(12) **Translation of European patent specification**

(11) **NO/EP 3068393 B1**

NORWAY

(19) NO

(51) Int Cl.

A61K 31/451 (2006.01) ***A61K 31/7068 (2006.01)***
A61K 31/706 (2006.01) ***A61P 35/02 (2006.01)***

Norwegian Industrial Property Office

(45)	Translation Published	2022.08.15
(80)	Date of The European Patent Office Publication of the Granted Patent	2022.03.09
(86)	European Application Nr.	14805743.3
(86)	European Filing Date	2014.11.11
(87)	The European Application's Publication Date	2016.09.21
(30)	Priority	2013.11.11, US, 201361902717 P
(84)	Designated Contracting States:	AL; AT; BE; BG; CH; CY; CZ; DE; DK; EE; ES; FI; FR; GB; GR; HR; HU; IE; IS; IT; LI; LT; LU; LV; MC; MK; MT; NL; NO; PL; PT; RO; RS; SE; SI; SK; SM; TR
	Designated Extension States:	BA; ME
(73)	Proprietor	Amgen Inc., One Amgen Center Drive, Thousand Oaks, California 91320-1799, USA
(72)	Inventor	CAENEPEEL, Sean, 2090 Stonehill Circle, Thousand Oaks, CA 91360, USA CANON, Jude, 13240 Fiji Way, Unit A, Marina Del Rey, California 90292, USA HUGHES, Paul, 909 14th Street 1, Santa Monica, California 90403, USA OLINER, Jonathan D., P.O Box 55, Garrett Park, MD 20896, USA RICKLES, Richard J., 10 Knowles Farm Road, Arlington, Massachusetts 02474, USA SAIKI, Anne Y., 4473 Cedarglen Court, Moorpark, California 93021, USA
(74)	Agent or Attorney	BRYN AARFLOT AS, Stortingsgata 8, 0161 OSLO, Norge

(54) Title **COMBINATION THERAPY INCLUDING AN MDM2 INHIBITOR AND ONE OR MORE ADDITIONAL PHARMACEUTICALLY ACTIVE AGENTS FOR THE TREATMENT OF CANCERS**

(56) References Cited:

US-A1-2012 196 823, US-A1-2012 077 683, US-A1-2011 319 378, US-A1-2013 245 039,
ZHANG W ET AL: "Blockade of mitogen-activated protein kinase/extracellular signal-regulated kinase kinase and murine double minute synergistically induces Apoptosis in acute myeloid leukemia via BH3-only proteins Puma and Bim", CANCER RESEARCH, vol. 70, no. 6, 15 March 2010 (2010-03-15) , pages 2424-2434, XP002740443, ISSN: 1538-7445, DOI: 10.1158/0008-5472.CAN-09-0878
JI Z ET AL: "p53 rescue through HDM2 antagonism suppresses melanoma growth and potentiates MEK inhibition", JOURNAL OF INVESTIGATIVE DERMATOLOGY, NATURE PUBLISHING GROUP, US, vol. 132, no. 2, 1 February 2012 (2012-02-01), pages 356-364, XP002694638, ISSN: 1523-1747, DOI: 10.1038/JID.2011.313 [retrieved on 2011-10-13]

