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(54) Title **THERAPEUTIC COMBINATIONS OF A BTK INHIBITOR AND A BCL-2 INHIBITOR**

(56) References

Cited:

WO-A1-2015/061752, WO-A1-2013/010868, WO-A1-2014/168975  
HANTSCHER O: "Targeting BCR-ABL and JAK2 in Ph+ ALL", BLOOD 20150226 AMERICAN SOCIETY OF HEMATOLOGY USA, vol. 125, no. 9, 26 February 2015 (2015-02-26), pages 1362-1363, XP008177695, ISSN: 0006-4971  
STEPHENS DEBORAH M ET AL: "Changing The Treatment Paradigm For Previously Treated Chronic Lymphocytic Leukemia Patients With Del(17p) Karyotype", BLOOD, vol. 122, no. 21, November 2013 (2013-11), page 2872, XP008177696, & 55TH ANNUAL MEETING OF THE AMERICAN-SOCIETY-OF-HEMATOLOGY; NEW ORLEANS, LA, USA; DECEMBER 07 -10, 2013

- J. SCHWAMB ET AL: "B-cell receptor triggers drug sensitivity of primary CLL cells by controlling glucosylation of ceramides", *BLOOD*, vol. 120, no. 19, 8 November 2012 (2012-11-08), pages 3978-3985, XP055218383, US ISSN: 0006-4971, DOI: 10.1182/blood-2012-05-431783
- L. A. MATHEWS GRINER ET AL: "High-throughput combinatorial screening identifies drugs that cooperate with ibrutinib to kill activated B-cell-like diffuse large B-cell lymphoma cells", *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES*, vol. 111, no. 6, 27 January 2014 (2014-01-27), pages 2349-2354, XP055218384, US ISSN: 0027-8424, DOI: 10.1073/pnas.1311846111
- GRISAFI DAVIDE ET AL: "Ibrutinib: from bench side to clinical implications", *MEDICAL ONCOLOGY, SCIENCE AND TECHNOLOGY LETTERS*, NORTHWOOD, GB, vol. 32, no. 9, 30 July 2015 (2015-07-30), pages 1-10, XP035522374, ISSN: 1357-0560, DOI: 10.1007/S12032-015-0669-9 [retrieved on 2015-07-30]
- G. K. PHILIPS ET AL: "Therapeutic uses of anti-PD-1 and anti-PD-L1 antibodies", *INTERNATIONAL IMMUNOLOGY*, vol. 27, no. 1, 16 October 2014 (2014-10-16), pages 39-46, XP055217958, GB ISSN: 0953-8178, DOI: 10.1093/intimm/dxu095
- E KLYUCHNIKOV ET AL: "Allogeneic hematopoietic cell transplantation for diffuse large B cell lymphoma: who, when and how?", *BONE MARROW TRANSPLANTATION*, vol. 49, no. 1, 27 May 2013 (2013-05-27), pages 1-7, XP055217963, GB ISSN: 0268-3369, DOI: 10.1038/bmt.2013.72
- JENNIFER L. YORI ET AL: "Abstract LB-221: Inhibition of rapamycin-induced feedback activation of AKT with dasatinib induces complete tumor regression in a preclinical model of breast cancer.", *CANCER RESEARCH*, vol. 73, no. 8, Suppl. 1, 15 April 2013 (2013-04-15), - 10 April 2013 (2013-04-10), pages LB-221, XP055217951, US ISSN: 0008-5472, DOI: 10.1158/1538-7445.AM2013-LB-221
- D'CRUZ OJ ET AL: "Novel Bruton's tyrosine kinase inhibitors currently in development", *ONCOTARGETS AND THERAPY*, vol. 6, 6 March 2013 (2013-03-06), pages 161-176, XP055217561, GB ISSN: 1178-6930, DOI: 10.2147/OTT.S33732
