What is claimed is:

1. Use of an EZH2 inhibitor in the manufacture of a medicament for the treatment of a germinal center-derived lymphoma.

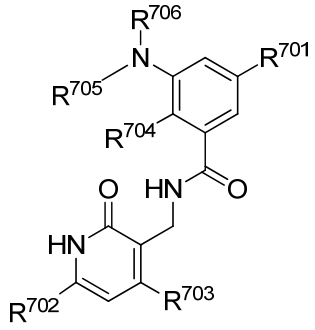
2. The use of claim 1, wherein the germinal center-derived lymphoma is an EZH2 wild type germinal center B-cell lymphoma.

3. The use of claim 1, wherein the germinal center-derived lymphoma is an EZH2 mutant germinal center B-cell lymphoma.

4. The use of any one of the preceding claims, wherein the germinal center-derived lymphoma is diffuse large B-cell lymphoma, follicular lymphoma, Burkitt's lymphoma or Non-Hodgkin's Lymphoma of germinal center B cell subtype.

5. The use of any one of the preceding claims, wherein the EZH2 inhibitor is to be administered orally.

6. The use of any one of the preceding claims, wherein the EZH2 inhibitor is of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof; wherein

R^{701} is H, F, OR^{707}, NHR^{707}, $-(C\equiv C)-(CH_2)_{n7}-R^{708}$, phenyl, 5- or 6-membered heteroaryl, C_{3-8} cycloalkyl, or 4-7 membered heterocycloalkyl containing 1-3 heteroatoms, wherein the phenyl, 5- or 6-membered heteroaryl, C_{3-8} cycloalkyl or 4-7 membered heterocycloalkyl each independently is optionally substituted with one or more groups selected from halo, C_{1-3} alkyl, OH, O-C_{1-6} alkyl, NH-C_{1-6} alkyl, and, C_{1-3} alkyl substituted with C_{3-8} cycloalkyl or 4-7 membered heterocycloalkyl containing 1-3 heteroatoms, wherein each of the O-C_{1-6} alkyl and

NH-C_{1-6} alkyl is optionally substituted with hydroxyl, O-C_{1-3} alkyl or NH-C_{1-3} alkyl, each of the O-C_{1-3} alkyl and NH-C_{1-3} alkyl being optionally further substituted with O-C_{1-3} alkyl or NH-C_{1-3} alkyl;

each of R^{702} and R^{703}, independently is H, halo, C_{1-4} alkyl, C_{1-6} alkoxyl or C_6-C_{10} aryloxy, each optionally substituted with one or more halo;

each of R^{704} and R^{705}, independently is C_{1-4} alkyl;

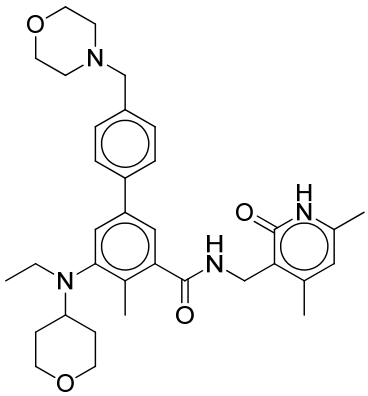
R^{706} is cyclohexyl substituted by N(C_{1-4} alkyl)$_2$ wherein one or both of the C_{1-4} alkyl is optionally substituted with C_{1-6} alkoxy; or R^{706} is tetrahydropyranyl;

R^{707} is C_{1-4} alkyl optionally substituted with one or more groups selected from hydroxyl, C_{1-4} alkoxy, amino, mono- or di-C_{1-4} alkylamino, C_{3-8} cycloalkyl, and 4-7 membered heterocycloalkyl containing 1-3 heteroatoms, wherein the C_{3-8} cycloalkyl or 4-7 membered heterocycloalkyl each independently is further optionally substituted with C_{1-3} alkyl;

R^{708} is C_{1-4} alkyl optionally substituted with one or more groups selected from OH, halo, and C_{1-4} alkoxy, 4-7 membered heterocycloalkyl containing 1-3 heteroatoms, or O-C_{1-6} alkyl, wherein the 4-7 membered heterocycloalkyl can be optionally further substituted with OH or C_{1-6} alkyl; and

n_7 is 0, 1 or 2.

