Claims

1. A method for preparation of a medicamentto improve the efficacy and/or reduce the side effects of the administration of a substituted hexitol derivative for treatment of non-small-cell lung carcinoma (NSCLC) or glioblastoma multiforme (GBM) 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 the substituted hexitol derivative for treatment of NSCLC or GBM; and

(b) modifying the factor or parameter to improve the efficacy and/or reduce the side effects of the administration of the substituted hexitol derivative by preparation of a medicament for treatment of NSCLC or GBM, wherein the medicament is adapted to be used together with administration of a therapeutically effective quantity of ionizing radiation for treatment of NSCLC or GBM.

2. The method of claim 1 wherein the substituted hexitol derivative is selected from the group consisting of dianhydrogalactitol, derivatives of dianhydrogalactitol, diacetyldianhydrogalactitol, and derivatives of diacetyldianhydrogalactitol.

3. The method of claim 2 wherein the substituted hexitol derivative is dianhydrogalactitol.

4. The method of claim 1 wherein the method improves the efficacy and/or reduces the side effects of the administration of a substituted hexitol derivative for treatment of non-small-cell lung carcinoma (NSCLC) when used together with administration of a therapeutically effective quantity of ionizing radiation for treatment of NSCLC.

5. The method of claim 1 wherein the method improves the efficacy and/or reduces the side effects of the administration of a substituted hexitol derivative for treatment of glioblastoma multiforme (GBM) when used together with administration of a therapeutically effective quantity of ionizing radiation for treatment of GBM.

6. The method of claim 1 wherein the factor or parameter is selected from the group consisting of:

(a) dose modification;
(b) route of administration;
(c) schedule of administration;
(d) administration to promote preferential accumulation in brain tissue;
(e) selection of disease stage;
(f) patient selection;
(g) patient/disease phenotype;
(h) patient/disease genotype;
(i) pre/post-treatment preparation
(j) toxicity management;
(k) pharmacokinetic/pharmacodynamic monitoring;

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(l) drug combinations;
(m) chemosensitization;
(n) chemopotentiation;
(o) post-treatment patient management;
(p) alternative medicine/therapeutic support;
(q) bulk drug product improvements;
(r) diluent systems;
(s) solvent systems;
(t) excipients;
(u) dosage forms;
(v) drug delivery systems;
(w) drug conjugate forms;
(x) prodrugs;
(y) multiple drug systems;
(z) biotherapeutic enhancement;
(aa) biotherapeutic resistance modulation;
(ab) radiation therapy enhancement;
(ac) novel mechanisms of action;
(ad) selective target cell population therapeutics;
(ae) use with ionizing radiation;
(af) use with an agent that counteracts myelosuppression; and
(ag) use with an agent that increases the ability of the substituted hexitol to pass through the blood-brain barrier to treat brain metastases of NSCLC.

7. The method of claim 7 wherein the substituted hexitol derivative is dianhydrogalactitol.

8. The method of claim 6 wherein the substituted hexitol derivative is dianhydrogalactitol and wherein the improvement is made by dose modification and the dose modification is at least one dose modification selected from the group consisting of:
(i) continuous i.v. infusion for hours to days;
(ii) biweekly administration;
(iii) doses greater than 5 mg/m^2/day;
(iv) progressive escalation of dosing from 1 mg/m^2/day based on patient tolerance;
(v) use of caffeine to modulate metabolism;
(vi) use of isoniazid to modulate metabolism;
(vii) selected and intermittent boosting of dosage administration;
(viii) administration of single and multiple doses escalating from 5 mg/m^2/day via bolus;
(ix) oral dosages of below 30 mg/m^2;
(x) oral dosages of above 130 mg/m^2;
(xi) oral dosages up to 40 mg/m^2 for 3 days and then a nadir/recovery period of 18-21 days;
(xii) dosing at a lower level for an extended period;
(xiii) dosing at a higher level;

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

(xv) the use of the substituted hexitol derivative as a single cytotoxic agent at 30 mg/m^2/day × 5 days, repeated monthly;

(xvi) dosing at 3 mg/kg;

(xvii) the use of a substituted hexitol derivative in combination therapy, at 30 mg/m^2/day × 5 days; and

(xviii) dosing at 40 mg/day × 5 days in adult patients, repeated every two weeks.

9. The method of claim 6 wherein the substituted hexitol derivative is dianhydrogalactitol and 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:

(i) topical administration;
(ii) oral administration;
(iii) slow release oral delivery;
(iv) intrathecal administration;
(v) intraarterial administration;
(vi) continuous infusion;
(vii) intermittent infusion;
(viii) intravenous administration, such as intravenous administration for 30 minutes;
(ix) administration through a longer infusion; and
(x) administration through IV push.

10. The method of claim 6 wherein the substituted hexitol derivative is dianhydrogalactitol and 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:

(i) daily administration;
(ii) weekly administration;
(iii) weekly administration for three weeks;
(iv) biweekly administration;
(v) biweekly administration for three weeks with a 1-2 week rest period;
(vi) intermittent boost dose administration; and
(vii) daily administration for one week for multiple weeks.

11. The method of claim 6 wherein the substituted hexitol derivative is dianhydrogalactitol and wherein the improvement is made by selection of disease stage and wherein the selection of disease stage is at least one selection of disease stage selected from the group consisting of:

(i) use in an appropriate disease stage for NSCLC or GBM;
(ii) use with an angiogenesis inhibitor to prevent or limit metastatic spread;
(iii) use for newly diagnosed disease;

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(iv) use for recurrent disease; and
(v) use for resistant or refractory disease.

12. The method of claim 6 wherein the substituted hexitol derivative is dianhydrogalactitol and wherein the improvement is made by patient selection and the patient selection is at least one patient selection carried out by a criterion selected from the group consisting of:

(i) 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;

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

(iii) selecting patients intolerant of GI toxicities;

(iv) 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.

