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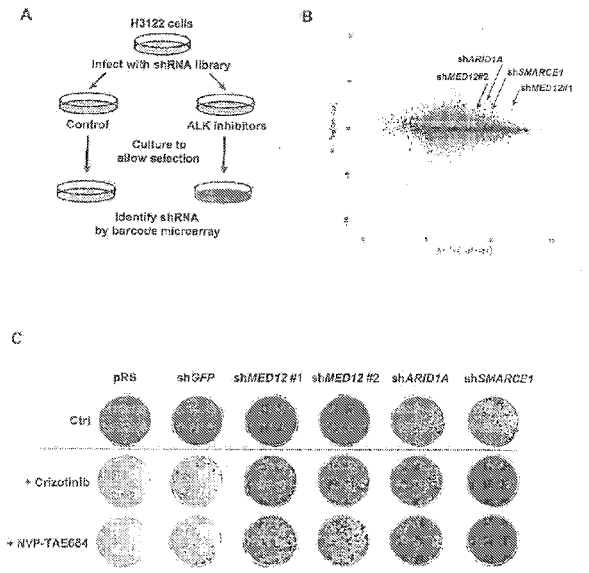
Published:

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

[Continued on next page]

(54) **Title**: METHODS AND COMPOSITIONS FOR PREDICTING RESISTANCE TO ANTICANCER TREATMENT WITH PROTEIN KINASE INHIBITORS

Fig 1



(57) **Abstract**: The instant application provides methods and related compositions pertaining to the identification of resistance to anticancer treatment in a patient. In a particular embodiment, the invention provides biomarkers for the identification of resistance to anticancer treatment in a lung cancer patient, wherein a reduced expression of a MEDIATOR and/or SW1/SNF complex gene in the lung cancer cells of the patient indicates that the lung cancer cells in the patient may be resistant to treatment with a receptor tyrosine kinase inhibitor, such as gefitinib and/or erlotinib. In some embodiments, the invention relates to methods and related compositions for predicting resistance to anticancer treatment by detecting the expression levels of one or more TGF-beta pathway nucleic acids and/or proteins.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
INV. C12Q1/68
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)
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, Sequence Search, 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	WO 2010/123982 A2 (FOX CHASE CANCER CT [US]; GODWIN ANDREW [US]; EISENBERG BURTON [US]; S) 28 October 2010 (2010-10-28) claim 1; table 2 ----- -/--	1-7, 19-27, 32-40, 43,44, 47,49, 51,52, 55,57, 59, 62-73, 77-94

[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
7 November 2012	14/11/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Santagati, Fabio

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/032202

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.:

4-7, 26, 27, 40, 47, 52, 55, 59, 127-153(completely); 1-3, 19-25, 32-39, 43 44, 49, 51, 57, 62-73, 77-94(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.

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2009/062199 A1 (FOX CHASE CANCER CT [US]; ASTSATUROV IGOR [US]; GOLEMIS ERICA A [US];) 14 May 2009 (2009-05-14) claims 23, 24; table 2	1-7, 19-27, 32-40, 43,44, 71-73, 77-81, 86-94
A	B. DAI ET AL: "STAT3 Mediates Resistance to MEK Inhibitor through MicroRNA miR-17", CANCER RESEARCH, vol. 71, no. 10, 28 March 2011 (2011-03-28), pages 3658-3668, XP55034370, ISSN: 0008-5472, DOI: 10.1158/0008-5472.CAN-10-3647 the whole document	1-7, 19-27, 32-40, 43,44, 71-73, 77-81, 86-94
Y	B. LUO ET AL: "Highly parallel identification of essential genes in cancer cells", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, vol. 105, no. 51, 23 December 2008 (2008-12-23), pages 20380-20385, XP55034447, ISSN: 0027-8424, DOI: 10.1073/pnas.0810485105 figure 4d	1-7, 19-27, 32-40, 43,44, 47,49, 51,52, 55,57, 59, 62-73, 77-94
A	QUENTMEIER HILMAR ET AL: "BCR-ABL1-independent PI3Kinase activation causing imatinib-resistance", JOURNAL OF HEMATOLOGY & ONCOLOGY, BIOMED CENTRAL LTD, LONDON UK, vol. 4, no. 1, 7 February 2011 (2011-02-07), page 6, XP021091168, ISSN: 1756-8722, DOI: 10.1186/1756-8722-4-6 figure 4	22-25
X	WO 2010/015538 A2 (HOFFMANN LA ROCHE [CH]; DELMAR PAUL [CH]; DELORD JEAN-PIERRE [FR]; ROC) 11 February 2010 (2010-02-11) claim 1; table 2	1-7, 19-27, 32-40, 43,44, 71-73, 77-81, 86-94

