What is claimed is:

1. A method for the treatment of a malignancy wherein the malignancy is characterized by resistance to at least one tyrosine kinase inhibitor (TKI) due to: (1) at least one mutation in a gene encoding a protein that is a target of at least one TKI; or (2) the presence of at least one additional gene in either a wild-type or mutated state encoding a product that confers resistance to the therapeutic effects of at least one TKI, the method comprising the administration of a therapeutically effective quantity of an alkylating hexitol derivative, wherein the additional gene in either a wild-type or mutated state encoding a product that confers resistance to the therapeutic effects of at least one TKI is *AHI-1*, and wherein the resistance to at least one TKI is due to a mutation in the kinase domain of ABL1 protein that is part of a BCR-ABL fusion protein that is a target of TKIs.

2. The method of claim 1 wherein the *AHI-1* gene is mutated as the result of a proviral insertion.

3. The method of claim 1 wherein the alkylating hexitol derivative is selected from the group consisting of dianhydrogalactitol, a derivative or analog of dianhydrogalactitol, diacetyldianhydrogalactitol, a derivative or analog of diacetyldianhydrogalactitol, dibromodulcitol, and a derivative or analog of dibromodulcitol.

4. The method of claim 3 wherein the alkylating hexitol derivative is selected from the group consisting of dianhydrogalactitol and a derivative or analog of dianhydrogalactitol.

5. The method of claim 4 wherein the alkylating hexitol derivative is dianhydrogalactitol.

6. The method of claim 3 wherein the alkylating hexitol derivative is selected from the group consisting of diacetyldianhydrogalactitol and a derivative or analog of diacetyldianhydrogalactitol.

7. The method of claim 6 wherein the alkylating hexitol derivative is diacetyldianhydrogalactitol.

8. The method of claim 3 wherein the alkylating hexitol derivative is selected from the group consisting of dibromodulcitol and a derivative or analog of dibromodulcitol.

9. The method of claim 8 wherein the alkylating hexitol derivative is dibromodulcitol.

10. The method of claim 1 further comprising the step of administering a therapeutically effective quantity of a BH3 mimetic to the subject.

11. The method of claim 10 wherein the BH3 mimetic is selected from the group consisting of:

(a) peptides;
(b) modified peptides;
(c) terpyridine-based peptidomimetics;
(d) terephthalamide-based peptidomimetics;
(e) benzoylurea-based peptidomimetics;
(f) obatoclax;
(g) TW37;
(h) an analog or derivative of TW37;
(i) (-) gossypol;
(j) gossypol derivatives;
(k) isoxazolidine derivatives;
(l) A-385358;
(m) an analog or derivative of A-385358;
(n) ABT-737;
(o) an analog or derivative of ABT-737;
(p) ABT-263;
(q) an analog or derivative of ABT-263;
(r) TM-1206; and
(s) an analog or derivative of TM-1206.

12. The method of claim 10 wherein the BH3 mimetic is a BH3 mimetic in which binding occurs between a hydrophobic groove on a binding partner for BH3 and the BH3 mimetic.

13. The method of claim 10 wherein the BH3 mimetic is a BH3 mimetic that adopts a helical structure or a structure seen by a binding partner as equivalent to a helical structure on binding to a hydrophobic groove located on a binding partner.

14. The method of claim 10 wherein the BH3 mimetic is a BH3 mimetic possessing hydrophobic amino acid residues with a spacing of i, i +3, i + 7, and i + 11 that interact at four hydrophobic pockets on a binding partner for BH3.

15. The method of claim 1 further comprising the step of administering a therapeutically effective quantity of a tyrosine kinase inhibitor to the subject.

16. The method of claim 15 further comprising the step of administering a therapeutically effective quantity of a BH3 mimetic to the subject.

17. The method of claim 1 further comprising the step of administering a therapeutically effective quantity of a JAK2 inhibitor to the subject.

18. The method of claim 17 further comprising the step of administering a therapeutically effective quantity of a tyrosine kinase inhibitor to the subject.

19. The method of claim 17 further comprising the step of administering a therapeutically effective quantity of a BH3 mimetic to the subject.

20. The method of claim 1 further comprising the step of administering a therapeutically effective quantity of a STAT5 inhibitor to the subject.

21. The method of claim 20 further comprising the step of administering a therapeutically effective quantity of a tyrosine kinase inhibitor to the subject.

22. The method of claim 20 further comprising the step of administering a therapeutically effective quantity of a BH3 mimetic to the subject.

23. The method of claim 1 further comprising the step of administering a therapeutically effective quantity of an Src kinase inhibitor to the subject.

24. The method of claim 23 further comprising the step of administering a therapeutically effective quantity of a tyrosine kinase inhibitor to the subject.

25. The method of claim 23 further comprising the step of administering a therapeutically effective quantity of a BH3 mimetic to the subject.

26. The method of claim 1 further comprising the step of administering a therapeutically effective quantity of a combination of kinase inhibitors to the subject to treat the malignancy; wherein the combination of kinase inhibitors is

a combination selected from the group consisting of: (1) a JAK2 inhibitor and a STAT5 inhibitor; (2) a JAK2 inhibitor and a Src inhibitor; (3) a STAT5 inhibitor and a Src inhibitor; and (4) a JAK2 inhibitor, a STAT5 inhibitor, and a Src inhibitor to the subject.

27. The method of claim 26 further comprising the step of administering a therapeutically effective quantity of a tyrosine kinase inhibitor to the subject.

28. The method of claim 26 further comprising the step of administering a therapeutically effective quantity of a BH3 mimetic to the subject.

29. A method for the treatment of a malignancy in a subject suffering from a malignancy who has a germline deletion polymorphism conferring resistance to thymidine kinase inhibitors (TKIs) comprising the step of administering a therapeutically effective quantity of a therapeutic agent selected from the group consisting of dianhydrogalactitol, a derivative or analog of dianhydrogalactitol, diacetyldianhydrogalactitol, a derivative or analog of diacetyldianhydrogalactitol, dibromodulcitol, and a derivative or analog of dibromodulcitol to the subject to treat the malignancy.

30. The method of claim 29 wherein the malignancy is chronic myelogenous leukemia (CML).

31. The method of claim 29 wherein the malignancy is non small cell lung carcinoma (NSCLC).

32. The method of claim 29 wherein the malignancy is triple-negative breast cancer.

33. The method of claim 29 wherein the therapeutic agent is selected from the group consisting of dianhydrogalactitol and a derivative or analog of dianhydrogalactitol.

34. The method of claim 33 wherein the therapeutic agent is dianhydrogalactitol.

35. The method of claim 33 wherein the therapeutic agent is a derivative or analog of dianhydrogalactitol.

36. The method of claim 35 wherein the derivative or analog of dianhydrogalactitol is a derivative of dianhydrogalactitol that is selected from the group consisting of: (i) a derivative of dianhydrogalactitol that has one or both of the

hydrogens of the two hydroxyl groups of dianhydrogalactitol replaced with lower alkyl; (ii) a derivative of dianhydrogalactitol that has one or more of the hydrogens attached to the two epoxide rings replaced with lower alkyl; (iii) a derivative of dianhydrogalactitol that has one or both of the methyl groups present in dianhydrogalactitol and that are attached to the same carbons that bear the hydroxyl groups replaced with C_2-C_6 lower alkyl; and (iv) a derivative of dianhydrogalactitol that has one or both of the methyl groups present in dianhydrogalactitol and that are attached to the same carbons that bear the hydroxyl groups substituted with a halo group by replacing a hydrogen of the methyl group with a halo group.

37. The method of claim 29 wherein the therapeutic agent is selected from the group consisting of diacetyldianhydrogalactitol and a derivative or analog of diacetyldianhydrogalactitol.

38. The method of claim 37 wherein the therapeutic agent is diacetyldianhydrogalactitol.

39. The method of claim 37 wherein the therapeutic agent is a derivative or analog of diacetyldianhydrogalactitol.

40. The method of claim 39 wherein the derivative or analog of diacetyldianhydrogalactitol is a derivative of diacetyldianhydrogalactitol that is selected from the group consisting of: (i) a derivative of diacetyldianhydrogalactitol that has one or both of the methyl groups that are part of the acetyl moieties replaced with C_2-C_6 lower alkyl; (ii) a derivative of diacetyldianhydrogalactitol that has one or both of the hydrogens attached to the epoxide ring replaced with lower alkyl; (iii) a derivative of diacetyldianhydrogalactitol that has one or both of the methyl groups attached to the same carbons that bear the acetyl groups replaced with C_2-C_6 lower alkyl; and (iv) a derivative of diacetyldianhydrogalactitol that has one or both of the methyl groups that are attached to the same carbons that bear the hydroxyl groups substituted with a halo group by replacing a hydrogen of the methyl group with a halo group.

41. The method of claim 29 wherein the therapeutic agent is selected from the group consisting of dibromodulcitol and a derivative or analog of dibromodulcitol.

42. The method of claim 41 wherein the therapeutic agent is dibromodulcitol.

43. The method of claim 41 wherein the therapeutic agent is a derivative or analog of dibromodulcitol.

44. The method of claim 43 wherein the derivative or analog of dibromodulcitol is a derivative of dibromodulcitol that is selected from the group consisting of: (i) a derivative of dibromodulcitol that has one or more of the hydrogens replaced with lower alkyl; and (ii) a derivative of dibromodulcitol that has one or both of the bromo groups replaced with another halo group selected from the group consisting of chloro, fluoro, and iodo.

45. The method of claim 29 further including a step of confirming whether a particular subject suffering from a malignancy has a germline deletion polymorphism conferring resistance to TKIs.

46. The method of claim 45 wherein the step of confirming whether a particular subject suffering from a malignancy has a germline deletion polymorphism conferring resistance to TKIs is performed by DNA-paired end tag (DNA-PET) analysis.

47. The method of claim 29 wherein the germline DNA deletion polymorphism is a germline DNA deletion polymorphism of 2903 bp located in the *BIM* gene.

48. The method of claim 47 wherein the germline DNA deletion polymorphism causes a splicing variation that leads to expression of an isoform of BIM protein that lacks a BH3 domain and thus inhibits the induction of apoptosis.

49. The method of claim 29 further comprising the step of administering a therapeutically effective quantity of a BH3 mimetic to the subject.

50. The method of claim 49 wherein the BH3 mimetic is selected from the group consisting of:

(a) peptides;
(b) modified peptides;
(c) terpyridine-based peptidomimetics;
(d) terephthalamide-based peptidomimetics;
(e) benzoylurea-based peptidomimetics;
(f) obatoclax;
(g) TW37;
(h) an analog or derivative of TW37;

(i) (-) gossypol;

(j) gossypol derivatives;

(k) isoxazolidine derivatives;

(l) A-385358;

(m) an analog or derivative of A-385358;

(n) ABT-737;

(o) an analog or derivative of ABT-737;

(p) ABT-263;

(q) an analog or derivative of ABT-263;

(r) TM-1206; and

(s) an analog or derivative of TM-1206.

51. The method of claim 49 wherein the BH3 mimetic is a BH3 mimetic in which binding occurs between a hydrophobic groove on a binding partner for BH3 and the BH3 mimetic.

52. The method of claim 49 wherein the BH3 mimetic is a BH3 mimetic that adopts a helical structure or a structure seen by a binding partner as equivalent to a helical structure on binding to a hydrophobic groove located on a binding partner.

53. The method of claim 49 wherein the BH3 mimetic is a BH3 mimetic possessing hydrophobic amino acid residues with a spacing of i, i +3, i + 7, and i + 11 that interact at four hydrophobic pockets on a binding partner for BH3.

54. The method of claim 50 wherein the BH3 mimetic is a peptide.

55. The method of claim 50 wherein the BH3 mimetic is a modified peptide.

56. The method of claim 55 wherein the modified peptide is a stapled BID BH3 helix.

57. The method of claim 50 wherein the BH3 mimetic is a terpyridine-based peptidomimetic.

58. The method of claim 50 wherein the BH3 mimetic is a terephthalamide-based peptidomimetic.

59. The method of claim 50 wherein the BH3 mimetic is a benzoylurea-based peptidomimetic.

60. The method of claim 50 wherein the BH3 mimetic is obatoclax.

61. The method of claim 50 wherein the BH3 mimetic is TW-37.

62. The method of claim 50 wherein the BH3 mimetic is an analog or derivative of TW-37.

63. The method of claim 50 wherein the BH3 mimetic is (-) gossypol.

64. The method of claim 50 wherein the BH3 mimetic is a gossypol derivative.

65. The method of claim 50 wherein the BH3 mimetic is A-385358.

66. The method of claim 50 wherein the BH3 mimetic is an analog or derivative of A-385358.

67. The method of claim 50 wherein the BH3 mimetic is ABT-737.

68. The method of claim 50 wherein the BH3 mimetic is an analog or derivative of ABT-737.

69. The method of claim 50 wherein the BH3 mimetic is ABT-263.

70. The method of claim 50 wherein the BH3 mimetic is an analog or derivative of ABT-737.

71. The method of claim 50 wherein the BH3 mimetic is TM-1206.

72. The method of claim 50 wherein the BH3 mimetic is an analog or derivative of TM-1206.

73. The method of claim 49 wherein the method further comprises administering a therapeutically effective quantity of a tyrosine kinase inhibitor to the subject.