(v) selecting patients characterized by carrying extra copies of the EGFR gene for NSCLC;

(vi) selecting patients characterized by methylation or lack of methylation of the promoter of the MGMT gene;

(vii) selecting patients characterized by an unmethylated promoter region of MGMT (O^6-methylguanine methyltransferase);

(viii) selecting patients characterized by a methylated promoter region of MGMT;

(ix) selecting patients characterized by a high expression of MGMT;

(x) selecting patients characterized by a low expression of MGMT;

(xi) selecting patients characterized by a mutation in EGFR;

(xii) selecting patients being administered a platinum-based drug as combination therapy;

(xiii) selecting patients who do not have EGFR mutations and thus are less likely to respond to tyrosine kinase inhibitors (TKI);

(xiv) selecting patients who have become resistant to TKI treatment;

(xv) selecting patients who have the *BIM* co-deletion mutation and thus are less likely to respond to TKI treatment;

(xvi) selecting patients who have become resistant to platinum-based drug treatment; and

(xvii) selecting patients with brain metastases.

13. The method of claim 12 wherein the criterion is selecting patients characterized by a mutation in EGFR and the mutation in EGFR is EGFR Variant III.

14. The method of claim 6 wherein the substituted hexitol derivative is dianhydrogalactitol and wherein the improvement is made by analysis of patient or disease phenotype and the analysis of patient or disease phenotype is a method of analysis of patient or disease phenotype carried out by a method selected from the group consisting of:

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(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 jun, and a protein kinase;

(c) surrogate compound dosing; and

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

15. The method of claim 7 wherein the substituted hexitol derivative is dianhydrogalactitol and wherein the improvement is made by analysis of patient or disease genotype and wherein the method of analysis of patient or disease genotype is a method of analysis of patient or disease genotype carried out by a method selected from the group consisting of:

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

(ii) use of a gene chip;

(iii) use of gene expression analysis;

(iv) use of single nucleotide polymorphism (SNP) analysis;

(v) measurement of the level of a metabolite or a metabolic enzyme;

(vi) determination of copy number of the EGFR gene;

(vii) determination of status of methylation of promoter of MGMT gene;

(viii) determination of the existence of an unmethylated promoter region of the MGMT gene;

(ix) determination of the existence of a methylated promoter region of the MGMT gene;

(x) determination of the existence of high expression of MGMT; and

(xi) determination of the existence of low expression of MGMT.

16. The method of claim 15 wherein the method is use of single nucleotide polymorphism (SNP) analysis and wherein the SNP analysis is carried out on a gene selected from the group consisting of histone deacetylase, ornithine decarboxylase, VEGF, a prostate specific gene, c-Jun, and a protein kinase.

17. The method of claim 6 wherein the substituted hexitol derivative is dianhydrogalactitol and wherein the improvement is made by pre/post-treatment preparation and wherein the pre/post-treatment preparation is a method of pre/post treatment preparation selected from the group consisting of:

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

(ii) the use of a diuretic;

(iii) the use of a uricosuric;

(iv) the use of uricase;

(v) the non-oral use of nicotinamide;

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

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

(viii) the use of caffeine;

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(ix) the use of leucovorin rescue;
(x) infection control; and
(xi) the use of an anti-hypertensive agent.

18. The method of claim 6 wherein the substituted hexitol derivative is dianhydrogalactitol and wherein the improvement is made by toxicity management and wherein the toxicity management is a method of toxicity management selected from the group consisting of:

(i) the use of colchicine or an analog thereof;
(ii) the use of a diuretic;
(iii) the use of a uricosuric;
(iv) the use of uricase;
(v) the non-oral use of nicotinamide;
(vi) the use of a sustained-release form of nicotinamide;
(vii) the use of an inhibitor of poly-ADP ribose polymerase;
(viii) the use of caffeine;
(ix) the use of leucovorin rescue;
(x) the use of sustained-release allopurinol;
(xi) the non-oral use of allopurinol;
(xii) the use of bone marrow transplants;
(xiii) the use of a blood cell stimulant;
(xiv) the use of blood or platelet infusions;
(xv) the administration of an agent selected from the group consisting of filgrastim, G-CSF, and GM-CSF;
(xvi) the application of a pain management technique;
(xvii) the administration of an anti-inflammatory agent;
(xviii) the administration of fluids;
(xix) the administration of a corticosteroid;
(xx) the administration of an insulin control medication;
(xxi) the administration of an antipyretic;
(xxii) the administration of an anti-nausea treatment;
(xxiii) the administration of an anti-diarrheal treatment;
(xxiv) the administration of N-acetylcysteine; and
(xxv) the administration of an antihistamine.

19. The method of claim 6 wherein the substituted hexitol derivative is dianhydrogalactitol and wherein the improvement is made by pharmacokinetic/pharmacodynamic monitoring and wherein the pharmacokinetic/pharmacodynamic monitoring is a method selected from the group consisting of:

(i) multiple determinations of blood plasma levels; and
(ii) multiple determinations of at least one metabolite in blood or urine.

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20. The method of claim 6 wherein the substituted hexitol derivative is dianhydrogalactitol and wherein the improvement is made by drug combination and wherein the drug combination is a drug combination selected from the group consisting of:

(i) use with topoisomerase inhibitors;
(ii) use with fraudulent nucleosides;
(iii) use with fraudulent nucleotides;
(iv) use with thymidylate synthetase inhibitors;
(v) use with signal transduction inhibitors;
(vi) use with cisplatin or platinum analogs;
(vii) use with monofunctional alkylating agents;
(viii) use with bifunctional alkylating agents;
(ix) use with alkylating agents that damage DNA at a different place than does dianhydrogalactitol;
(x) use with anti-tubulin agents;
(xi) use with antimetabolites;
(xii) use with berberine;
(xiii) use with apigenin;
(xiv) use with amonafide;
(xv) use with colchicine or analogs;
(xvi) use with genistein;
(xvii) use with etoposide;
(xviii) use with cytarabine;
(xix) use with camptothecins;
(xx) use with vinca alkaloids;
(xxi) use with 5-fluorouracil;
(xxii) use with curcumin;
(xxiii) use with NF-κB inhibitors;
(xxiv) use with rosmarinic acid;
(xxv) use with mitoguazone;
(xxvi) use with tetrandrine;
(xxvii) use with temozolomide;
(xxviii) use with VEGF inhibitors;
(xxix) use with cancer vaccines;
(xxx) use with EGFR inhibitors;
(xxxi) use with tyrosine kinase inhibitors;
(xxxii) use with poly (ADP-ribose) polymerase (PARP) inhibitors; and
(xxxiii) use with ALK inhibitors.

