CLAIMS

1. An antibody or an epitope-binding fragment thereof that specifically binds to an EphA2 receptor and comprising at least one heavy chain and at least one light chain, wherein said heavy chain comprises three sequential complementarity-determining regions having amino acid sequences represented by SEQ ID NOS: 1, 2, and 3, and wherein said light chain comprises three sequential complementarity-determining regions having amino acid sequences represented by SEQ ID NOS: 4, 5, and 6.

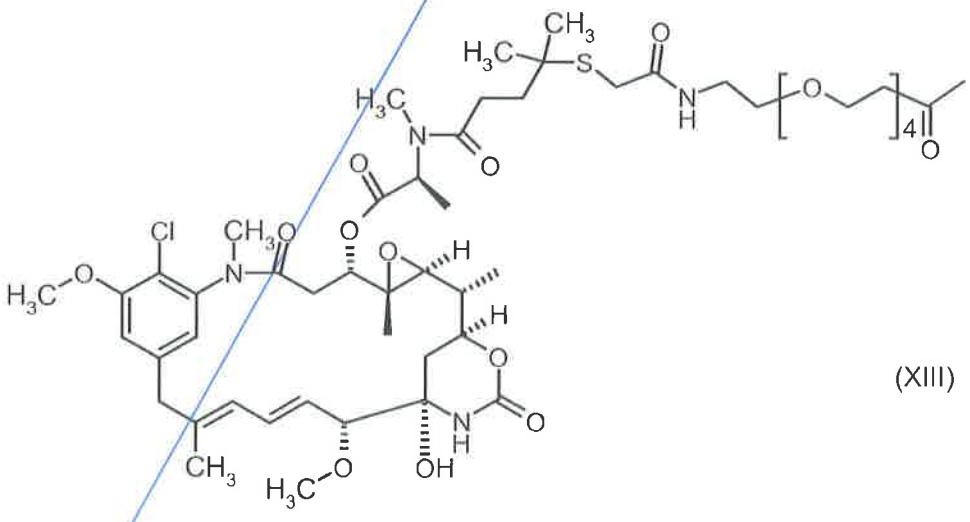
2. An antibody or an epitope-binding fragment thereof according to claim 1, wherein said monoclonal antibody or epitope-binding fragment thereof is a humanized or resurfaced antibody or epitope-binding fragment thereof.

3. An antibody or an epitope-binding fragment thereof according to claim 1, wherein said heavy chain comprises an amino acid sequence consisting of SEQ ID NO: 12 and wherein said light chain comprises an amino acid sequence consisting of SEQ ID NO: 14.

4. An antibody or an epitope-binding fragment thereof according to claim 1, wherein said heavy chain consists in an amino acid sequence SEQ ID NO: 18, and wherein said light chain consists in an amino acid sequence SEQ ID NO: 16.

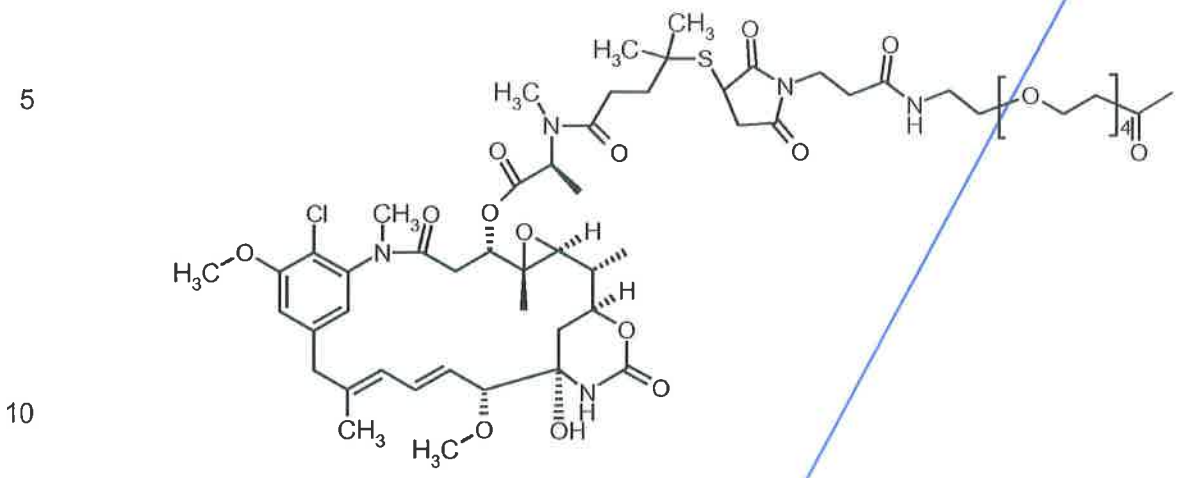
5. A conjugate of an antibody or an epitope-binding fragment according to claims 1-4, wherein said conjugate comprises a cytotoxic agent chosen between:

a) the maytansinoid of formula (XIII):