74. The method of claim 73 wherein the tyrosine kinase inhibitor is selected from the group consisting of imatinib, bosutinib, nilotinib, and dasatinib.

75. The method of claim 74 wherein the tyrosine kinase inhibitor is imatinib.

76. The method of claim 74 wherein the tyrosine kinase inhibitor is selected from the group consisting of erlotinib, afatinib, and dacomitinib.

77. The method of claim 49 wherein the method further comprises administering a therapeutically effective quantity of a JAK2 inhibitor to the subject.

78. The method of claim 77 wherein the JAK2 inhibitor is selected from the group consisting of (E)-N-benzyl-2-cyano-3-(3,4-dihydroxyphenyl)acrylamide (AG490), ruxolitinib, tofacitinib, tofacitinib citrate, N-tert-

butyl-3-(5-methyl-2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenylamino)pyrimidin-4-ylamino)benzenesulfonamide (TG-101348), (S)-5-chloro-N2-(1-(5-fluoropyrimidin-2-yl)ethyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (AZD1480), N-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide (CYT387), baricitinib, (S,E)-3-(6-bromopyridin-2-yl)-2-cyano-N-(1-phenylethyl)acrylamide (WP1066), S-ruxolitinib, N-tert-butyl-3-(5-methyl-2-(4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)benzenesulfonamide (TG101209), N-[3-(4-methyl-1-piperazinyl)phenyl]-8-[4-(methylsulfonyl)phenyl]-[1,2,4]triazolo[1,5-a]pyridin-2-amine (CEP33779), 8-(3,5-difluoro-4-(morpholinomethyl)phenyl)-2-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)quinoxaline (NVP-BSK805), (S)-5-fluoro-2-(1-(4-fluorophenyl)ethylamino)-6-(5-methyl-1H-pyrazol-3-ylamino)nicotinonitrile (AZ 960), 3-(4-chloro-2-fluorobenzyl)-2-methyl-N-(3-methyl-1H-pyrazol-5-yl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine (LY2784544), 1-cyclopropyl-3-(3-(5-(morpholinomethyl)-1H-benzo[d]imidazol-2-yl)-1H-pyrazol-4-yl)urea (AT9283), pacritinib (SB1518), (S)-N-(4-(2-((4-morpholinophenyl)amino)pyrimidin-4-yl)phenyl)pyrrolidine-2-carboxamide (XL019), and N-tert-butyl-3-(5-methyl-2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenylamino)pyrimidin-4-ylamino)benzenesulfonamide (TG101348).

79. The method of claim 49 wherein the method further comprises the step of administering a therapeutically effective quantity of a STAT5 inhibitor to the subject.

80. The method of claim 79 wherein the STAT5 inhibitor is selected from the group consisting of N'-((4-oxo-4H-chromen-3-yl)methylene)nicotinohydrazide and pimozide.

81. The method of claim 49 wherein the method further comprises the step of administering a therapeutically effective quantity of a Src inhibitor to the subject.

82. The method of claim 81 wherein the Src inhibitor is selected from the group consisting of dasatinib, saracatinib, bosutinib, N-benzyl-2-(5-(4-(2-morpholinoethoxy)phenyl)pyridin-2-yl)acetamide (KX2-391), CGP76030, and 4-methyl-3-(1-methyl-6-(pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino)-N-(3-(trifluoromethyl)phenyl)benzamide (NVP-BHG712).

83. The method of claim 49 wherein the method further comprises the step of administering a therapeutically effective quantity of a combination of kinase inhibitors to the subject, 1) a JAK2 inhibitor and a STAT5 inhibitor; (2) a JAK2 inhibitor and a Src inhibitor; (3) a STAT5 inhibitor and a Src inhibitor; and (4) a JAK2 inhibitor, a STAT5 inhibitor, and a Src inhibitor.

84. A method for combining screening for a germline deletion polymorphism conferring resistance to TKI therapy, and, if the germline deletion polymorphism is found to exist, treatment of a malignancy resistant to TKIs in a subject comprising the steps of:

(a) screening for the germline deletion polymorphism in a subject with a malignancy; and

(b) if the germline deletion polymorphism is found to exist in the subject with the malignancy, administering a therapeutically effective quantity of a therapeutic agent selected from the group consisting of dianhydrogalactitol, a derivative or analog of dianhydrogalactitol, diacetyldianhydrogalactitol, a derivative or analog of diacetyldianhydrogalactitol, dibromodulcitol, and a derivative or analog of dibromodulcitol to the subject to treat the malignancy.

85. The method of claim 84 wherein the germline deletion polymorphism conferring resistance to TKI therapy is a deletion of 2903 bp located in the *BIM* gene.

86. The method of claim 84 wherein the germline DNA deletion polymorphism causes a splicing variation that leads to expression of an isoform of BIM protein that lacks a BH3 domain and thus inhibits the induction of apoptosis.

87. The method of claim 84 wherein the step of screening for the germline deletion polymorphism in a subject with a malignancy is performed by DNA-paired end tag (DNA-PET) analysis.

88. The method of claim 84 wherein the malignancy is chronic myelogenous leukemia (CML).

89. The method of claim 84 wherein the malignancy is non small cell lung carcinoma (NSCLC).

90. The method of claim 84 wherein the malignancy is triple-negative breast cancer.

91. The method of claim 84 wherein the therapeutic agent is selected from the group consisting of dianhydrogalactitol and a derivative or analog of dianhydrogalactitol.

92. The method of claim 91 wherein the therapeutic agent is dianhydrogalactitol.

93. The method of claim 84 wherein the therapeutic agent is selected from the group consisting of diacetyldianhydrogalactitol and a derivative or analog of diacetyldianhydrogalactitol.

94. The method of claim 93 wherein the therapeutic agent is diacetyldianhydrogalactitol.

95. The method of claim 84 wherein the therapeutic agent is selected from the group consisting of dibromodulcitol and a derivative or analog of dibromodulcitol.

96. The method of claim 95 wherein the therapeutic agent is dibromodulcitol.

97. The method of claim 84 further comprising the step of administering a therapeutically effective quantity of a BH3 mimetic to the subject.

98. The method of claim 97 wherein the BH3 mimetic is selected from the group consisting of:

(a) peptides;
(b) modified peptides;
(c) terpyridine-based peptidomimetics;
(d) terephthalamide-based peptidomimetics;
(e) benzoylurea-based peptidomimetics;
(f) obatoclax;
(g) TW37;
(h) an analog or derivative of TW37;
(i) (-) gossypol;
(j) gossypol derivatives;
(k) isoxazolidine derivatives;
(l) A-385358;
(m) an analog or derivative of A-385358;
(n) ABT-737;

(o) an analog or derivative of ABT-737;

(p) ABT-263;

(q) an analog or derivative of ABT-263

(r) TM-1206; and

(s) an analog or derivative of TM-1206.

99. The method of claim 97 wherein the BH3 mimetic is a BH3 mimetic in which binding occurs between a hydrophobic groove on a binding partner for BH3 and the BH3 mimetic.

100. The method of claim 97 wherein the BH3 mimetic is a BH3 mimetic that adopts a helical structure or a structure seen by a binding partner as equivalent to a helical structure on binding to a hydrophobic groove located on a binding partner.

101. The method of claim 97 wherein the BH3 mimetic is a BH3 mimetic possessing hydrophobic amino acid residues with a spacing of i, i +3, i + 7, and i + 11 that interact at four hydrophobic pockets on a binding partner for BH3.

102. The method of claim 98 wherein the BH3 mimetic is ABT-737.

103. The method of claim 84 wherein the method further comprises administering a therapeutically effective quantity of a tyrosine kinase inhibitor to the subject.

104. The method of claim 103 wherein the tyrosine kinase inhibitor is selected from the group consisting of imatinib, bosutinib, nilotinib, and dasatinib.

105. The method of claim 104 wherein the tyrosine kinase inhibitor is imatinib.

106. The method of claim 103 wherein the tyrosine kinase inhibitor is selected from the group consisting of erlotinib, afatinib, and dacomitinib.

107. A method for the treatment of a malignancy in a subject suffering from a malignancy associated with a mutation in or a dysregulation of the *AHI1* gene comprising the step of administering a therapeutically effective quantity of a therapeutic agent selected from the group consisting of dianhydrogalactitol, a derivative or analog of dianhydrogalactitol, diacetyldianhydrogalactitol, a derivative or analog of diacetyldianhydrogalactitol, dibromodulcitol, and a derivative or analog of dibromodulcitol to the subject to treat the malignancy.

108. The method of claim 107 wherein the malignancy is chronic myelocytic leukemia.

109. The method of claim 107 wherein the therapeutic agent is selected from the group consisting of dianhydrogalactitol and a derivative or analog of dianhydrogalactitol.

110. The method of claim 109 wherein the therapeutic agent is dianhydrogalactitol.

111. The method of claim 109 wherein the therapeutic agent is a derivative or analog of dianhydrogalactitol.

112. The method of claim 111 wherein the derivative or analog of dianhydrogalactitol is a derivative of dianhydrogalactitol that is selected from the group consisting of: (i) a derivative of dianhydrogalactitol that has one or both of the hydrogens of the two hydroxyl groups of dianhydrogalactitol replaced with lower alkyl; (ii) a derivative of dianhydrogalactitol that has one or more of the hydrogens attached to the two epoxide rings replaced with lower alkyl; (iii) a derivative of dianhydrogalactitol that has one or both of the methyl groups present in dianhydrogalactitol and that are attached to the same carbons that bear the hydroxyl groups replaced with C_2-C_6 lower alkyl; and (iv) a derivative of dianhydrogalactitol that has one or both of the methyl groups present in dianhydrogalactitol and that are attached to the same carbons that bear the hydroxyl groups substituted with a halo group by replacing a hydrogen of the methyl group with a halo group.

113. The method of claim 107 wherein the therapeutic agent is selected from the group consisting of diacetyldianhydrogalactitol and a derivative or analog of diacetyldianhydrogalactitol.

114. The method of claim 113 wherein the therapeutic agent is diacetyldianhydrogalactitol.

115. The method of claim 113 wherein the therapeutic agent is a derivative or analog of diacetyldianhydrogalactitol.

116. The method of claim 115 wherein the derivative or analog of diacetyldianhydrogalactitol is a derivative of diacetyldianhydrogalactitol that is selected from the group consisting of: (i) a derivative of diacetyldianhydrogalactitol that has one or both of the methyl groups that are part of the acetyl moieties replaced with C_2-C_6 lower alkyl; (ii) a derivative of diacetyldianhydrogalactitol that

has one or both of the hydrogens attached to the epoxide ring replaced with lower alkyl; (iii) a derivative of diacetyldianhydrogalactitol that has one or both of the methyl groups attached to the same carbons that bear the acetyl groups replaced with C_2-C_6 lower alkyl; and (iv) a derivative of diacetyldianhydrogalactitol that has one or both of the methyl groups that are attached to the same carbons that bear the hydroxyl groups substituted with a halo group by replacing a hydrogen of the methyl group with a halo group..

117. The method of claim 107 wherein the therapeutic agent is selected from the group consisting of dibromodulcitol and a derivative or analog of dibromodulcitol.

118. The method of claim 117 wherein the therapeutic agent is dibromodulcitol.

119. The method of claim 117 wherein the therapeutic agent is a derivative or analog of dibromodulcitol.

120. The method of claim 119 wherein the derivative or analog of dibromodulcitol is a derivative of dibromodulcitol that is selected from the group consisting of: (i) a derivative of dibromodulcitol that has one or more of the hydrogens replaced with lower alkyl; and (ii) a derivative of dibromodulcitol that has one or both of the bromo groups replaced with another halo group selected from the group consisting of chloro, fluoro, and iodo.

121. The method of claim 107 further comprising the administration of a therapeutically effective quantity of an agent that modulates the expression or activity of either the *AHI1* gene or the AHI1 protein.

122. The method of claim 121 wherein the agent that modulates the expression or activity of either the *AHI1* gene or the AHI1 protein is an agent that modulates the expression of the *AHI1* gene.

123. The method of claim 122 wherein the agent that modulates the expression of the *AHI1* gene modulates the expression of the *AHI1* gene at the level of transcription.

124. The method of claim 122 wherein the agent that modulates the expression of the *AHI1* gene modulates the expression of the *AHI1* gene at the level of translation.

125. The method of claim 123 wherein the agent that modulates the expression of the *AHI1* gene at the level of transcription is selected from the group consisting of short interfering RNA (siRNA), microRNA (miRNA), and synthetic hairpin RNA (shRNA), antisense nucleic acids, and complementary DNA (cDNA).

126. The method of claim 125 wherein the agent that modulates the expression of the *AHI1* gene at the level of transcription is siRNA.

127. The method of claim 121 wherein the agent that modulates the expression or activity of either the *AHI1* gene or the AHI1 protein is an agent that inhibits the activity of the AHI1 protein.

128. The method of claim 127 wherein the agent that inhibits the activity of the AHI1 protein is an antibody that specifically binds the AHI1 protein.

129. The method of claim 127 wherein the agent that inhibits the activity of the AHI1 protein is an antibody that specifically binds a receptor for the AHI1 protein.

130. The method of claim 127 wherein the agent that inhibits the activity of the AHI1 protein is an antagonist of a receptor that specifically binds the AHI1 protein.