- GIROTTI MARIA ROMINA ET AL: "No longer an untreatable disease: How targeted and immunotherapies have changed the management of melanoma patients", *MOLECULAR ONCOLOGY, ELSEVIER, AMSTERDAM, NL*, vol. 8, no. 6, 15 August 2014 (2014-08-15), pages 1140-1158, XP029054008, ISSN: 1574-7891, DOI: 10.1016/J.MOLONC.2014.07.027
- QINGJIE LIU ET AL: "Design and synthesis of carbazole carboxamides as promising inhibitors of Bruton's tyrosine kinase (BTK) and Janus kinase 2 (JAK2)", *BIOORGANIC & MEDICINAL CHEMISTRY LETTERS*, vol. 25, no. 19, 6 August 2015 (2015-08-06), pages 4265-4269, XP055218382, AMSTERDAM, NL ISSN: 0960-894X, DOI: 10.1016/j.bmcl.2015.07.102
- D. CHIRON ET AL: "Cell-Cycle Reprogramming for PI3K Inhibition Overrides a Relapse-Specific C481S BTK Mutation Revealed by Longitudinal Functional Genomics in Mantle Cell Lymphoma", *CANCER DISCOVERY*, vol. 4, no. 9, 31 July 2014 (2014-07-31), pages 1022-1035, XP055218352, US ISSN: 2159-8274, DOI: 10.1158/2159-8290.CD-14-0098
- BIN CHEN ET AL: "Rapamycin Enhances the Anti-Cancer Effect of Dasatinib by Suppressing Src/PI3K/mTOR Pathway in NSCLC Cells", *PLOS ONE*, vol. 10, no. 6, 10 June 2015 (2015-06-10), page e0129663, XP055218386, US ISSN: 1932-6203, DOI: 10.1371/journal.pone.0129663
- ZHANG QING ET AL: "[Effect of PI3K[delta] inhibitor CAL-101 on myeloma cell lines and preliminary study of synergistic effects with other new drugs].", *ZHONGHUA XUE YE XUE ZA ZHI = ZHONGHUA XUEYEXUE ZAZHI* OCT 2014, vol. 35, no. 10, October 2014 (2014-10), pages 926-930, XP008177739, ISSN: 0253-2727
- VAN DEN AKKER EMILE ET AL: "The Btk inhibitor LFM-A13 is a potent inhibitor of Jak2 kinase activity", *BIOLOGICAL CHEMISTRY*, vol. 385, no. 5, May 2004 (2004-05), pages 409-413, XP008177694, ISSN: 1431-6730
- IDIT SAGIV-BARFI ET AL: "Therapeutic antitumor immunity by checkpoint blockade is enhanced by ibrutinib, an inhibitor of both BTK and ITK", *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES*, vol. 112, no. 9, 17 February 2015 (2015-02-17), pages E966-E972, XP055217955, US ISSN: 0027-8424, DOI: 10.1073/pnas.1500712112
- SONGDEJ NATTHAPOL ET AL: "GIST Treatment Options after Tyrosine Kinase Inhibitors", *CURRENT TREATMENT OPTIONS IN ONCOLOGY* MAY 2005, SPRINGER US, BOSTON, vol. 15, no. 3, 22 June 2014 (2014-06-22), pages 493-506, XP035381545, ISSN: 1527-2729, DOI: 10.1007/S11864-014-0295-3 [retrieved on 2014-06-22]
- BRIAN J. PARK ET AL: "Dasatinib synergizes with both cytotoxic and signal transduction inhibitors in heterogeneous breast cancer cell lines - Lessons for design of combination targeted therapy", *CANCER LETTERS*, vol. 320, no. 1, 2 February 2012 (2012-02-02), pages 104-110, XP055217954, US ISSN: 0304-3835, DOI: 10.1016/j.canlet.2012.01.039

