

CLAIMS

1. ~~— A method of selecting an individual as suitable for treatment with an anti-CD25 ADC, wherein the individual is selected for treatment with the anti-CD25 ADC if the individual has been treated with an anti-BCL-2 agent, a mTOR inhibitor, or a secondary agent.~~

2. ~~— A method of selecting an individual as suitable for treatment with an anti-CD25 ADC, wherein the individual is selected for treatment with the anti-CD25 ADC if the individual is being treated with an anti-BCL-2 agent, a mTOR inhibitor, or a secondary agent.~~

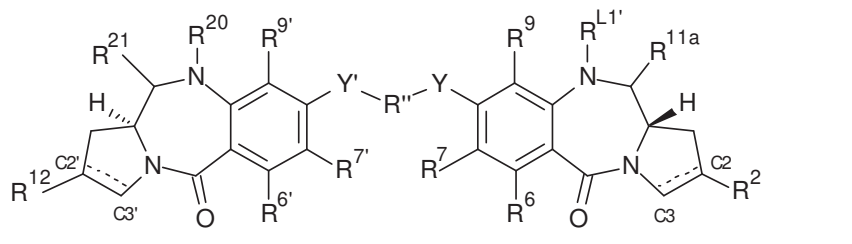
3. ~~— The method according to any one of the preceding claims, wherein the individual is selected for treatment if the individual is refractory to treatment, or further treatment, with the anti-BCL-2 agent, mTOR inhibitor, or secondary agent.~~

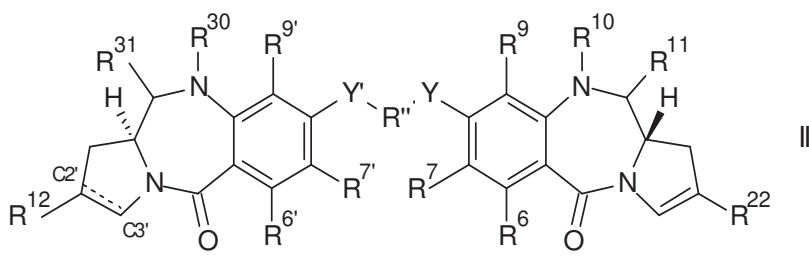
4. ~~— A method for treating a disorder in an individual, the method comprising:
(i) selecting an individual as suitable for treatment by a method according to any one of claims 1 to 3; and
(ii) administering to the individual an effective amount of the anti-CD25 ADC.~~

5. ~~— The method according to claim 4, further comprising administering a an anti-BCL-2 agent, a mTOR inhibitor, or a secondary agent in combination with the anti-CD25 ADC.~~

16. AUse of an anti-CD25 antibody drug conjugate (ADC) in the manufacture of a medicament for use in combination therapy ~~method for treating a disorder in an individual, wherein said medicament is to be administered in combination with anthe method comprising administering to the individual an effective amount of an anti-CD25 ADC and an anti-BCL-2 agent;~~
~~, a mTOR inhibitor, or a secondary agent~~ wherein the anti-CD25 ADC comprises an antibody that binds to CD25 and a pyrrolobenzodiazepine (PBD) warhead; optionally wherein the PBD warhead comprises a PBD dimer.

2. The use according to claim 1, wherein the anti-CD25 ADC is a conjugate of formula L - (D^L)_p, where D^L is of formula I or II:





wherein:

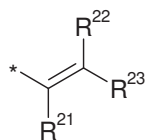
L is the antibody (Ab) which binds to CD25;

when there is a double bond present between C2' and C3', R¹² is selected from the group consisting of:

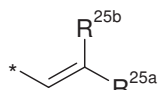
(ia) C₅₋₁₀ aryl group, optionally substituted by one or more substituents selected from the group comprising: halo, nitro, cyano, ether, carboxy, ester, C₁₋₇ alkyl, C₃₋₇ heterocyclyl and bis-oxy-C₁₋₃ alkylene;

(ib) C₁₋₅ saturated aliphatic alkyl;

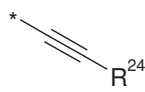
(ic) C₃₋₆ saturated cycloalkyl;



(id) , wherein each of R²¹, R²² and R²³ are independently selected from H, C₁₋₃ saturated alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl and cyclopropyl, where the total number of carbon atoms in the R¹² group is no more than 5;

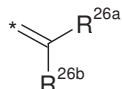


(ie) , wherein one of R^{25a} and R^{25b} is H and the other is selected from: phenyl, which phenyl is optionally substituted by a group selected from halo, methyl, methoxy; pyridyl; and thiophenyl; and



