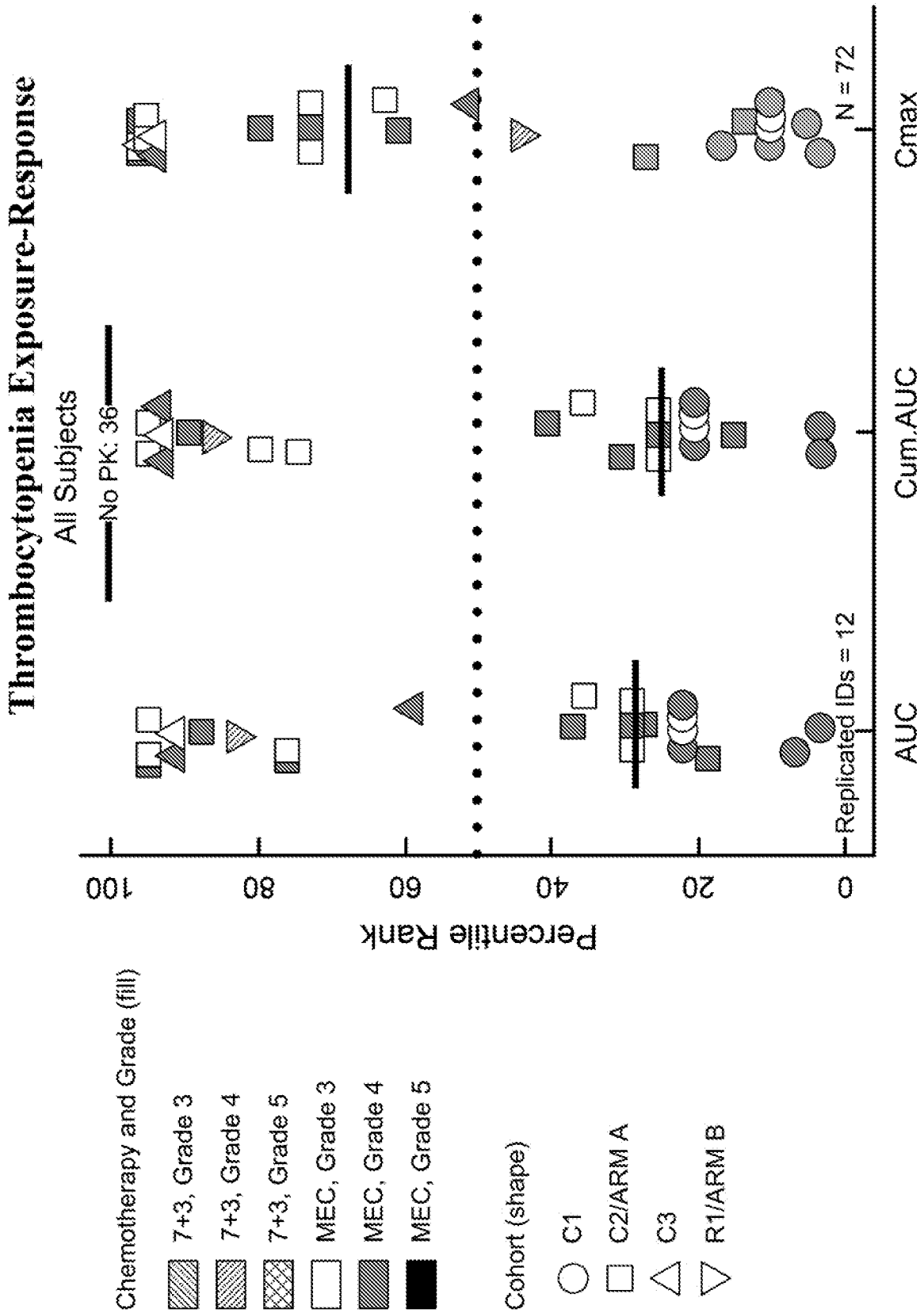

Thrombocytopenia Exposure-Response
All Subjects
No PK: 36
Percentile Rank
100
80
60
40
20
0
Replicated IDs = 12
AUC
Cum.AUC
Cmax
N = 72
Chemotherapy and Grade (fill)
7+3, Grade 3
7+3, Grade 4
7+3, Grade 5
MEC, Grade 3
MEC, Grade 4
MEC, Grade 5
Cohort (shape)
C1
C2/ARM A
C3
R1/ARM B