131. The method of claim 127 wherein the agent that modulates the expression or activity of either the *AHI1* gene or the AHI1 protein is an agent that inhibits a transcription factor that has a binding site in the *AHI1* gene promoter.

132. The method of claim 131 wherein the transcription factor that has a binding site in the *AHI1* gene promoter is selected from the group consisting of RFX1, POU2F1, POU2F1a, Nkx2-5, Evi-1, and RSRFC4.

133. A method to improve the efficacy and/or reduce the side effects of the administration of an alkylating hexitol derivative for treatment of a malignancy selected from a TKI-resistant malignancy and a malignancy associated with mutation or dysregulation of the *AHI1* gene comprising the steps of:

(a) identifying at least one factor or parameter associated with the efficacy and/or occurrence of side effects of the administration of an alkylating hexitol derivative for treatment of a TKI-resistant malignancy or for treatment of a malignancy associated with a mutation in or dysregulation of the *AHI1* gene; and

(b) modifying the factor or parameter to improve the efficacy and/or reduce the side effects of the administration of the alkylating hexitol derivative for

treatment of the TKI-resistant malignancy or the malignancy associated with a mutation in or dysregulation of the *AHI1* gene.

134. The method of claim 133 wherein the malignancy is a TKI-resistant malignancy and wherein the resistance to TKI is due to: (1) at least one mutation in a gene encoding a protein that is a target of at least one TKI; or (2) the presence of at least one additional gene in either a wild-type or mutated state encoding a product that confers resistance to the therapeutic effects of at least one TKI, wherein the additional gene in either a wild-type or mutated state encoding a product that confers resistance to the therapeutic effects of at least one TKI is *AHI-1*, and wherein the resistance to at least one TKI is due to a mutation in the kinase domain of ABL1 protein that is part of a BCR-ABL fusion protein that is a target of TKIs.

135. The method of claim 133 wherein the malignancy is a malignancy associated with a mutation or dysregulation of the *AHI1* gene.

136. The method of claim 135 wherein the factor or parameter is selected from the group consisting of:

(1) dose modification;
(2) route of administration;
(3) schedule of administration;
(4) indications for use;
(5) selection of disease stage;
(6) other indications;
(7) patient selection;
(8) patient/disease phenotype;
(9) patient/disease genotype;
(10) pre/post-treatment preparation
(11) toxicity management;
(12) pharmacokinetic/pharmacodynamic monitoring;
(13) drug combinations;
(14) chemosensitization;
(15) chemopotentiation;
(16) post-treatment patient management;
(17) alternative medicine/therapeutic support;

(18) bulk drug product improvements;

(19) diluent systems;

(20) solvent systems;

(21) excipients;

(22) dosage forms;

(23) dosage kits and packaging;

(24) drug delivery systems;

(25) drug conjugate forms;

(26) compound analogs;

(27) prodrugs;

(28) multiple drug systems;

(29) biotherapeutic enhancement;

(30) biotherapeutic resistance modulation;

(31) radiation therapy enhancement;

(32) novel mechanisms of action;

(33) selective target cell population therapeutics; and

(34) use with an agent enhancing its activity.

137. The method of claim 136 wherein the improvement is made by dose modification and the dose modification is at least one dose modification selected from the group consisting of:

(a) continuous i.v. infusion for hours to days;

(b) biweekly administration;

(c) doses greater than 5 mg/m^2/day;

(d) progressive escalation of dosing from 1 mg/m^2/day based on patient tolerance;

(e) use of caffeine to modulate metabolism;

(f) use of isonazid to modulate metabolism;

(g) selected and intermittent boosting of dosage administration;

(h) administration of single and multiple doses escalating from 5mg/m^2/day via bolus;

(i) oral dosages of below 30 mg/m^2;

(j) oral dosages of above 130 mg/m^2;

(k) oral dosages up to 40 mg/m^2 for 3 days and then a nadir/recovery period of 18-21 days;

(l) dosing at a lower level for an extended period (e.g., 21 days);

(m) dosing at a higher level;

(n) dosing with a nadir/recovery period longer than 21 days;

(o) the use of an alkylating hexitol derivative as a single cytotoxic agent;

(p) immediate release dosing;

(q) slow release dosing; and

(r) controlled release dosing.

138. The method of claim 136 wherein the improvement is made by route of administration and the route of administration is at least one route of administration selected from the group consisting of:

(a) topical administration;

(b) oral administration;

(c) slow release oral delivery;

(d) intrathecal administration;

(e) intraarterial administration;

(f) continuous infusion;

(g) intermittent infusion;

(h) intravenous administration, such as intravenous administration for 30 minutes;

(i) administration through a longer infusion;

(j) administration through IV push; and

(k) intraperitoneal administration.

139. The method of claim 136 wherein the improvement is made by schedule of administration and the schedule of administration is at least one schedule of administration selected from the group consisting of:

(a) daily administration;

(b) weekly administration;

(c) weekly administration for three weeks;

(d) biweekly administration;

(e) biweekly administration for three weeks with a 1-2 week rest period;

(f) intermittent boost dose administration; and

(g) daily administration for one week for multiple weeks.

140. The method of claim 136 wherein the improvement is made by selection of disease stage and the selection of disease stage is at least one selection of disease stage selected from the group consisting of:

(a) use in an appropriate disease stage for a TKI-resistant malignancy;

(b) use for newly diagnosed disease;

(c) use for recurrent disease;

(d) use for resistant or refractory disease;

(e) use for treatment of an *AHI1*-associated malignancy;

(f) use for treatment of triple-negative breast cancer; and

(g) use for treatment of metastatic disease.

141. The method of claim 136 wherein the improvement is made by patient selection and the patient selection is a patient selection carried out by a criterion selected from the group consisting of:

(a) selecting patients with a disease condition characterized by a high level of a metabolic enzyme selected from the group consisting of histone deacetylase and ornithine decarboxylase;

(b) selecting patients with a low or high susceptibility to a condition selected from the group consisting of thrombocytopenia and neutropenia;

(c) selecting patients intolerant of GI toxicities;

(d) selecting patients characterized by over- or under-expression of a gene selected from the group consisting of c-Jun, a GPCR, a signal transduction protein, VEGF, a prostate-specific gene, and a protein kinase;

(e) selecting patients based on the *BIM* co-deletion; and

(f) selecting patients based on a mutation in or dysregulation of *AHI1*.

142. The method of claim 136 wherein the improvement is made by analysis of patient or disease phenotype and the analysis of patient or disease phenotype is carried out by a method selected from the group consisting of:

(a) use of a diagnostic tool, a diagnostic technique, a diagnostic kit, or a diagnostic assay to confirm a patient's particular phenotype;

(b) use of a method for measurement of a marker selected from the group consisting of histone deacetylase, ornithine decarboxylase, VEGF, a protein that is a gene product of a prostate specific gene, a protein that is a gene product of jun, a protein kinase, desmoglein-3, and a caspase-derived neo-epitope;

(c) surrogate compound dosing; and

(d) low dose pre-testing for enzymatic status.

143. The method of claim 136 wherein the improvement is made by analysis of patient or disease genotype and the analysis of patient or disease genotype is carried out by a method selected from the group consisting of:

(a) use of a diagnostic tool, a diagnostic technique, a diagnostic kit, or a diagnostic assay to confirm a patient's particular genotype;

(b) use of a gene chip;

(c) use of gene expression analysis;

(d) use of single nucleotide polymorphism (SNP) analysis; and

(e) measurement of the level of a metabolite or a metabolic enzyme.

144. The method of claim 136 wherein the improvement is made by pre/post-treatment preparation and the pre/post-treatment preparation is a method of pre/post treatment preparation selected from the group consisting of:

(a) the use of colchicine or an analog thereof;

(b) the use of a uricosuric;

(c) the use of uricase;

(d) the non-oral use of nicotinamide;

(e) the use of a sustained-release form of nicotinamide;

(f) the use of an inhibitor of poly-ADP ribose polymerase;

(g) the use of caffeine;

(h) the use of leucovorin rescue;

(i) infection control; and

(j) the use of an anti-hypertensive agent.

145. The method of claim 136 wherein the improvement is made by toxicity management and the toxicity management is a method of toxicity management selected from the group consisting of:

(a) the use of colchicine or an analog thereof;

(b) the use of a uricosuric;

(c) the use of uricase;

(d) the non-oral use of nicotinamide;

(e) the use of a sustained-release form of nicotinamide;

(f) the use of an inhibitor of poly-ADP ribose polymerase;

(g) the use of caffeine;

(h) the use of leucovorin rescue;

(i) the use of sustained-release allopurinol;

(j) the non-oral use of allopurinol;

(k) the use of bone marrow transplants;

(l) the use of a blood cell stimulant;

(m) the use of blood or platelet infusions;

(n) the administration of an agent selected from the group consisting of filgrastim (Neupogen®), G-CSF, and GM-CSF;

(o) the application of a pain management technique;

(p) the administration of an anti-inflammatory agent;

(q) the administration of fluids;

(r) the administration of a corticosteroid;

(s) the administration of an insulin control medication;

(t) the administration of an antipyretic;

(u) the administration of an anti-nausea treatment;

(v) the administration of an anti-diarrheal treatment;

(w) the administration of N-acetylcysteine;

(x) the administration of an antihistamine; and

(y) the administration of agents for reduction of gastric toxicity.

146. The method of claim 136 wherein the improvement is made by pharmacokinetic/pharmacodynamic monitoring and the

pharmacokinetic/pharmacodynamic monitoring is a method selected from the group consisting of:

(a) multiple determinations of blood plasma levels; and

(b) multiple determinations of at least one metabolite in blood or urine.

147. The method of claim 136 wherein the improvement is made by drug combination and the drug combination is a drug combination selected from the group consisting of:

(c) use with thymidylate synthetase inhibitors;

(d) use with signal transduction inhibitors;

(e) use with cisplatin or platinum analogs;

(f) use with alkylating agents;

(g) use with anti-tubulin agents;

(h) use with antimetabolites;

(i) use with berberine;

(j) use with apigenin;

(k) use with colchicine or an analog thereof;

(l) use with genistein;

(m) use with etoposide;

(n) use with cytarabine;

(o) use with camptothecins;

(p) use with vinca alkaloids;

(q) use with topoisomerase inhibitors;

(r) use with 5-fluorouracil;

(s) use with curcumin;

(t) use with NF-κB inhibitors;

(u) use with rosmarinic acid;

(v) use with mitoguazone;

(w) use with meisoindigo;

(x) use with imatinib;

(y) use with dasatinib;

(z) use with nilotinib;

(aa) use with epigenetic modulators;

(ab) use with transcription factor inhibitors;

(ac) use with taxol;

(ad) use with homoharringtonine;

(ae) use with pyridoxal;

(af) use with spirogermanium;

(ag) use with caffeine;

(ah) use with nicotinamide;

(ai) use with methylglyoxalbisguanylhydrazone;

(aj) use with Rho kinase inhibitors;

(ak) use with 1,2,4-benzotriazine oxides;

(al) use with an alkylglycerol;

(am) use with an inhibitor of a Mer, Ax1, or Tyro-3 receptor kinase;

(an) use with an inhibitor of ATR kinase;

(ao) use with a modulator of Fms kinase, Kit kinase, MAP4K4 kinase, TrkA kinase, or TrkB kinase;

(ap) use with endoxifen;

(aq) use with a mTOR inhibitor;

(ar) use with an inhibitor of Mnk1a kinase, Mkn1b kinase, Mnk2a kinase, or Mnk2b kinase;

(as) use with a modulator of pyruvate kinase M2;

(at) use with a modulator of phosphoinositide 3-kinases;

(au) use with a cysteine protease inhibitor;

(av) use with phenformin;

(aw) use with Sindbis virus-based vectors;

(ax) use with peptidomimetics that act as mimetics of Smac and inhibit IAPs to promote apoptosis;

(ay) use with a Raf kinase inhibitor;

(az) use with a nuclear transport modulator;

(ba) use with an acid ceramidase inhibitor and a choline kinase inhibitor;

(bb) use with tyrosine kinase inhibitors;

(bc) use with anti-CS1 antibodies;

(bd) use with inhibitors of protein kinase CK2;

(be) use with anti-guanylyl cyclase C (GCC) antibodies;

(bf) use with histone deacetylase inhibitors;

(bg) use with cannabinoids;

(bh) use with glucagon-like peptide-1 (GLP-1) receptor agonists;

(bi) use with inhibitors of Bcl-2 or Bcl-xL;

(bj) use with Stat3 pathway inhibitors;

(bk) use with inhibitors of polo-like kinase 1 (Plk1);

(bl) use with GBPAR1 activators;

(bm) use with modulators of serine-threonine protein kinase and poly(ADP-ribose) polymerase (PARP) activity;

(bn) use with taxanes;

(bo) use with inhibitors of dihydrofolate reductase;

(bp) use with inhibitors of aromatase;

(bq) use with benzimidazole-based anti-neoplastic agents;

(br) use with an O6-methylguanine-DNA-methyltransferase (MGMT) inhibitor;

(bs) use with CCR9 inhibitors;

(bt) use with acid sphingomyelinase inhibitors;

(bu) use with peptidomimetic macrocycles;