(if) , where R²⁴ is selected from: H; C₁₋₃ saturated alkyl; C₂₋₃ alkenyl; C₂₋₃ alkynyl; cyclopropyl; phenyl, which phenyl is optionally substituted by a group selected from halo, methyl, methoxy; pyridyl; and thiophenyl;

when there is a single bond present between C2' and C3',



R¹² is , where R^{26a} and R^{26b} are independently selected from H, F, C₁₋₄ saturated alkyl, C₂₋₃ alkenyl, which alkyl and alkenyl groups are optionally substituted by a group selected from C₁₋₄ alkyl amido and C₁₋₄ alkyl ester; or, when one of R^{26a} and R^{26b} is H, the other is selected from nitrile and a C₁₋₄ alkyl ester;

R⁶ and R⁹ are independently selected from H, R, OH, OR, SH, SR, NH₂, NHR, NRR', nitro, Me₃Sn and halo;

where R and R' are independently selected from optionally substituted C₁₋₁₂ alkyl, C₃₋₂₀ heterocyclyl and C₅₋₂₀ aryl groups;

R⁷ is selected from H, R, OH, OR, SH, SR, NH₂, NHR, NHRR', nitro, Me₃Sn and halo;

R'' is a C₃₋₁₂ alkylene group, which chain may be interrupted by one or more heteroatoms, e.g. O, S, NR^{N2} (where R^{N2} is H or C₁₋₄ alkyl), and/or aromatic rings, e.g. benzene or pyridine;

Y and Y' are selected from O, S, or NH;

R^{6'}, R^{7'}, R^{9'} are selected from the same groups as R⁶, R⁷ and R⁹ respectively;

R^{L1'} is a linker for connection to the antibody (Ab);

R^{11a} is selected from OH, OR^A, where R^A is C₁₋₄ alkyl, and SO₂M, where z is 2 or 3 and M is a monovalent pharmaceutically acceptable cation;

R²⁰ and R²¹ either together form a double bond between the nitrogen and carbon atoms to which they are bound or;

R²⁰ is selected from H and R^C, where R^C is a capping group;

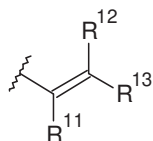
R²¹ is selected from OH, OR^A and SO₂M;

when there is a double bond present between C2 and C3, R² is selected from the group consisting of:

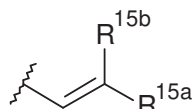
(ia) C₅₋₁₀ aryl group, optionally substituted by one or more substituents selected from the group comprising: halo, nitro, cyano, ether, carboxy, ester, C₁₋₇ alkyl, C₃₋₇ heterocyclyl and bis-oxy-C₁₋₃ alkylene;

(ib) C₁₋₅ saturated aliphatic alkyl;

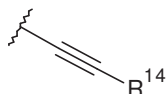
(ic) C₃₋₆ saturated cycloalkyl;



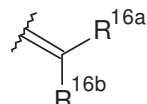
(id) _____, wherein each of R¹¹, R¹² and R¹³ are independently selected from H, C₁₋₃ saturated alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl and cyclopropyl, where the total number of carbon atoms in the R² group is no more than 5;



(ie) _____, wherein one of R^{15a} and R^{15b} is H and the other is selected from: phenyl, which phenyl is optionally substituted by a group selected from halo, methyl, methoxy; pyridyl; and thiophenyl; and

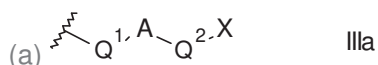


(if) _____, where R¹⁴ is selected from: H; C₁₋₃ saturated alkyl; C₂₋₃ alkenyl; C₂₋₃ alkynyl; cyclopropyl; phenyl, which phenyl is optionally substituted by a group selected from halo, methyl, methoxy; pyridyl; and thiophenyl;
when there is a single bond present between C2 and C3,



R² is _____, where R^{16a} and R^{16b} are independently selected from H, F, C₁₋₄ saturated alkyl, C₂₋₃ alkenyl, which alkyl and alkenyl groups are optionally substituted by a group selected from C₁₋₄ alkyl amido and C₁₋₄ alkyl ester; or, when one of R^{16a} and R^{16b} is H, the other is selected from nitrile and a C₁₋₄ alkyl ester;