FIG. 13C

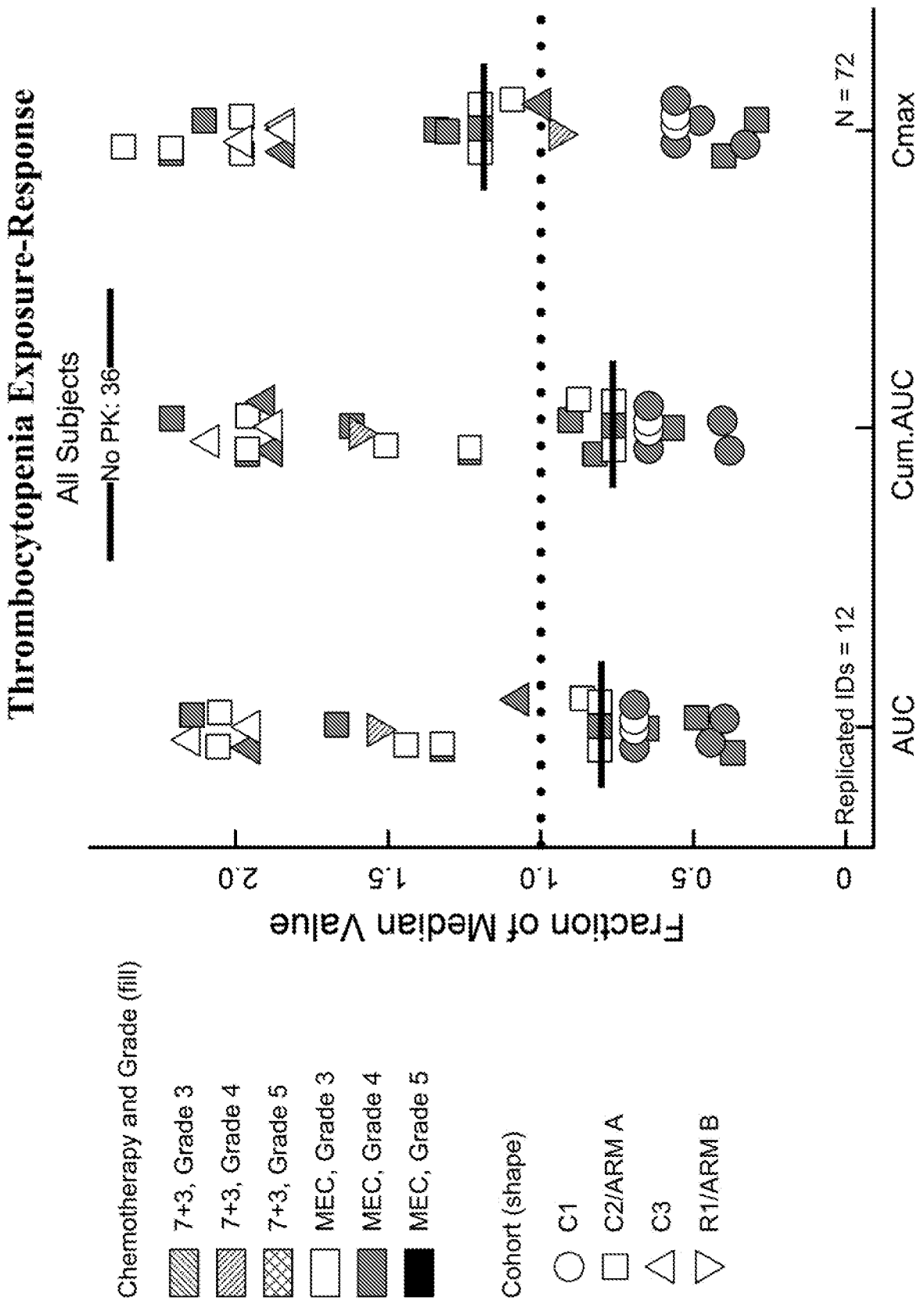

Thrombocytopenia Exposure-Response
All Subjects
No PK: 36
Fraction of Median Value
0
0.5
1.0
1.5
2.0
Replicated IDs = 12
AUC
Cum.AUC
Cmax
N = 72
Chemotherapy and Grade (fill)
7+3, Grade 3
7+3, Grade 4
7+3, Grade 5
MEC, Grade 3
MEC, Grade 4
MEC, Grade 5
Cohort (shape)
C1
C2/ARM A
C3
R1/ARM B

FIG. 13D

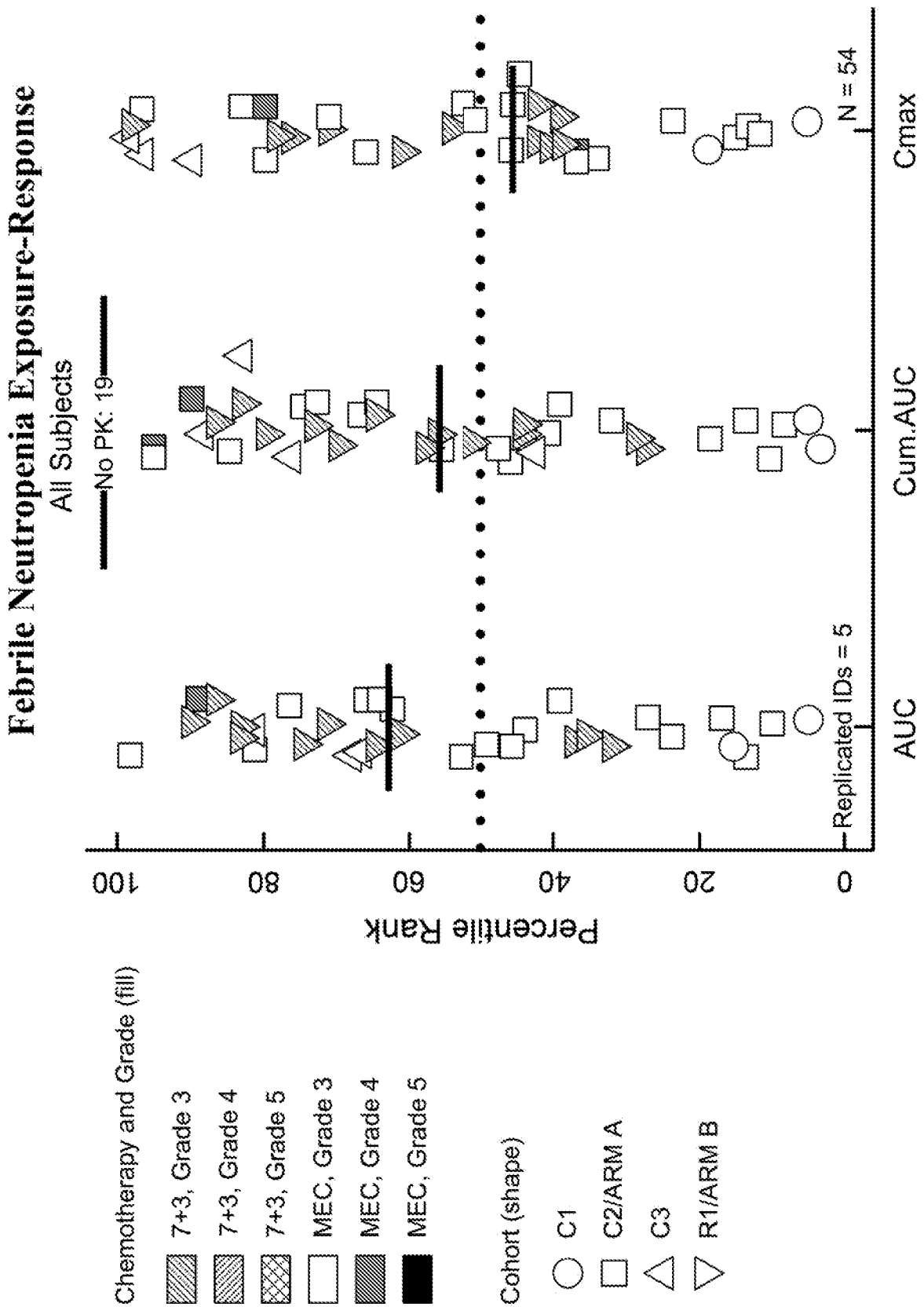

Febrile Neutropenia Exposure-Response
All Subjects
No PK: 19
Percentile Rank
0
20
40
60
80
100
Replicated IDs = 5
AUC
Cum.AUC
Cmax
N = 54
Chemotherapy and Grade (fill)
7+3, Grade 3
7+3, Grade 4
7+3, Grade 5
MEC, Grade 3
MEC, Grade 4
MEC, Grade 5
Cohort (shape)
C1
C2/ARM A
C3
R1/ARM B