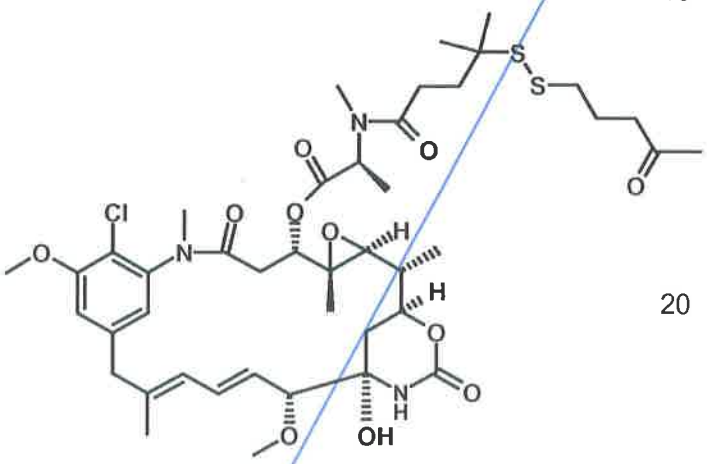
(XIII)

b) the maytansinoid of formula (XIV):



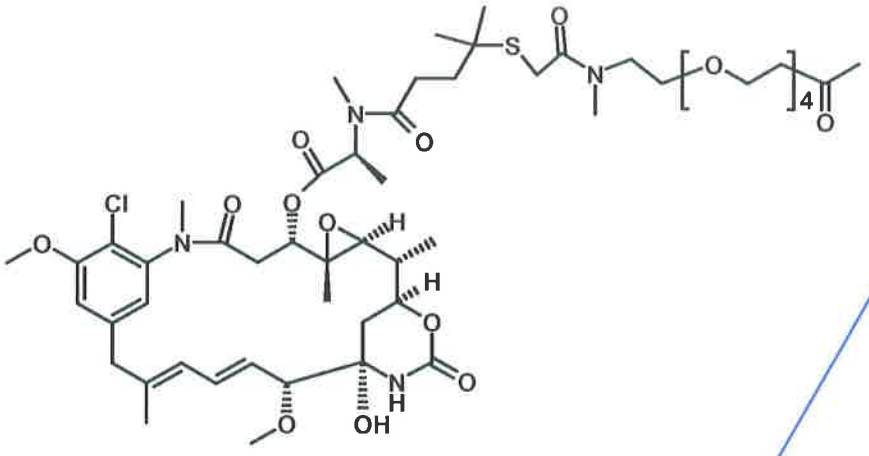
(XIV)

c) the maytansinoid of formula (XXIV):



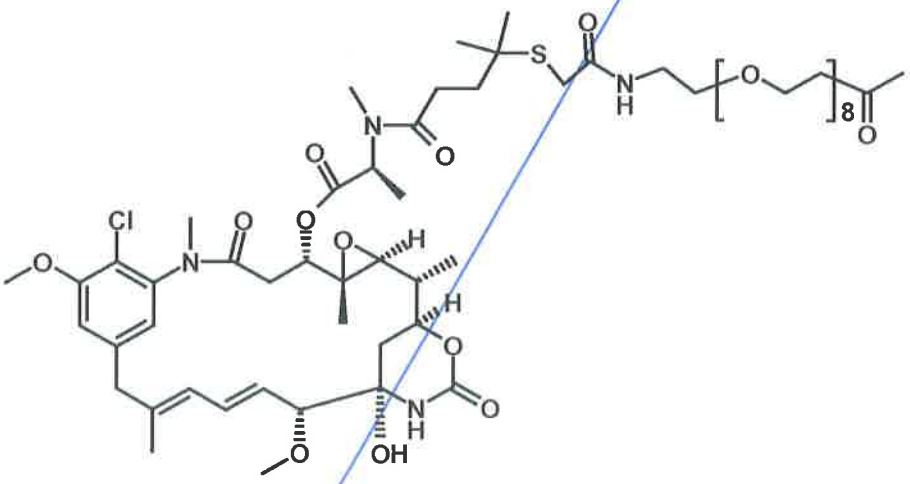
(XXIV)

d) the maytansinoid of formula (XXV):



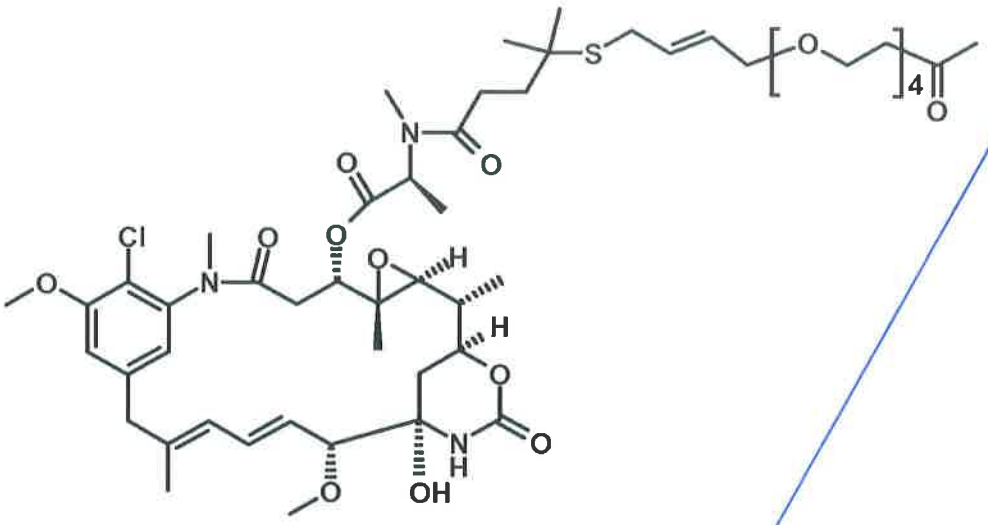
(XXV)

e) the maytansinoid of formula (XXVI):