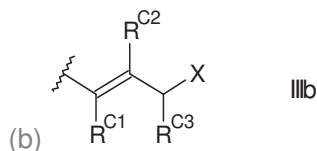
R²² is of formula IIIa, formula IIIb or formula IIIc;



where A is a C₅₋₇ aryl group, and either

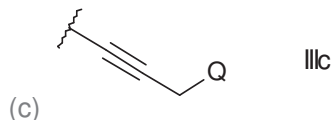
(i) Q¹ is a single bond, and Q² is selected from a single bond and -Z-(CH₂)_n-, where Z is selected from a single bond, O, S and NH and n is from 1 to 3; or

(ii) Q¹ is -CH=CH-, and Q² is a single bond;



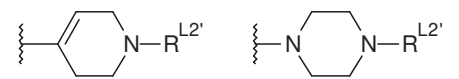
where;

R^{C1}, R^{C2} and R^{C3} are independently selected from H and unsubstituted C₁₋₂ alkyl;



where Q is selected from O-R^{L2'}, S-R^{L2'} and NR^N-R^{L2'}, and R^N is selected from H, methyl and ethyl

X is selected from the group comprising: O-R^{L2'}, S-R^{L2'}, CO₂-R^{L2'}, CO-R^{L2'}, NH-C(=O)-R^{L2'},

, NHNH-R^{L2'}, CONHNH-R^{L2'}, NR^N-R^{L2'}, wherein R^N is selected from the group comprising H and C₁₋₄ alkyl;

R^{L2'} is a linker for connection to the antibody (Ab);

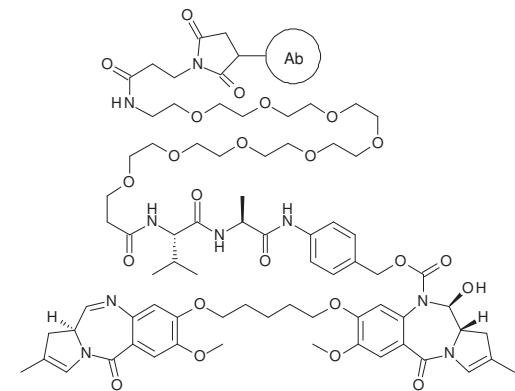
R¹⁰ and R¹¹ either together form a double bond between the nitrogen and carbon atoms to which they are bound or;

R¹⁰ is H and R¹¹ is selected from OH, OR^A and SO₂M;

R³⁰ and R³¹ either together form a double bond between the nitrogen and carbon atoms to which they are bound or;

R³⁰ is H and R³¹ is selected from OH, OR^A and SO₂M.

3. The use according to claim 1 or 2, wherein the anti-CD25 ADC has the chemical structure:



, wherein Ab is the antibody that binds to CD25.

4. The use according to any one of claims 1-3, wherein the anti-CD25 ADC comprises an antibody having:

(i) a VH domain comprising a VH CDR1 with the amino acid sequence of SEQ ID NO.3, a VH CDR2 with the amino acid sequence of SEQ ID NO.4, and a VH CDR3 with the amino acid sequence of SEQ ID NO.5;

(ii) a VH domain having the sequence according to SEQ ID NO. 1;

(iii) a VL domain having a VL CDR1 with the amino acid sequence of SEQ ID NO.6, a VL CDR2 with the amino acid sequence of SEQ ID NO.7, and a VL CDR3 with the amino acid sequence of SEQ ID NO.8; and / or

(iv) a VL domain having the sequence according to SEQ ID NO. 2.

5. The use according to any one of claims 1-3, wherein the anti-CD25 ADC is ADCT-301.

7. ~~The method according to claim 6, wherein the individual is selected for treatment according to a method according to any one of claims 1 to 3.~~

68. ~~The use method according to any preceding claim one of claims 5 to 7, wherein the treatment comprises administering the anti-CD25 ADC before the anti-BCL-2 agent, mTOR inhibitor, or secondary agent simultaneous with the anti-BCL-2 agent, mTOR inhibitor, or secondary agent, or after the anti-BCL-2 agent, mTOR inhibitor, or secondary agent.~~

9. ~~The method according to any previous claim, wherein the treatment further comprises administering a chemotherapeutic agent.~~

10. ~~The method according to any previous claim, wherein the individual is human.~~

711. ~~The use method according to any preceding claim, wherein the individual:~~

~~(i) has a disorder or has been determined to have a disorder;~~

~~(ii)~~

12. ~~The method according to claim 11, wherein the individual has, or has been has been determined to have, a cancer which expresses CD25 or CD25+ tumour-associated non-tumour cells, such as CD25+ infiltrating cells;~~