FIG. 13E

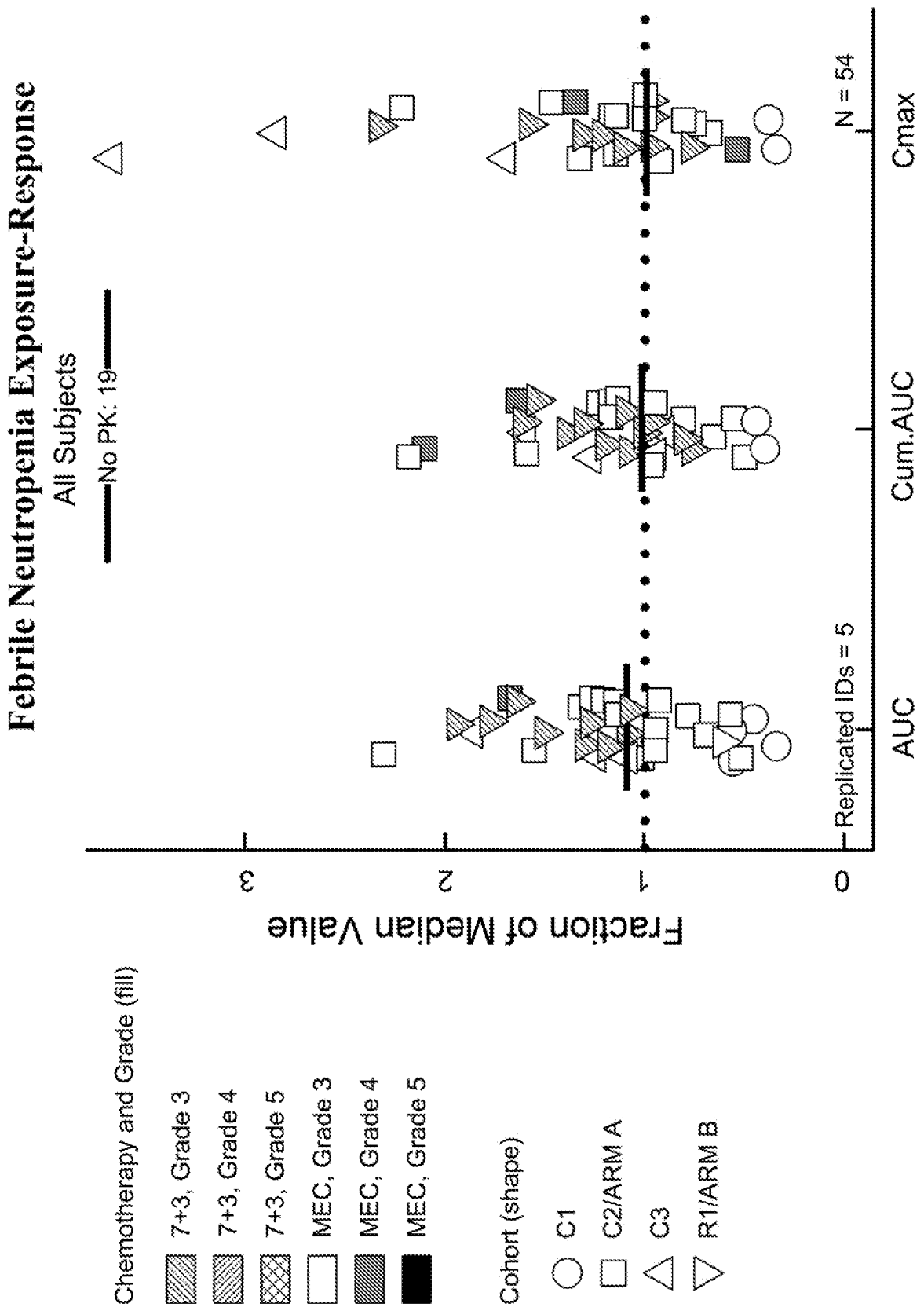

Febrile Neutropenia Exposure-Response
All Subjects
No PK: 19
Fraction of Median Value
0
1
2
3
Replicated IDs = 5
AUC
Cum.AUC
Cmax
N = 54
Chemotherapy and Grade (fill)
7+3, Grade 3
7+3, Grade 4
7+3, Grade 5
MEC, Grade 3
MEC, Grade 4
MEC, Grade 5
Cohort (shape)
C1
C2/ARM A
C3
R1/ARM B

FIG. 13F

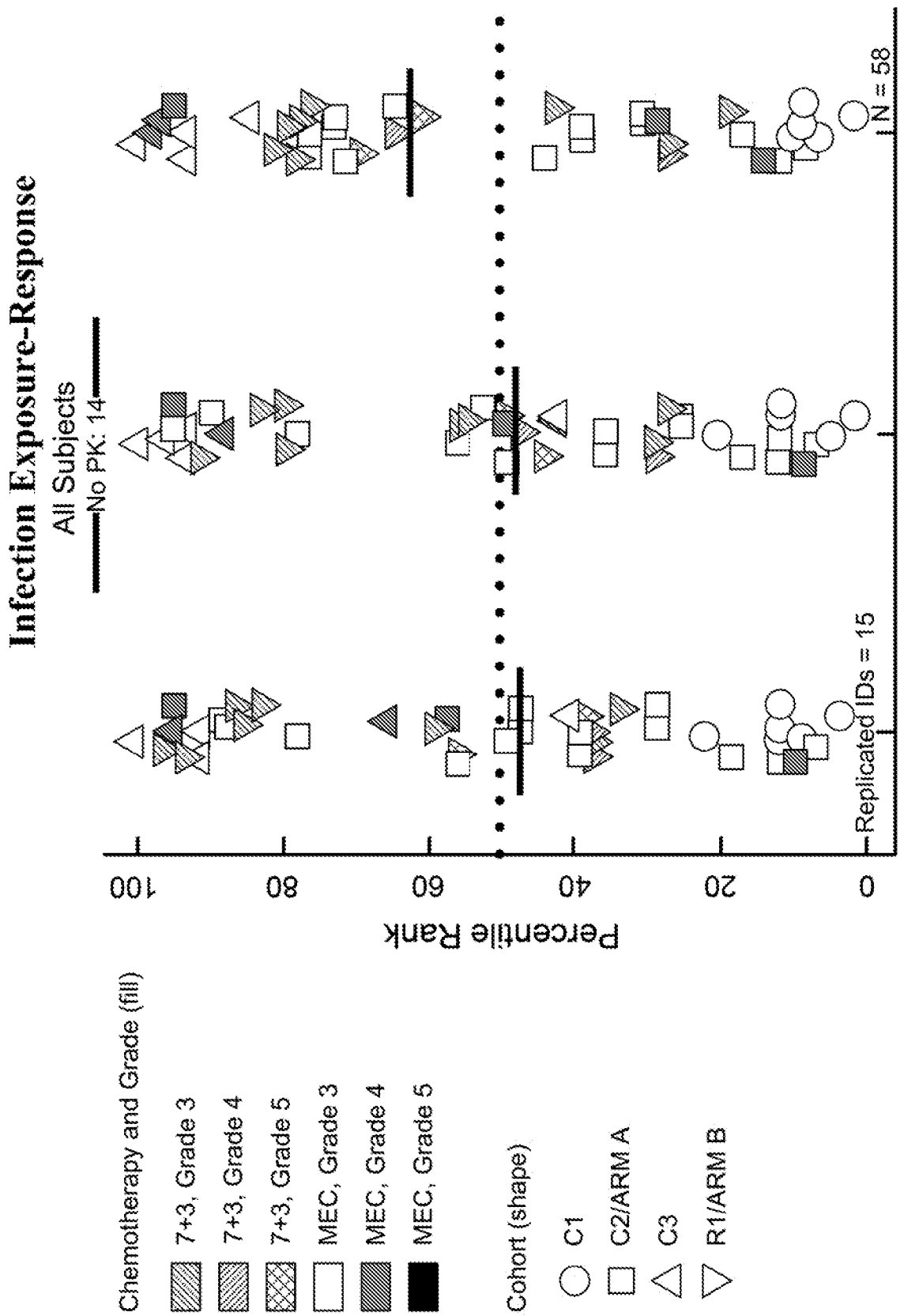

Infection Exposure-Response
All Subjects
No PK: 14
Percentile Rank
0
20
40
60
80
100
Replicated IDs = 15
AUC
Cum.AUC
Cmax
N = 58
Chemotherapy and Grade (fill)
7+3, Grade 3
7+3, Grade 4
7+3, Grade 5
MEC, Grade 3
MEC, Grade 4
MEC, Grade 5
Cohort (shape)
C1
C2/ARM A
C3
R1/ARM B