21. The method of claim 6 wherein the substituted hexitol derivative is dianhydrogalactitol and wherein the improvement is made by chemosensitization or chemopotentiation and the chemosensitization or chemopotentiation is the use of a substituted hexitol derivative as a chemosensitizer or chemopotentiator in combination with an agent selected from the group consisting of:

(i) topoisomerase inhibitors;
(ii) fraudulent nucleosides;
(iii) fraudulent nucleotides;

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(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) colchicine or analogs;
(xiv) genistein;
(xv) etoposide;
(xvi) cytarabine;
(xvii) camptothecins;
(xviii) vinca alkaloids;
(xix) topoisomerase inhibitors;
(xx) 5-fluorouracil;
(xxi) curcumin;
(xxii) NF-κB inhibitors;
(xxiii) rosmarinic acid;
(xxiv) mitoguazone;
(xxv) tetrandrine;
(xxvi) a tyrosine kinase inhibitor;
(xxvii) an inhibitor of EGFR; and
(xxviii) an inhibitor of PARP.

22. The method of claim 6 wherein the substituted hexitol derivative is dianhydrogalactitol and wherein the improvement is made by post-treatment management and the post-treatment management is a method selected from the group consisting of:

(i) a therapy associated with pain management;
(ii) administration of an anti-emetic;
(iii) an anti-nausea therapy;
(iv) administration of an anti-inflammatory agent;
(v) administration of an anti-pyretic agent; and
(vi) administration of an immune stimulant.

23. The method of claim 6 wherein the substituted hexitol derivative is dianhydrogalactitol and 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 administration of a herbal medication created either synthetically or through extraction.

24. The method of claim 6 wherein the substituted hexitol derivative is dianhydrogalactitol and 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:

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(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.

25. The method of claim 6 wherein the substituted hexitol derivative is dianhydrogalactitol and wherein the improvement is made by use of a diluent and the diluent is a diluent selected from the group consisting of:

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

26. The method of claim 6 wherein the substituted hexitol derivative is dianhydrogalactitol and 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:

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

27. The method of claim 6 wherein the substituted hexitol derivative is dianhydrogalactitol and wherein the improvement is made by use of an excipient and the excipient is an excipient selected from the group consisting of:

(i) mannitol;
(ii) albumin;
(iii) EDTA;
(iv) sodium bisulfite;
(v) benzyl alcohol;
(vi) a carbonate buffer; and
(vii) a phosphate buffer.

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28. The method of claim 6 wherein the substituted hexitol derivative is dianhydrogalactitol and 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:

(i) tablets;
(ii) capsules;
(iii) topical gels;
(iv) topical creams;
(v) patches;
(vi) suppositories; and
(vii) lyophilized dosage fills.

29. The method of claim 6 wherein the substituted hexitol derivative is dianhydrogalactitol and 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:

(i) nanocrystals;
(ii) bioerodible polymers;
(iii) liposomes;
(iv) slow release injectable gels; and
(v) microspheres.

30. The method of claim 6 wherein the substituted hexitol derivative is dianhydrogalactitol and wherein the improvement is made by use of a drug conjugate form and the drug conjugate form is selected from the group consisting of:

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

31. The method of claim 6 wherein the substituted hexitol derivative is dianhydrogalactitol and wherein the substituted hexitol derivative is in the form of a prodrug system and wherein the prodrug system is a prodrug system selected from the group consisting of:

(i) the use of enzyme sensitive esters;
(ii) the use of dimers;
(iii) the use of Schiff bases;
(iv) the use of pyridoxal complexes; and
(v) the use of caffeine complexes.

32. The method of claim 6 wherein the substituted hexitol derivative is dianhydrogalactitol and 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:

(i) use of multi-drug resistance inhibitors;
(ii) use of specific drug resistance inhibitors;
(iii) use of specific inhibitors of selective enzymes;

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(iv) use of signal transduction inhibitors;
(v) use of repair inhibition; and
(vi) use of topoisomerase inhibitors with non-overlapping side effects.

33. The method of claim 6 wherein the substituted hexitol derivative is dianhydrogalactitol and wherein the improvement is made by biotherapeutic enhancement and the biotherapeutic enhancement is 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:

(i) cytokines;
(ii) lymphokines;
(iii) therapeutic antibodies;
(iv) antisense therapies;
(v) gene therapies;
(vi) ribozymes;
(vii) RNA interference; and
(viii) vaccines.

34. The method of claim 6 wherein the substituted hexitol derivative is dianhydrogalactitol and wherein the improvement is made by biotherapeutic resistance modulation and the biotherapeutic resistance modulation is use against NSCLC resistant to a therapeutic agent or technique selected from the group consisting of:

(i) biological response modifiers;
(ii) cytokines;
(iii) lymphokines;
(iv) therapeutic antibodies;
(v) antisense therapies;
(vi) gene therapies;
(vii) ribozymes;
(viii) RNA interference; and
(ix) vaccines.

35. The method of claim 6 wherein the substituted hexitol derivative is dianhydrogalactitol and 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:

(i) hypoxic cell sensitizers;
(ii) radiation sensitizers/protectors;
(iii) photosensitizers;
(iv) radiation repair inhibitors;
(e) thiol depleters;
(f) vaso-targeted agents;
(g) DNA repair inhibitors;
(h) radioactive seeds;
(i) radionuclides;
(j) radiolabeled antibodies; and

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(k) brachytherapy.