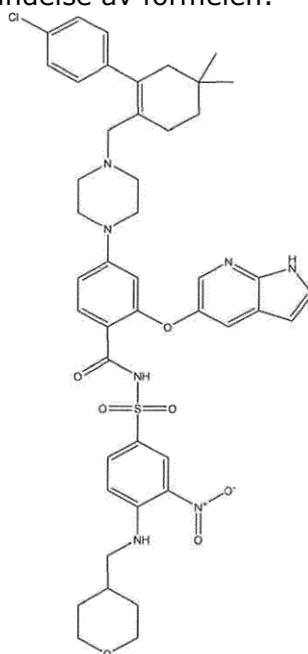
Enclosed is a translation of the patent claims in Norwegian. Please note that as per the Norwegian Patents Acts, section 66i the patent will receive protection in Norway only as far as there is agreement between the translation and the language of the application/patent granted at the EPO. In matters 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/>

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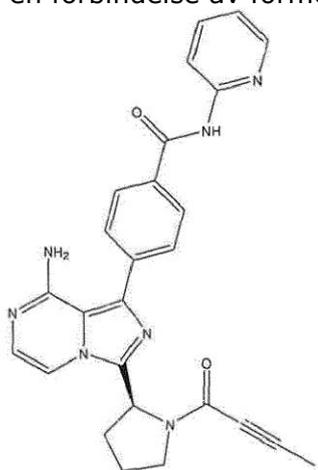
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**Patentkrav**

- 5 **1.** Farmasøytisk kombinasjon omfattende (1) en B-cellelymfom-2-inhibitor (BCL-2-inhibitor) eller et farmasøytisk akseptabelt salt derav, og (2) en Brutons tyrosinkinaseinhibitor (BTK-inhibitor) eller et farmasøytisk akseptabelt salt derav, for anvendelse i behandlingen av kreft hos et menneskeindivid, hvori BCL-2-inhibitoren er en forbindelse av formelen:



og BTK-inhibitoren er en forbindelse av formelen:



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**2.** Den farmasøytiske kombinasjonen for anvendelse ifølge krav 1, hvori BCL-2-inhibitoren skal administreres før administrering av BTK-inhibitoren.

5 **3.** Den farmasøytiske kombinasjonen for anvendelse ifølge krav 1, hvori BCL-2-inhibitoren skal administreres samtidig med administreringen av BTK-inhibitoren.

**4.** Den farmasøytiske kombinasjonen for anvendelse ifølge krav 1, hvori BCL-2-inhibitoren skal administreres til individet etter administrering av BTK-inhibitoren.

10

**5.** Den farmasøytiske kombinasjonen for anvendelse ifølge et hvilket som helst foregående krav, hvori kombinasjonen videre omfatter et anti-CD20-antistoff valgt fra gruppen som består av rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab og ibritumomab.

15

**6.** Den farmasøytiske kombinasjonen for anvendelse ifølge et hvilket som helst foregående krav, hvori kreften er en hematologisk malignitet valgt fra gruppen som består av kronisk lymfatisk leukemi (CLL), liten lymfatisk leukemi (SLL), non-Hodgkins lymfom (NHL), diffust storcellet B-cellelymfom (DLBCL), follikulært lymfom (FL), mantelcellelymfom (MCL), Hodgkins lymfom, akutt lymfatisk leukemi fra B-celler (B-ALL), Burkitts lymfom, Waldenströms makroglobulinemi (WM), multippelt myelom og myelofibrose.