FIG. 13G

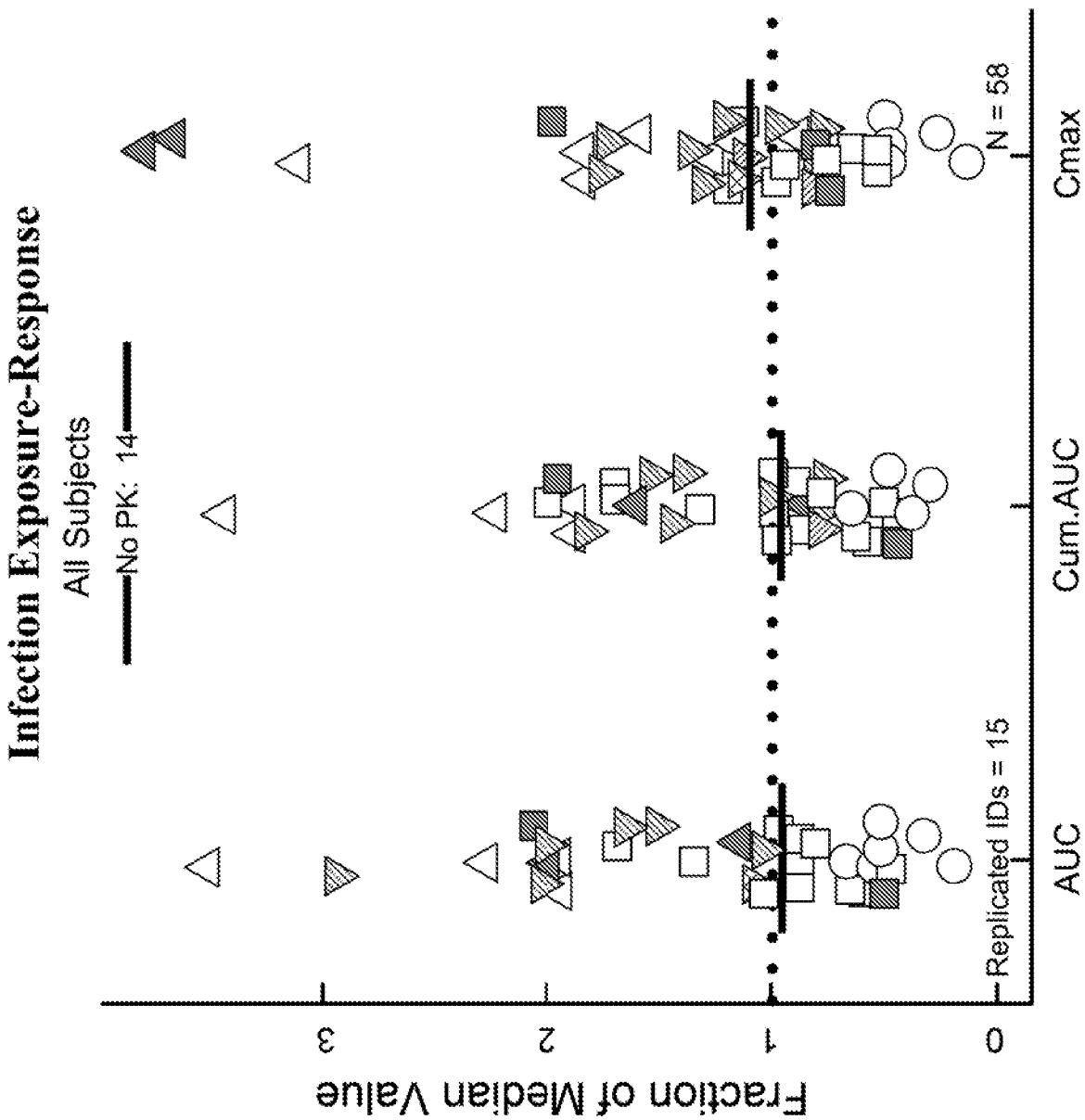

Infection Exposure-Response
All Subjects
No PK: 14
Fraction of Median Value
0
1
2
3
Replicated IDs = 15
AUC
Cum.AUC
Cmax
N = 58
Chemotherapy and Grade (fill)
7+3, Grade 3
7+3, Grade 4
7+3, Grade 5
MEC, Grade 3
MEC, Grade 4
MEC, Grade 5
Cohort (shape)
C1
C2/ARM A
C3
R1/ARM B

FIG. 13H

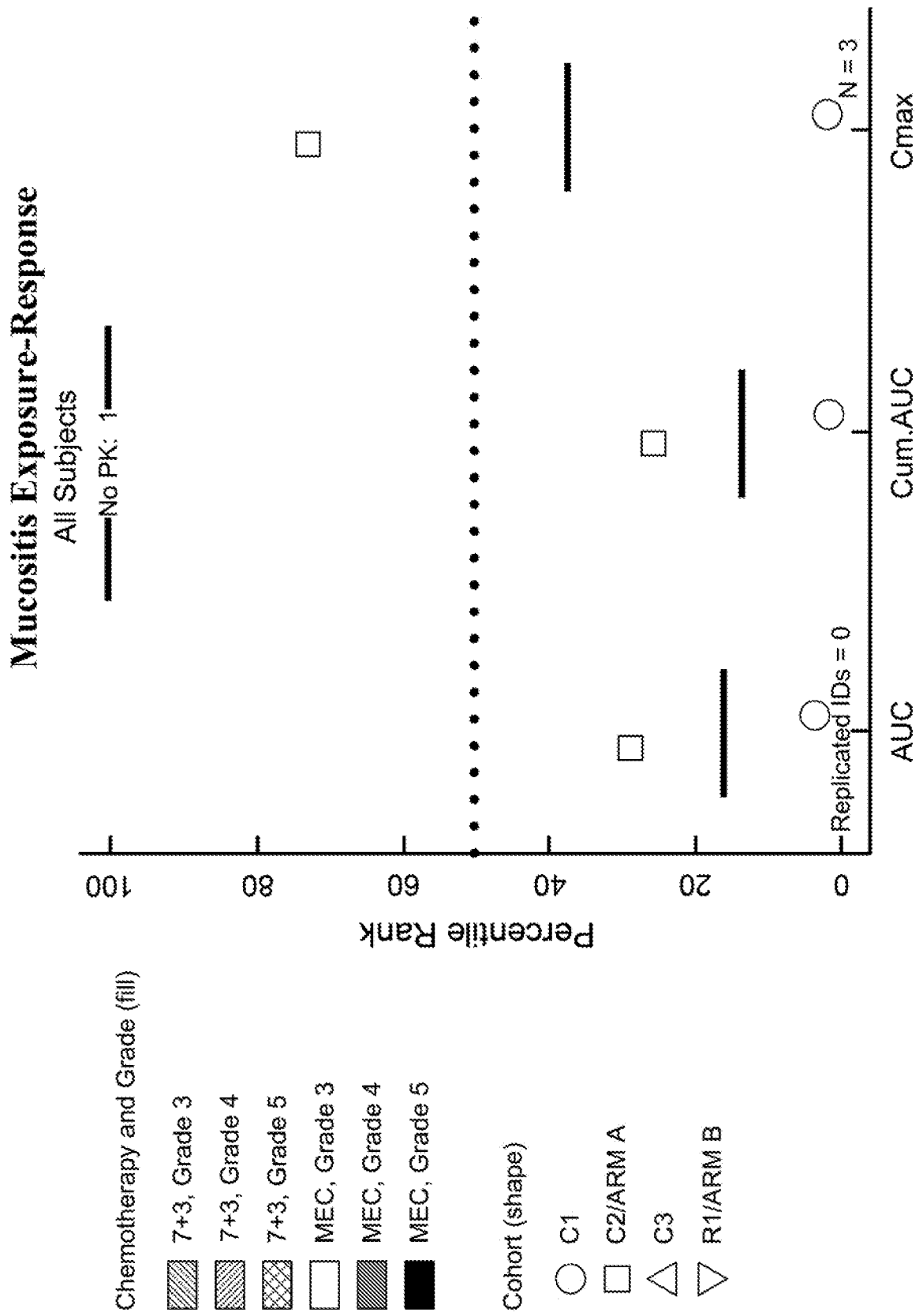

Mucositis Exposure-Response
All Subjects
No PK: 1
Percentile Rank
0
20
40
60
80
100
Replicated IDs = 0
AUC
Cum.AUC
Cmax
N = 3
Chemotherapy and Grade (fill)
7+3, Grade 3
7+3, Grade 4
7+3, Grade 5
MEC, Grade 3
MEC, Grade 4
MEC, Grade 5
Cohort (shape)
C1
C2/ARM A
C3
R1/ARM B

