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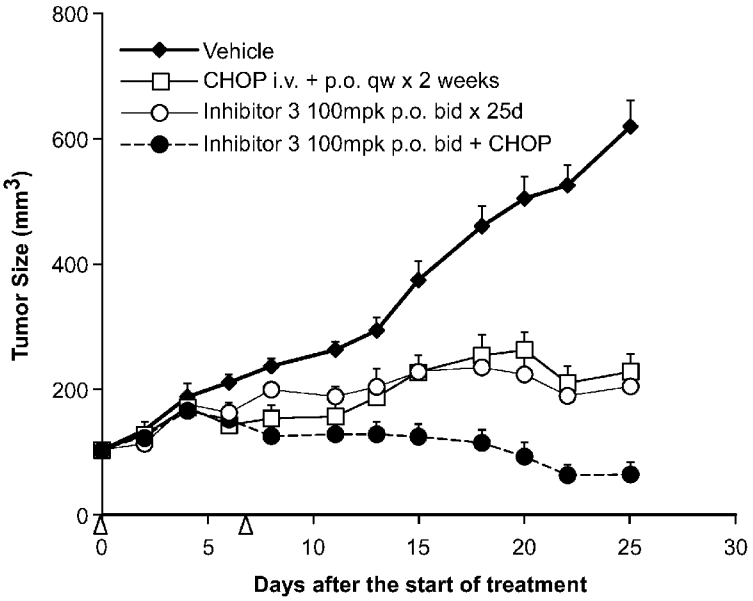
[Continued on next page]

(54) Title: COMBINATIONS OF EZH2 INHIBITORS WITH FURTHER AGENTS FOR USE IN THE TREATMENT OF CANCER

(57) Abstract: Provided herein are methods methods of treating cancer using an effective amount of an EZH2 inhibitor and an effective amount of a second agent. Also provided are compositions comprising an EZH2 inhibitor and an effective amount of a second agent.

FIG. 1



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TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

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INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/404 A61K31/4045 A61K31/52 A61K31/573 A61P35/00
ADD.

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)
A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, FSTA, INSPEC, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2015/085325 A1 (EPIZYME INC [US]) 11 June 2015 (2015-06-11) claims 1,2,4,13,17 page 10, paragraph 048 -----	1,3, 13-15, 17,28,30
X	WO 2013/155464 A1 (EPIZYME INC [US]) 17 October 2013 (2013-10-17) claims 3,5,12,35-37 page 1, paragraph 002 -----	1,3, 13-17,30

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* 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
16 December 2016	24/01/2017

Name and mailing address of the ISA/	Authorized officer
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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BALASUBRAMANIAN VIDYA ET AL: "CPI-169, a novel and potent EZH2 inhibitor, synergizes with CHOP in vivo and achieves complete regression in lymphoma xenograft models", CANCER RESEARCH, vol. 74, no. 19, Suppl. S, October 2014 (2014-10), page 1697, XP002761414, & 105TH ANNUAL MEETING OF THE AMERICAN-ASSOCIATION-FOR-CANCER-RESEARCH (AACR); SAN DIEGO, CA, USA; APRIL 05 -09, 2014 abstract -----	1,3,11, 14,15
X	KNUTSON SARAH K ET AL: "Synergistic Anti-Tumor Activity of EZH2 Inhibitors and Glucocorticoid Receptor Agonists in Models of Germinal Center Non-Hodgkin Lymphomas", PLOS ONE, vol. 9, no. 12, December 2014 (2014-12), pages 1-22, XP002761415, page 1, abstract -----	1,3, 13-15
X	WO 2009/058102 A1 (AGENCY SCIENCE TECH & RES [SG]; YU QIANG [SG]) 7 May 2009 (2009-05-07) paragraphs [0231], [0249], [0259] -----	1,3,16
X	ROY B C ET AL: "Role of bacterial infection in the epigenetic regulation of Wnt antagonist WIF1 by PRC2 protein EZH2", ONCOGENE, vol. 34, no. 34, 8 December 2014 (2014-12-08), pages 1-12, XP002765289, DOI: 10.1038/onc.2014.386 page 1, abstract -----	1,3,16
X	FISKUS WARREN ET AL: "Combined Targeting of Chromatin Modifying Enzymes LSD1, EZH2 and Histone Deacetylases (HDACs) Has Superior Efficacy Against Human Mantle Cell Lymphoma Cells", BLOOD, vol. 118, no. 21, 18 November 2011 (2011-11-18), page 2429, XP002765290, & 53RD ANNUAL MEETING AND EXPOSITION OF THE AMERICAN-SOCIETY-OF-HEMATOLOGY (ASH); SAN DIEGO, CA, USA; DECEMBER 10 -13, 2011 abstract -----	1,3,7,15

