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14 January 2016

(54) Title: USE OF DIANHYDROGALACTITOL AND ANALOGS OR DERIVATIVES THEREOF TO TREAT NON-SMALL-CELL CARCINOMA OF THE LUNG AND OVARIAN CANCER

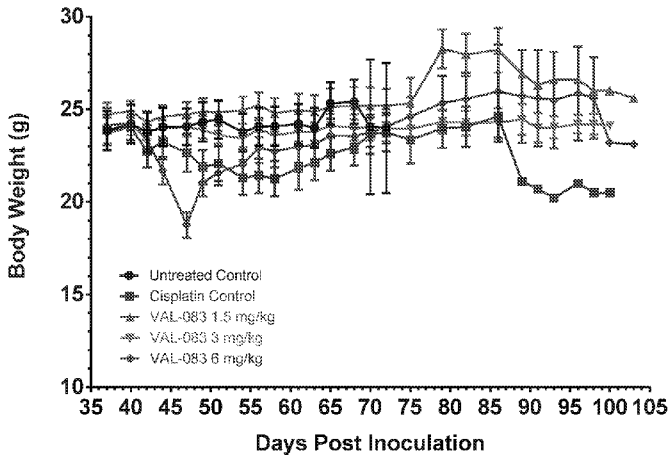

Figure 1

(57) Abstract: The use of dianhydrogalactitol provides a novel therapeutic modality for the treatment of non-small-cell lung carcinoma (NSCLC) and ovarian cancer. Dianhydrogalactitol acts as an alkylating agent on DNA that creates N^7 methylation. Dianhydrogalactitol is effective in suppressing the growth of cancer stem cells and is active against tumors that are refractory to temozolomide, cisplatin, and thymidine kinase inhibitors; the drug acts independently of the MGMT repair mechanism. Dianhydrogalactitol can be used together with other anti-neoplastic agents and can possess additive or super-additive effects.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2015/024462

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 38/12 (2015.01)
CPC - A61K 31/336 (2015.07)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 31/47, 31/336, 38/12, 45/06; A61P 35/00, 35/02; C12N 9/12; C12Q 1/00, 1/68 (2015.01)
CPC - A61K 31/47, 31/336, 45/06; C12Q 1/6886, 2600/118, 2600/156, 2600/16 (2015.07)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - A61K 31/47, 31/336, 45/06; C12Q 1/6886, 2600/118, 2600/156, 2600/16 (2015.07) (keyword delimited)
USPC - 424/649; 514/393, 475

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Orbit, Google Patents, Google Scholar.
Search terms used: dianhydrogalactitol nsclc lung cancer intravenous therapeutically effective amount inassignee:Del inassignee:Mar ininventor:bacha dose dosage optimal OR suboptimal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014/004376 A2 (DEL MAR PHARMACEUTICALS) 03 January 2014 (03.01.2014) entire document	1-5, 7-10, 83, 84, 86, 87, 122-128
A	WO 2013/110058 A2 (BACHA et al) 25 July 2013 (25.07.2013) entire document	1-5, 7-10, 83, 84, 86, 87, 122-128
A	US 2002/0037328 A1 (BROWN) 28 March 2002 (28.03.2002) entire document	1-5, 7-10, 83, 84, 86, 87, 122-128
A	WO 2012/024367 A2 (DEL MAR PHARMACEUTICALS) 23 February 2012 (23.02.2012) entire document	1-5, 7-10, 83, 84, 86, 87, 122-128
P, X	"VAL-083: NSCLC Historical Review & Strategy for Product Differentiation," DelMar Pharmaceuticals, November 2014, Pgs. 1-24. Retrieved from the Internet:<http://www.delmarpharma.com/VAL-083-NSCLC1411.pdf> on 05 August 2015 (05.08.2015). entire document	1-5, 7-10, 83, 84, 86, 87, 122-128

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
05 August 2015	19 AUG 2015
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2015/024462

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-5, 7-10, 83, 84, 86, 87, and 122-128 will be searched to the extent that they read on NSCLC, dianhydrogalactitol, and continuous i.v. infusion for hours to days dose modification.