(XXVI)

f) the maytansinoid of formula (XXVII):



(XXVII)

6. A conjugate according to claim 5, wherein said cytotoxic agent is covalently bound to the antibody.

7. A conjugate according to any of claims 5 or 6, wherein the cytotoxic agent is the maytansinoid of formula (XIII).

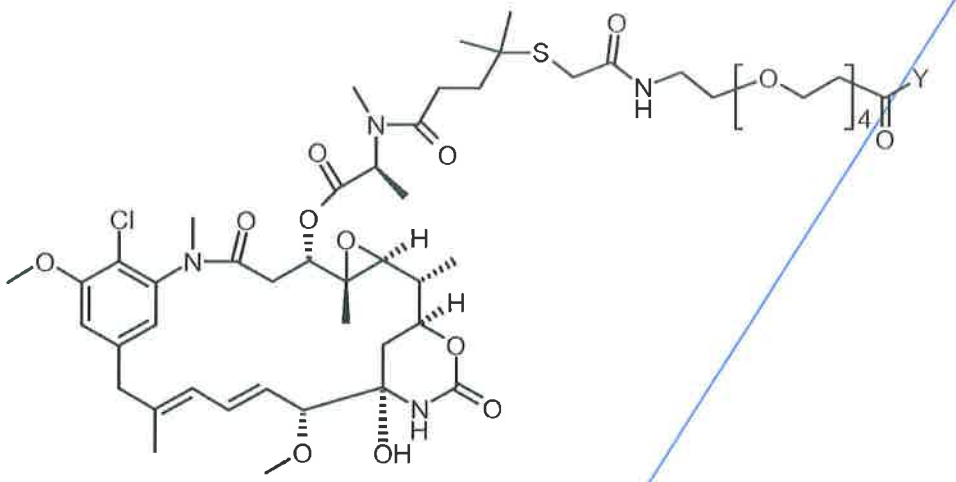
8. A method for preparing a conjugate comprising the steps of:

(i) bringing into contact an optionally-buffered aqueous solution of a cell-binding agent with a solution of a cytotoxic compound;

(ii) then optionally separating the conjugate which was formed in (i) from the unreacted reagents and any aggregate which may be present in the solution;

wherein the cell-binding agent is an antibody according to claims 1-4, and a cytotoxic agent chosen between:

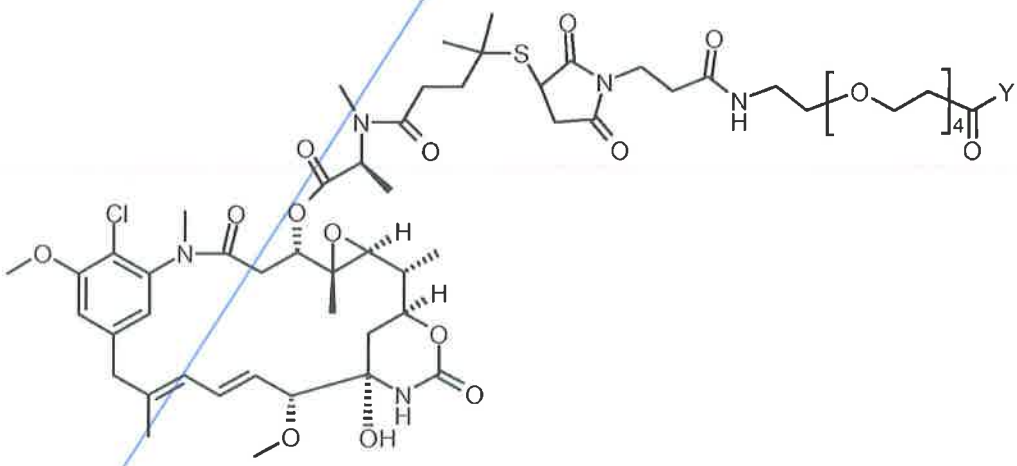
the compound of formula (XVII):



(XVII)

wherein Y is N-succinimidyloxy, N-sulfosuccinimidyloxy, N-phthalimidyloxy, N-sulfophthalimidyloxy, 2-nitrophenyloxy, 4-nitrophenyloxy, 2,4-dinitrophenyloxy, 3-sulfonyl-4-nitrophenyloxy, 3-carboxy-4-nitrophenyloxy, imidazolyl, or halogen atom; and

the compound of formula (XVIII):