FIG. 13I

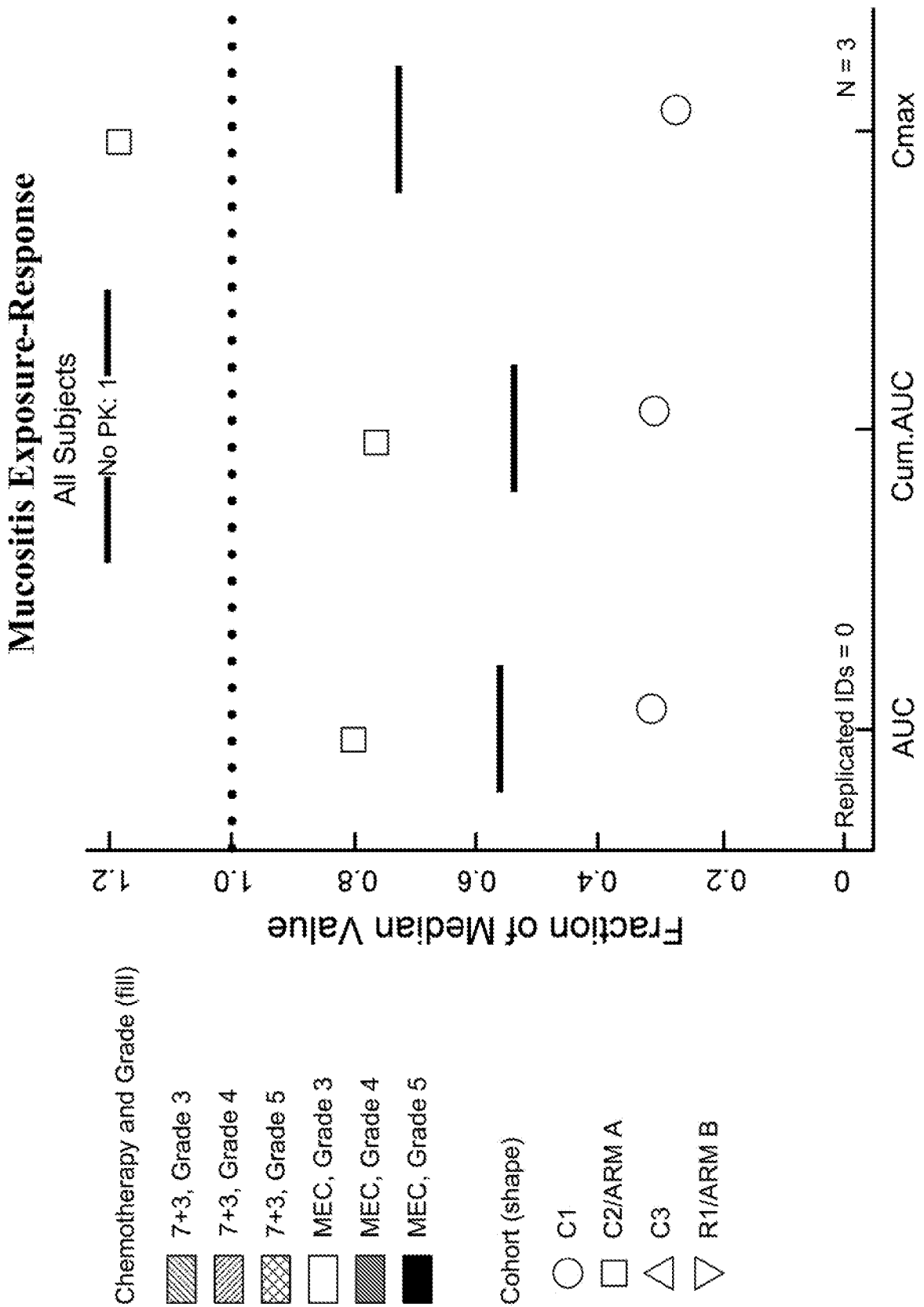

Mucositis Exposure-Response
All Subjects
No PK: 1
Fraction of Median Value
0
0.2
0.4
0.6
0.8
1.0
1.2
Replicated IDs = 0
AUC
Cum.AUC
Cmax
N = 3
Chemotherapy and Grade (fill)
7+3, Grade 3
7+3, Grade 4
7+3, Grade 5
MEC, Grade 3
MEC, Grade 4
MEC, Grade 5
Cohort (shape)
C1
C2/ARM A
C3
R1/ARM B

