



SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, KM, ML, MR, NE, SN, TD, TG).

— *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))*

Published:

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

(88) Date of publication of the international search report:

31 August 2017

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/065447

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.: 1-24, 27, 31, 32, 36-56(all partially)
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:
see FURTHER INFORMATION sheet PCT/ISA/210

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.:

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.:
25, 26(completely); 1-24, 27, 31, 32, 36-56(partially)

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/US2016/065447

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/5377 C12Q1/68 A61P35/02
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 C12Q
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, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	S. K. KNUTSON ET AL: "Selective Inhibition of EZH2 by EPZ-6438 Leads to Potent Antitumor Activity in EZH2-Mutant Non-Hodgkin Lymphoma", MOLECULAR CANCER THERAPEUTICS, vol. 13, no. 4, 1 April 2014 (2014-04-01), pages 842-854, XP055247668, US ISSN: 1535-7163, DOI: 10.1158/1535-7163.MCT-13-0773 abstract; table 1 ----- -/--	1-27,31, 32,36-56

Further documents are listed in the continuation of Box C.

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 19 May 2017	Date of mailing of the international search report 26/07/2017
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Borst, Markus

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2016/065447

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	V RIBRAG: "Phase 1 Study of Tazemetostat (EPZ-6438), an Inhibitor of Enhancer of Zeste-Homolog 2 (EZH2): Preliminary Safety and Activity in Relapsed or Refractory Non-Hodgkin Lymphoma (NHL) Patients", 57TH ANNUAL MEETING OF THE AMERICAN-SOCIETY-OF-HEMATOLOGY; ORLANDO, FL, USA, 3 December 2015 (2015-12-03), XP055362197, abstract; section "Results"	1-27,31, 32,36-56
Y	M. TESTONI ET AL: "Genetic lesions in diffuse large B-cell lymphomas", ANNALS OF ONCOLOGY., vol. 26, no. 6, 20 January 2015 (2015-01-20), pages 1069-1080, XP055361604, NL ISSN: 0923-7534, DOI: 10.1093/annonc/mdv019 figure 2	1-27,31, 32,36-56
Y	LAURA PASQUALUCCI ET AL: "Inactivating mutations of acetyltransferase genes in B-cell lymphoma", NATURE, vol. 471, no. 7337, 10 March 2011 (2011-03-10), pages 189-195, XP055361688, United Kingdom ISSN: 0028-0836, DOI: 10.1038/nature09730 section "EP300 mutations in DLBCL and follicular lymphoma & Laura Pasqualucci ET AL: "Inactivating mutations of acetyltransferase genes in B-cell lymphoma SUPPLEMENTARY INFORMATION", NATURE, vol. 471, no. 7337, 10 March 2011 (2011-03-10), pages 189-195, XP055362291, United Kingdom ISSN: 0028-0836, DOI: 10.1038/nature09730 1-27, 31-32, 36-56	1-27,31, 32,36-56

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 25, 26(completely); 1-24, 27, 31, 32, 36-56(partially)

EHZ2 inhibitor for use in treating cancer in a patient carrying at least one mutation occurring in a sequence of EP300 gene or a sequence encoding histone acetyl transferase p300, wherein the mutation results in a substitution of tyrosine (Y) for aspartic acid (D) at position 1467 of histone acetyltransferase p300 (D1467Y) or in a substitution of serine (S) for phenylalanine (F) at position 1289 of histone acetyltransferase p300 (F1289S)

2. claims: 28-30(completely); 1-24, 27, 31, 32, 36-56(partially)

EHZ2 inhibitor for use in treating cancer in a patient carrying at least one mutation occurring in a sequence of a CREB binding protein gene or in a sequence encoding CREBBP, wherein EP300 gene or a sequence encoding histone acetyl transferase p300, wherein the mutation results in a substitution of phosphate (P) for threonine (T) at position 1494 of CREBBP (T1494P) or in a substitution of arginine (R) for Leucine (L) at position 1446 of CREBBP (L1446R) or in a substitution of Leucine (L) for phosphate (P) at position 1499 of CREBBP (P1499L)

3. claims: 33-35(completely); 1-24, 27, 31, 32, 36-56(partially)

EHZ2 inhibitor for use in treating cancer in a patient carrying at least one mutation occurring in a sequence of EZH2 protein, wherein the mutation results in a substitution of any amino acid other than tyrosine (Y) for tyrosine (Y) at position 64 (Y641X) or in a substitution of any amino acid other than alanine (A) for alanine (A) at position 682 (A682X), or in a substitution of any amino acid other than alanine (A) for alanine (A) at position 692 (A692X), or in a substitution of tyrosine (Y) for Leucine (L) at position 646 (Y646F/H/N/S)

4. claims: 1-24, 27, 31, 32, 36-56(all partially)

EHZ2 inhibitor for use in treating cancer in a patient carrying at least one mutation occurring in a sequence of STAT6, wherein the mutation results in a substitution of glycine (G)/alanine (A)/histidine (H)/tyrosine (Y) for aspartate (D) at position 419 (D419G/A/H/Y) or in a substitution of arginine (R) for glutamine (Q) at position 286 Q286R, or in a substitution of serine (S) for asparagine (N) at position 417 (N417S), or in a substitution of arginine (R) for cysteine (C) at position 371 (C371R), or in a substitution of lysine (K) for glutamate (E) at position

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

377 (E377K)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 1-24, 27, 31, 32, 36-56(all partially)

Claims 1-56 are directed to the treatment of cancer in a patient having at least one mutation in one or more sequences encoding a huge list of proteins. Tables 1-9 and figures 15-16 list genes of mutant cancer genes. From tables 15, 17-19 and figures 9, 10, 19-22 it emanates that the same gene mutations frequently occur in the responder as well as in the non-responder group. This means that in the absence of a further characterisation of the mutation, i.e. by defining the position and the change of amino acid, it is not predictable whether the patient will or will not respond to EZH2 inhibitor therapy. In fact as outlined in the application itself [0116] mutations can induce a gain as well as a loss of function and, hence, depending on their biological effect may increase or decrease responsiveness to cancer treatment. Since the problem to be solved with the application on file is to provide an effective cancer therapy, the disclosure provided can be considered sufficient only insofar as the specific mutations characterising a responder or non-responder group are disclosed. This requirement is fulfilled for the following specific mutations:

- p300 D1467Y and F1289S (claims 25-26)
-
- CREBBP T1494P, L1446R and P1499L (claims 28-30)
- EZH2 Y641X, A682X, A692X (claims 33-35) and Y646F/H/N/S (table 16)
- STAT6 D419G/A/H/Y;
- Q286R; N417S; R371C; K377E (table 20 and claim 38, 47).

The subject-matter of claims 1-24, 27, 31-32, 36-56, therefore, is not sufficiently disclosed (Article 5 PCT) nor supported by the description (Article 6 PCT), insofar as the mutations are not characterised therein. In view of this lack of disclosure and support a meaningful search can be performed only for the subject-matter claims 25-26, 28-30, 33-35 (whole claims) and for claims 1-24, 27, 31-32, 36-56 insofar as they cover the aforementioned mutations (partial claims). Due to the concomitant lack of unity the scope of the search will be further limited to those inventions for which search fees have been paid.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guidelines C-IV, 7.2), should the problems which led to the Article 17(2) declaration be overcome.