7. The use of any one of the preceding claims, wherein the EZH2 inhibitor is EPZ-6438 having the following formula:



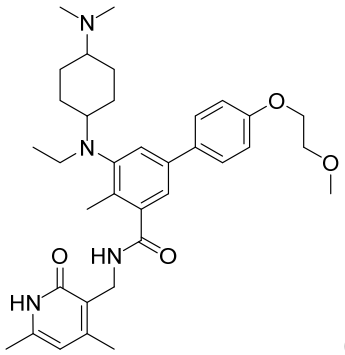
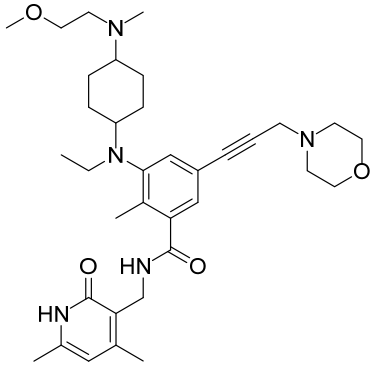
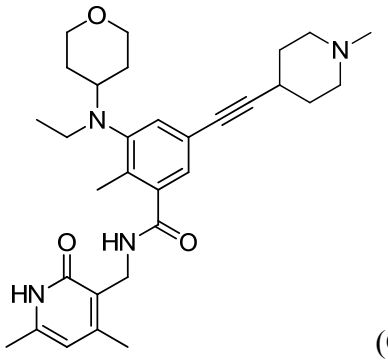
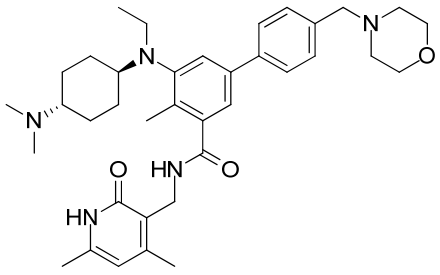
(EPZ-6438) or a pharmaceutically acceptable salt thereof.

8. The use of any one of the preceding claims, wherein the EZH2 inhibitor is to be administered at a dose of about 100 mg to about 3200 mg daily.

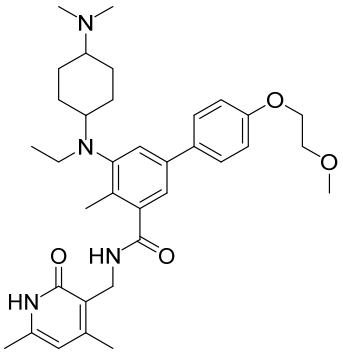
9. The use of any one of the preceding claims, wherein the EZH2 inhibitor is to be administered at a dose of about 100 mg BID to about 1600 mg BID.

10. The use of any one of the preceding claims, wherein the EZH2 inhibitor is to be administered at a dose of about 100 mg BID, 200 mg BID, 400 mg BID, 800 mg BID, or about 1600 mg BID.

11. The use of any one of the preceding claims, wherein the EZH2 inhibitor is:


(A),

(B)

(C) or

(D), or a pharmaceutically acceptable salt thereof.

12. The use of any one of the preceding claims, wherein the EZH2 inhibitor is:



(A) or a pharmaceutically acceptable salt thereof.

13. The use of any one of the preceding claims, wherein the medicament is to be used in combination with a standard of care agent.

14. The use of claim 13, wherein the standard of care agent is one or more components of R-CHOP, a BCL inhibitor, or a BCR inhibitor, optionally the standard of care agent is selected from GDC0068, GSK1070916, GSK2126458, GSK690693, and JQ1.

15. The use of claim 13 or 14, wherein the EZH2 inhibitor and the standard of care agent are to be administered simultaneously or sequentially.

16. The use of claim 13 or 14, wherein the EZH2 inhibitor is to be administered prior to administration of the standard of care agent.

17. The use of claim 13 or 14, wherein the standard of care agent is to be administered prior to administration of the EZH2 inhibitor.