(bv) use with cholanic acid amides;

(bw) use with substituted oxazaphosphorines;

(bx) use with anti-TWEAK receptor antibodies;

(by) use with an ErbB3 binding protein;

(bz) use with a glutathione S-transferase-activated anti-neoplastic compound;

(ca) use with substituted phosphorodiamidates;

(cb) use with inhibitors of MEKK protein kinase;

(cd) use with COX-2 inhibitors;

(ce) use with cimetidine and a cysteine derivative;

(cf) use with anti-IL-6 receptor antibody;

(cg) use with an antioxidant;

(ch) use with an isoxazole inhibitor of tubulin polymerization;

(ci) use with PARP inhibitors;

(cj) use with Aurora protein kinase inhibitors;

(ck) use with peptides binding to prostate-specific membrane antigen;

(cl) use with CD19 binding agents;

(cm) use with benzodiazepines;

(cn) use with Toll-like receptor (TLR) agonists;

(co) use with bridged bicyclic sulfamides;

(cp) use with inhibitors of epidermal growth factor receptor kinase;

(cq) use with a ribonuclease of the T2 family having actin-binding activity;

(cr) use with myrsinoic acid A or an analog thereof;

(cs) use with inhibitors of a cyclin-dependent kinase;

(ct) use with inhibitors of the interaction between p53 and MDM2;

(cu) use with inhibitors of the receptor tyrosine kinase MET;

(cv) use with largazole or largazole analogs;

(cw) use with inhibitors of AKT protein kinase;

(cx) use with 2′-fluoro-5-methyl-β-L-arabinofuranosyluridine or L-deoxythymidine;

(cy) use with HSP90 modulators;

(cz) use with inhibitors of JAK kinases;

(da) use with inhibitors of PDK1 protein kinase;

(db) use with PDE4 inhibitors;

(de) use with inhibitors of proto-oncogene c-Met tyrosine kinase;

(df) use with inhibitors of indoleamine 2,3-dioxygenase;

(dg) use with agents that inhibit expression of ATDC (TRIM29);

(dh) use with proteomimetic inhibitors of the interaction of nuclear receptor with coactivator peptides;

(di) use with antagonists of XIAP family proteins;

(dj) use with tumor-targeted superantigens;

(dk) use with inhibitors of Pim kinases;

(dl) use with inhibitors of CHK1 or CHK2 kinases;

(dm) use with inhibitors of angiopoietin-like 4 protein;

(dn) use with Smo antagonists;

(do) use with nicotinic acetylcholine receptor antagonists;

(dp) use with farnesyl protein transferase inhibitors;

(dq) use with adenosine A3 receptor antagonists;

(dr) use with a cancer vaccine;

(ds) use with a JAK2 inhibitor; and

(dt) use with a Src inhibitor.

148. The method of claim 136 wherein the improvement is made by drug combination and the drug combination is a drug combination selected from the group consisting of:

(i) use with ACE inhibitors;

(ii) use with adenosine kinase inhibitors;

(iii) use with adrenal cortex antagonists;

(iv) use with AKT pathway inhibitors;

(v) use with angiogenesis inhibitors;

(vi) use with angiostatic steroids;

(vii) use with anti-androgens;

(viii) use with anti-estrogens;

(ix) use with anti-hypercalcemia agents;

(x) use with apoptosis inhibitors;

(xi) use with ATI receptor antagonists;

(xii) use with aurora kinase inhibitors;

(xiii) use with aromatase inhibitors;

(xiv) use with bisphosphonates;

(xv) use with Bruton's tyrosine kinase inhibitors;

(xvi) use with calcineurin inhibitors;

(xvii) use with CaM kinase II inhibitors;

(xviii) use with CD45 tyrosine phosphatase inhibitors;

(xix) use with CDC25 phosphatase inhibitors;

(xx) use with CHK kinase inhibitors;

(xxi) use with compounds targeting/decreasing a protein or lipid kinase activity;

(xxii) use with compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase;

(xxiii) use with compounds which induce cell differentiation processes;

(xxiv) use with cRAF kinase inhibitors;

(xxv) use with cyclin dependent kinase inhibitors;

(xxvi) use with cysteine protease inhibitors;

(xxvii) use with DNA intercalators;

(xxviii) use with DNA strand breakers;

(xxix) use with E3 ligase inhibitors;

(xxx) use with EDG binders;

(xxxi) use with endocrine hormones;

(xxxii) use with farnesyltransferase inhibitors;

(xxxiii) use with Flk-1 kinase inhibitors;

(xxxiv) use Flt-3 inhibitors;

(xxxv) use with gonadorelin agonists;

(xxxvi) heparanase inhibitors;

(xxxvii) use with histone deacetylase (HDAC) inhibitors;

(xxxviii) use with HSP90 inhibitors;

(xxxix) use with IκBα inhibitors;

(xl) use with insulin receptor tyrosine kinase inhibitors;

(xli) use with c-Jun N-terminal kinase inhibitors;

(xlii) use with microtubule binding agents;

(xliii) use with mitogen-activated protein (MAP) kinase inhibitors;

(xliv) use with MDM2 inhibitors;

(xlv) use with MEK inhibitors;

(xlvi) use with methionine aminopeptidase inhibitors;

(xlvii) use with MMP inhibitors;

(xlviii) use with NGFR tyrosine kinase inhibitors;

(xlix) use with p38 MAP kinase inhibitors;

(l) use with p56 tyrosine kinase inhibitors;

(li) use with PDGFR tyrosine kinase inhibitors;

(lii) use with phosphatidylinositol 3-kinase inhibitors;

(liii) use with phosphatase inhibitors;

(liv) use with platinum agents;

(lv) use with protein phosphatase inhibitors;

(lvi) use with PKC inhibitors;

(lvii) use with PKC delta kinase inhibitors;

(lviii) use with polyamine synthesis inhibitors;

(lix) use with proteasome inhibitors;

(lx) use with PTP1B inhibitors;

(lxi) use with protein tyrosine kinase inhibitors;

(lxii) use with SRC family tyrosine kinase inhibitors;

(lxiii) use with Syk tyrosine kinase inhibitors;

(lxiv) use with Janus (JAK-2 and/or JAK-3) tyrosine kinase inhibitors;

(lxv) use with inhibitors of Ras oncogenic isoforms;

(lxvi) use with retinoids;

(lxvii) use with ribonucleotide reductase inhibitors;

(lxviii) use with RNA polymerase II elongation inhibitors;

(lxix) use with S-adenosylmethionine decarboxylase inhibitors;

(lxx) use with serine/threonine kinase inhibitors;

(lxxi) use with compounds which target, decrease, or inhibit the activity or function of serine/threonine mTOR kinase;

(lxxii) use with somatostatin receptor antagonists;

(lxxiii) use with telomerase inhibitors;

(lxxiv) use with topoisomerase inhibitors;

(lxxv) use with VEGFR tyrosine kinase inhibitors; and

(lxxvi) use with RANKL inhibitors.

149. The method of claim 136 wherein the improvement is made by chemosensitization and the chemosensitization comprises the use of an alkylating hexitol derivative as a chemosensitizer in combination with an agent selected from the group consisting of:

(a) topoisomerase inhibitors;
(b) fraudulent nucleosides;
(c) fraudulent nucleotides;
(d) thymidylate synthetase inhibitors;
(e) signal transduction inhibitors;
(f) cisplatin or platinum analogs;
(g) alkylating agents;
(h) anti-tubulin agents;
(i) antimetabolites;
(j) berberine;
(k) apigenin;
(l) colchicine or an analog of colchicine;
(m) genistein;
(n) etoposide;
(o) cytarabine;
(p) camptothecin;
(q) vinca alkaloids;
(r) 5-fluorouracil;
(s) curcumin;
(t) NF-κB inhibitors;
(u) rosmarinic acid; and
(v) mitoguazone.

150. The method of claim 136 wherein the improvement is made by chemopotentiation and the chemopotentiation comprises the use of an alkylating hexitol derivative as a chemopotentiator in combination with an agent selected from the group consisting of:

(a) fraudulent nucleosides;
(b) fraudulent nucleotides;
(c) thymidylate synthetase inhibitors;

(d) signal transduction inhibitors;
(e) cisplatin or platinum analogs;
(f) alkylating agents;
(g) anti-tubulin agents;
(h) antimetabolites;
(i) berberine;
(j) apigenin;
(k) colchicine or analogs of colchicine;
(l) genistein;
(m) etoposide;
(n) cytarabine;
(o) camptothecins;
(p) vinca alkaloids;
(q) topoisomerase inhibitors;
(r) 5-fluorouracil;
(s) curcumin;
(t) NF-κB inhibitors;
(u) rosmarinic acid;
(v) mitoguazone; and
(w) a biotherapeutic.

151. The method of claim 136 wherein the improvement is made by post-treatment management and the post-treatment management is a method selected from the group consisting of:

(a) a therapy associated with pain management;
(b) nutritional support;
(c) administration of an anti-emetic;
(d) an anti-nausea therapy;
(e) administration of an anti-inflammatory agent;
(f) administration of an anti-pyretic agent; and
(g) administration of an immune stimulant.

152. The method of claim 136 wherein the improvement is made by alternative medicine/post-treatment support and the alternative medicine/post-treatment support is a method selected from the group consisting of:

(a) hypnosis;

(b) acupuncture;

(c) meditation;

(d) a herbal medication created either synthetically or through extraction; and

(e) applied kinesiology.

153. The method of claim 156 wherein the alternative medicine/post-treatment support is a herbal medication created either synthetically or through extraction and the herbal medication created either synthetically or through extraction is selected from the group consisting of:

(a) a NF-κB inhibitor;

(b) a natural anti-inflammatory;

(c) an immunostimulant;

(d) an antimicrobial; and

(e) a flavonoid, isoflavone, or flavone.

154. The method of claim 153 wherein the herbal medication created either synthetically or through extraction is a NF-κB inhibitor, and the NF-κB inhibitor is selected from the group consisting of parthenolide, curcumin, and rosmarinic acid.

155. The method of claim 153 wherein the herbal medication created either synthetically or through extraction is a natural anti-inflammatory, and the natural anti-inflammatory is selected from the group consisting of rhein and parthenolide.

156. The method of claim 153 wherein the herbal medication created either synthetically or through extraction is an immunostimulant, and the immunostimulant is a product found in or isolated from Echinacea.

157. The method of claim 153 wherein the herbal medication created either synthetically or through extraction is an anti-microbial, and the anti-microbial is berberine.

158. The method of claim 153 wherein the herbal medication created either synthetically or through extraction is a flavonoid, isoflavone, or flavone, and the flavonoid or flavone is selected from the group consisting of apigenenin, genistein, genistin, 6″-O-malonylgenistin, 6″-O-acetylgenistin, daidzein, daidzin, 6″-

O-malonyldaidzin, 6''-O-acetylgenistin, glycitein, glycitin, 6''-O-malonylglycitin, and 6-O-acetylglycitin.

159. The method of claim 136 wherein the improvement is made by a bulk drug product improvement and the bulk drug product improvement is a bulk drug product improvement selected from the group consisting of:

(a) salt formation;

(b) preparation as a homogeneous crystal structure;

(c) preparation as a pure isomer;

(d) increased purity;

(e) preparation with lower residual solvent content; and

(f) preparation with lower residual heavy metal content.

160. The method of claim 136 wherein the improvement is made by use of a diluent and the diluent is a diluent selected from the group consisting of:

(a) an emulsion;

(b) dimethylsulfoxide (DMSO);

(c) N-methylformamide (NMF)

(d) dimethylformamide (DMF)

(e) dimethylacetamide (DMA);

(f) ethanol;

(g) benzyl alcohol;

(h) dextrose-containing water for injection;

(i) Cremophor;

(j) cyclodextrin and

(k) PEG.

161. The method of claim 136 wherein the improvement is made by use of a solvent system and the solvent system is a solvent system selected from the group consisting of:

(a) an emulsion;

(b) DMSO;

(c) NMF;

(d) DMF;

(e) DMA;

(f) ethanol;

(g) benzyl alcohol;

(h) dextrose-containing water for injection;

(i) Cremophor;

(j) PEG; and

(k) salt systems.

162. The method of claim 136 wherein the improvement is made by use of an excipient and the excipient is an excipient selected from the group consisting of:

(a) mannitol;

(b) albumin;

(c) EDTA;

(d) sodium bisulfite;

(e) benzyl alcohol;

(f) carbonate buffers;

(g) phosphate buffers;

(h) PEG;

(i) vitamin A;

(j) vitamin D;

(k) vitamin E;

(l) esterase inhibitors;

(m) cytochrome P450 inhibitors;

(n) multi-drug resistance (MDR) inhibitors;

(o) organic resins;

(p) detergents;

(q) perillyl alcohol or an analog thereof; and

(r) activators of channel-forming receptors.

163. The method of claim 136 wherein the improvement is made by use of a dosage form and the dosage form is a dosage form selected from the group consisting of:

(a) tablets;

(b) capsules;

(c) topical gels;

(d) topical creams;

(e) patches;

(f) suppositories;

(g) lyophilized dosage fills;

(h) immediate-release formulations;

(i) slow-release formulations;

(j) controlled-release formulations; and

(k) liquid in capsules.