FIG. 13J

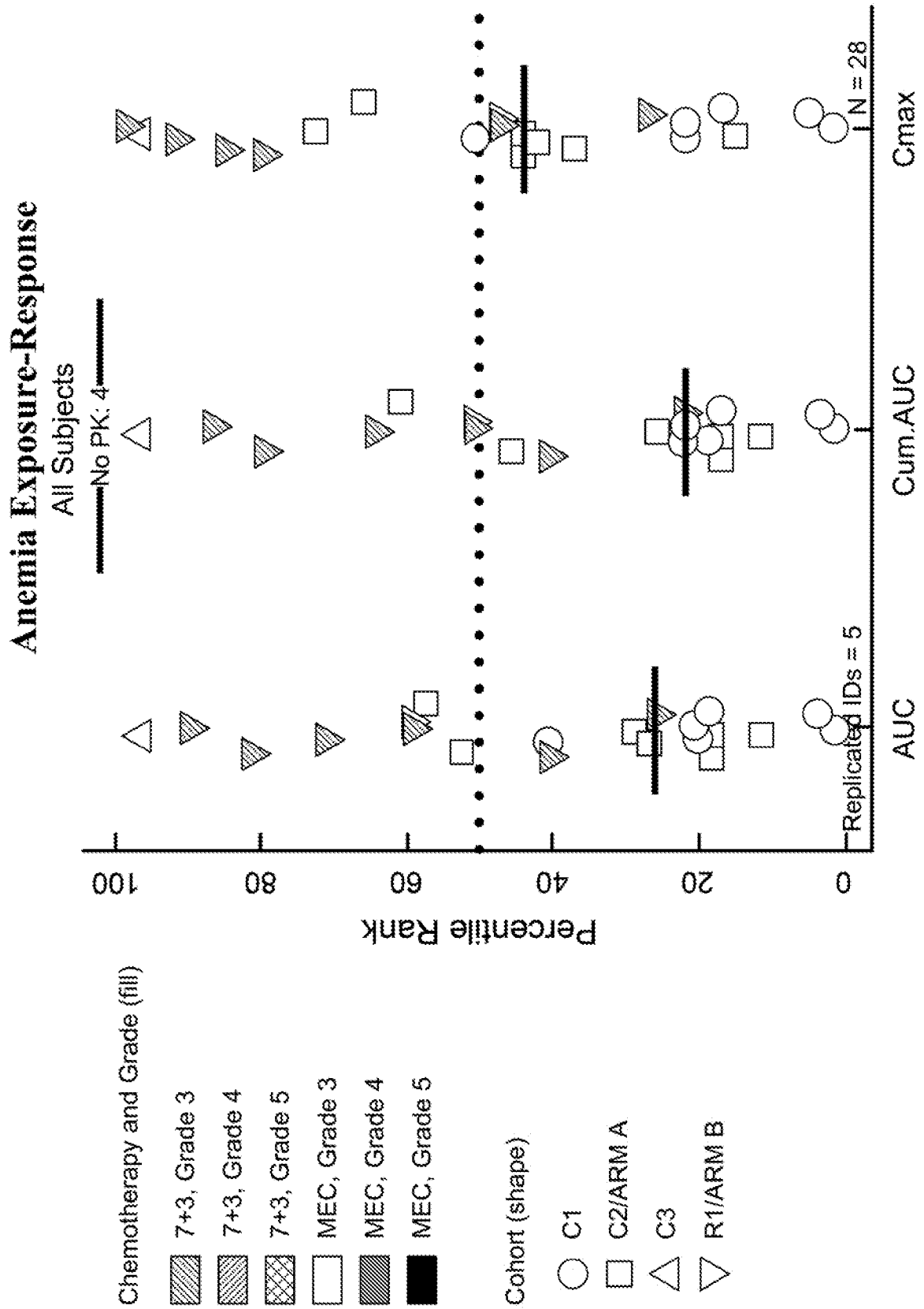

Anemia Exposure-Response
All Subjects
No PK: 4
Percentile Rank
0
20
40
60
80
100
Replicated IDs = 5
AUC
Cum.AUC
Cmax
N = 28
Chemotherapy and Grade (fill)
7+3, Grade 3
7+3, Grade 4
7+3, Grade 5
MEC, Grade 3
MEC, Grade 4
MEC, Grade 5
Cohort (shape)
C1
C2/ARM A
C3
R1/ARM B

FIG. 13K

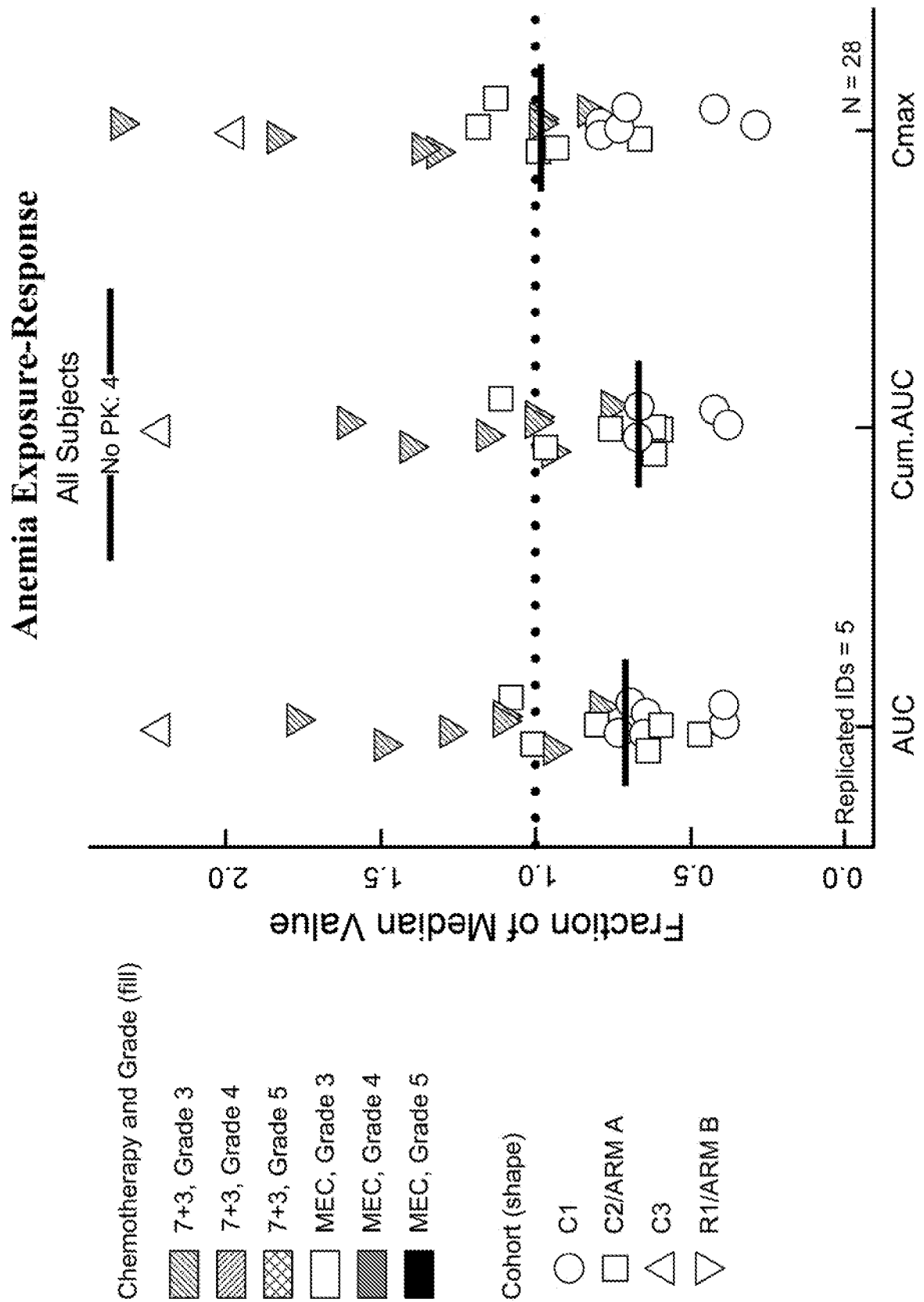

Anemia Exposure-Response
All Subjects
No PK: 4
Fraction of Median Value
0.0
0.5
1.0
1.5
2.0
Replicated IDs = 5
AUC
Cum.AUC
Cmax
N = 28
Chemotherapy and Grade (fill)
7+3, Grade 3
7+3, Grade 4
7+3, Grade 5
MEC, Grade 3
MEC, Grade 4
MEC, Grade 5
Cohort (shape)
C1
C2/ARM A
C3
R1/ARM B

