CLAIMS

1. Use of one or more metal chelators in the manufacture of a medicament for treating a proliferative disease in a mammalian subject; wherein said one or more metal chelators are broad-spectrum metal chelators; and wherein said medicament is to be administered to the subject in combination with an anti-cancer therapy and optionally at least one antioxidant, vitamin, or essential mineral.

2. The use of claim 1, wherein the antioxidant, vitamin(s) or mineral(s) is/are chosen from zinc, selenium, magnesium, rubidium and vitamin C;
preferably wherein at least one or at least two of zinc, selenium, magnesium, and vitamin C are administered;
more preferably wherein zinc, selenium, magnesium, and vitamin C are administered.

3. The use of claim 1 or claim 2, ~~wherein the one or more metal chelators are broad-spectrum metal chelators;~~
~~preferably~~ wherein at least one of the one or more metal chelators is/are capable of chelating at least two metals;
~~more~~ preferably wherein the one or more metal chelators is/are administered in an amount effective to reduce the levels of the at least two metals.

4. The use of any one of claim~~s~~ 1-3 wherein the one or more metal chelators are chosen from EDTA (such as Ca-EDTA), dimercaptosuccinic acid (DMSA), 2,3-dimercapto-1-propanesulfonic acid (DMPS), BAL, N-acetylcysteine (NAC), ~~deferasirox, deferiprone, deferoxamine,~~ pentetate calcium trisodium (Ca-DPTA), pentetate zinc trisodium (Zn-DPTA), ~~trientine, tetrathiomolybdate,~~ and dexrazoxane;

or wherein the metal chelator is chosen from dimercaptosuccinic acid (DMSA), 2,3-dimercapto-1-propanesulfonic acid (DMPS), N-(2,3-dimercaptopropyl)-

phthalamidic acid (DMPA), pentetate calcium trisodium (Ca-DTPA), and dimercaprol (BAL).

5. The use of any one of claims 1-3, wherein the metal chelator is a dithiol chelator;

or wherein the metal chelator is chosen from dimercaptosuccinic acid (DMSA), 2,3-dimercapto-1-propanesulfonic acid (DMPS), N-(2,3-dimercaptopropyl)-phthalamidic acid (DMPA);

~~or wherein the metal chelator is an iron chelator;~~

~~or wherein the metal chelator is deferasirox, deferiprone, or deferoxamine;~~

or wherein the metal chelator is N-acetyl-cysteine (NAC) or a gadolinium chelator, such as a bifunctional gadolinium(III) chelator;

~~or wherein the metal chelator is a copper chelator, preferably wherein the copper chelator is trientine or tetrathiomolybdate;~~

or wherein the metal chelator is dexrazoxane.

6. The use of any one of claims 1-5, wherein the disease is chosen from cancer, a myeloproliferative neoplasm (MPN), myelodysplastic syndrome (MDS), bone marrow disease; bone marrow failure; and a cytopenia such as an idiopathic cytopenia;

preferably wherein the disease is cancer;

more preferably, wherein the cancer has relapsed or is refractory to a previous treatment.

7. The use of claim 6, wherein the cancer is a hematologic malignancy;

preferably wherein the cancer is a leukemia;

more preferably wherein the leukemia is chosen from acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML).

8. The use of claim 7, wherein the ~~leukemia~~hematologic malignancy is AML.

9. The use of any one of claims 1-8, wherein the anti-cancer therapy is chosen from a chemotherapy, an epigenetic therapy, an immunotherapy, or a targeted cancer therapy;
preferably wherein the anti-cancer therapy is a chemotherapy;
~~m~~more preferably wherein the chemotherapy comprises one or more agents chosen from mylotarg, cladribine, idarubicin, and cytarabine.

10. The use of claim 9, wherein the chemotherapy comprises cladribine, idarubicin, and cytarabine ("CLIA");

or- wherein the chemotherapy comprises mylotarg, cladribine, idarubicin, and cytarabine ("CLIA-M").