164. The method of claim 136 wherein the improvement is made by use of dosage kits and packaging and the dosage kits and packaging are dosage kits and packaging selected from the group consisting of the use of amber vials to protect from light and the use of stoppers with specialized coatings to improve shelf-life stability.

165. The method of claim 136 wherein the improvement is made by use of a drug delivery system and the drug delivery system is a drug delivery system selected from the group consisting of:

(a) oral dosage forms;

(b) nanocrystals;

(c) nanoparticles;

(d) cosolvents;

(e) slurries;

(f) syrups;

(g) bioerodible polymers;

(h) liposomes;

(i) slow-release injectable gels;

(j) microspheres; and

(k) targeting compositions with epidermal growth factor receptor-binding peptides.

166. The method of claim 136 wherein the improvement is made by use of a drug conjugate form and the drug conjugate form is a drug conjugate form selected from the group consisting of:

(a) a polymer system;

(b) polylactides;

(c) polyglycolides;

(d) amino acids;

(e) peptides;

(f) multivalent linkers;

(g) immunoglobulins;

(h) cyclodextrin polymers;

(i) modified transferrin;

(j) hydrophobic or hydrophobic-hydrophilic polymers;

(k) conjugates with a phosphonoformic acid partial ester;

(l) conjugates with a cell-binding agent incorporating a charged cross-linker; and

(m) conjugates with β-glucuronides through a linker.

167. The method of claim 136 wherein the improvement is made by use of a compound analog and the compound analog is a compound analog selected from the group consisting of:

(a) alteration of side chains to increase or decrease lipophilicity;

(b) addition of an additional chemical functionality to alter a property selected from the group consisting of reactivity, electron affinity, and binding capacity; and

(c) alteration of salt form.

168. The method of claim 136 wherein the improvement is made by use of a prodrug system and the prodrug system is a prodrug system selected from the group consisting of:

(a) the use of enzyme sensitive esters;

(b) the use of dimers;

(c) the use of Schiff bases;

(d) the use of pyridoxal complexes;

(e) the use of caffeine complexes;

(f) the use of nitric oxide-releasing prodrugs;

(g) the use of prodrugs with fibroblast activation protein α-cleavable oligopeptides;

(h) the use of prodrugs that are products of reaction with an acetylating or carbamylating agent;

(i) the use of prodrugs that are hexanoate conjugates;

(j) the use of prodrugs that are polymer-agent conjugates; and

(k) the use of prodrugs that are subject to redox activation.

169. The method of claim 136 wherein the improvement is made by use of a multiple drug system and the multiple drug system is a multiple drug system selected from the group consisting of:

(a) inhibitors of multi-drug resistance;

(b) specific drug resistance inhibitors;

(c) specific inhibitors of selective enzymes;

(d) signal transduction inhibitors;

(e) meisoindigo;

(f) imatinib;

(g) hydroxyurea;

(h) dasatinib;

(i) capecitabine;

(j) nilotinib;

(k) repair inhibition agents; and

(l) topoisomerase inhibitors with non-overlapping side effects.

170. The method of claim 136 wherein the improvement is made by biotherapeutic enhancement and the biotherapeutic enhancement is be performed by use in combination as sensitizers potentiators with a therapeutic agent or technique that is a therapeutic agent or technique selected from the group consisting of:

(a) biological response modifiers;

(b) cytokines;

(c) lymphokines;

(d) therapeutic antibodies;

(e) antisense therapies;

(f) gene therapies;

(g) ribozymes; and

(h) RNA interference.

171. The method of claim 136 wherein the improvement is made by use of biotherapeutic resistance modulation and the biotherapeutic resistance modulation is use against a TKI-resistant malignancy also resistant to a therapeutic agent or technique selected from the group consisting of:

(a) biological response modifiers;

(b) cytokines;

(c) lymphokines;

(d) therapeutic antibodies;

(e) antisense therapies;

(f) gene therapies;

(g) ribozymes; and

(h) RNA interference.

172. The method of claim 136 wherein the improvement is made by use of biotherapeutic resistance modulation and the biotherapeutic resistance modulation is use against a malignancy associated with dysregulation of the *AHI1* gene that is also resistant to a therapeutic agent or technique selected from the group consisting of:

(a) biological response modifiers;

(b) cytokines;

(c) lymphokines;

(d) therapeutic antibodies;

(e) antisense therapies;

(f) gene therapies;

(g) ribozymes; and

(h) RNA interference.

173. The use of claim 136 wherein the improvement is made by radiation therapy enhancement and the radiation therapy enhancement is a radiation therapy enhancement agent or technique selected from the group consisting of:

(a) use with hypoxic cell sensitizers;

(b) use with radiation sensitizers/protectors;

(c) use with photosensitizers;

(d) use with radiation repair inhibitors;

(e) use with thiol depleting agents;

(f) use with vaso-targeted agents;

(g) use with DNA repair inhibitors;

(h) use with radioactive seeds;

(i) use with radionuclides;

(j) use with radiolabeled antibodies; and

(k) use with brachytherapy.

174. The method of claim 136 wherein the improvement is by use of a novel mechanism of action and the novel mechanism of action is a novel mechanism of action that is a therapeutic interaction with a target or mechanism selected from the group consisting of:

(a) inhibitors of poly-ADP ribose polymerase;

(b) agents that affect vasculature;

(c) agents that promote vasodilation;

(d) oncogenic targeted agents;

(e) signal transduction inhibitors;

(f) agents inducing EGFR inhibition;

(g) agents inducing Protein Kinase C inhibition;

(h) agents inducing Phospholipase C downregulation;

(i) agents including jun downregulation;

(j) agents modulating expression of histone genes;

(k) agents modulating expression of VEGF;

(l) agents modulating expression of ornithine decarboxylase;

(m) agents modulating expression of jun D;

(n) agents modulating expression of v-jun;

(o) agents modulating expression of GPCRs;

(p) agents modulating expression of protein kinase A;

(q) agents modulating expression of protein kinases other than protein kinase A;

(r) agents modulating expression of telomerase;

(s) agents modulating expression of prostate specific genes; and

(t) agents modulating expression of histone deacetylase.

175. The method of claim 136 wherein the improvement is made by use of selective target cell population therapeutics and the use of selective target cell population therapeutics is a use selected from the group consisting of:

(a) use against radiation sensitive cells;

(b) use against radiation resistant cells; and

(c) use against energy depleted cells.

176. The method of claim 136 wherein the improvement is made by use with an agent to enhance the activity of the alkylating hexitol derivative and the agent to enhance the activity of the alkylating hexitol derivative is selected from the group consisting of:

(a) nicotinamide;

(b) caffeine;

(c) tetandrine; and

(d) berberine.

177. A composition to improve the efficacy and/or reduce the side effects of suboptimally administered drug therapy employing an alkylating hexitol derivative for the treatment of a TKI resistant malignancy or a malignancy associated with mutation in or dysregulation of the *AHI1* gene comprising an alternative selected from the group consisting of:

(a) a therapeutically effective quantity of a modified alkylating hexitol derivative or a derivative, analog, or prodrug of an alkylating hexitol derivative or a modified alkylating hexitol derivative, wherein the modified alkylating hexitol derivative or the derivative, analog or prodrug of the modified alkylating hexitol derivative possesses increased therapeutic efficacy or reduced side effects for treatment of a TKI-resistant malignancy or a malignancy associated with mutation in or dysregulation of the *AHI1* gene as compared with an unmodified alkylating hexitol derivative;

(b) a composition comprising:

(i) a therapeutically effective quantity of an alkylating hexitol derivative, a modified alkylating hexitol derivative, or a derivative, analog, or prodrug of an alkylating hexitol derivative or a modified alkylating hexitol derivative; and

(ii) at least one additional therapeutic agent, therapeutic agent subject to chemosensitization, therapeutic agent subject to chemopotentiation, diluent, excipient, solvent system, or drug delivery system, wherein the composition possesses increased therapeutic efficacy or reduced side effects for treatment of a TKI-resistant malignancy or a malignancy associated with mutation in or dysregulation of the *AHI1* gene as compared with an unmodified alkylating hexitol derivative;

(c) a therapeutically effective quantity of an alkylating hexitol derivative, a modified alkylating hexitol derivative, or a derivative, analog, or prodrug of an alkylating hexitol derivative or a modified alkylating hexitol derivative that is incorporated into a dosage form, wherein an alkylating hexitol derivative, a modified alkylating hexitol derivative, or a derivative, analog, or prodrug of an alkylating hexitol derivative or a modified alkylating hexitol derivative incorporated into the dosage form possesses increased therapeutic efficacy or reduced side effects for treatment of a TKI-resistant malignancy or a malignancy associated with mutation in or dysregulation of the *AHI1* gene as compared with an unmodified alkylating hexitol derivative;

(d) a therapeutically effective quantity of an alkylating hexitol derivative, a modified alkylating hexitol derivative, or a derivative, analog, or prodrug of an alkylating hexitol derivative or a modified alkylating hexitol derivative that is incorporated into a dosage kit and packaging, wherein an alkylating hexitol derivative, a modified alkylating hexitol derivative, or a derivative, analog, or prodrug of an alkylating hexitol derivative or a modified alkylating hexitol derivative incorporated into the dosage kit and packaging possesses increased therapeutic efficacy or reduced side effects for treatment of a TKI-resistant malignancy or a malignancy associated with mutation in or dysregulation of the *AHI1* gene as compared with an unmodified alkylating hexitol derivative; and

(e) a therapeutically effective quantity of an alkylating hexitol derivative, a modified alkylating hexitol derivative, or a derivative, analog, or prodrug of an alkylating hexitol derivative or a modified alkylating hexitol derivative that is subjected to a bulk drug product improvement, wherein the an alkylating hexitol derivative, a modified alkylating hexitol derivative, or a derivative, analog, or prodrug of an alkylating hexitol derivative or a modified alkylating hexitol derivative subject to

the bulk drug product improvement possesses increased therapeutic efficacy or reduced side effects for treatment of a TKI-resistant malignancy or a malignancy associated with mutation in or dysregulation of the *AHI1* gene as compared with an unmodified alkylating hexitol derivative.

178. The composition of claim 177 wherein the composition possesses increased therapeutic efficacy or reduced side effects for treatment of a TKI-resistant malignancy and wherein the resistance to TKI is due to: (1) at least one mutation in a gene encoding a protein that is a target of at least one TKI; or (2) the presence of at least one additional gene in either a wild-type or mutated state encoding a product that confers resistance to the therapeutic effects of at least one TKI, wherein the additional gene in either a wild-type or mutated state encoding a product that confers resistance to the therapeutic effects of at least one TKI is *AHI-1*, and wherein the resistance to at least one TKI is due to a mutation in the kinase domain of ABL1 protein that is part of a BCR-ABL fusion protein that is a target of TKIs.

179. The composition of claim 177 wherein the composition possesses increased therapeutic efficacy or reduced side effects for treatment of a malignancy associated with mutation in or dysregulation of the *AHI1* gene.

180. The composition of claim 177 wherein the composition comprises a drug combination comprising:

(i) an alkylating hexitol derivative, a modified alkylating hexitol derivative, or a derivative, analog, or prodrug of an alkylating hexitol derivative or a modified alkylating hexitol derivative; and

(ii) an additional therapeutic agent selected from the group consisting of:

(a) topoisomerase inhibitors;
(b) fraudulent nucleosides;
(c) fraudulent nucleotides;
(d) thymidylate synthetase inhibitors;
(e) signal transduction inhibitors;
(f) cisplatin or platinum analogs;
(g) alkylating agents;
(h) anti-tubulin agents;

(i) antimetabolites;
(j) berberine;
(k) apigenin;
(l) amonafide;
(m) vinca alkaloids;
(n) 5-fluorouracil;
(o) curcumin;
(p) NF-κB inhibitors;
(q) rosmarinic acid;
(r) mitoguazone;
(s) tetrandrine;
(t) a JAK2 inhibitor;
(u) a STAT5 inhibitor; and
(v) a Src inhibitor.

181. The composition of claim 177 wherein the composition comprises a drug combination comprising:

(a) an alkylating hexitol derivative, a modified alkylating hexitol derivative, or a derivative, analog, or prodrug of an alkylating hexitol derivative or a modified alkylating hexitol derivative; and

(b) a BH3 mimetic.

182. The composition of claim 181 wherein the BH3 mimetic is a BH3 mimetic selected from the group consisting of:

(i) peptides;
(ii) modified peptides;
(iii) terpyridine-based peptidomimetics;
(iv) terephthalamide-based peptidomimetics;
(v) benzoylurea-based peptidomimetics;
(vi) obatoclax;
(vii) TW37;
(viii) an analog or derivative of TW37;
(ix) (-) gossypol;
(x) gossypol derivatives;
(xi) isoxazolidine derivatives;

(xii) A-385358;

(xiii) an analog or derivative of A-385358;

(xiv) ABT-737;

(xv) an analog or derivative of ABT-737;

(xvi) ABT-263;

(xvii) an analog or derivative of ABT-263;

(xviii) TM-1206; and

(xix) an analog or derivative of TM-1206.

183. The composition of claim 177 wherein the composition comprises a drug combination comprising:

(a) an alkylating hexitol derivative, a modified alkylating hexitol derivative, or a derivative, analog, or prodrug of an alkylating hexitol derivative or a modified alkylating hexitol derivative; and

(b) an agent that modulates the expression of the *AHI1* gene or modulates the activity of AHI1 protein.