KOJIMA KENSUKE ET AL: "Mitogen-activated protein kinase kinase inhibition enhances nuclear proapoptotic function of p53 in acute myelogenous leukemia cells", CANCER RESEARCH 1 APR 2007, vol. 67, no. 7, 1 April 2007 (2007-04-01), pages 3210-3219, XP002740444, ISSN: 0008-5472
J. M. GOZGIT ET AL: "Potent Activity of Ponatinib (AP24534) in Models of FLT3-Driven Acute Myeloid Leukemia and Other Hematologic Malignancies", MOLECULAR CANCER THERAPEUTICS, vol. 10, no. 6, 11 April 2011 (2011-04-11) , pages 1028-1035, XP055056925, ISSN: 1535-7163, DOI: 10.1158/1535-7163.MCT-10-1044
LONG JIANTING ET AL: "Multiple distinct molecular mechanisms influence sensitivity and resistance to MDM2 inhibitors in adult acute myelogenous leukemia", BLOOD 8 JUL 2010, vol. 116, no. 1, 8 July 2010 (2010-07-08), pages 71-80, XP002740447, ISSN: 1528-0020
FENG JIANHUA ET AL: "Stabilization of Mdm2 via decreased ubiquitination is mediated by protein kinase B/Akt-dependent phosphorylation", THE JOURNAL OF BIOLOGICAL CHEMISTRY 20 AUG 2004, vol. 279, no. 34, 20 August 2004 (2004-08-20), pages 35510-35517, XP002740653, ISSN: 0021-9258
ZAULI GIORGIO ET AL: "Dasatinib plus Nutlin-3 shows synergistic antileukemic activity in both p53 wild-type and p53 mutated B chronic lymphocytic leukemias by inhibiting the Akt pathway", CLINICAL CANCER RESEARCH : AN OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH 15 FEB 2011, vol. 17, no. 4, 15 February 2011 (2011-02-15), pages 762-770, XP002740448, ISSN: 1078-0432
TIANJUN ZHOU ET AL: "Structural Mechanism of the Pan-BCR-ABL Inhibitor Ponatinib (AP24534): Lessons for Overcoming Kinase Inhibitor Resistance", CHEMICAL BIOLOGY & DRUG DESIGN, vol. 77, no. 1, 30 November 2010 (2010-11-30), pages 1-11, XP055065379, ISSN: 1747-0277, DOI: 10.1111/j.1747-0285.2010.01054.x
KHOURY H JEAN ET AL: "Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure", BLOOD 12 APR 2012, vol. 119, no. 15, 12 April 2012 (2012-04-12), pages 3403-3412, XP002740449, ISSN: 1528-0020
KOJIMA KENSUKE ET AL: "Concomitant inhibition of MDM2 and Bcl-2 protein function synergistically induce mitochondrial apoptosis in AML", CELL CYCLE (GEORGETOWN, TEX.) DEC 2006, vol. 5, no. 23, December 2006 (2006-12), pages 2778-2786, XP002740450, ISSN: 1551-4005
BOSE P ET AL: "Mcl-1 as a therapeutic target in acute myelogenous leukemia (AML)", LEUKEMIA RESEARCH REPORTS 2013 ELSEVIER LTD GBR, vol. 2, no. 1, 22 January 2013 (2013-01-22), pages 12-14, XP002740451, ISSN: 2213-0489
LU WENGE ET AL: "Activation of p53 by roscovitine-mediated suppression of MDM2 expression", ONCOGENE, NATURE PUBLISHING GROUP, GB, vol. 20, no. 25, 31 May 2001 (2001-05-31), pages 3206-3216, XP002292792, ISSN: 0950-9232, DOI: 10.1038/SJ.ONC.1204412
KAO CHIA-LI ET AL: "Rapamycin increases the p53/MDM2 protein ratio and p53-dependent apoptosis by translational inhibition of mdm2 in cancer cells", CANCER LETTERS 28 DEC 2009, vol. 286, no. 2, 28 December 2009 (2009-12-28), pages 250-259, XP002740446, ISSN: 1872-7980
CHITHRA D PALANI ET AL: "Histone deacetylase inhibitors enhance the anticancer activity of nutlin-3 and induce p53 hyperacetylation and downregulation of MDM2 and MDM4 gene expression", INVESTIGATIONAL NEW DRUGS ; THE JOURNAL OF NEW ANTICANCER AGENTS, KLUWER ACADEMIC PUBLISHERS, BO, vol. 30, no. 1, 3 August 2010 (2010-08-03) , pages 25-36, XP035000732, ISSN: 1573-0646, DOI: 10.1007/S10637-010-9510-7
NAGMA KHAN ET AL: "Determination of the class and isoform selectivity of small-molecule histone deacetylase inhibitors", BIOCHEMICAL JOURNAL, vol. 409, no. 2, 15 January 2008 (2008-01-15), page 581, XP055074060, ISSN: 0264-6021, DOI: 10.1042/BJ20070779
MARTINELLI E ET AL: "Antitumor activity of pimasertib, a selective MEK 1/2 inhibitor, in combination with PI3K/mTOR inhibitors or with multi-targeted kinase inhibitors in pimasertib-resistant human lung and colorectal cancer cells", INTERNATIONAL JOURNAL OF CANCER. JOURNAL INTERNATIONAL DU CANCER NOV 2013, vol. 133, no. 9, 30 April 2013 (2013-04-30), pages 2089-2101, XP002740445, ISSN: 1097-0215
FALCHOOK G S ET AL: "Activity of the oral MEK inhibitor trametinib in patients with advanced melanoma: a phase 1 dose-escalation trial", LANCET ONCOLOGY, LANCET PUBLISHING GROUP, LONDON, GB, vol. 13, no. 8, 1 August 2012 (2012-08-01) , pages 782-789, XP002727794, ISSN: 1470-2045, DOI: 10.1016/S1470-2045(12)70269-3 [retrieved on 2012-07-16]