~~(iii)~~

13. ~~The method according to any previous claim, wherein the individual is undergoing treatment with an anti-BCL-2 agent, a mTOR inhibitor, or a secondary agent.~~

~~(iv)~~

14. ~~The method according to any previous claim, wherein the individual has undergone treatment with an anti-BCL-2 agent; and /or, a mTOR inhibitor, or a secondary agent.~~

~~(v)~~

15. ~~The method according to any previous claim, wherein the individual is refractory to treatment, or further treatment, with the anti-BCL-2 agent, mTOR inhibitor, or secondary agent.~~

~~16. The method according to any one of the preceding claims, wherein the treatment has increased efficacy as compared to monotherapy with either the anti-CD25 ADC or anti-BCL 2 agent, mTOR inhibitor, or secondary agent alone.~~

~~17. The method according to any preceding claim, wherein the anti-CD25 ADC is ADCx25 or ADCT-301.~~

~~818. The usemethod according to any previous claim, wherein the disorder is a proliferative disease.~~

~~919. The usemethod of claim 18, wherein the disorder is cancer, or is selected from the group comprising:~~

~~Hodgkin's and non-Hodgkin's Lymphoma, including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), Mantle Cell lymphoma (MCL), chronic lymphatic lymphoma (CLL), Marginal Zone B-cell lymphoma (MZBL);~~

~~leukemias such as Hairy cell leukemia (HCL), Hairy cell leukemia variant (HCL-v), Acute Myeloid Leukaemia (AML), anaplastic large cell lymphoma (ALCL), and Acute Lymphoblastic Leukaemia (ALL) such as Philadelphia chromosome-positive ALL (Ph+ALL) or Philadelphia chromosome-negative ALL (Ph-ALL);~~

~~pancreatic cancer, breast cancer, colorectal cancer, gastric and oesophageal cancer, leukemia and lymphoma, melanoma, non-small cell lung cancer, ovarian cancer, hepatocellular carcinoma, renal cell carcinoma, and head and neck cancer.~~

~~1020. The usemethod according to any previous claim, wherein the individual has, or ~~has been~~ has been determined to have, a disorder characterised by the presence of:~~

~~(i) a neoplasm comprising both CD25+ve and CD25-ve cells; or~~

~~(ii)~~

~~21. The method according to any previous claim, wherein the individual has, or has been has been determined to have, a disorder characterised by the presence of a neoplasm comprising, or composed of, CD25-ve neoplastic cells.~~

~~1122. The usemethod according to ~~either of claims 20 or 21~~ 10, wherein the neoplasm is all or part of a solid tumour.~~

~~1223. The usemethod according to claim 11 ~~of statement 22~~, wherein the solid tumour is associated with CD25+ve infiltrating cells;~~

~~optionally wherein the solid tumour is associated with high levels of CD25+ve infiltrating cells.~~

~~1324. The use according to claim 12 ~~method of statement 23~~, wherein the solid tumour is selected from the group consisting of pancreatic cancer, breast cancer (including triple negative breast cancer), colorectal cancer, gastric and oesophageal cancer, melanoma, non-small cell lung cancer, ovarian cancer, hepatocellular carcinoma, renal cell carcinoma, bladder, and head and neck cancer.~~

~~25. The method according to any previous claim, wherein the disorder is selected from the group comprising:~~

~~Hodgkin's and non-Hodgkin's Lymphoma, including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, (FL), Mantle Cell lymphoma (MCL), chronic lymphatic lymphoma (CLL), Marginal Zone B-cell lymphoma (MZBL);~~

~~leukemias such as Hairy cell leukemia (HCL), Hairy cell leukemia variant (HCL-v), Acute Myeloid Leukaemia (AML), anaplastic large cell lymphoma (ALCL), and Acute Lymphoblastic Leukaemia (ALL) such as Philadelphia chromosome-positive ALL (Ph+ALL) or Philadelphia chromosome-negative ALL (Ph-ALL);~~

~~pancreatic cancer, breast cancer, colorectal cancer, gastric and oesophageal cancer, leukemia and lymphoma, melanoma, non-small cell lung cancer, ovarian cancer, hepatocellular carcinoma, renal cell carcinoma, and head and neck cancer.~~

~~26. The method according to any one of claims 1 to 25, wherein the secondary agent is bendamustine.~~