36. The method of claim 6 wherein the substituted hexitol derivative is dianhydrogalactitol and wherein the improvement is made by use of a novel mechanism of action and the novel mechanism of action is a therapeutic interaction with a target or mechanism selected from the group consisting of:

(i) inhibitors of poly-ADP ribose polymerase;
(ii) agents that affect vasculature or vasodilation;
(iii) oncogenic targeted agents;
(iv) signal transduction inhibitors;
(v) EGFR inhibition;
(vi) protein kinase C inhibition;
(vii) phospholipase C downregulation;
(viii) Jun downregulation;
(ix) histone genes;
(x) VEGF;
(xi) ornithine decarboxylase;
(xii) ubiquitin C;
(xiii) Jun D;
(xiv) v-Jun;
(xv) GPCRs;
(xvi) protein kinase A;
(xvii) protein kinases other than protein kinase A;
(xviii) prostate specific genes;
(xix) telomerase;
(xx) histone deacetylase; and
(xxi) tyrosine kinase inhibitors.

37. The method of claim 6 wherein the substituted hexitol derivative is dianhydrogalactitol and 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:

(i) use against radiation sensitive cells;
(ii) use against radiation resistant cells; and
(iii) use against energy depleted cells.

38. The method of claim 1 wherein the ionizing radiation is administered in a manner selected from the group consisting of:

(a) administered concurrently with the substituted hexitol derivative;
(b) administered separately from the substituted hexitol derivative;
(c) administered in a single dose; and
(d) administered in fractionated doses.

39. The method of claim 1 wherein the radiation dosage is from about 40 Gy to about 79.2 Gy.

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40. The method of claim 39 wherein the radiation dosage is about 60 Gy.

41. The method of claim 1 wherein the radiation is administered by a method selected from the group consisting of high-energy X-rays, high-energy electrons from a linear accelerator unit, and gamma rays from a cobalt-60-based device.

42. The method of claim 1 wherein the radiation is administered to treat NSCLC.

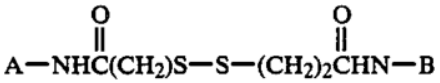
43. The method of claim 1 wherein the radiation is administered to treat GBM.

44. The method of claim 43 wherein the method further comprises administration of trans sodium crocetinate as a radiosensitizer.

45. The method of claim 6 wherein the substituted hexitol derivative is dianhydrogalactitol and wherein the substituted hexitol derivative is dianhydrogalactitol and wherein the improvement is made by use of an agent that counteracts myelosuppression and the agent that counteracts myelosuppression is a dithiocarbamate.

46. The method of claim 6 wherein the substituted hexitol derivative is dianhydrogalactitol and wherein the improvement is made by use with an agent that increases the ability of the substituted hexitol to pass through the blood-brain barrier to treat brain metastases of NSCLC and the agent that increases the ability of the substituted hexitol to pass through the blood-brain barrier is an agent selected from the group consisting of:

(i) a chimeric peptide of the structure of Formula (D-III):



(D-III)

wherein: (A) A is somatostatin, thyrotropin releasing hormone (TRH), vasopressin, alpha interferon, endorphin, muramyl dipeptide or ACTH 4-9 analogue; and (B) B is insulin, IGF-I, IGF-II, transferrin, cationized (basic) albumin or prolactin; or a chimeric peptide of the structure of Formula (D-III) wherein the disulfide conjugating bridge between A and B is replaced with a bridge of Subformula (D-III(a)):

$$A\text{-}NH(CH_2)_2S\text{-}S\text{-}B \text{ (cleavable linkage)}$$

(D-III(a)),

wherein the bridge is formed using cysteamine and EDAC as the bridge reagents; or a chimeric peptide of the structure of Formula (D-III) wherein the disulfide conjugating bridge between A and B is replaced with a bridge of Subformula (D-III(b)):

$$A\text{-}NH{=}CH(CH_2)_3CH{=}NH\text{-}B \text{ (non-cleavable linkage)}$$

(D-III(b)),

wherein the bridge is formed using glutaraldehyde as the bridge reagent;

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(ii) a composition comprising either avidin or an avidin fusion protein bonded to a biotinylated substituted hexitol derivative to form an avidin-biotin-agent complex including therein a protein selected from the group consisting of insulin, transferrin, an anti-receptor monoclonal antibody, a cationized protein, and a lectin;

(iii) a neutral liposome that is pegylated and incorporates the substituted hexitol derivative, wherein the polyethylene glycol strands are conjugated to at least one transportable peptide or targeting agent;

(iv) a humanized murine antibody that binds to the human insulin receptor linked to the substituted hexitol derivative through an avidin-biotin linkage; and

(v) a fusion protein comprising a first segment and a second segment: the first segment comprising a variable region of an antibody that recognizes an antigen on the surface of a cell that after binding to the variable region of the antibody undergoes antibody-receptor-mediated endocytosis, and, optionally, further comprises at least one domain of a constant region of an antibody; and the second segment comprising a protein domain selected from the group consisting of avidin, an avidin mutein, a chemically modified avidin derivative, streptavidin, a streptavidin mutein, and a chemically modified streptavidin derivative, wherein the fusion protein is linked to the substituted hexitol by a covalent link to biotin.

47. The method of claim 6 wherein the substituted hexitol derivative is dianhydrogalactitol and wherein the improvement is made by use of an agent that suppresses the growth of cancer stem cells.