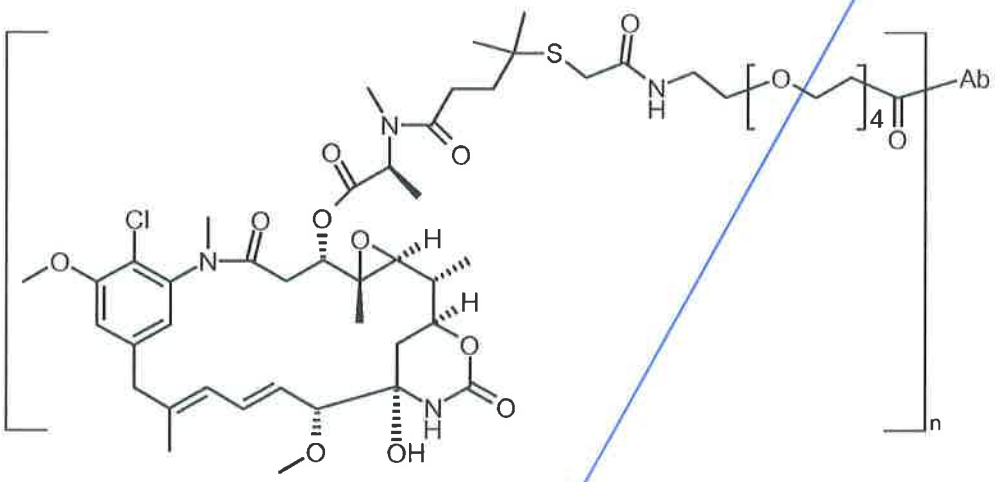
(XVIII)

wherein Y is N-succinimidyloxy, N-sulfosuccinimidyloxy, N-phthalimidyloxy, N-sulfophthalimidyloxy, 2-nitrophenyloxy, 4-nitrophenyloxy, 2,4-dinitrophenyloxy, 3-

sulfonyl-4-nitrophenyloxy, 3-carboxy-4-nitrophenyloxy, imidazolyl, or halogen atom; and

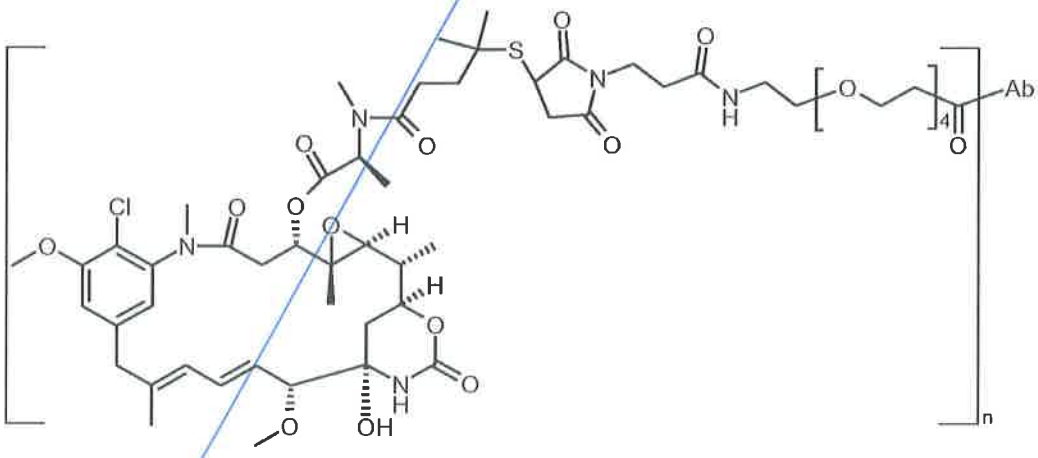
9. A conjugate obtainable by the method of claim 8.

10. A conjugate according to claim 9, said conjugate having a structure chosen between the structures of the formula (XV):



(XV)

and of the formula (XVI):



(XVI)

wherein Ab is an antibody according to claims 1-3 and n is an integer comprised between 1 and 15.

11. The antibody-drug conjugate of claim 10 wherein n is comprised between 4 and 7.

12. The antibody-drug conjugate of claim 11 having the structure of formula (XV).

13. A pharmaceutical composition containing an antibody or epitope-binding fragment thereof according to any of claims 1-4, or a conjugate according to any of claims 6, 7 and 8, and a pharmaceutically acceptable carrier or excipient.

14. An antibody or epitope-binding fragment thereof according to any of claims 1-4, or a conjugate according to any of claims 5, 6, and 7, for use as a medicament.

15. The use of an antibody or epitope-binding fragment thereof according to any of claims 1-4, or a conjugate according to any of claims 5, 6, and 7, to make a medicament to treat cancer.

16. The use of claim 15 wherein the cancer is chosen between carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, ovary, pancreas, stomach, cervix, thyroid and skin; including squamous cell carcinoma ; hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Burkitt's lymphoma ; hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias and promyelocytic leukemia; tumors of mesenchymal origin, including fibrosarcoma and rhabdomyoscarcoma; other tumors, including melanoma, seminoma, tetratocarcinoma, neuroblastoma and glioma; tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma, and schwannomas; tumors of mesenchymal origin, including fibrosarcoma, rhabdomyoscarama, and osteosarcoma; and other tumors, including melanoma, xeroderma pigmentosum, keratoactanthoma, seminoma, thyroid follicular cancer and teratocarcinoma.

17. An antibody or an epitope-binding fragment thereof according to claims 1-4, wherein the paratope of said monoclonal antibody or epitope-binding fragment thereof comprises in the light chain: Arg35 of Loop L1, Tyr54, Arg58 and Asp60 of L2.

18. An antibody or an epitope-binding fragment thereof according to claims 1-4, wherein the paratope of said monoclonal antibody or epitope-binding fragment thereof comprises in the heavy chain: Thr30, Ala31, Tyr32 and Tyr33 of Loop H1,

Asn52, Tyr54, Asn55 and Phe57 of H2 and Glu99, Phe100, Tyr101, Gly102, Tyr103 and Tyr105 of H3.