FIG. 13L

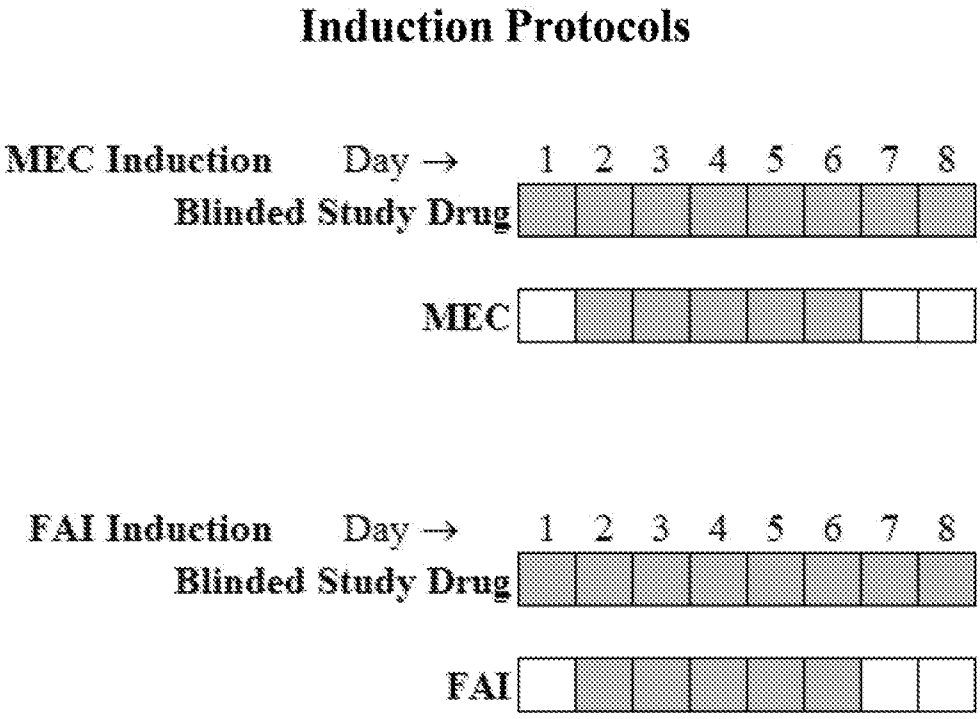

Induction Protocols
MEC Induction
Day →
1 2 3 4 5 6 7 8
Blinded Study Drug
MEC
FAI Induction
Day →
1 2 3 4 5 6 7 8
Blinded Study Drug
FAI