48. The method of claim 47 wherein the agent that suppresses the growth of cancer stem cells is selected from the group consisting of: (1) naphthoquinones; (2) VEGF-DLL4 bispecific antibodies; (3) farnesyl transferase inhibitors; (4) gamma-secretase inhibitors; (5) anti-TIM3 antibodies; (6) tankyrase inhibitors; (7) Wnt pathway inhibitors other than tankyrase inhibitors; (8) camptothecin-binding moiety conjugates; (9) Notch1 binding agents, including antibodies; (10) oxabicycloheptanes and oxabicycloheptenes; (11) inhibitors of the mitochondrial electron transport chains or the mitochondrial tricarboxylic acid cycle; (12) Axl inhibitors; (13) dopamine receptor antagonists; (14) anti-RSPO1 antibodies; (15) inhibitors or modulators of the Hedgehog pathway; (16) caffeic acid analogs and derivatives; (17) Stat3 inhibitors; (18) GRP-94-binding antibodies; (19) Frizzled receptor polypeptides; (20) immunoconjugates with cleavable linkages; (21) human prolactin, growth hormone, or placental lactogen; (22) anti-prominin-1 antibody; (23) antibodies specifically binding N-cadherin; (24) DR5 agonists; (25) anti-DLL4 antibodies or binding fragments thereof; (26) antibodies specifically binding GPR49; (27) DDR1 binding agents; (28) LGR5 binding agents; (29) telomerase-activating compounds; (30) fingolimod plus anti-CD74 antibodies or fragments thereof; (31) an antibody that prevents the binding of CD47 to SIPRα or a CD47 mimetic; (32) thienopyranone kinase inhibitors for inhibition of PI-3 kinases; (33) cancer-stem-cell-binding peptides; (34) diphtheria toxin-interleukin 3 conjugates; (35) inhibitors of histone deacetylase; (36) progesterone or analogs thereof; (37) antibodies binding the negative regulatory region (NRR) of Notch2; (38) inhibitors of HGFIN; (39) immunotherapeutic peptides; (40) inhibitors of CSCPK or related kinases; (41) imidazo[1,2-a]pyrazine derivatives as α-helix mimetics; (42) antibodies directed to an epitope of variant Heterogeneous Ribonucleoprotein G (HnRNPG); (43) antibodies binding TES7 antigen; (44) antibodies binding the ILR3α subunit; (45) ifenprodil tartrate and other compounds with a similar activity; (46) antibodies binding SALL4; (47) antibodies binding Notch4; (48) bispecific

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antibodies binding both NBR1 and Cep55; (49) Smo inhibitors; (50) peptides blocking or inhibiting interleukin-1 receptor 1; (51) antibodies specific for CD47 or CD19; (52) histone methyltransferase inhibitors; (53) antibodies specifically binding Lg5; (54) antibodies specifically binding EFNA1; (55) phenothiazine derivatives; (56) HDAC inhibitors plus AKT inhibitors; (57) ligands binding to cancer-stem-line-specific cell surface antigen stem cell markers; (58) Notch receptor agonists; (59) binding agents binding human MET; (60) PDGFR-β inhibitors; (61) pyrazolo compounds with histone demethylase activity; (62) heterocyclic substituted 3-heteroaryidenyl-2-indolinone derivatives; (63) albumin-binding arginine deiminase fusion proteins; (64) hydrogen-bond surrogate peptides and peptidomimetics that reactivate p53; (65) prodrugs of 2-pyrrolinodoxorubicin conjugated to antibodies; (66) targeted cargo proteins; (67) bisacodyl and analogs thereof; (68) N^1-cyclic amine-N^5-substituted phenyl biguanide derivative; (69) fibulin-3 protein; (70) modulators of SCFSkp2; (71) inhibitors of Slingshot-2; (72) monoclonal antibodies specifically binding DCLK1 protein; (73) antibodies or soluble receptors that modulate the Hippo pathway; (74) selective inhibitors of CDK8 and CDK19; (75) antibodies and antibody fragments specifically binding IL-17; (76) antibodies specifically binding FRMD4A; (77) monoclonal antibodies specifically binding the ErbB-3 receptor; (78) antibodies that specifically bind human RSPO3 and modulate β-catenin activity; (79) esters of 4,9-dihydroxy-naphtho[2,3-b]furans; (80) CCR5 antagonists; (81) antibodies that specifically bind the extracellular domain of human C-type lectin-like molecule (CLL-1); (82) anti-hypertension compounds; (83) anthraquinone radiosensitizer agents plus ionizing radiation; (84) CDK-inhibiting pyrrolopyrimidinone derivatives; (85) analogs of CC-1065 and conjugates thereof; (86) antibodies specifically binding to the protein Notum; (87) CDK8 antagonists; (88) bHLH proteins and nucleic acids encoding them; (89) inhibitors of the histone methyltransferase EZH2; (90) sulfonamides inhibiting carbonic anhydrase isoforms; (91) antibodies specifically binding DEspR; (92) antibodies specifically binding human leukemia inhibitory factor (LIF); (93) doxovir; (94) inhibitors of mTOR; (95) antibodies specifically binding FZD10; (96) naphthofurans; (97) death receptor agonists; (98) tigecycline; (99) strigolactones and strigolactone analogs; and (100) compounds inducing methuosis.

49. A composition to improve the efficacy and/or reduce the side effects of suboptimally administered drug therapy employing a substituted hexitol derivative for the treatment of NSCLC or GBM comprising an alternative selected from the group consisting of:

(a) a therapeutically effective quantity of a derivative or prodrug of a substituted hexitol derivative, wherein the derivative or prodrug of the substituted hexitol derivative possesses increased therapeutic efficacy or reduced side effects for treatment of NSCLC or GBM;

(b) a composition comprising:

(i) a therapeutically effective quantity of a substituted hexitol derivative or a derivative or prodrug of a substituted hexitol derivative; and

(ii) at least one additional therapeutic agent, therapeutic agent subject to chemosensitization, therapeutic agent subject to chemopotentiation, diluent, excipient, solvent system, drug delivery system, agent to counteract myelosuppression, or agent that increases the ability of the substituted hexitol to pass through the blood-brain barrier, wherein the composition possesses increased therapeutic efficacy or reduced side effects for treatment of NSCLC or GBM;

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(c) a therapeutically effective quantity of a substituted hexitol derivative or a derivative or prodrug of a substituted hexitol derivative that is incorporated into a dosage form, wherein the substituted hexitol derivative or the derivative or prodrug of a substituted hexitol derivative incorporated into the dosage form possesses increased therapeutic efficacy or reduced side effects for treatment of NSCLC or GBM as compared with an unmodified substituted hexitol derivative; and

(d) a therapeutically effective quantity of a substituted hexitol derivative or a derivative or prodrug of a substituted hexitol that is subjected to a bulk drug product improvement, wherein the substituted hexitol derivative or the derivative or prodrug of the substituted hexitol derivative or a modified substituted hexitol derivative subjected to the bulk drug product improvement possesses increased therapeutic efficacy or reduced side effects for treatment of NSCLC or GBM as compared with an unmodified substituted hexitol derivative, wherein the composition is adapted for use together with administration of a therapeutically effective quantity of ionizing radiation for treatment of NSCLC or GBM;
wherein the substituted hexitol derivative is dianhydrogalactitol or diacetyldianhydrogalactitol.