19. An antibody or an epitope-binding fragment thereof according to claims 1-4, wherein said monoclonal antibody or epitope-binding fragment thereof comprises mutation at the position: Thr H28.

20. An antibody or an epitope-binding fragment thereof according to claims 1-4, wherein said monoclonal antibody or epitope-binding fragment thereof comprises mutation at one of few of the following positions on the light chain: 35, 26 to 31, 34 to 37, 55, 56, 57, 59 and 94 to 102.

21. An antibody or an epitope-binding fragment thereof according to claims 1-4, wherein said monoclonal antibody or epitope-binding fragment thereof comprises mutation at one of few of the following positions on the heavy chain: 28, 54 and 57.

22. An antibody or an epitope-binding fragment thereof according to claims 1-4, which specifically binds to an epitope of human EphA2 receptor comprising residues Gly49, Lys50, Gly51, Asp53, Cys70, Asn71, Val72, Met73, Ser74, Gly75, Gln77, Phe108, Pro109, Gly110, Gly111, Ser113 and Ser114.of the LBD from the extra-cellular domain of EphA2 receptor , or a conservatively substituted form thereof.

23. A conjugate according to any of claims 6, 7 and 8 having an average DAR above 4, the DAR being measured with a UV spectrophotometer and determined by the following equation DAR = c_D / c_A

with :

$$c_D = [(\varepsilon_{A280} \times A_{252}) - (\varepsilon_{A252} \times A_{280})] / [(\varepsilon_{D252} \times \varepsilon_{A280}) - (\varepsilon_{A252} \times \varepsilon_{D280})]$$

$$c_A = [A_{280} - (c_D \times \varepsilon_{D280})] / \varepsilon_{A280}$$

ε_{D252} = 26,159 $M^{-1}cm^{-1}$

ε_{D280} = 5,180 $M^{-1}cm^{-1}$

ε_{A280} = 224,000 M^{-1} cm^{-1}

ε_{A252} = 82,880 $M^{-1}cm^{-1}$

A_{252} and A_{280} being the absorbances of the conjugate measured on the UV spectrophotometer at respectively 252 and 280 nm

24. , A conjugate according to claim 23 having an average DAR comprised between 4 and 10 or 5 and 8.

25. A conjugate according to claim 23 having an average DAR comprised between 5.9 and 7.5.

26. An article of manufacture comprising:

- a) a packaging material
- b) an antibody or epitope-binding fragment thereof according to any of claims 1-4, or a conjugate according to any of claims 6 to 8 and 23 to 25, and
- c) a label or package insert contained within said packaging material indicting that said antibody or epitope-binding fragment thereof is effective for treating cancer.

CLAIMS

1. An antibody or an epitope-binding fragment thereof that specifically binds to an EphA2 receptor and comprising at least one heavy chain and at least one light chain, wherein said heavy chain comprises a sequence having at 95% homology with an amino acid sequence consisting of SEQ ID NO: 12, comprises three sequential complementarity-determining regions having amino acid sequences represented by SEQ ID NOS: 1, 2, and 3 and comprises an arginine residue in position 74, and wherein said light chain comprises a sequence having a 95% homology with an amino acid sequence consisting of SEQ ID NO: 14, comprises three sequential complementarity-determining regions having amino acid sequences represented by SEQ ID NOS: 4, 5, and 6 with the provision that when conjugated to a cytotoxic agent, conjugation does not affect the affinity of said antibody.

2. An antibody or an epitope-binding fragment thereof according to claim 1, wherein when conjugated to a cytotoxic agent, the K_D is not significantly different for drug-to-antibody ratios ranging from 5.6 to 8.4 from the one of the naked antibody.

3. An antibody or an epitope-binding fragment thereof according to claim 1 or 2, wherein heavy chain comprises a sequence having 97% homology with an amino acid sequence consisting of SEQ ID NO: 12 and light chain comprises a sequence having 97% homology with an amino acid sequence consisting of SEQ ID NO: 14.

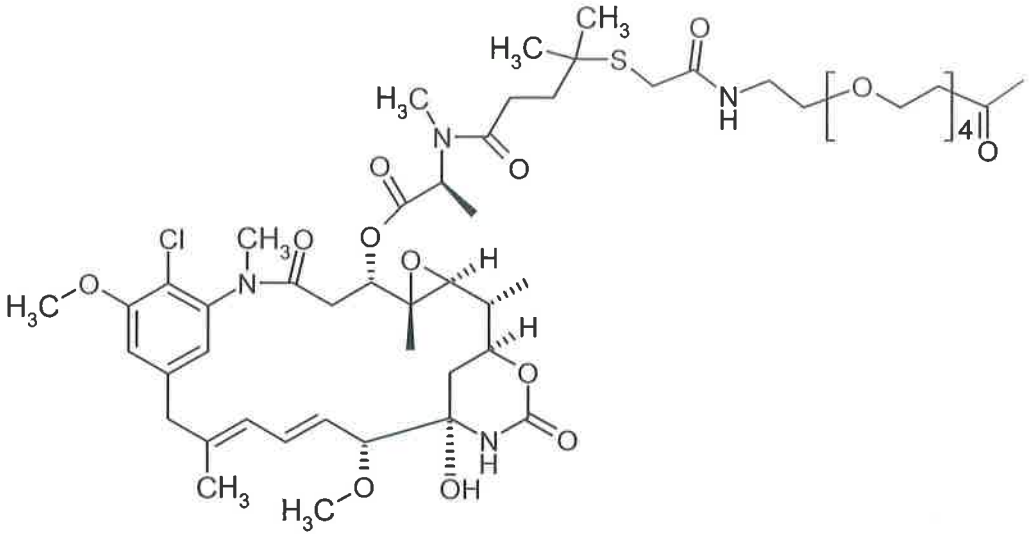
4. An antibody or an epitope-binding fragment thereof according to any of claims 1-3, wherein said monoclonal antibody or epitope-binding fragment thereof is a humanized or resurfaced antibody or epitope-binding fragment thereof.