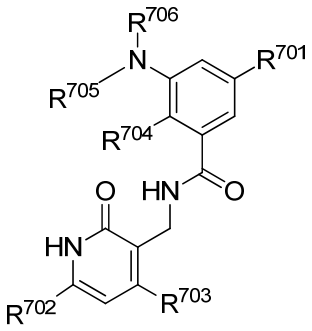
18. Use of an EZH2 inhibitor in the manufacture of a medicament for the treatment of Primary Mediastinal Large B-Cell Lymphoma (PMBCL).

19. The use of claim 18, wherein the PMBCL is a mutant EZH2.

20. The use of claim 18, wherein the PMBCL is wild-type EZH2.

21. The use of any one of claims 18-20, wherein the EZH2 inhibitor is to be administered orally.

22. The use of any one of claims 18-21, wherein the EZH2 inhibitor is of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof; wherein

R^{701} is H, F, OR^{707}, NHR^{707}, $-(C\equiv C)-(CH_2)_{n7}-R^{708}$, phenyl, 5- or 6-membered heteroaryl, C_{3-8} cycloalkyl, or 4-7 membered heterocycloalkyl containing 1-3 heteroatoms, wherein the phenyl, 5- or 6-membered heteroaryl, C_{3-8} cycloalkyl or 4-7 membered heterocycloalkyl each independently is optionally substituted with one or more groups selected from halo, C_{1-3} alkyl, OH, O-C_{1-6} alkyl, NH-C_{1-6} alkyl, and, C_{1-3} alkyl substituted with C_{3-8} cycloalkyl or 4-7 membered heterocycloalkyl containing 1-3 heteroatoms, wherein each of the O-C_{1-6} alkyl and NH-C_{1-6} alkyl is optionally substituted with hydroxyl, O-C_{1-3} alkyl or NH-C_{1-3} alkyl, each of the O-C_{1-3} alkyl and NH-C_{1-3} alkyl being optionally further substituted with O-C_{1-3} alkyl or NH-C_{1-3} alkyl;

each of R^{702} and R^{703}, independently is H, halo, C_{1-4} alkyl, C_{1-6} alkoxyl or C_6-C_{10} aryloxy, each optionally substituted with one or more halo;

each of R^{704} and R^{705}, independently is C_{1-4} alkyl;

R^{706} is cyclohexyl substituted by N(C_{1-4} alkyl)$_2$ wherein one or both of the C_{1-4} alkyl is optionally substituted with C_{1-6} alkoxy; or R^{706} is tetrahydropyranyl;

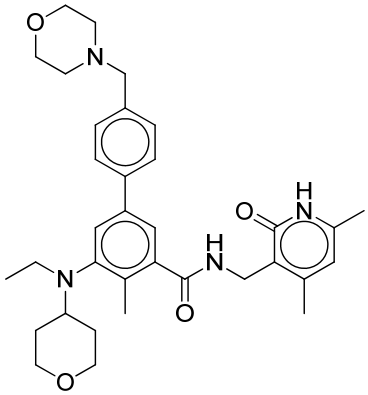
R^{707} is C_{1-4} alkyl optionally substituted with one or more groups selected from hydroxyl, C_{1-4} alkoxy, amino, mono- or di-C_{1-4} alkylamino, C_{3-8} cycloalkyl, and 4-7 membered heterocycloalkyl containing 1-3 heteroatoms, wherein the C_{3-8} cycloalkyl or 4-7 membered heterocycloalkyl each independently is further optionally substituted with C_{1-3} alkyl;

R^{708} is C_{1-4} alkyl optionally substituted with one or more groups selected from OH, halo, and C_{1-4} alkoxy, 4-7 membered heterocycloalkyl containing 1-3 heteroatoms, or O-C_{1-6} alkyl,

wherein the 4-7 membered heterocycloalkyl can be optionally further substituted with OH or C_{1-6} alkyl; and

n_7 is 0, 1 or 2.