~~27. The method according to any one of claims 1 to 25, wherein the secondary agent is a phosphoinositide 3-kinase inhibitor.~~

~~28. The method according to claim 27, wherein the phosphoinositide 3-kinase inhibitor is copanlisib, idelalisib, duvelisib, Taselisib, Buparlisib, Alpelisib, Umbralisib, Dactolisib, or Voxtalisib.~~

~~29. The method according to claim 27, wherein the phosphoinositide 3-kinase inhibitor is copanlisib or idelalisib.~~

~~30. The method according to any one of claims 1 to 25, wherein the secondary agent is a proteasome inhibitor.~~

~~31. The method according to claim 30, wherein the proteasome inhibitor is bortezomib, carfilzomib, ixazomib, Oprozomib, or Salinosporamide A.~~

~~32. The method according to claim 30, wherein the wherein the proteasome inhibitor is bortezomib.~~

~~33. The method according to any one of claims 1 to 25, wherein the secondary agent is an anti-folate.~~

~~34. The method according to claim 33, wherein the anti-folate is pralatrexate, methotrexate, pemetrexed, or raltitrexed.~~

~~35. The method according to claim 33, wherein the anti-folate is pralatrexate.~~

~~36. The method according to any one of claims 1 to 25, wherein the secondary agent is a HDAC inhibitor.~~

~~37. The method according to claim 36, wherein the HDAC inhibitor is romidepsin, vorinostat, Abexinostat, belinostat (PXD101), LAQ824, panobinostat (LBH589), entinostat (MS-275), tacedinaline (CI994), or mocetinostat (MGCD0103).~~

~~38. The method according to claim 36, wherein the HDAC inhibitor is romidepsin or vorinostat.~~

~~3914. The use method according to any preceding one of claims 1 to 25, wherein the anti-BCL-2 agent is selected from the group consisting of: Venetoclax (ABT-199), navitoclax (ABT-263), ABT-737, S55746/BCL201, and oblimersen (G3139).~~

~~4015. The use method according to claim 3914, wherein the anti-BCL-2 agent is Venetoclax.~~

~~16. A composition comprising an anti-CD25 ADC and an anti-BCL-2 agent, wherein the anti-CD25 ADC and anti-BCL-2 agent are defined according to any one of claims 1-15.~~

~~17. The use of the composition of claim 16 in the manufacture of a medicament for treating a disorder in an individual, wherein the treatment is as defined in any one of claims 1-15.~~

~~41. The method according to any one of claims 1 to 25, wherein the mTOR inhibitor is everolimus (RAD001), sirolimus (Rapamycin), CCI-779 (temsirolimus), ridaforolimus (AP-23573), NVP-BEZ235 (dactolisib), BGT226, SF1126, Gedatolisib, Omipalisib, XL765, KU-0063794, oleuropein aglycone, AZD8055, AZD2014, AZD 3147, sapanisertib (INK128/MLN0128), OSI027, torin 1, torin 2, torkinib (PP242), WYE687, ETP45658, PF05212384, PF04691502, XL388, eCF309, Rapalink 1, or Rapalink 2.~~

~~42. The method according to claim 41, wherein the mTOR inhibitor is Everolimus.~~

~~43. An anti-CD25 ADC for use in a method of treatment according to any one of claims 4 to 42.~~

~~44. A composition comprising an anti-CD25 ADC, for use in a method of treatment according to any one of claims 4 to 42.~~

~~45. An anti-BCL-2 agent, a mTOR inhibitor, or a secondary agent for use in a method of treatment according to any one of claims 5 to 42.~~

~~46. A composition comprising an anti-BCL-2 agent, a mTOR inhibitor, or a secondary agent for use in a method of treatment according to any one of claims 5 to 42.~~

~~47. Use of an anti-CD25 ADC in the manufacture of a medicament for treating a disorder in an individual, wherein the treatment comprises the method of any one of claims 4 to 42.~~

48. — ~~Use of an anti-BCL-2 agent, a mTOR inhibitor, or a secondary agent in the manufacture of a medicament for treating a disorder in an individual, wherein the treatment comprises the method of any one of claims 5 to 42.~~

49. — ~~A kit comprising:~~

~~a first medicament comprising an anti-CD25 ADC;~~

~~a package insert comprising instructions for administration of the first medicament according to the method of any one of claims 4 to 42.~~

50. — ~~The kit according to claim 49, further comprising:~~

~~A second medicament comprising an anti-BCL-2 agent, a mTOR inhibitor, or a secondary agent.~~