5. An antibody or an epitope-binding fragment thereof according to any of claims 1-4, wherein said heavy chain comprises an amino acid sequence consisting of SEQ ID NO: 12 and wherein said light chain comprises an amino acid sequence consisting of SEQ ID NO: 14.

6. An antibody or an epitope-binding fragment thereof according to any of claims 1-5, wherein said heavy chain consists in an amino acid sequence SEQ ID NO: 18, and wherein said light chain consists in an amino acid sequence SEQ ID NO: 16.

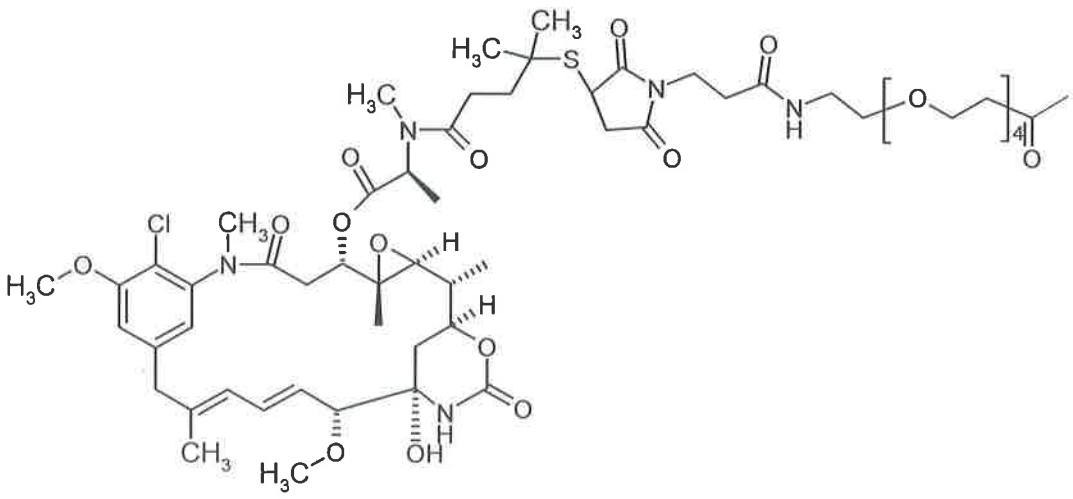
7. A conjugate of an antibody or an epitope-binding fragment according to claims 1-6, wherein said conjugate comprises a cytotoxic agent chosen between:

a) the maytansinoid of formula (XIII):



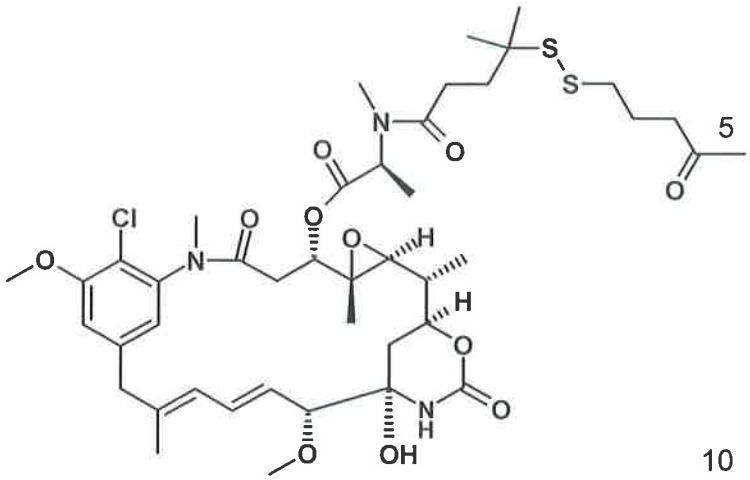
(XIII)

b) the maytansinoid of formula (XIV):



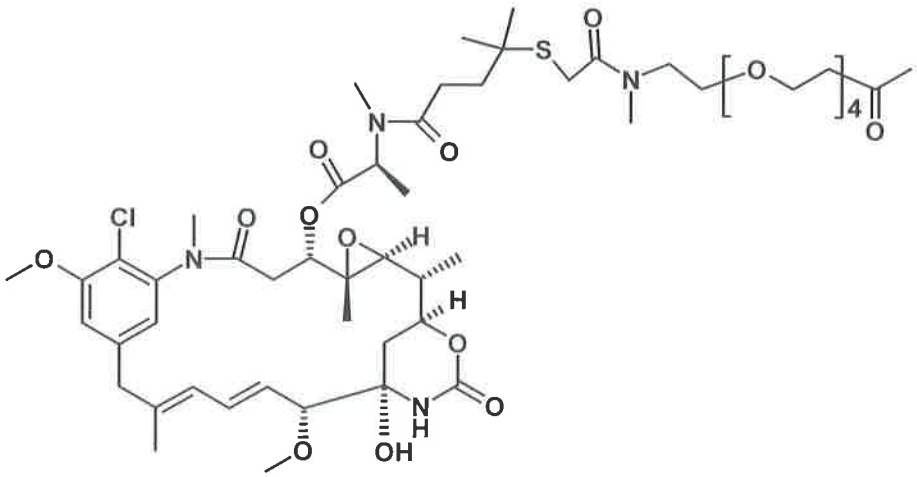
(XIV)

c) the maytansinoid of formula (XXIV):