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2015/024462

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-153 are drawn to compositions and methods to improve the efficacy and/or reduce the side effects of the administration of a substituted hexitol derivative for treatment of a malignancy.

The first invention of Group I+ is restricted to compositions and methods to improve the efficacy and/or reduce the side effects of the administration of a substituted hexitol derivative for treatment of a malignancy, 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; 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; wherein the malignancy is selected to be non-small-cell lung carcinoma (NSCLC), and the substituted hexitol derivative is selected to be dianhydrogalactitol; and the factor or parameter is selected to be dose modification, specifically, the dose modification has been selected to be continuous i.v. infusion for hours to days. It is believed that claims 1-5, 7-10, 83, 84, 86, 87, and 122-128 read on this first named invention and thus these claims will be searched without fee to the extent that they read on NSCLC, dianhydrogalactitol, and continuous i.v. infusion for hours to days dose modification.

Applicant is invited to elect additional malignancies and/or factors/parameters to improve efficacy and/or reduce the side effects, and/or substituted hexitol derivatives to be searched in a specifor each composition or method to be searched in a specific combination by paying additional fee for each set of election. An exemplary election would be compositions and methods to improve the efficacy and/or reduce the side effects of the administration of a substituted hexitol derivative for treatment of a malignancy, 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; 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; wherein the malignancy is selected to be ovarian cancer, and the substituted hexitol derivative is selected to be diacetyldianhydrogalactitol; and the factor or parameter is selected to be route of administration.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 the lack the same or corresponding technical features for the following reasons:

The Groups I+ formulas do not share a significant structural element, requiring the selection of alternatives for the malignancy to be treated "treatment of a malignancy selected from the group consisting of non-small-cell lung carcinoma (NSCLC) and ovarian cancer"; the substituted hexitol derivative, "wherein the substituted hexitol derivative is selected from the group consisting of galactitols, substituted galacitols, dulcitols, and substituted dulcitols", and the factor or parameter associated with the efficacy and/or occurrence of side effects, "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; (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) dosage kits and packaging; (w) drug delivery systems; (x) drug conjugate forms; (y) compound analogs; (z) prodrugs; (aa) multiple drug systems; (ab) biotherapeutic enhancement; (ac) biotherapeutic resistance modulation; (ad) radiation therapy enhancement; (ae) novel mechanisms of action; (af) selective target cell population therapeutics; (ag) use with ionizing radiation; (ah) use with an agent that counteracts myelosuppression; and (aj) 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".

The Groups I+ share the technical features of compositions and methods to improve the efficacy and/or reduce the side effects of the administration of a substituted hexitol derivative for treatment of a malignancy of non-small-cell lung carcinoma (NSCLC) and ovarian cancer 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 the malignancy; 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 for treatment of the malignancy. However, these shared technical features do not represent a contribution over the prior art.

Specifically, WO 2013/110058 A2 to Bacha et al. discloses compositions and methods to improve the efficacy and/or reduce the side effects of the administration of a substituted hexitol derivative for treatment of a malignancy of non-small-cell lung carcinoma (NSCLC) and ovarian cancer (the present invention is a composition to improve the efficacy and/or reduce the side effects of suboptimally administered drug therapy employing a substituted hexitol derivative, Para. [0039]; a method to improve the efficacy and/or reduce the side effects of the administration of a substituted hexitol derivative for treatment, Para. [0036]; ovarian cancer, Para. [0227]; non-small cell lung cancer, Para. [0069]) 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 the malignancy (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, Para. [0036]); 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 for treatment of the malignancy (modifying the factor or parameter to improve the efficacy and/or reduce the side effects of the administration of the substituted hexitol derivative for treatment, Para. [0036]).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical features.