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	"Affymetrix Human Genome U133 Plus 2.0 Array", GENE EXPRESSION OMNIBUS, 7 November 2003 (2003-11-07), XP002627319, [retrieved on 2003-11-07] the whole document	47,49, 51,52
A	WO 02/44420 A2 (WYETH CORP [US]; GILLIS KIMBERLY A [US]; ZHANG YIXIAN [US]) 6 June 2002 (2002-06-06) the whole document	47,49, 51,52
X	WO 2006/104761 A2 (EXAGEN DIAGNOSTICS INC [US]; DAVIS LISA [US]; TANG LEI [US]) 5 October 2006 (2006-10-05) sequences 1-188	55,57, 59, 62-70, 82-85
X	WO 2004/046386 A1 (GENOMIC HEALTH INC [US]; VALL D HEBRON UNIVERSITY HOSPI [ES]; BAKER JO) 3 June 2004 (2004-06-03) claim 2; examples 1, 2; table 3	127-153
X,P	WO 2011/112678 A1 (DANA FARBER CANCER INST INC [US]; BROAD INST INC [US]; GARRAWAY LEVI A) 15 September 2011 (2011-09-15) claims 1, 6; tables 4, 5	127-135
X	WO 2008/086342 A2 (SQUIBB BRISTOL MYERS CO [US]; HUANG FEI [US]; CLARK EDWIN A [US]; WANG) 17 July 2008 (2008-07-17) paragraph [0058]; claim 13e; table 2	127-135
X	HONG C C ET AL: "Receptor tyrosine kinase AXL is induced by chemotherapy drugs and overexpression of AXL confers drug resistance in acute myeloid leukemia", CANCER LETTERS, NEW YORK, NY, US, vol. 268, no. 2, 18 September 2008 (2008-09-18), pages 314-324, XP023612548, ISSN: 0304-3835, DOI: 10.1016/J.CANLET.2008.04.017 [retrieved on 2008-05-27] the whole document	127-135

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KATRIINA PELTOLA ET AL: "Pim-1 Kinase Expression Predicts Radiation Response in Squamocellular Carcinoma of Head and Neck and Is under the Control of Epidermal Growth Factor Receptor", NEOPLASIA, vol. 11, no. 7, 1 July 2009 (2009-07-01), pages 629-636, XP55043023, DOI: 10.1593/neo.81038 the whole document -----	127-135
A	A. V. TUTTER ET AL: "Role for Med12 in Regulation of Nanog and Nanog Target Genes", JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 284, no. 6, 1 January 2008 (2008-01-01), pages 3709-3718, XP55042934, ISSN: 0021-9258, DOI: 10.1074/jbc.M805677200 figures 2, 4 -----	127-154

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2012/032202

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WO 2009062199 A1	14-05-2009	US 2010239656 A1	23-09-2010
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		WO 2008086342 A2	17-07-2008

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 4-7, 26, 27, 40, 47, 52, 55, 59(completely); 1-3, 19-25, 32-39, 43, 44, 49, 51, 57, 62-73, 77-94(partially)

   Method of evaluating and/or predicting resistance to anticancer treatment in a patient in need thereof, comprising (a) measuring expression levels or detecting an inactivating mutation or measuring activity of one or more SWI/SNF complex nucleic acid and/or proteins in the patient. A microarray comprising probes complementary to a gene of the SWI/SNF complex. A kit comprising a pair of primers specific for a gene of the SWI/SNF complex.

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2. claims: 8-11, 28-30, 41, 48, 53, 56, 60, 115-126(completely); 1-3, 19-25, 32-39, 43, 44, 49, 51, 57, 62-73, 77-94(partially)

   Method of evaluating and/or predicting resistance to anticancer treatment in a patient in need thereof, comprising (a) measuring expression levels or detecting an inactivating mutation or measuring activity of one or more MEDIATOR complex nucleic acid and/or proteins in the patient. A microarray comprising probes complementary to a gene of the MEDIATOR complex. A kit comprising a pair of primers speific for a gene of the MEDIATOR complex. Method of evaluating and/or predicting resistance to anticancer treatment in a patient in need thereof, comprising (a) measuring expression levels of MED12 and one or more markers of an EMT-like phenotype.

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3. claims: 12-18, 31, 42, 45, 46, 50, 54, 58, 61, 74-76(completely); 19-25, 32-39, 51, 62-70, 77-94(partially)

   Method of evaluating and/or predicting resistance to anticancer treatment in a patient in need thereof, comprising (a) measuring expression levels or detecting an inactivating mutation or measuring activity of one or more RAS-GAP nucleic acid and/or proteins in the patient. A microarray comprising probes complementary to a RAS-GAP gene. A kit comprising a pair of primers specific for a RAS-GAP gene.

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4. claims: 95-113, 154

   Method of treating resistance to one or more inhibitors of ERK activation in a patient in need thereof, comprising administering to the patient at least one inhibitor of the TGF-beta pathway in combination with the one or more inhibitors of ERK activation. Method of evaluating and/or

predicting resistance to anticancer treatment in a patient in need thereof, comprising (a) measuring expression levels, or detecting inactivating mutations or measuring activity of one or more TGFbeta pathway nucleic acid and/or proteins. method of identifying an inhibitor of ERK activation, comprising: measuring MED12/TGFbeta binding in the presence and absence of a test compound.

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5. claim: 114

Method of identifying an inhibitor of TGFbeta pathway activation, comprising: measuring MED12/TGFbeta binding in the presence and absence of a test compound.

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6. claims: 127-153

Method of evaluating and/or predicting resistance to anticancer treatment in a patient in need thereof comprising: measuring expression levels of one or more MED12KD signature nucleic acid and/or proteins.