11. The use of any one of claims 1-9, wherein the anti-cancer therapy is an immunotherapy;
preferably wherein the immunotherapy is chosen from a monoclonal antibody and an immune checkpoint inhibitor;
or wherein the immunotherapy is chosen from rituximab, ofatumumab, or blinatumomab, inotuzumab, gemtuzumab ozogamicin, ipilumumab, and an immune checkpoint inhibitor targeting PD-1/PD-L1.

12. The use of claim 11, wherein the immune checkpoint inhibitor targeting PD-1/PD-L1 is chosen from nivolumab, pembrolizumab, atezolizumab, avelumab, and durvalumab.

13. The use of any one of claims 1-9, wherein the anti-cancer therapy is a targeted therapy;

preferably wherein the targeted therapy is chosen from a FLT3 inhibitor, a BCR-ABL tyrosine kinase inhibitor, a JAK-2 inhibitor, an IDH1 or IDH2 inhibitor, a BCL-2 inhibitor, and gemtuzumab ozogamicin.

14. The use of any one of claims 1-13, wherein the subject is a human; preferably wherein the human subject:
a) has a cancer; and
b) has elevated levels of one or more, or two or more, metals as compared to healthy subjects;
or wherein elevated levels of one or more metals are measured in the bone marrow and/or the serum.

15. The use of claim 14, wherein the metal(s) is/are chosen from chosen from arsenic (As), aluminum (Al), antimony (Sb), Barium (Ba), boron (B), cadmium (Cd), Cerium (Ce), Chromium (Cr), lead (Pb), mercury (Hg), neodymium (Nd), Nickel (Ni), tin (Sn), titanium (Ti), uranium (U), and vanadium (V);
or wherein the human subject has decreased levels of at least one of calcium (Ca), magnesium (Mg), selenium (Se), zinc (Zn) and rubidium (Rb);
preferably wherein the elevated and/or reduced levels are with respect to the median values in a non-diseased population.

16. The use of any one of claims 1-15, wherein the said use results in the reduction or clearance of one or more mutations or cytogenetic abnormalities in the cancer.

~~17. Use of one or more metal chelators and at least one antioxidant, vitamin, or essential mineral in the manufacture of a medicament for the reduction or clearance of one or more mutations or cytogenetic abnormalities in the cancer cells of a subject with cancer.~~

~~18. A method of diagnosing a subject with a chelation therapy responsive proliferative disease, comprising:~~

~~i) measuring the levels of two or more metals in one or more samples of the subject's serum or bone marrow;~~

~~ii) comparing the levels of each of the two or more metals in the sample(s) to each of two or more corresponding median reference values of the same metals obtained from healthy patients; and~~

~~iii) if the levels of the two or more metals in the sample(s) are higher than the median reference values, classifying the subject as having a chelation therapy responsive proliferative disease.~~

17~~19~~. Use of one or more broad spectrum metal chelators ~~and at least one of zinc, selenium, magnesium, rubidium and/or vitamin C~~ in the manufacture of a medicament for treating a chelation therapy-responsive proliferative disease in a subject;~~-~~ wherein said one or more broad-spectrum metal chelators is administered in combination with an anti-cancer therapy wherein said subject is diagnosed as having a chelation therapy-responsive proliferative disease according to the method comprising the steps of:

i) measuring the levels of two or more metals in one or more samples of the subject's serum or bone marrow;

ii) comparing the levels of each of the two or more metals in the sample(s) to each of two or more corresponding median reference values of the same metals obtained from healthy patients; and

iii) if the levels of the two or more metals in the sample(s) are higher than the median reference values, classifying the subject as having a chelation therapy - responsive proliferative disease.

~~of claim 18.~~

18~~20~~. A pharmaceutical composition or pharmaceutical combination comprising

(i) one or more broad-spectrum metal chelators;

(ii) ~~at least one antioxidant, vitamin, or essential mineral and/or (iii)~~ at least one anti-cancer pharmacologic therapy; and

(iii~~v~~) a pharmaceutically acceptable excipient.