184. The composition of claim 177 wherein the composition comprises a drug combination comprising:

(a) an alkylating hexitol derivative, a modified alkylating hexitol derivative, or a derivative, analog, or prodrug of an alkylating hexitol derivative or a modified alkylating hexitol derivative;

(b) an agent that modulates the expression of the *AHI1* gene or modulates the activity of AHI1 protein; and

(c) a BH3 mimetic.

185. The composition of claim 177 wherein the composition comprises:

(a) an alkylating hexitol derivative, a modified alkylating hexitol derivative, or a derivative, analog, or prodrug of an alkylating hexitol derivative or a modified alkylating hexitol derivative; and

(b) a therapeutic agent subject to chemosensitization selected from the group consisting of:

(i) topoisomerase inhibitors;

(ii) fraudulent nucleosides;

(iii) fraudulent nucleotides;

(iv) thymidylate synthetase inhibitors;
(v) signal transduction inhibitors;
(vi) cisplatin or platinum analogs;
(vii) alkylating agents;
(viii) anti-tubulin agents;
(ix) antimetabolites;
(x) berberine;
(xi) apigenin;
(xii) colchicine or an analog of colchicine;
(xiii) genistein;
(xiv) etoposide;
(xv) cytarabine;
(xvi) camptothecin;
(xvii) vinca alkaloids;
(xviii) 5-fluorouracil;
(xix) curcumin;
(xx) NF-κB inhibitors;
(xxi) rosmarinic acid; and
(xxii) mitoguazone;

wherein the alkylating hexitol derivative, a modified alkylating hexitol derivative, or a derivative, analog, or prodrug of an alkylating hexitol derivative or a modified alkylating hexitol derivative acts as a chemosensitizer.

186. The composition of claim 177 wherein the composition comprises:

(a) an alkylating hexitol derivative, a modified alkylating hexitol derivative, or a derivative, analog, or prodrug of an alkylating hexitol derivative or a modified alkylating hexitol derivative; and

(b) a therapeutic agent subject to chemopotentiation selected from the group consisting of:

(i) topoisomerase inhibitors;
(ii) fraudulent nucleosides;
(iii) fraudulent nucleotides;
(iv) thymidylate synthetase inhibitors;

(v) signal transduction inhibitors;
(vi) cisplatin or platinum analogs;
(vii) alkylating agents;
(viii) anti-tubulin agents;
(ix) antimetabolites;
(x) berberine;
(xi) apigenin;
(xii) amonafide;
(xiii) vinca alkaloids;
(xiv) 5-fluorouracil;
(xv) curcumin;
(xvi) NF-κB inhibitors;
(xvii) rosmarinic acid;
(xviii) mitoguazone; and
(xix) tetrandrine;

wherein the alkylating hexitol derivative, a modified alkylating hexitol derivative, or a derivative, analog, or prodrug of an alkylating hexitol derivative or a modified alkylating hexitol derivative acts as a chemopotentiator.

187. The composition of claim 177 wherein the alkylating hexitol derivative, a modified alkylating hexitol derivative, or a derivative, analog, or prodrug of an alkylating hexitol derivative or a modified alkylating hexitol derivative is subjected to a bulk drug product improvement, wherein the bulk drug product improvement is selected from the group consisting of:

(i) salt formation;
(ii) preparation as a homogeneous crystal structure;
(iii) preparation as a pure isomer;
(iv) increased purity;
(v) preparation with lower residual solvent content; and
(vi) preparation with lower residual heavy metal content.

188. The composition of claim 177 wherein the composition comprises an alkylating hexitol derivative, a modified alkylating hexitol derivative, or a derivative, analog, or prodrug of an alkylating hexitol derivative or a modified

alkylating hexitol derivative and a diluent, wherein the diluent is selected from the group consisting of:

(i) an emulsion;
(ii) dimethylsulfoxide (DMSO);
(iii) N-methylformamide (NMF)
(iv) dimethylformamide (DMF)
(v) dimethylacetamide (DMA);
(vi) ethanol;
(vii) benzyl alcohol;
(viii) dextrose-containing water for injection;
(ix) Cremophor;
(x) cyclodextrins; and
(xi) PEG.

189. The composition of claim 177 wherein the composition comprises an alkylating hexitol derivative, a modified alkylating hexitol derivative, or a derivative, analog, or prodrug of an alkylating hexitol derivative or a modified alkylating hexitol derivative and a solvent system, wherein the solvent system is selected from the group consisting of:

(i) an emulsion;
(ii) DMSO;
(iii) NMF;
(iv) DMF;
(v) DMA;
(vi) ethanol;
(vii) benzyl alcohol;
(viii) dextrose-containing water for injection;
(ix) Cremophor;
(x) PEG, and
(xi) salt systems.

190. The composition of claim 177 wherein the composition comprises an alkylating hexitol derivative, a modified alkylating hexitol derivative, or a derivative, analog, or prodrug of an alkylating hexitol derivative or a modified

alkylating hexitol derivative and an excipient, wherein the excipient is selected from the group consisting of:

(i) mannitol;
(ii) albumin;
(iii) EDTA;
(iv) sodium bisulfite;
(v) benzyl alcohol;
(vi) carbonate buffers;
(vii) phosphate buffers;
(viii) PEG;
(ix) vitamin A;
(x) vitamin D;
(xi) vitamin E;
(xii) esterase inhibitors;
(xiii) cytochrome P450 inhibitors;
(xiv) multi-drug resistance (MDR) inhibitors;
(xv) organic resins;
(xvi) detergents;
(xvii) perillyl alcohol or an analog thereof; and
(xviii) activators of channel-forming receptors.

191. The composition of claim 177 wherein the alkylating hexitol derivative, modified alkylating hexitol derivative, or derivative, analog, or prodrug of an alkylating hexitol derivative or modified alkylating hexitol derivative is incorporated into a dosage form selected from the group consisting of:

(i) tablets;
(ii) capsules;
(iii) topical gels;
(iv) topical creams;
(v) patches;
(vi) suppositories;
(vii) lyophilized dosage fills;
(viii) immediate-release formulations;
(ix) slow-release formulations;

(x) controlled-release formulations; and

(xi) liquid in capsules.

192. The composition of claim 177 wherein the alkylating hexitol derivative, modified alkylating hexitol derivative, or derivative, analog, or prodrug of an alkylating hexitol derivative or modified alkylating hexitol derivative is incorporated into a dosage kit and packaging selected from the group consisting of amber vials to protect from light and stoppers with specialized coatings to improve shelf-life stability.

193. The composition of claim 177 wherein the composition comprises:

(a) an alkylating hexitol derivative, modified alkylating hexitol derivative, or derivative, analog, or prodrug of an alkylating hexitol derivative or modified alkylating hexitol derivative; and

(b) a drug delivery system, wherein the drug delivery system is selected from the group consisting of:

(i) oral dosage forms;

(ii) nanocrystals;

(iii) nanoparticles;

(iv) cosolvents;

(v) slurries;

(vi) syrups;

(vii) bioerodible polymers;

(viii) liposomes;

(ix) slow-release injectable gels;

(x) microspheres; and

(xi) targeting compositions with epidermal growth factor receptor-binding peptides.

194. The composition of claim 177 wherein the therapeutic agent is a modified alkylating hexitol derivative, and the modification is selected from the group consisting of:

(a) alteration of side chains to increase or decrease lipophilicity;

(b) addition of an additional chemical functionality to alter a property selected from the group consisting of reactivity, electron affinity, and binding capacity; and

(c) alteration of salt form.

195. The composition of claim 177 wherein therapeutic agent is an alkylating hexitol derivative, modified alkylating hexitol derivative, or derivative, analog, or prodrug of an alkylating hexitol derivative or modified alkylating hexitol derivative and the therapeutic agent is present in the composition in a drug conjugate form selected from the group consisting of:

(i) a polymer system;

(ii) polylactides;

(iii) polyglycolides;

(iv) amino acids;

(v) peptides;

(vi) multivalent linkers;

(vii) immunoglobulins;

(viii) cyclodextrin polymers;

(ix) modified transferrin;

(x) hydrophobic or hydrophobic-hydrophilic polymers;

(xi) conjugates with a phosphonoformic acid partial ester;

(xii) conjugates with a cell-binding agent incorporating a charged cross-linker; and

(xiii) conjugates with β-glucuronides through a linker.

196. The composition of claim 177 wherein the therapeutic agent is an alkylating hexitol derivative, modified alkylating hexitol derivative, or derivative or analog of an alkylating hexitol derivative or modified alkylating hexitol derivative and the therapeutic agent is in the form of a prodrug system, wherein the prodrug system is selected from the group consisting of:

(i) enzyme sensitive esters;

(ii) dimers;

(iii) Schiff bases;

(iv) pyridoxal complexes;

(v) caffeine complexes;

(vi) nitric oxide-releasing prodrugs;

(vii) prodrugs with fibroblast activation protein α-cleavable oligopeptides

(viii) products of reaction with an acylating or carbamylating agent;

(ix) hexanoate conjugates;

(x) polymer-agent conjugates; and

(xi) prodrugs that are subject to redox activation.

197. The composition of claim 177 wherein the therapeutic agent is an alkylating hexitol derivative, modified alkylating hexitol derivative, or derivative, analog, or prodrug of an alkylating hexitol derivative or modified alkylating hexitol derivative and the composition further comprises at least one additional therapeutic agent to form a multiple drug system, wherein the at least one additional therapeutic agent is selected from the group consisting of:

(i) an inhibitor of multi-drug resistance;

(ii) a specific drug resistance inhibitor;

(iii) a specific inhibitor of a selective enzyme;

(iv) a signal transduction inhibitor;

(v) an inhibitor of a repair enzyme; and

(vi) a topoisomerase inhibitor with non-overlapping side effects.

198. The composition of claim 177 wherein the alkylating hexitol derivative is selected from the group consisting of dianhydrogalactitol, a derivative or analog of dianhydrogalactitol, diacetyldianhydrogalactitol, a derivative or analog of diacetyldianhydrogalactitol, dibromodulcitol, and a derivative or analog of dibromodulcitol.

199. The composition of claim 198 wherein the alkylating hexitol derivative is dianhydrogalactitol.

200. The composition of claim 198 wherein the alkylating hexitol derivative is a derivative or analog of dianhydrogalactitol.

201. The composition of claim 200 wherein the derivative or analog of dianhydrogalactitol is a derivative of dianhydrogalactitol that is selected from the group consisting of: (i) a derivative of dianhydrogalactitol that has one or both of the

hydrogens of the two hydroxyl groups of dianhydrogalactitol replaced with lower alkyl; (ii) a derivative of dianhydrogalactitol that has one or more of the hydrogens attached to the two epoxide rings replaced with lower alkyl; (iii) a derivative of dianhydrogalactitol that has one or both of the methyl groups present in dianhydrogalactitol and that are attached to the same carbons that bear the hydroxyl groups replaced with C_2-C_6 lower alkyl; and (iv) a derivative of dianhydrogalactitol that has one or both of the methyl groups present in dianhydrogalactitol and that are attached to the same carbons that bear the hydroxyl groups substituted with a halo group by replacing a hydrogen of the methyl group with a halo group.

202. The composition of claim 198 wherein the alkylating hexitol derivative is diacetyldianhydrogalactitol.

203. The composition of claim 198 wherein the alkylating hexitol derivative is a derivative or analog of diacetyldianhydrogalactitol.

204. The composition of claim 203 wherein the derivative or analog of diacetyldianhydrogalactitol is a derivative of diacetyldianhydrogalactitol that is selected from the group consisting of: (i) a derivative of diacetyldianhydrogalactitol that has one or both of the methyl groups that are part of the acetyl moieties replaced with C_2-C_6 lower alkyl; (ii) a derivative of diacetyldianhydrogalactitol that has one or both of the hydrogens attached to the epoxide ring replaced with lower alkyl; (iii) a derivative of diacetyldianhydrogalactitol that has one or both of the methyl groups attached to the same carbons that bear the acetyl groups replaced with C_2-C_6 lower alkyl; and (iv) a derivative of diacetyldianhydrogalactitol that has one or both of the methyl groups that are attached to the same carbons that bear the hydroxyl groups substituted with a halo group by replacing a hydrogen of the methyl group with a halo group.

205. The composition of claim 198 wherein the alkylating hexitol derivative is dibromodulcitol.

206. The composition of claim 198 wherein the alkylating hexitol derivative is a derivative or analog of dibromodulcitol.

207. The composition of claim 206 wherein the derivative or analog of dibromodulcitol is derivative of dibromodulcitol that is selected from the group consisting of: (i) a derivative of dibromodulcitol that has one or more of the hydrogens replaced with lower alkyl; and (ii) a derivative of dibromodulcitol that has

one or both of the bromo groups replaced with another halo group selected from the group consisting of chloro, fluoro, and iodo.