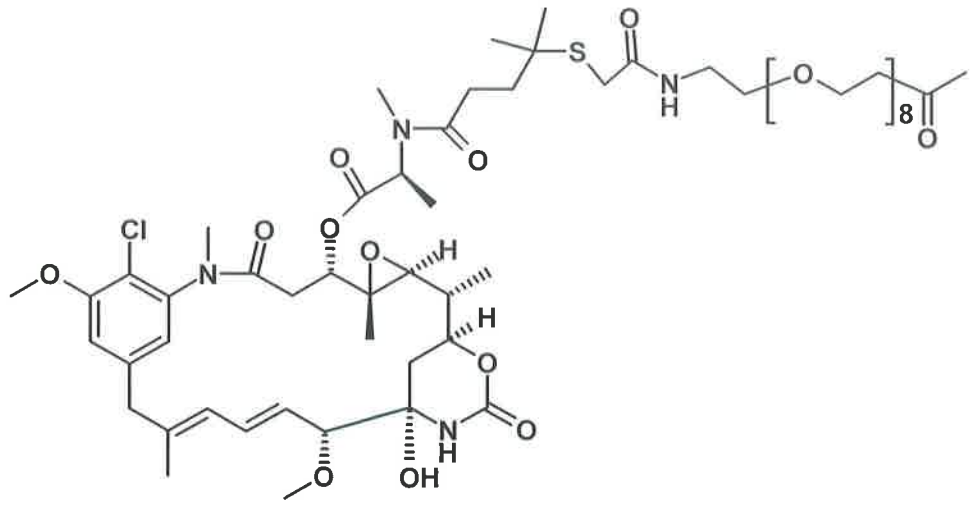
(XXIV)

d) the maytansinoid of formula (XXV):



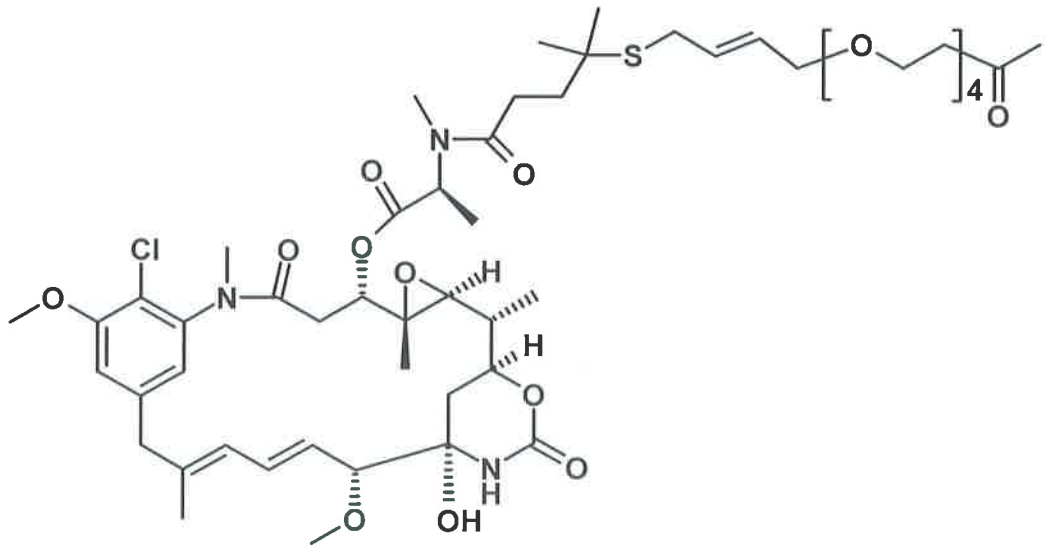
(XXV)

e) the maytansinoid of formula (XXVI):



(XXVI)

f) the maytansinoid of formula (XXVII):



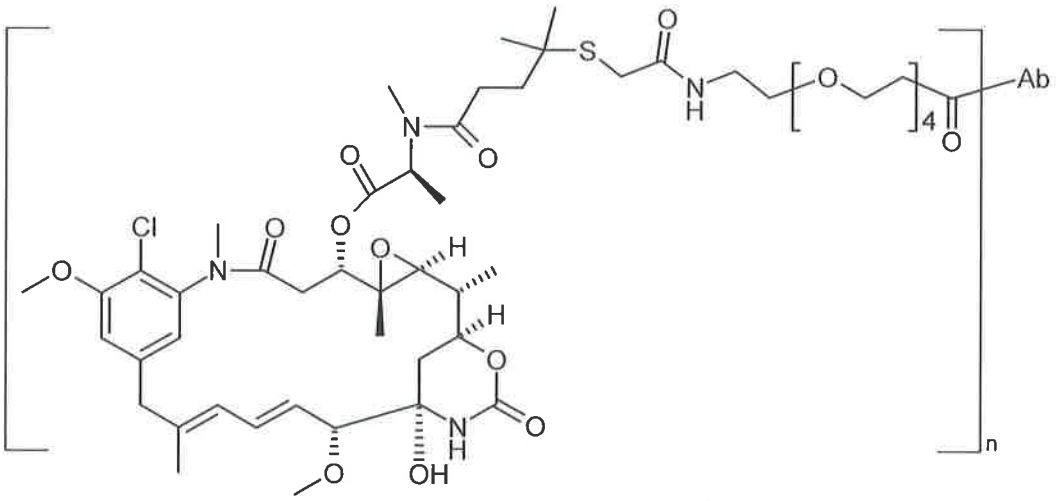
(XXVII)