-/--

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ZHANG KEJIE ET AL: "Reversing Metabolic and Epigenetic Cellular Alterations to Overcome Chemo-Resistance in Aggressive B Cell Lymphomas", BLOOD, vol. 120, no. 21, 16 November 2012 (2012-11-16), page 1305, XP002765291, & 54TH ANNUAL MEETING AND EXPOSITION OF THE AMERICAN-SOCIETY-OF-HEMATOLOGY (ASH); ATLANTA, GA, USA; DECEMBER 08 -11, 2012 abstract ----- GUPTA MAMTA ET AL: "SHP1 Suppression In Diffuse Large B Cell Lymphoma Is Regulated Through Promoter Hypermethylation At Novel CpG2 Island and H3K27 Trimethylation Histone Mark", BLOOD, vol. 122, no. 21, 15 November 2013 (2013-11-15), page 632, XP002765292, & 55TH ANNUAL MEETING OF THE AMERICAN-SOCIETY-OF-HEMATOLOGY; NEW ORLEANS, LA, USA; DECEMBER 07 -10, 2013 abstract ----- D. SASAKI ET AL: "Overexpression of enhancer of zeste homolog 2 with trimethylation of lysine 27 on histone H3 in adult T-cell leukemia/lymphoma as a target for epigenetic therapy", HAEMATOLOGICA, THE HEMATOLOGY JOURNAL : OFFICIAL ORGAN OF THE EUROPEAN HEMATOLOGY ASSOCIATION, vol. 96, no. 5, 1 May 2011 (2011-05-01), pages 712-719, XP055313186, IT ISSN: 0390-6078, DOI: 10.3324/haematol.2010.028605 page 712, abstract ----- A. CHASE ET AL: "Aberrations of EZH2 in Cancer", CLINICAL CANCER RESEARCH, vol. 17, no. 9, 2 March 2011 (2011-03-02), pages 2613-2618, XP055169734, ISSN: 1078-0432, DOI: 10.1158/1078-0432.CCR-10-2156 page 2616, left-hand column, last paragraph page 2616, right-hand column, paragraph 1 ----- -/--	1,3,15 1,3,7,15 1,3,7,15 1,3,7, 15,16

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YAMAGUCHI J ET AL: "Histone deacetylase inhibitor (SAHA) and repression of EZH2 synergistically inhibit proliferation of gallbladder carcinoma", CANCER SCIENCE, JAPANESE CANCER ASSOCIATION, TOKYO, JP, vol. 101, no. 2, 1 February 2010 (2010-02-01), pages 355-362, XP002718696, ISSN: 1347-9032, DOI: 10.1111/J.1349-7006.2009.01387.X [retrieved on 2009-10-06] page 355, abstract -----	1,3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/044157

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 additional 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 an 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.:

1, 3, 4, 7, 11-17, 19, 20, 23(completely); 28-30(partially)

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.:

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 4, 20(completely); 1, 3, 11-17, 19, 28-30(partially)

   An EZH2 inhibitor in combination with a phthalimide for use in the treatment of cancer

   ---

2. claims: 5, 21(completely); 1, 3, 11-17, 19, 28-30(partially)

   An EZH2 inhibitor in combination with an anti-inflammatory steroid for use in the treatment of cancer

   ---

3. claims: 6, 22(completely); 1, 3, 11-17, 19, 28-30(partially)

   An EZH2 inhibitor in combination with a PI3K inhibitor for use in the treatment of cancer

   ---

4. claims: 8, 24, 25(completely); 1, 3, 11-17, 19, 28-30(partially)

   An EZH2 inhibitor in combination with an LSD1 inhibitor for use in the treatment of cancer

   ---

5. claims: 7, 23(completely); 1, 3, 11-17, 19, 28-30(partially)

   An EZH2 inhibitor in combination with a histone deacetylase inhibitor for use in the treatment of cancer

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6. claims: 9, 26(completely); 1, 3, 11-17, 19, 28-30(partially)

   An EZH2 inhibitor in combination with CHOP (cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone) or CHOP and rituximab for use in the treatment of cancer

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7. claims: 1, 11-17, 28-30(all partially)

   An EZH2 inhibitor in combination with prednisolone for use in the treatment of cancer

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8. claims: 1, 11-17, 28-30(all partially)

   An EZH2 inhibitor in combination with bortezomib for use in the treatment of cancer

   ---

9. claims: 1, 11-17, 28-30(all partially)

   An EZH2 inhibitor in combination with a bromodomain-targeted

compound for use in the treatment of cancer
---

10. claims: 1, 11-17, 28-30(all partially)

An EZH2 inhibitor in combination with ibrutinib for use in the treatment of cancer
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11. claims: 2, 10, 18, 27(completely); 11-17, 28-30(partially)

An EZH2 inhibitor in combination with an alkylating neoplastic agent for use in the treatment of cancer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/044157

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2015085325 A1	11-06-2015	AU 2014360078 A1	09-06-2016
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