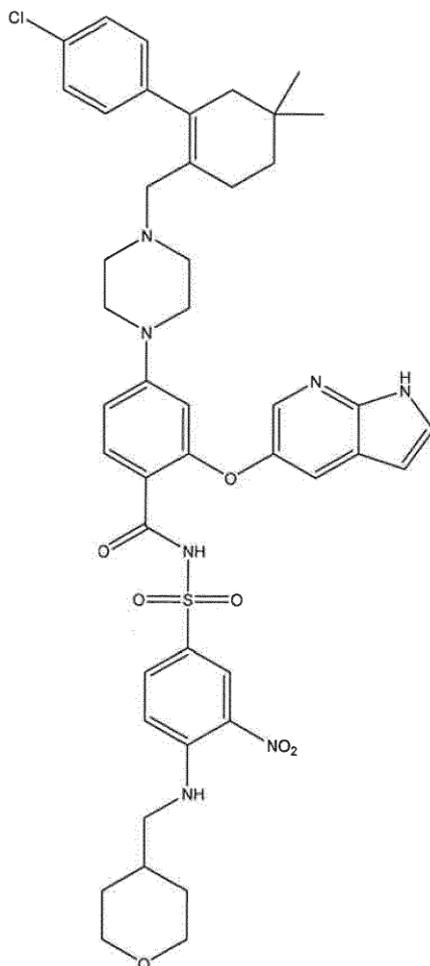
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**7.** Farmasøytisk sammensetning omfattende (1) en BCL-2-inhibitor eller et farmasøytisk akseptabelt salt derav; og (2) en BTK-inhibitor eller et farmasøytisk akseptabelt salt derav for anvendelse i behandlingen av kreft hos et menneskeindivid, hvori BCL-2-inhibitoren er en forbindelse av formelen:

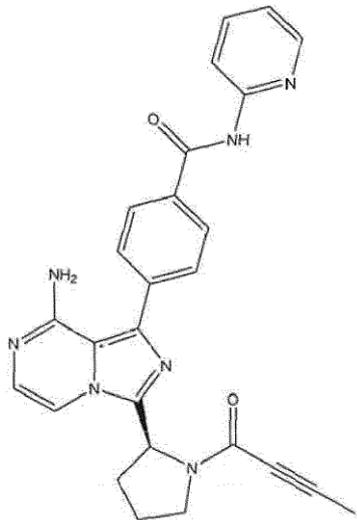
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og BTK-inhibitoren er en forbindelse av formelen:



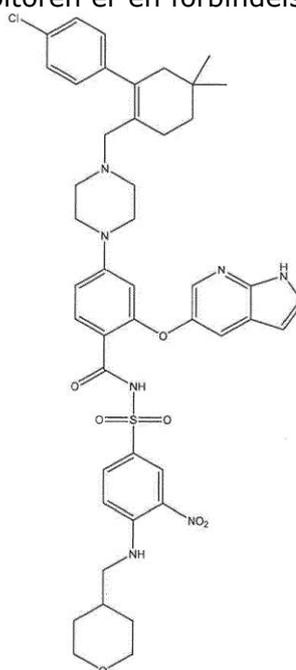
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5 **8.** Den farmasøytiske sammensetningen for anvendelse ifølge krav 7, omfattende en mengde av BTK-inhibitoren valgt fra gruppen som består av 5 mg, 10 mg, 12.5 mg, 15 mg, 20 mg, 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 375 mg, 400 mg, 425 mg, 450 mg, 475 mg, 500 mg, 525 mg og 550 mg.

10 **9.** Den farmasøytiske sammensetningen for anvendelse ifølge krav 7, omfattende en mengde av BCL-2-inhibitoren valgt fra gruppen som består av 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 375 mg, 400 mg, 425 mg, 450 mg, 475 mg og 500 mg.

15 **10.** Sett omfattende (1) en sammensetning omfattende en BCL-2-inhibitor eller et farmasøytisk akseptabelt salt derav; og (2) en sammensetning omfattende en BTK-inhibitor eller et farmasøytisk akseptabelt salt derav, hvori settet er for samtidig administrering av en BCL-2-inhibitor og en BTK-inhibitor, enten samtidig eller separat for anvendelse i behandlingen av kreft hos et menneskeindivid, hvori BCL-2-inhibitoren er en forbindelse av formelen:



20 og BTK-inhibitoren er en forbindelse av formelen:

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