WANG ET AL: "Clinical experience of MEK inhibitors in cancer therapy", BIOCHIMICA ET BIOPHYSICA ACTA. MOLECULAR CELL RESEARCH, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 1773, no. 8, 1 August 2007 (2007-08-01), pages 1248-1255, XP022181677, ISSN: 0167-4889, DOI: 10.1016/J.BBAMCR.2006.11.009
LIU DINGXIE ET AL: "Potent inhibition of thyroid cancer cells by the MEK inhibitor PD0325901 and its potentiation by suppression of the PI3K and NF-kappaB pathways", THYROID : OFFICIAL JOURNAL OF THE AMERICAN THYROID ASSOCIATION AUG 2008, vol. 18, no. 8, August 2008 (2008-08), pages 853-864, XP002740459, ISSN: 1050-7256
FLAHERTY KEITH T ET AL: "Combined BRAF and MEK Inhibition in Melanoma with BRAF V600 Mutations", NEW ENGLAND JOURNAL OF MEDICINE, MASSACHUSETTS MEDICAL SOCIETY, US , vol. 367, no. 18 1 November 2012 (2012-11-01), pages 1694-1703, XP002725869, ISSN: 0028-4793, DOI: 10.1056/NEJMOA1210093 Retrieved from the Internet: URL:http://www.nejm.org/doi/pdf/10.1056/NE JMoa1210093 [retrieved on 2012-09-29]
J. G. GREGER ET AL: "Combinations of BRAF, MEK, and PI3K/mTOR Inhibitors Overcome Acquired Resistance to the BRAF Inhibitor GSK2118436 Dabrafenib, Mediated by NRAS or MEK Mutations", MOLECULAR CANCER THERAPEUTICS, vol. 11, no. 4, 1 April 2012 (2012-04-01), pages 909-920, XP055057160, ISSN: 1535-7163, DOI: 10.1158/1535-7163.MCT-11-0989
KOJIMA KENSUKE ET AL: "Mdm2 inhibitor Nutlin-3a induces p53-mediated apoptosis by transcription-dependent and transcription-independent mechanisms and may overcome Atm-mediated resistance to fludarabine in chronic lymphocytic leukemia", BLOOD 1 AUG 2006, vol. 108, no. 3, 1 August 2006 (2006-08-01), pages 993-1000, XP055140017, ISSN: 0006-4971
JI ZHENYU ET AL: "Vemurafenib synergizes with nutlin-3 to deplete survivin and suppresses melanoma viability and tumor growth", CLINICAL CANCER RESEARCH : AN OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH 15 AUG 2013, vol. 19, no. 16, 27 June 2013 (2013-06-27) , pages 4383-4391, XP002734225, ISSN: 1078-0432
GILES FRANCIS ET AL: "MK-0457, a novel aurora kinase and BCR-ABL inhibitor, is active against BCR-ABL T315I mutant chronic myelogenous leukemia (CML)", BLOOD, AMERICAN SOCIETY OF HEMATOLOGY, US, vol. 108, no. 11, Part 1, 1 November 2006 (2006-11-01), page 52a, XP009124755, ISSN: 0006-4971