Claims

1. A method for preparation of a medicament for the treatment of a malignancy wherein the malignancy is characterized by resistance to at least one tyrosine kinase inhibitor (TKI) due to: (1) at least one mutation in a gene encoding a protein that is a target of at least one TKI; or (2) the presence of at least one additional gene in either a wild-type or mutated state encoding a product that confers resistance to the therapeutic effects of at least one TKI, the wherein the medicament comprises a therapeutically effective quantity of an alkylating hexitol derivative, wherein the additional gene in either a wild-type or mutated state encoding a product that confers resistance to the therapeutic effects of at least one TKI is *AHI-1*, and wherein the resistance to at least one TKI is due to a mutation in the kinase domain of ABL1 protein that is part of a BCR-ABL fusion protein that is a target of TKIs.

2. The method of claim 1 wherein the *AHI-1* gene is mutated as the result of a proviral insertion.

3. The method of claim 1 wherein the alkylating hexitol derivative is selected from the group consisting of dianhydrogalactitol, a derivative or analog of dianhydrogalactitol, diacetyldianhydrogalactitol, a derivative or analog of diacetyldianhydrogalactitol, dibromodulcitol, and a derivative or analog of dibromodulcitol.

4. The method of claim 3 wherein the alkylating hexitol derivative is selected from the group consisting of dianhydrogalactitol and a derivative or analog of dianhydrogalactitol.

5. The method of claim 4 wherein the alkylating hexitol derivative is dianhydrogalactitol.

6. The method of claim 1 wherein the medicament further comprises a therapeutically effective quantity of a BH3 mimetic.

7. The method of claim 6 wherein the BH3 mimetic is selected from the group consisting of:

(a) peptides;
(b) modified peptides;
(c) terpyridine-based peptidomimetics;
(d) terephthalamide-based peptidomimetics;
(e) benzoylurea-based peptidomimetics;
(f) obatoclax;
(g) TW37;
(h) an analog or derivative of TW37;
(i) (-) gossypol;
(j) gossypol derivatives;
(k) isoxazolidine derivatives;
(l) A-385358;

(m) an analog or derivative of A-385358;
(n) ABT-737;
(o) an analog or derivative of ABT-737;
(p) ABT-263;
(q) an analog or derivative of ABT-263;
(r) TM-1206; and
(s) an analog or derivative of TM-1206.

8. The method of claim 1 wherein the medicament further comprises a therapeutic agent selected from the group consisting of a tyrosine kinase inhibitor, a JAK2 inhibitor, and a STAT5 inhibitor.

9. A method for preparing of a medicament for the treatment of a malignancy in a subject suffering from a malignancy who has a germline deletion polymorphism conferring resistance to thymidine kinase inhibitors (TKIs) wherein the medicament comprises therapeutically effective quantity of a therapeutic agent selected from the group consisting of dianhydrogalactitol, a derivative or analog of dianhydrogalactitol, diacetyldianhydrogalactitol, a derivative or analog of diacetyldianhydrogalactitol, dibromodulcitol, and a derivative or analog of dibromodulcitol.

10. The method of claim 9 wherein the malignancy is selected from the group consisting of chronic myelogenous leukemia (CML), non small cell lung carcinoma (NSCLC), and triple-negative breast cancer.

11. The method of claim 9 wherein the therapeutic agent is selected from the group consisting of dianhydrogalactitol and a derivative or analog of dianhydrogalactitol.

12. The method of claim 10 wherein the therapeutic agent is dianhydrogalactitol.

13. The method of claim 9 wherein the germline DNA deletion polymorphism causes a splicing variation that leads to expression of an isoform of BIM protein that lacks a BH3 domain and thus inhibits the induction of apoptosis wherein the germline DNA deletion polymorphism is a germline DNA deletion polymorphism of 2903 bp located in the *BIM* gene.

14. The method of claim 13 wherein the germline DNA deletion polymorphism causes a splicing variation that leads to expression of an isoform of BIM protein that lacks a BH3 domain and thus inhibits the induction of apoptosis.

15. The method of claim 9 wherein the medicament further comprises a therapeutically effective quantity of a BH3 mimetic.

16. The method of claim 15 wherein the BH3 mimetic is selected from the group consisting of:
(a) peptides;
(b) modified peptides;

(c) terpyridine-based peptidomimetics;
(d) terephthalamide-based peptidomimetics;
(e) benzoylurea-based peptidomimetics;
(f) obatoclax;
(g) TW37;
(h) an analog or derivative of TW37;
(i) (-) gossypol;
(j) gossypol derivatives;
(k) isoxazolidine derivatives;
(l) A-385358;
(m) an analog or derivative of A-385358;
(n) ABT-737;
(o) an analog or derivative of ABT-737;
(p) ABT-263;
(q) an analog or derivative of ABT-263;
(r) TM-1206; and
(s) an analog or derivative of TM-1206.

17. The method of claim 9 wherein the medicament further comprises a therapeutically effective quantity of a tyrosine kinase inhibitor.

18. The method of claim 17 wherein the tyrosine kinase inhibitor is selected from the group consisting of erlotinib, afatinib, dacomitinib, imatinib, bosutinib, nilotinib, and dasatinib.

19. The method of claim 9 wherein the medicament further comprises a therapeutically effective quantity of a JAK2 inhibitor.

20. The method of claim 19 wherein the JAK2 inhibitor is selected from the group consisting of (E)-N-benzyl-2-cyano-3-(3,4-dihydroxyphenyl)acrylamide (AG490), ruxolitinib, tofacitinib, tofacitinib citrate, N-tert-butyl-3-(5-methyl-2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenylamino)pyrimidin-4-ylamino)benzenesulfonamide (TG-101348), (S)-5-chloro-N2-(1-(5-fluoropyrimidin-2-yl)ethyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine (AZD1480), N-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide (CYT387), baricitinib, (S,E)-3-(6-bromopyridin-2-yl)-2-cyano-N-(1-phenylethyl)acrylamide (WP1066), S-ruxolitinib, N-tert-butyl-3-(5-methyl-2-(4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)benzenesulfonamide (TG101209), N-[3-(4-methyl-1-piperazinyl)phenyl]-8-[4-(methylsulfonyl)phenyl]-[1,2,4]triazolo[1,5-a]pyridin-2-amine (CEP33779), 8-(3,5-difluoro-4-(morpholinomethyl)phenyl)-2-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)quinoxaline (NVP-BSK805), (S)-5-fluoro-2-(1-(4-fluorophenyl)ethylamino)-6-(5-methyl-1H-pyrazol-3-ylamino)nicotinonitrile (AZ 960), 3-(4-chloro-2-fluorobenzyl)-2-methyl-N-(3-methyl-1H-pyrazol-5-yl)-8-(morpholinomethyl)imidazo[1,2-b]pyridazin-6-amine (LY2784544), 1-cyclopropyl-3-(3-(5-(morpholinomethyl)-1H-benzo[d]imidazol-2-yl)-1H-pyrazol-4-yl)urea (AT9283), pacritinib (SB1518), (S)-N-(4-(2-((4-morpholinophenyl)amino)pyrimidin-4-yl)phenyl)pyrrolidine-2-carboxamide (XL019), and N-tert-butyl-3-(5-methyl-2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenylamino)pyrimidin-4-ylamino)benzenesulfonamide (TG101348).

21. The method of claim 9 wherein the medicament further comprises a therapeutically effective quantity of a STAT5 inhibitor.

22. The method of claim 21 wherein the STAT5 inhibitor is selected from the group consisting of N′-((4-oxo-4H-chromen-3-yl)methylene)nicotinohydrazide and pimozide.

23. The method of claim 9 wherein the medicament further comprises a therapeutically effective quantity of a Src inhibitor.

24. The method of claim 23 wherein the Src inhibitor is selected from the group consisting of dasatinib, saracatinib, bosutinib, N-benzyl-2-(5-(4-(2-morpholinoethoxy)phenyl)pyridin-2-yl)acetamide (KX2-391), CGP76030, and 4-methyl-3-(1-methyl-6-(pyridin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino)-N-(3-(trifluoromethyl)phenyl)benzamide (NVP-BHG712).

25. A method for preparation of a medicament for the treatment of a malignancy in a subject suffering from a malignancy associated with a mutation in or a dysregulation of the *AHI1* gene wherein the medicament comprises a therapeutically effective quantity of a therapeutic agent selected from the group consisting of dianhydrogalactitol, a derivative or analog of dianhydrogalactitol, diacetyldianhydrogalactitol, a derivative or analog of diacetyldianhydrogalactitol, dibromodulcitol, and a derivative or analog of dibromodulcitol.

26. The method of claim 25 wherein the therapeutic agent is dianhydrogalactitol.

27. The method of claim 25 wherein the malignancy is chronic myelocytic leukemia.

28. The method of claim 25 wherein the medicament further comprises a therapeutically effective quantity of an agent that modulates the expression or activity of either the *AHI1* gene or the AHI1 protein.

29. The method of claim 28 wherein the agent that modulates the expression or activity of either the *AHI1* gene or the AHI1 protein is an agent that modulates the expression of the *AHI1* gene.

30. The method of claim 28 wherein the agent that modulates the expression or activity of either the *AHI1* gene or the AHI1 protein is an agent that inhibits the activity of the AHI1 protein.

31. The method of claim 1, 9, or 25 wherein the medicament is a drug combination further comprising a therapeutic agent selected from the group consisting of:

(a) thymidylate synthetase inhibitors;
(b) signal transduction inhibitors;
(c) cisplatin or platinum analogs;

(d) alkylating agents;
(e) anti-tubulin agents;
(f) antimetabolites;
(g) berberine;
(h) apigenin;
(i) colchicine or an analog thereof;
(j) genistein;
(k) etoposide;
(l) cytarabine;
(m) camptothecins;
(n) vinca alkaloids;
(o) topoisomerase inhibitors;
(p) 5-fluorouracil;
(q) curcumin;
(r) NF-κB inhibitors;
(s) rosmarinic acid;
(t) mitoguazone;
(u) meisoindigo;
(v) imatinib;
(w) dasatinib;
(x) nilotinib;
(y) epigenetic modulators;
(z) transcription factor inhibitors;
(aa) taxol;
(ab) homoharringtonine;
(ac) pyridoxal;
(ad) spirogermanium;
(ae) caffeine;
(af) nicotinamide;
(ag) methylglyoxalbisguanylhydrazone;
(ah) Rho kinase inhibitors;
(ai) 1,2,4-benzotriazine oxides;
(aj) an alkylglycerol;
(ak) an inhibitor of a Mer, Ax1, or Tyro-3 receptor kinase;
(al) an inhibitor of ATR kinase;
(am) a modulator of Fms kinase, Kit kinase, MAP4K4 kinase, TrkA kinase, or TrkB kinase;
(an) endoxifen;
(ao) a mTOR inhibitor;
(ap) an inhibitor of Mnk1a kinase, Mkn1b kinase, Mnk2a kinase, or Mnk2b kinase;
(aq) a modulator of pyruvate kinase M2;
(ar) a modulator of phosphoinositide 3-kinases;
(as) a cysteine protease inhibitor;
(at) phenformin;
(au) Sindbis virus-based vectors;

(av) peptidomimetics that act as mimetics of Smac and inhibit IAPs to promote apoptosis;
(aw) a Raf kinase inhibitor;
(ax) a nuclear transport modulator;
(ay) an acid ceramidase inhibitor and a choline kinase inhibitor;
(az) tyrosine kinase inhibitors;
(ba) anti-CS1 antibodies;
(bb) inhibitors of protein kinase CK2;
(bc) anti-guanylyl cyclase C (GCC) antibodies;
(bd) histone deacetylase inhibitors;
(be) cannabinoids;
(bf) glucagon-like peptide-1 (GLP-1) receptor agonists;
(bg) inhibitors of Bcl-2 or Bcl-xL;
(bh) Stat3 pathway inhibitors;
(bi) inhibitors of polo-like kinase 1 (Plk1);
(bj) GBPAR1 activators;
(bk) modulators of serine-threonine protein kinase and poly(ADP-ribose) polymerase (PARP) activity;
(bl) taxanes;
(bm) inhibitors of dihydrofolate reductase;
(bn) inhibitors of aromatase;
(bo) benzimidazole-based anti-neoplastic agents;
(bp) an O6-methylguanine-DNA-methyltransferase (MGMT) inhibitor;
(bq) CCR9 inhibitors;
(br) acid sphingomyelinase inhibitors;
(bs) peptidomimetic macrocycles;
(bt) cholanic acid amides;
(bu) substituted oxazaphosphorines;
(bv) anti-TWEAK receptor antibodies;
(bw) an ErbB3 binding protein;
(bx) a glutathione S-transferase-activated anti-neoplastic compound;
(by) substituted phosphorodiamidates;
(bz) inhibitors of MEKK protein kinase;
(ca) COX-2 inhibitors;
(cb) cimetidine and a cysteine derivative;
(cc) anti-IL-6 receptor antibody;
(cd) an antioxidant;
(ce) an isoxazole inhibitor of tubulin polymerization;
(cf) PARP inhibitors;
(cg) Aurora protein kinase inhibitors;
(ch) peptides binding to prostate-specific membrane antigen;
(ci) CD19 binding agents;
(cj) benzodiazepines;
(ck) Toll-like receptor (TLR) agonists;
(cl) bridged bicyclic sulfamides;
(cm) inhibitors of epidermal growth factor receptor kinase;

(cn) a ribonuclease of the T2 family having actin-binding activity;
(co) myrsinoic acid A or an analog thereof;
(cp) inhibitors of a cyclin-dependent kinase;
(cq) inhibitors of the interaction between p53 and MDM2;
(cr) inhibitors of the receptor tyrosine kinase MET;
(cs) largazole or largazole analogs;
(ct) inhibitors of AKT protein kinase;
(cu) 2′-fluoro-5-methyl-β-L-arabinofuranosyluridine or L-deoxythymidine;
(cv) HSP90 modulators;
(cw) inhibitors of JAK kinases;
(cx) inhibitors of PDK1 protein kinase;
(cy) PDE4 inhibitors;
(cz) inhibitors of proto-oncogene c-Met tyrosine kinase;
(da) inhibitors of indoleamine 2,3-dioxygenase;
(db) agents that inhibit expression of ATDC (TRIM29);
(dc) proteomimetic inhibitors of the interaction of nuclear receptor with coactivator peptides;
(dd) antagonists of XIAP family proteins;
(de) tumor-targeted superantigens;
(df) inhibitors of Pim kinases;
(dg) inhibitors of CHK1 or CHK2 kinases;
(dh) inhibitors of angiopoietin-like 4 protein;
(di) Smo antagonists;
(dj) nicotinic acetylcholine receptor antagonists;
(dk) farnesyl protein transferase inhibitors;
(dl) adenosine A3 receptor antagonists;
(dm) a cancer vaccine;
(dn) a JAK2 inhibitor; and
(do) a Src inhibitor.