50. The composition of claim 49 wherein the composition possesses increased therapeutic efficacy or reduced side effects for treatment of NSCLC when administered together with administration of a therapeutically effective quantity of ionizing radiation for treatment of NSCLC.

51. The composition of claim 49 wherein the composition possesses increased therapeutic efficacy or reduced side effects for treatment of GBM when administered together with administration of a therapeutically effective quantity of ionizing radiation for treatment of GBM.

52. The composition of claim 49 wherein the unmodified substituted hexitol derivative is dianhydrogalactitol.

53. The composition of claim 49 wherein the composition comprises a drug combination comprising:

(a) dianhydrogalactitol; and

(b) an additional therapeutic agent 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) monofunctional alkylating agents;
(viii) bifunctional alkylating agents;
(ix) alkylating agents that damage DNA at a different place than does dianhydrogalactitol;
(x) anti-tubulin agents;
(xi) antimetabolites;
(xii) berberine;

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(xiii) apigenin;
(xiv) amonafide;
(xv) colchicine or analogs;
(xvi) genistein;
(xvii) etoposide;
(xviii) cytarabine;
(xix) camptothecins;
(xx) vinca alkaloids;
(xxi) 5-fluorouracil;
(xxii) curcumin;
(xxiii) NF-κB inhibitors;
(xxiv) rosmarinic acid;
(xxv) mitoguazone;
(xxvi) tetrandrine;
(xxvii) temozolomide;
(xxviii) VEGF inhibitors;
(xxix) cancer vaccines;
(xxx) EGFR inhibitors;
(xxxi) tyrosine kinase inhibitors;
(xxxii) poly (ADP-ribose) polymerase (PARP) inhibitors;
(xxxiii) ALK inhibitors; and
(xxxiv) agents for the suppression of proliferation of cancer stem cells.

54. The composition of claim 49 wherein the composition comprises:
(a) dianhydrogalactitol; and
(b) a therapeutic agent subject to chemosensitization or 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) colchicine or analogs;
(xiv) genistein;
(xv) etoposide;
(xvi) cytarabine;
(xvii) camptothecins;
(xviii) vinca alkaloids;
(xix) topoisomerase inhibitors;

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(xx) 5-fluorouracil;
(xxi) curcumin;
(xxii) NF-κB inhibitors;
(xxiii) rosmarinic acid;
(xxiv) mitoguazone;
(xxv) tetrandrine;
(xxvi) a tyrosine kinase inhibitor;
(xxvii) an inhibitor of EGFR; and
(xxviii)an inhibitor of PARP;

wherein the substituted hexitol derivative acts as a chemosensitizer or chemopotentiator.

55. The composition of claim 49 wherein the substituted hexitol derivative is dianhydrogalactitol and wherein the dianhydrogalactitol is subjected to a bulk drug product improvement, wherein the bulk drug product improvement is 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.

56. The composition of claim 49 wherein the composition comprises dianhydrogalactitol and a diluent, wherein the diluent is selected from the group consisting of:

(a) an emulsion;
(b) dimethylsulfoxide (DMSO);
(c) N-methylformamide (NMF)
(d) DMF;
(e) ethanol;
(f) benzyl alcohol;
(g) dextrose-containing water for injection;
(h) Cremophor;
(i) cyclodextrin; and
(j) PEG.

57. The composition of claim 49 wherein the composition comprises dianhydrogalactitol and a solvent system, wherein the solvent system is selected from the group consisting of:

(a) an emulsion;
(b) dimethylsulfoxide (DMSO);
(c) N-methylformamide (NMF)
(d) DMF;
(e) ethanol;
(f) benzyl alcohol;
(g) dextrose-containing water for injection;
(h) Cremophor;

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(i) cyclodextrin; and
(j) PEG.

58. The composition of claim 49 wherein the composition comprises dianhydrogalactitol and an excipient, wherein the excipient is selected from the group consisting of:

(a) mannitol;
(b) albumin;
(c) EDTA;
(d) sodium bisulfite;
(e) benzyl alcohol;
(f) a carbonate buffer; and
(g) a phosphate buffer.

59. The composition of claim 49 wherein the substituted hexitol derivative is dianhydrogalactitol and wherein the dianhydrogalactitol is incorporated into a dosage form selected from the group consisting of:

(a) tablets;
(b) capsules;
(c) topical gels;
(d) topical creams;
(e) patches;
(f) suppositories; and
(g) lyophilized dosage fills.

60. The composition of claim 49 wherein the composition comprises dianhydrogalactitol and a drug delivery system selected from the group consisting of:

(a) nanocrystals;
(b) bioerodible polymers;
(c) liposomes;
(d) slow release injectable gels; and
(e) microspheres.

61. The composition of claim 49 wherein the substituted hexitol derivative is dianhydrogalactitol and wherein the dianhydrogalactitol is present in the composition in a drug conjugate form selected from the group consisting of:

(a) a polymer system;
(b) polylactides;
(c) polyglycolides;
(d) amino acids;
(e) peptides; and
(f) multivalent linkers.

62. The composition of claim 49 wherein the substituted hexitol derivative is dianhydrogalactitol and wherein the dianhydrogalactitol is in the form of a prodrug system, wherein the prodrug system is selected from the group consisting of:

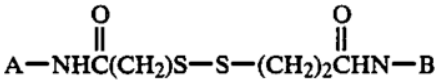
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(a) enzyme sensitive esters;
(b) dimers;
(c) Schiff bases;
(d) pyridoxal complexes; and
(e) caffeine complexes.