Enclosed is a translation of the patent claims in Norwegian. Please note that as per the Norwegian Patents Acts, section 66i the patent will receive protection in Norway only as far as there is agreement between the translation and the language of the application/patent granted at the EPO. In matters concerning the validity of the patent, language of the application/patent granted at the EPO will be used as the basis for the decision. The patent documents published by the EPO are available through Espacenet (http://worldwide.espacenet.com) or via the search engine on our website here: https://search.patentstyret.no/

PATENTKRAV

1. 2-((3R,5R,6S)-5-(3-klorfenyl)-6-(4-klorfenyl)-1-((S)-1-(isopropylsulfonyl)-3-metylbutan-2-yl)-3-metyl-2-oksopiperidin-3-yl)eddiksyre for bruk i en fremgangsmåte for behandling av akutt myelogen leukemi, idet nevnte fremgangsmåte omfatter administrering, til en pasient med behov for det, av en effektiv mengde av 2-((3R,5R,6S)-5-(3-klorfenyl)-6-(4-klorfenyl)-1-((S)-1-(isopropylsulfonyl)-3-metylbutan-2-yl)-3-metyl-2-oksopiperidin-3-yl)eddiksyre og decitabin.

2. 2-((3R,5R,6S)-5-(3-klorfenyl)-6-(4-klorfenyl)-1-((S)-1-(isopropylsulfonyl)-3-metylbutan-2-yl)-3-metyl-2-oksopiperidin-3-yl)eddiksyre for bruk i en fremgangsmåte for behandling av akutt myelogen leukemi, idet nevnte fremgangsmåte omfatter administrering, til en pasient med behov for det, av en effektiv mengde av 2-((3R,5R,6S)-5-(3-klorfenyl)-6-(4-klorfenyl)-1-((S)-1-(isopropylsulfonyl)-3-metylbutan-2-yl)-3-metyl-2-oksopiperidin-3-yl)eddiksyre og cytarabin.

3. 2-((3R,5R,6S)-5-(3-klorfenyl)-6-(4-klorfenyl)-1-((S)-1-(isopropylsulfonyl)-3-metylbutan-2-yl)-3-metyl-2-oksopiperidin-3-yl)eddiksyre for bruk i en fremgangsmåte for behandling av akutt myelogen leukemi ifølge krav 1 eller 2, hvor den akutte myelogene leukemien har en FLT3-ITD-mutasjon.

4. En farmasøytisk sammensetning omfattende 2-((3R,5R,6S)-5-(3-klorfenyl)-6-(4-klorfenyl)-1-((S)-1-(isopropylsulfonyl)-3-metylbutan-2-yl)-3-metyl-2-oksopiperidin-3-yl)eddiksyre og decitabin for bruk i en fremgangsmåte for behandling av akutt myelogen leukemi.

5. En farmasøytisk sammensetning omfattende 2-((3R,5R,6S)-5-(3-klorfenyl)-6-(4-klorfenyl)-1-((S)-1-(isopropylsulfonyl)-3-metylbutan-2-yl)-3-metyl-2-oksopiperidin-3-yl)eddiksyre og cytarabin for bruk i en fremgangsmåte for behandling av akutt myelogen leukemi.

6. Et sett med farmasøytiske sammensetninger for bruk i en fremgangsmåte for behandling av akutt myelogen leukemi, idet nevnte sett omfatter separate farmasøytiske sammensetninger, idet én av de farmasøytiske sammensetningene omfatter 2-((3R,5R,6S)-5-(3-klorfenyl)-6-(4-klorfenyl)-1-((S)-1-(isopropylsulfonyl)-3-metylbutan-2-yl)-3-metyl-2-oksopiperidin-3-yl)eddiksyre, og den andre farmasøytiske sammensetningen omfatter decitabin.

7. Et sett med farmasøytiske sammensetninger for bruk i en fremgangsmåte for behandling av akutt myelogen leukemi, idet nevnte sett omfatter separate farmasøytiske sammensetninger, idet én av de farmasøytiske sammensetningene omfatter 2-((3R,5R,6S)-5-(3-klorfenyl)-6-(4-klorfenyl)-1-((S)-1-(isopropylsulfonyl)-3-metylbutan-2-yl)-3-metyl-2-oksopiperidin-3-yl)eddiksyre, og den andre farmasøytiske sammensetningen omfatter cytarabin.