FIG. 14A

Consolidation Protocols

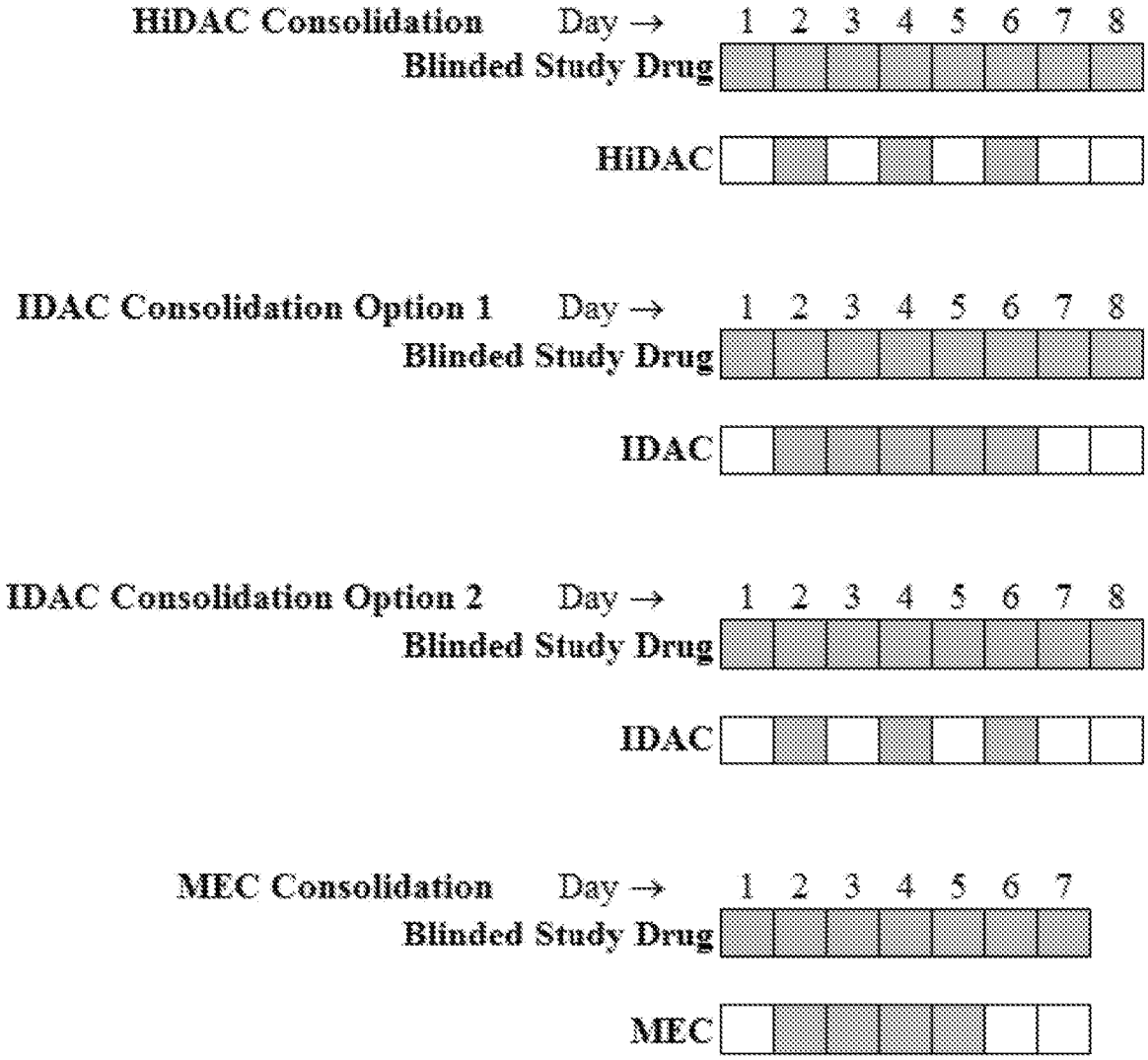


FIG. 14B

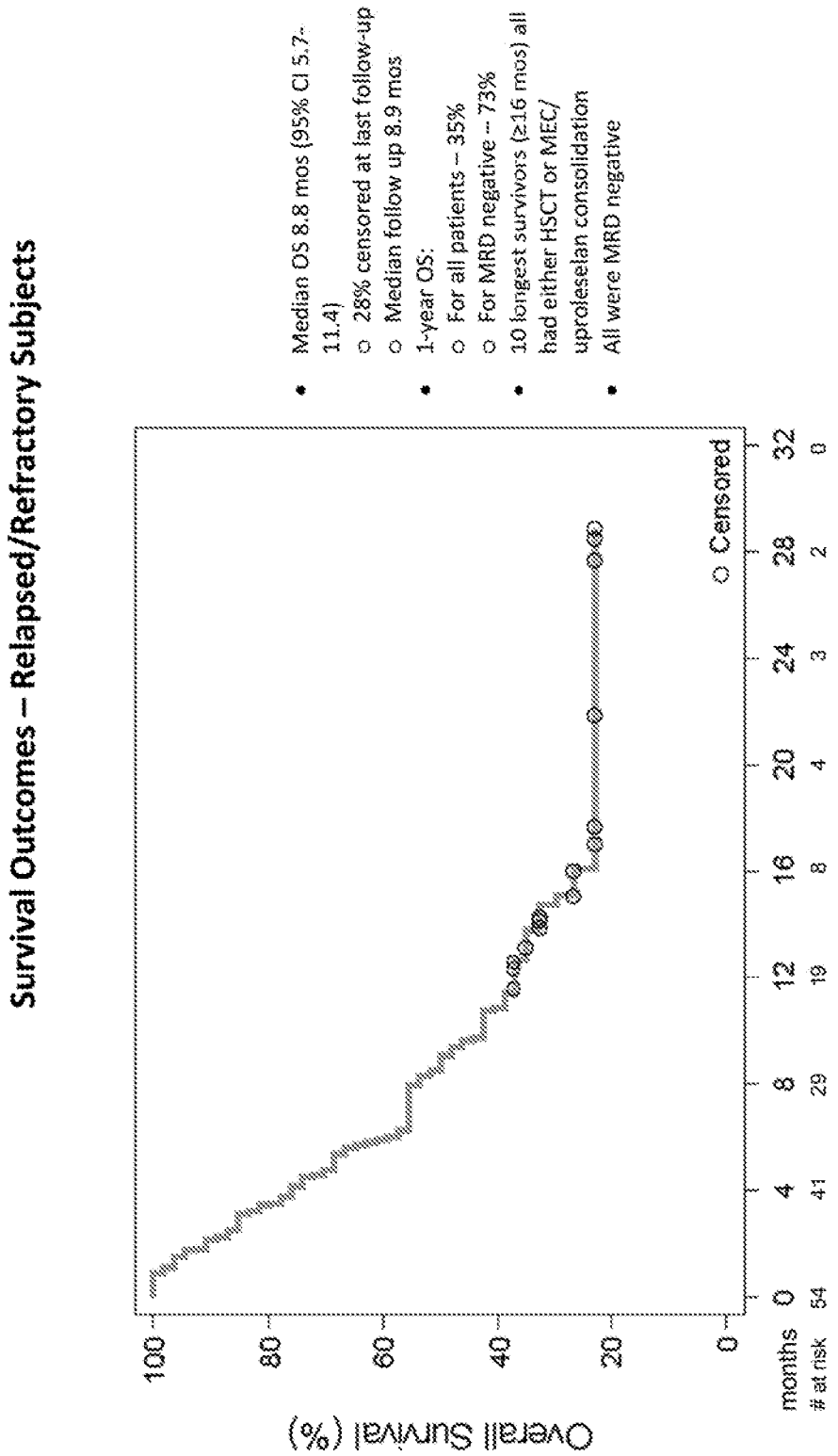

Survival Outcomes – Relapsed/Refractory Subjects
Median OS 8.8 mos (95% CI 5.7-11.4)
28% censored at last follow-up
Median follow up 8.9 mos
1-year OS:
For all patients – 35%
For MRD negative – 73%
10 longest survivors (≥16 mos) all had either HSCT or MEC/ uproleselan consolidation
All were MRD negative
Censored
Overall Survival (%)
100
80
60
40
20
0
months 0 4 8 12 16 20 24 28 32
at risk 54 41 29 19 8 4 3 2 0
RP2D (10mg/kg/dose) shown, N=54.

FIG. 15

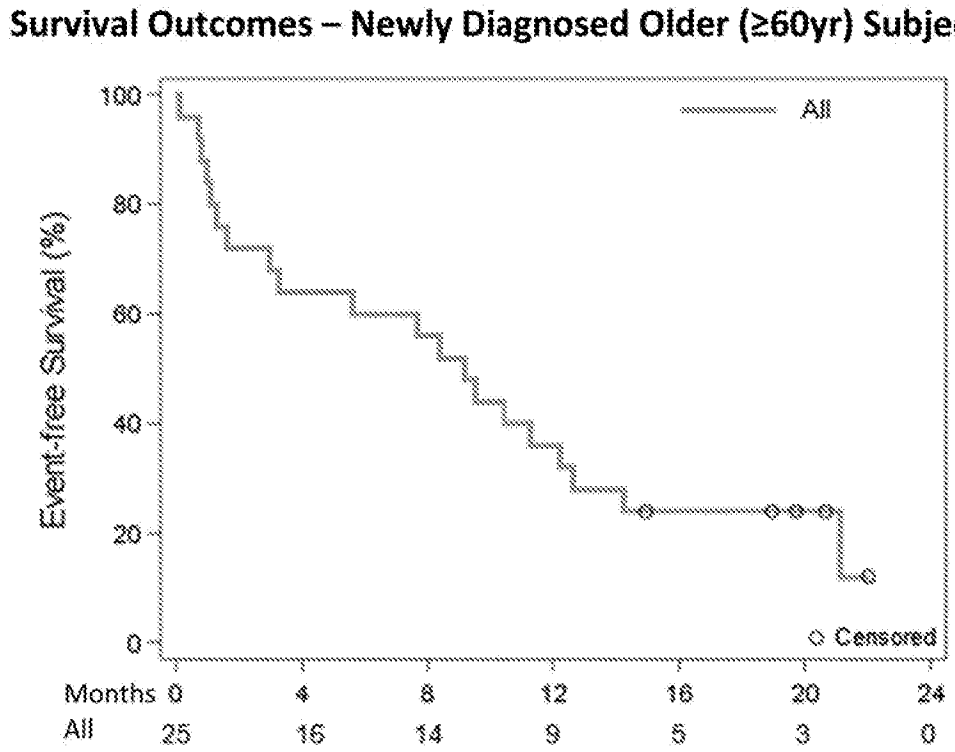


FIG. 16A

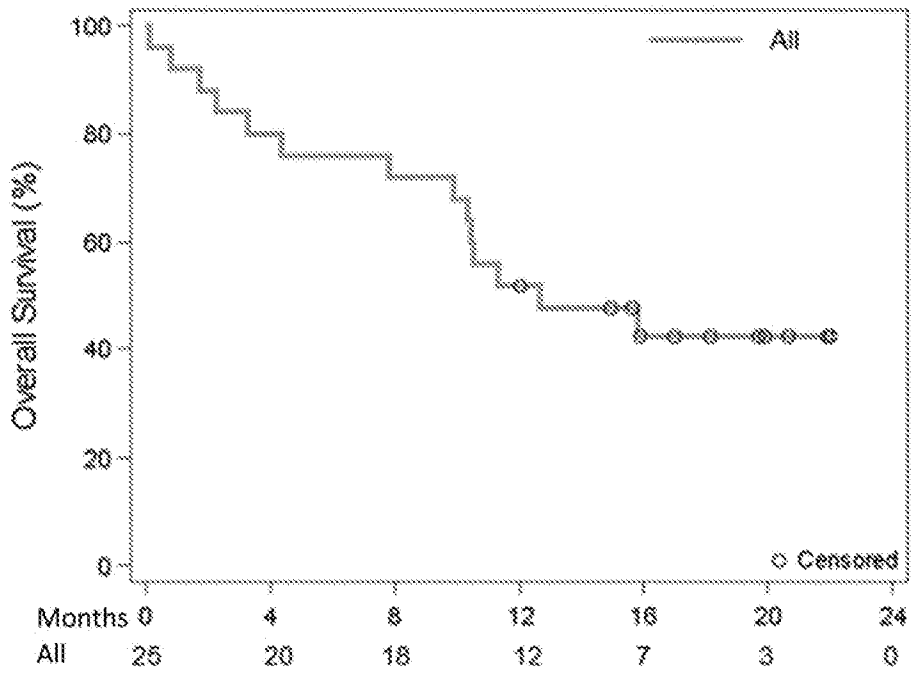


FIG. 16B