23. The use of any one of claims 18-22, wherein the EZH2 inhibitor is EPZ-6438 having the following formula:



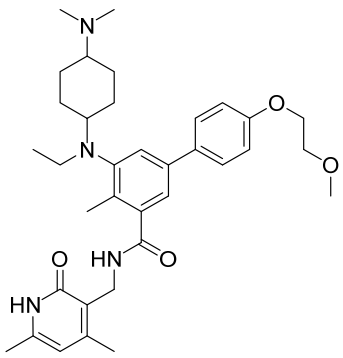
(EPZ-6438) or a pharmaceutically acceptable salt thereof.

24. The use of any one of claims 18-23, wherein the EZH2 inhibitor is to be administered at a dose of about 100 mg to about 3200 mg daily.

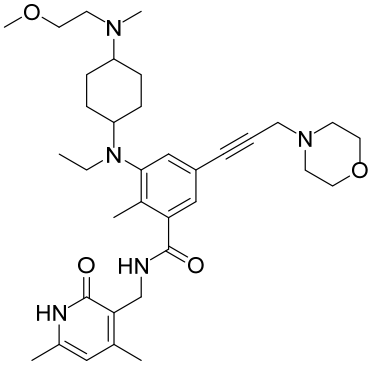
25. The use of any one of claims 18-24, wherein the EZH2 inhibitor is to be administered at a dose of about 100 mg BID to about 1600 mg BID.

26. The use of any one of claims 18-25, wherein the EZH2 inhibitor is to be administered at a dose of about 100 mg BID, 200 mg BID, 400 mg BID, 800 mg BID, or about 1600 mg BID.

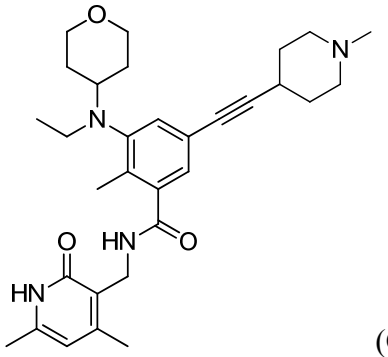
27. The use of any one of claims 18-26, wherein the EZH2 inhibitor is:



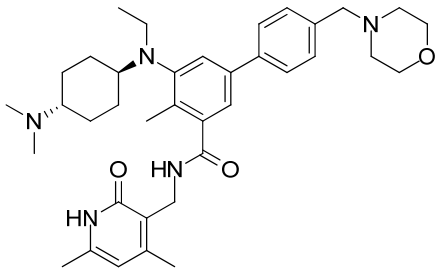
(A),



(B)

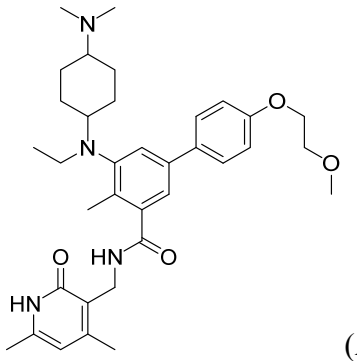


(C) or



(D), or a pharmaceutically acceptable salt thereof.

28. The use of any one of claims 18-27, wherein the EZH2 inhibitor is:



(A) or a pharmaceutically acceptable salt thereof.

29. The use of any one of claims 18-28, wherein the medicament is to be used in combination with a standard of care agent.

30. The use of claim 29, wherein the standard of care agent is one or more components of R-CHOP, a BCL inhibitor, or a BCR inhibitor, optionally the standard of care agent is selected from GDC0068, GSK1070916, GSK2126458, GSK690693, and JQ1.

31. The use of claim 29 or 30, wherein the EZH2 inhibitor and the standard of care agent are to be administered simultaneously or sequentially.

32. The use of claim 29 or 30, wherein the EZH2 inhibitor is to be administered prior to administration of the standard of care agent.

33. The use of claim 29 or 30, wherein the standard of care agent is to be administered prior to administration of the EZH2 inhibitor.

34. A method of selecting a patient for a use according to any one of the preceding claims, wherein the patient is selected based on the expression profile of one or more genes selected from the group consisting of EZH2, BCL6 and BCL2.

35. The method of claim 34, wherein the method further comprises a step of detecting levels of histone methylation in a skin biopsy.

36. The method of claim 35, wherein the histone methylation is H3K27 trimethylation.