63. The composition of claim 49 wherein the composition comprises dianhydrogalactitol and 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:
(a) an inhibitor of multi-drug resistance;
(b) a specific drug resistance inhibitor;
(c) a specific inhibitor of a selective enzyme;
(d) a signal transduction inhibitor;
(e) an inhibitor of a repair enzyme; and
(f) a topoisomerase inhibitor with non-overlapping side effects.

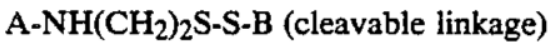
64. The composition of claim 49 wherein the composition comprises dianhydrogalactitol and an agent to counteract myelosuppression, wherein the agent to counteract myelosuppression is a dithiocarbamate.

65. The composition of claim 49 wherein the composition comprises dianhydrogalactitol and an agent that increases the ability of the substituted hexitol to pass through the blood-brain barrier, wherein the agent that increases the ability of the substituted hexitol to pass through the blood-brain barrier is selected from the group consisting of:
(a) a chimeric peptide of the structure of Formula (D-III):



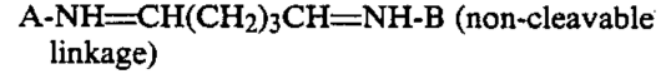
(D-III)

wherein: (A) A is somatostatin, thyrotropin releasing hormone (TRH), vasopressin, alpha interferon, endorphin, muramyl dipeptide or ACTH 4-9 analogue; and (B) B is insulin, IGF-I, IGF-II, transferrin, cationized (basic) albumin or prolactin; or a chimeric peptide of the structure of Formula (D-III) wherein the disulfide conjugating bridge between A and B is replaced with a bridge of Subformula (D-III(a)):



(D-III(a)),

wherein the bridge is formed using cysteamine and EDAC as the bridge reagents; or a chimeric peptide of the structure of Formula (D-III) wherein the disulfide conjugating bridge between A and B is replaced with a bridge of Subformula (D-III(b)):



(D-III(b)),

wherein the bridge is formed using glutaraldehyde as the bridge reagent;

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(b) a composition comprising either avidin or an avidin fusion protein bonded to a biotinylated substituted hexitol derivative to form an avidin-biotin-agent complex including therein a protein selected from the group consisting of insulin, transferrin, an anti-receptor monoclonal antibody, a cationized protein, and a lectin;

(c) a neutral liposome that is pegylated and incorporates the substituted hexitol derivative, wherein the polyethylene glycol strands are conjugated to at least one transportable peptide or targeting agent;

(d) a humanized murine antibody that binds to the human insulin receptor linked to the substituted hexitol derivative through an avidin-biotin linkage; and

(e) a fusion protein comprising a first segment and a second segment: the first segment comprising a variable region of an antibody that recognizes an antigen on the surface of a cell that after binding to the variable region of the antibody undergoes antibody-receptor-mediated endocytosis, and, optionally, further comprises at least one domain of a constant region of an antibody; and the second segment comprising a protein domain selected from the group consisting of avidin, an avidin mutein, a chemically modified avidin derivative, streptavidin, a streptavidin mutein, and a chemically modified streptavidin derivative, wherein the fusion protein is linked to the substituted hexitol by a covalent link to biotin.

66. The composition of claim 49 wherein the composition comprises dianhydrogalactitol and an agent that suppresses proliferation of cancer stem cells, wherein the agent that suppresses proliferation of cancer stem cells is selected from the group consisting of: (1) naphthoquinones; (2) VEGF-DLL4 bispecific antibodies; (3) farnesyl transferase inhibitors; (4) gamma-secretase inhibitors; (5) anti-TIM3 antibodies; (6) tankyrase inhibitors; (7) Wnt pathway inhibitors other than tankyrase inhibitors; (8) camptothecin-binding moiety conjugates; (9) Notch1 binding agents, including antibodies; (10) oxabicycloheptanes and oxabicycloheptenes; (11) inhibitors of the mitochondrial electron transport chains or the mitochondrial tricarboxylic acid cycle; (12) Axl inhibitors; (13) dopamine receptor antagonists; (14) anti-RSPO1 antibodies; (15) inhibitors or modulators of the Hedgehog pathway; (16) caffeic acid analogs and derivatives; (17) Stat3 inhibitors; (18) GRP-94-binding antibodies; (19) Frizzled receptor polypeptides; (20) immunoconjugates with cleavable linkages; (21) human prolactin, growth hormone, or placental lactogen; (22) anti-prominin-1 antibody; (23) antibodies specifically binding N-cadherin; (24) DR5 agonists; (25) anti-DLL4 antibodies or binding fragments thereof; (26) antibodies specifically binding GPR49; (27) DDR1 binding agents; (28) LGR5 binding agents; (29) telomerase-activating compounds; (30) fingolimod plus anti-CD74 antibodies or fragments thereof; (31) an antibody that prevents the binding of CD47 to SIPRα or a CD47 mimetic; (32) thienopyranone kinase inhibitors for inhibition of PI-3 kinases; (33) cancer-stem-cell-binding peptides; (34) diphtheria toxin-interleukin 3 conjugates; (35) inhibitors of histone deacetylase; (36) progesterone or analogs thereof; (37) antibodies binding the negative regulatory region (NRR) of Notch2; (38) inhibitors of HGFIN; (39) immunotherapeutic peptides; (40) inhibitors of CSCPK or related kinases; (41) imidazo[1,2-a]pyrazine derivatives as α-helix mimetics; (42) antibodies directed to an epitope of variant Heterogeneous Ribonucleoprotein G (HnRNPG); (43) antibodies binding TES7 antigen; (44) antibodies binding the ILR3α subunit; (45) ifenprodil tartrate and other compounds with a similar activity; (46) antibodies binding SALL4; (47) antibodies binding Notch4; (48) bispecific antibodies binding both NBR1 and Cep55; (49) Smo inhibitors; (50) peptides blocking or inhibiting interleukin-1 receptor 1; (51) antibodies specific for CD47 or CD19; (52) histone methyltransferase inhibitors; (53) antibodies

