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DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR,
KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME,
MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ,
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WO 2014/004376 A3

(54) **Title:** METHODS FOR TREATING TYROSINE-KINASE-INHIBITOR-RESISTANT MALIGNANCIES IN PATIENTS WITH GENETIC POLYMORPHISMS OR AHI1 DYSREGULATIONS OR MUTATIONS EMPLOYING DIANHYDROGALACTITOL, DIACETYLDIANHYDROGALACTITOL, DIBROMODULCITOL, OR ANALOGS OR DERIVATIVES THEREOF

(57) **Abstract:** Methods and compositions suitable for the treatment of malignancies in subjects with a germline deletion polymorphism that blocks the activity of thymidine kinase inhibitors in triggering apoptosis in tumor cells or in subjects having a mutation in or a dysregulation of the *AHI1* gene are disclosed. These methods employ an alkylating hexitol derivative such as dianhydrogalactitol, a derivative or analog of dianhydrogalactitol, diacetyldianhydrogalactitol, a derivative or analog of diacetyldianhydrogalactitol, dibromodulcitol, and a derivative or analog of dibromodulcitol. The compositions can include such alkylating hexitol derivatives. The methods can further include administration of a BH3 mimetic, and the compositions can further include a BH3 mimetic. In subjects having a dysregulation of the *AHI1* gene, the methods can further include the administration of an agent modulating the expression or activity of the *AHI1* gene or AHI1 protein, and the compositions can further include such an agent.

INTERNATIONAL SEARCH REPORT

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International application No.

PCT/US2013/047320

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 38/12 (2014.01)

USPC - 514/19.6

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 38/12; A61P 35/00, 35/02; C07K 7/08; C12Q 1/68 (2014.01)

USPC - 424/9.2; 435/6.14; 514/1.1, 18.9, 19.3, 19.4, 19.6, 19.9, 21.1; 530/300; 702/20

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

CPC - A61K 38/00, 49/0004; C12Q 1/6886; G06F 19/22 (2013.01)

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

Orbit, Google Patents, Google Scholar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X - Y	US 2007/0154931 A1 (RADICH et al.) 05 July 2007 (05.07.2007) entire document	1, 4-7, 17, 31, 32, 47 ----- 2, 3, 12-16, 18, 33-36, 48-56, 109-113
Y	ZHOU et al. "AHI-1 interacts with BCR-ABL and modulates BCR-ABL transforming activity and imatinib response of CML stem/progenitor cells" J. Exp. Med. Vol. 205(11): 2657-2671, 20 October 2008. entire document	2, 3, 35, 36, 109-113
Y	US 2012/0149648 A1 (NASH et al) 14 June 2012 (14.06.2012) entire document	12-16, 18, 33, 51-56
Y	US 2011/0287003 A1 (PATEL et al) 24 November 2011 (24.11.2011) entire document	34
Y	WO 2012/082074 A1 (RUAN et al) 21 June 2012 (21.06.2012) entire document	48-50
A	US 2012/0053063 A1 (RIGATTI et al) 01 March 2012 (01.03.2012) entire document	1-7, 12-18, 31-36, 47-56, 109-113
A	PONASSI et al. "A novel Bim-BH3-derived Bcl-XL inhibitor." Cell Cycle 7(20): 3211-3224. 15 October 2008. entire document	1-7, 12-18, 31-36, 47-56, 109-113
A	PELLICANO et al. "Assembling defenses against therapy-resistant leukemic stem cells: Bcl6 joins the ranks" J. Exp. Med. Vol. 208(11): 2155-2158. 24 October 2011. entire document	1-7, 12-18, 31-36, 47-56, 109-113

 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

07 January 2014

Date of mailing of the international search report

24 JAN 2014

Name and mailing address of the ISA/US

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2013/047320 24.01.2014
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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:

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.:
1-7, 12, 13-18, 31-36, 47-56, 109-113, limited to wherein the alkylating hexitol derivative is selected to be dianhydrogalactitol; and further comprising the step of administering a therapeutically effective quantity of a tyrosine kinase inhibitor to the subject, wherein the tyrosine kinase inhibitor is selected to be a BH3 mimetic, and wherein the BH3 mimetic is selected to be a peptide.

- 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.