32. The method of claim 1, 9, or 25 wherein the medicament is a drug conjugate form and the drug conjugate form is a drug conjugate form selected from the group consisting of:
(a) a polymer system;
(b) polylactides;
(c) polyglycolides;
(d) amino acids;
(e) peptides;
(f) multivalent linkers;
(g) immunoglobulins;
(h) cyclodextrin polymers;
(i) modified transferrin;
(j) hydrophobic or hydrophobic-hydrophilic polymers;
(k) conjugates with a phosphonoformic acid partial ester;

(l) conjugates with a cell-binding agent incorporating a charged cross-linker; and

(m) conjugates with β-glucuronides through a linker.

33. A composition to improve the efficacy and/or reduce the side effects of suboptimally administered drug therapy employing an alkylating hexitol derivative for the treatment of a TKI resistant malignancy or a malignancy associated with mutation in or dysregulation of the *AHI1* gene comprising an alternative selected from the group consisting of:

(a) a therapeutically effective quantity of a modified alkylating hexitol derivative or a derivative, analog, or prodrug of an alkylating hexitol derivative or a modified alkylating hexitol derivative, wherein the modified alkylating hexitol derivative or the derivative, analog or prodrug of the modified alkylating hexitol derivative possesses increased therapeutic efficacy or reduced side effects for treatment of a TKI-resistant malignancy or a malignancy associated with mutation in or dysregulation of the *AHI1* gene as compared with an unmodified alkylating hexitol derivative;

(b) a composition comprising:

(i) a therapeutically effective quantity of an alkylating hexitol derivative, a modified alkylating hexitol derivative, or a derivative, analog, or prodrug of an alkylating hexitol derivative or a modified alkylating hexitol derivative; and

(ii) at least one additional therapeutic agent, therapeutic agent subject to chemosensitization, therapeutic agent subject to chemopotentiation, diluent, excipient, solvent system, or drug delivery system, wherein the composition possesses increased therapeutic efficacy or reduced side effects for treatment of a TKI-resistant malignancy or a malignancy associated with mutation in or dysregulation of the *AHI1* gene as compared with an unmodified alkylating hexitol derivative;

(c) a therapeutically effective quantity of an alkylating hexitol derivative, a modified alkylating hexitol derivative, or a derivative, analog, or prodrug of an alkylating hexitol derivative or a modified alkylating hexitol derivative that is incorporated into a dosage form, wherein an alkylating hexitol derivative, a modified alkylating hexitol derivative, or a derivative, analog, or prodrug of an alkylating hexitol derivative or a modified alkylating hexitol derivative incorporated into the dosage form possesses increased therapeutic efficacy or reduced side effects for treatment of a TKI-resistant malignancy or a malignancy associated with mutation in or dysregulation of the *AHI1* gene as compared with an unmodified alkylating hexitol derivative;

(d) a therapeutically effective quantity of an alkylating hexitol derivative, a modified alkylating hexitol derivative, or a derivative, analog, or prodrug of an alkylating hexitol derivative or a modified alkylating hexitol derivative that is incorporated into a dosage kit and packaging, wherein an alkylating hexitol derivative, a modified alkylating hexitol derivative, or a derivative, analog, or prodrug of an alkylating hexitol derivative or a modified alkylating hexitol derivative incorporated into the dosage kit and packaging possesses increased therapeutic efficacy or reduced side effects for treatment of a TKI-resistant malignancy or a malignancy associated with mutation in or dysregulation of the *AHI1* gene as compared with an unmodified alkylating hexitol derivative; and

(e) a therapeutically effective quantity of an alkylating hexitol derivative, a modified alkylating hexitol derivative, or a derivative, analog, or prodrug of an alkylating hexitol derivative or a modified alkylating hexitol derivative that is subjected to a bulk drug product improvement, wherein the an alkylating hexitol derivative, a modified alkylating hexitol

derivative, or a derivative, analog, or prodrug of an alkylating hexitol derivative or a modified alkylating hexitol derivative subject to the bulk drug product improvement possesses increased therapeutic efficacy or reduced side effects for treatment of a TKI-resistant malignancy or a malignancy associated with mutation in or dysregulation of the *AHI1* gene as compared with an unmodified alkylating hexitol derivative.

34. The composition of claim 33 wherein the composition possesses increased therapeutic efficacy or reduced side effects for treatment of a TKI-resistant malignancy and wherein the resistance to TKI is due to: (1) at least one mutation in a gene encoding a protein that is a target of at least one TKI; or (2) the presence of at least one additional gene in either a wild-type or mutated state encoding a product that confers resistance to the therapeutic effects of at least one TKI, wherein the additional gene in either a wild-type or mutated state encoding a product that confers resistance to the therapeutic effects of at least one TKI is *AHI-1*, and wherein the resistance to at least one TKI is due to a mutation in the kinase domain of ABL1 protein that is part of a BCR-ABL fusion protein that is a target of TKIs.

35. The composition of claim 33 wherein the composition possesses increased therapeutic efficacy or reduced side effects for treatment of a malignancy associated with mutation in or dysregulation of the *AHI1* gene.

36. The composition of claim 33 wherein the composition comprises a drug combination comprising:

(i) an alkylating hexitol derivative, a modified alkylating hexitol derivative, or a derivative, analog, or prodrug of an alkylating hexitol derivative or a modified alkylating hexitol derivative; and

(ii) an additional therapeutic agent selected from the group consisting of:

- (a) topoisomerase inhibitors;
- (b) fraudulent nucleosides;
- (c) fraudulent nucleotides;
- (d) thymidylate synthetase inhibitors;
- (e) signal transduction inhibitors;
- (f) cisplatin or platinum analogs;
- (g) alkylating agents;
- (h) anti-tubulin agents;
- (i) antimetabolites;
- (j) berberine;
- (k) apigenin;
- (l) amonafide;
- (m) vinca alkaloids;
- (n) 5-fluorouracil;
- (o) curcumin;
- (p) NF-κB inhibitors;
- (q) rosmarinic acid;
- (r) mitoguazone;
- (s) tetrandrine;
- (t) a JAK2 inhibitor;

(u) a STAT5 inhibitor; and
(v) a Src inhibitor.

37. The composition of claim 33 wherein the composition comprises a drug combination comprising:

(a) an alkylating hexitol derivative, a modified alkylating hexitol derivative, or a derivative, analog, or prodrug of an alkylating hexitol derivative or a modified alkylating hexitol derivative; and

(b) a BH3 mimetic.

38. The composition of claim 37 wherein the BH3 mimetic is a BH3 mimetic selected from the group consisting of:

(i) peptides;
(ii) modified peptides;
(iii) terpyridine-based peptidomimetics;
(iv) terephthalamide-based peptidomimetics;
(v) benzoylurea-based peptidomimetics;
(vi) obatoclax;
(vii) TW37;
(viii) an analog or derivative of TW37;
(ix) (-) gossypol;
(x) gossypol derivatives;
(xi) isoxazolidine derivatives;
(xii) A-385358;
(xiii) an analog or derivative of A-385358;
(xiv) ABT-737;
(xv) an analog or derivative of ABT-737;
(xvi) ABT-263;
(xvii) an analog or derivative of ABT-263;
(xviii) TM-1206; and
(xix) an analog or derivative of TM-1206.

39. The composition of claim 33 wherein the composition comprises a drug combination comprising:

(a) an alkylating hexitol derivative, a modified alkylating hexitol derivative, or a derivative, analog, or prodrug of an alkylating hexitol derivative or a modified alkylating hexitol derivative; and

(b) an agent that modulates the expression of the *AHI1* gene or modulates the activity of AHI1 protein.

40. The composition of claim 33 wherein the composition comprises an alkylating hexitol derivative, a modified alkylating hexitol derivative, or a derivative, analog, or prodrug of an alkylating hexitol derivative or a modified alkylating hexitol derivative and an excipient, wherein the excipient is selected from the group consisting of:

(i) mannitol;
(ii) albumin;

(iii) EDTA;
(iv) sodium bisulfite;
(v) benzyl alcohol;
(vi) carbonate buffers;
(vii) phosphate buffers;
(viii) PEG;
(ix) vitamin A;
(x) vitamin D;
(xi) vitamin E;
(xii) esterase inhibitors;
(xiii) cytochrome P450 inhibitors;
(xiv) multi-drug resistance (MDR) inhibitors;
(xv) organic resins;
(xvi) detergents;
(xvii) perillyl alcohol or an analog thereof; and
(xviii) activators of channel-forming receptors.

41. The composition of claim 33 wherein the composition comprises:

(a) an alkylating hexitol derivative, modified alkylating hexitol derivative, or derivative, analog, or prodrug of an alkylating hexitol derivative or modified alkylating hexitol derivative; and

(b) a drug delivery system, wherein the drug delivery system is selected from the group consisting of:

(i) oral dosage forms;
(ii) nanocrystals;
(iii) nanoparticles;
(iv) cosolvents;
(v) slurries;
(vi) syrups;
(vii) bioerodible polymers;
(viii) liposomes;
(ix) slow-release injectable gels;
(x) microspheres; and
(xi) targeting compositions with epidermal growth factor receptor-binding peptides.

42. The composition of claim 33 wherein the therapeutic agent is an alkylating hexitol derivative, modified alkylating hexitol derivative, or derivative, analog, or prodrug of an alkylating hexitol derivative or modified alkylating hexitol derivative and the therapeutic agent is present in the composition in a drug conjugate form selected from the group consisting of:

(i) a polymer system;
(ii) polylactides;
(iii) polyglycolides;
(iv) amino acids;
(v) peptides;
(vi) multivalent linkers;

(vii) immunoglobulins;
(viii) cyclodextrin polymers;
(ix) modified transferrin;
(x) hydrophobic or hydrophobic-hydrophilic polymers;
(xi) conjugates with a phosphonoformic acid partial ester;
(xii) conjugates with a cell-binding agent incorporating a charged cross-linker; and
(xiii) conjugates with β-glucuronides through a linker.

43. The composition of claim 33 wherein the therapeutic agent is an alkylating hexitol derivative, modified alkylating hexitol derivative, or derivative or analog of an alkylating hexitol derivative or modified alkylating hexitol derivative and the therapeutic agent is in the form of a prodrug system, wherein the prodrug system is selected from the group consisting of:
(i) enzyme sensitive esters;
(ii) dimers;
(iii) Schiff bases;
(iv) pyridoxal complexes;
(v) caffeine complexes;
(vi) nitric oxide-releasing prodrugs;
(vii) prodrugs with fibroblast activation protein α-cleavable oligopeptides
(viii) products of reaction with an acylating or carbamylating agent;
(ix) hexanoate conjugates;
(x) polymer-agent conjugates; and
(xi) prodrugs that are subject to redox activation.

44. The composition of claim 33 wherein the therapeutic agent is an alkylating hexitol derivative, modified alkylating hexitol derivative, or derivative, analog, or prodrug of an alkylating hexitol derivative or modified alkylating hexitol derivative and the composition further comprises at least one additional therapeutic agent to form a multiple drug system, wherein the at least one additional therapeutic agent is selected from the group consisting of:
(i) an inhibitor of multi-drug resistance;
(ii) a specific drug resistance inhibitor;
(iii) a specific inhibitor of a selective enzyme;
(iv) a signal transduction inhibitor;
(v) an inhibitor of a repair enzyme; and
(vi) a topoisomerase inhibitor with non-overlapping side effects.

45. The composition of claim 33 wherein the alkylating hexitol derivative is selected from the group consisting of dianhydrogalactitol, a derivative or analog of dianhydrogalactitol, diacetyldianhydrogalactitol, a derivative or analog of diacetyldianhydrogalactitol, dibromodulcitol, and a derivative or analog of dibromodulcitol.

46. The composition of claim 45 wherein the alkylating hexitol derivative is dianhydrogalactitol.

47. The composition of claim 45 wherein the alkylating hexitol derivative is a derivative or analog of dianhydrogalactitol.