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specifically binding Lg5; (54) antibodies specifically binding EFNA1; (55) phenothiazine derivatives; (56) HDAC inhibitors plus AKT inhibitors; (57) ligands binding to cancer-stem-line-specific cell surface antigen stem cell markers; (58) Notch receptor agonists; (59) binding agents binding human MET; (60) PDGFR-β inhibitors; (61) pyrazolo compounds with histone demethylase activity; (62) heterocyclic substituted 3-heteroaryidenyl-2-indolinone derivatives; (63) albumin-binding arginine deiminase fusion proteins; (64) hydrogen-bond surrogate peptides and peptidomimetics that reactivate p53; (65) prodrugs of 2-pyrrolinodoxorubicin conjugated to antibodies; (66) targeted cargo proteins; (67) bisacodyl and analogs thereof; (68) N^1-cyclic amine-N^5-substituted phenyl biguanide derivative; (69) fibulin-3 protein; (70) modulators of SCFSkp2; (71) inhibitors of Slingshot-2; (72) monoclonal antibodies specifically binding DCLK1 protein; (73) antibodies or soluble receptors that modulate the Hippo pathway; (74) selective inhibitors of CDK8 and CDK19; (75) antibodies and antibody fragments specifically binding IL-17; (76) antibodies specifically binding FRMD4A; (77) monoclonal antibodies specifically binding the ErbB-3 receptor; (78) antibodies that specifically bind human RSPO3 and modulate β-catenin activity; (79) esters of 4,9-dihydroxy-naphtho[2,3-b]furans; (80) CCR5 antagonists; (81) antibodies that specifically bind the extracellular domain of human C-type lectin-like molecule (CLL-1); (82) anti-hypertension compounds; (83) anthraquinone radiosensitizer agents plus ionizing radiation; (84) CDK-inhibiting pyrrolopyrimidinone derivatives; (85) analogs of CC-1065 and conjugates thereof; (86) antibodies specifically binding to the protein Notum; (87) CDK8 antagonists; (88) bHLH proteins and nucleic acids encoding them; (89) inhibitors of the histone methyltransferase EZH2; (90) sulfonamides inhibiting carbonic anhydrase isoforms; (91) antibodies specifically binding DEspR; (92) antibodies specifically binding human leukemia inhibitory factor (LIF); (93) doxovir; (94) inhibitors of mTOR; (95) antibodies specifically binding FZD10; (96) naphthofurans; (97) death receptor agonists; (98) tigecycline; (99) strigolactones and strigolactone analogs; and (100) compounds inducing methuosis.

67. A method for preparation of a medicament for treatment of non-small-cell lung carcinoma (NSCLC) or glioblastoma multiforme (GBM) wherein the medicament comprises a therapeutically effective quantity of a substituted hexitol derivative selected from the group consisting of dianhydrogalactitol, derivatives of dianhydrogalactitol, diacetyldianhydrogalactitol, and derivatives of diacetyldianhydrogalactitol wherein the medicament is for use with a therapeutically effective quantity of radiation for the treatment of NSCLC or GBM.

68. The method of claim 67 wherein the substituted hexitol derivative is dianhydrogalactitol.

69. The method of claim 68 wherein the therapeutically effective quantity of dianhydrogalactitol is a quantity of dianhydrogalactitol that results in a dosage of from about 1 mg/m^2 to about 40 mg/m^2.

70. The method of claim 69 wherein the therapeutically effective quantity of dianhydrogalactitol is a quantity of dianhydrogalactitol that results in a dosage of from about 5 mg/m^2 to about 25 mg/m^2.

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71. The method of claim 68 wherein the dianhydrogalactitol is administered by a route selected from the group consisting of intravenous and oral.

72. The method of claim 67 wherein the medicament is for use with a further step selected from the group consisting of:

(a) administering a therapeutically effective quantity of temozolomide;

(b) administering a therapeutically effective quantity of bevacizumab;

(c) administering a therapeutically effective quantity of a corticosteroid;

(d) administering a therapeutically effective quantity of at least one chemotherapeutic agent selected from the group consisting of lomustine, a platinum-containing chemotherapeutic agent, vincristine, and cyclophosphamide;

(e) administering a therapeutically effective quantity of a tyrosine kinase inhibitor;

(f) administering a therapeutically effective quantity of an EGFR inhibitor;

(g) administering a therapeutically effective quantity of an agent that suppresses proliferation of cancer stem cells;

(h) administering a therapeutically effective quantity of a platinum-containing chemotherapeutic agent and wherein the platinum-containing chemotherapeutic agent is selected from the group consisting of carboplatin, iproplatin, oxaliplatin, tetraplatin, satraplatin, picoplatin, nedaplatin, and triplatin;

(i) administering a therapeutically effective quantity of an EGFR inhibitor and wherein the EGFR inhibitor affects wild-type binding sites or mutated binding sites;

(j) administering a therapeutically effective quantity of an agent that increases the ability of the substituted hexitol to pass through the blood-brain barrier;

(k) administering a therapeutically effective quantity of an agent that counteracts myelosuppression; and

(l) administering a therapeutically effective quantity of an agent that suppresses the growth of cancer stem cells.

73. The method of claim 67 wherein the medicament is to be administered with radiation in a manner selected from the group consisting of:

(a) administered concurrently with the substituted hexitol derivative;

(b) administered separately from the substituted hexitol derivative;

(c) administered in a single dose; and

(d) administered in fractionated doses.

74. The method of claim 67 wherein the radiation dosage is from about 40 Gy to about 79.2 Gy.

75. The method of claim 74 wherein the radiation dosage is about 60 Gy.

76. The method of claim 67 wherein the radiation is administered by a method selected from the group consisting of high-energy X-rays, high-energy electrons from a linear accelerator unit, and gamma rays from a cobalt-60-based device.

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77. The method of claim 67 wherein the medicament is to be administered with trans sodium crocetinate as a radiosensitizer.

78. The method of claim 68 wherein the dianhydrogalactitol:

(a) substantially suppresses the growth of cancer stem cells (CSCs);

(b) is effective in suppressing the growth of cancer cells possessing O^6-methylguanine-DNA methyltransferase (MGMT)-driven drug resistance; or

(c) is effective in suppressing the growth of cancer cells resistant to temozolomide.

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