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(54)	Title	METHOD FOR DETERMINING THE SUITABILITY OF INHIBITORS OF HUMAN EZH2 IN TREATMENT
(56)	References Cited:	WO-A1-2011/140324 WO-A2-2009/124137 US-A1- 2005 266 473 US-A1- 2008 222 741 US-A1- 2009 012 031 RYAN D MORIN ET AL: "Somatic mutations altering EZH2 (Tyr641) in follicular and diffuse large B-cell lymphomas of germinal-center origin", NATURE GENETICS, vol. 42, no. 2, 1 February 2010 (2010-02-01), pages 181-185, XP055101779, ISSN: 1061-4036, DOI: 10.1038/ng.518 T. B. MIRANDA ET AL: "DZNep is a global histone methylation inhibitor that reactivates developmental genes not silenced by DNA methylation", MOLECULAR CANCER THERAPEUTICS, vol. 8, no. 6, 1 June 2009 (2009-06-01), pages 1579-1588, XP055049435, ISSN: 1535-7163, DOI: 10.1158/1535-7163.MCT-09-0013

- RICHO VICTORIA M ET AL: "Lymphoma-Associated Mutations of EZH2 Result In a Change-of-Function", BLOOD, AMERICAN SOCIETY OF HEMATOLOGY, US, vol. 116, no. 21, 1 November 2010 (2010-11-01), page 312, XP009176070, ISSN: 0006-4971
- TIM J WIGLE ET AL: "The Y641C mutation of EZH2 alters substrate specificity for histone H3 lysine 27 methylation states", FEBS LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 585, no. 19, 9 August 2011 (2011-08-09), pages 3011-3014, XP028300045, ISSN: 0014-5793, DOI: 10.1016/J.FEBSLET.2011.08.018 [retrieved on 2011-08-17]
- C. J. SNEERING ET AL: "Coordinated activities of wild-type plus mutant EZH2 drive tumor-associated hypertrimethylation of lysine 27 on histone H3 (H3K27) in human B-cell lymphomas", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, vol. 107, no. 49, 7 December 2010 (2010-12-07), pages 20980-20985, XP55075961, ISSN: 0027-8424, DOI: 10.1073/pnas.1012525107
- D. B. YAP ET AL: "Somatic mutations at EZH2 Y641 act dominantly through a mechanism of selectively altered PRC2 catalytic activity, to increase H3K27 trimethylation", BLOOD, vol. 117, no. 8, 29 December 2010 (2010-12-29), pages 2451-2459, XP055075957, ISSN: 0006-4971, DOI: 10.1182/blood-2010-11-321208
- SHIVANI GARAPATY-RAO ET AL: "Identification of EZH2 and EZH1 Small Molecule Inhibitors with Selective Impact on Diffuse Large B Cell Lymphoma Cell Growth", CHEMISTRY & BIOLOGY, vol. 20, no. 11, 1 November 2013 (2013-11-01), pages 1329-1339, XP055101733, ISSN: 1074-5521, DOI: 10.1016/j.chembiol.2013.09.013
- QI WEI ET AL: "Selective inhibition of Ezh2 by a small molecule inhibitor blocks tumor cells proliferation.", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA 26 DEC 2012, vol. 109, no. 52, 26 December 2012 (2012-12-26), pages 21360-21365, XP002720302, ISSN: 1091-6490
- MIRANDA, TINA B. ET AL.: 'DZNep is a global histone methylation inhibitor that reactivates developmental genes not silenced by DNA methylation.' MOL CANCER THER. vol. 8, no. 6, 09 June 2009, pages 1579 - 1588, XP055049435
- YAP D.B. ET AL.: 'Somatic mutations at EZH2 Y641 act dominantly through a mechanism of selectively altered PRC2 catalytic activity, to increase H3-K27 trimethylation.' BLOOD vol. 117, no. 8, 29 December 2010, pages 2451 - 2459, XP055075957

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. Fremgangsmåte for å bestemme hvorvidt et individ som har eller er mistenkt for å ha kreft valgt fra lymfom og melanom er en kandidat for behandling med en hemmer av EZH2, omfattende;

å detektere en Y641-mutant av et EZH2-polypeptid, hvis den er til stede, i en prøve oppnådd fra individet;

hvor i nærværet av Y641-mutanten indikerer at individet er en kandidat for behandling med en hemmer av EZH2.
2. Fremgangsmåte ifølge krav 1, hvor i Y641-mutanten er valgt fra gruppen som består av Y641F, Y641H, Y641N, og Y641S.
3. Fremgangsmåte ifølge hvilket som helst av de foregående kravene, hvor i kreften er follikulært lymfom eller diffust storcellet B-cellelymfom (DLBCL)
4. Fremgangsmåte ifølge hvilket som helst av de foregående kravene, hvor i

detekteringen av Y641-mutanten av EZH2 er ved:
 - a. helgenomsekvensering,
 - b. målregionsekvensering som detekterer en nukleinsyre som koder for Y641-mutanten av EZH2-polypeptidet,
 - c. et antistoff som binder spesifikt til et polypeptid eller fragment derav som er karakteristisk for Y641-mutanten av EZH2-polypeptidet; eller
 - d. en nukleinsyreprobe som hybridiserer til en nukleinsyre som koder for et polypeptid eller fragment derav som er karakteristisk for Y641-mutanten av EZH2-polypeptidet.
5. Fremgangsmåten ifølge krav 4, hvor i målregionsekvenseringen omfatter forsterking av minst en del av nukleinsyren med minst én PCR-primer.
6. Fremgangsmåte ifølge hvilket som helst av kravene 1 til 5, hvor i hemmeren av EZH2

- a. hemmer trimetylering av H3-K27, eller
- b. hemmer histonmetyltransferaseaktiviteten til Y641-mutanten av EZH2, eventuelt hvori hemmingen er selektiv hemming.