8. A conjugate according to claim 5, wherein said cytotoxic agent is covalently bound to the

antibody.

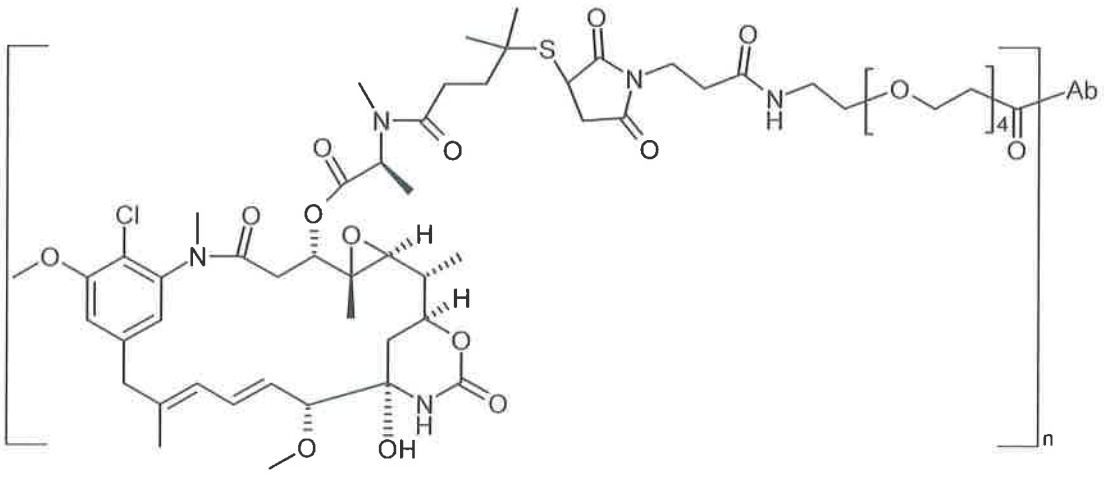
9. A conjugate according to any of claims 7 or 8, wherein the cytotoxic agent is the maytansinoid of formula (XIII).

10. A conjugate according to any of claims 7-9, said conjugate having a structure chosen between the structures of the formula (XV):



(XV)

and of the formula (XVI):



(XVI)

wherein Ab is an antibody according to claims 1-6 and n is an integer comprised between 1 and 15.

11. The antibody-drug conjugate of claim 10 wherein n is comprised between 4 and 7.

12. The antibody-drug conjugate of claim 11 having the structure of formula (XV).

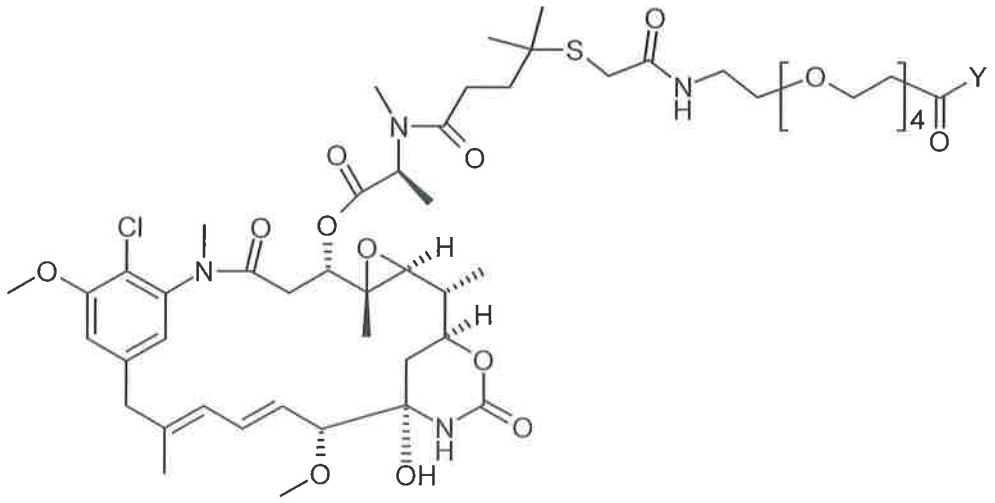
13. A method for preparing a conjugate comprising the steps of:

(i) bringing into contact an optionally-buffered aqueous solution of a cell-binding agent with a solution of a cytotoxic compound;

(ii) then optionally separating the conjugate which was formed in (i) from the unreacted reagents and any aggregate which may be present in the solution;

wherein the cell-binding agent is an antibody according to claims 1-4, and a cytotoxic agent chosen between:

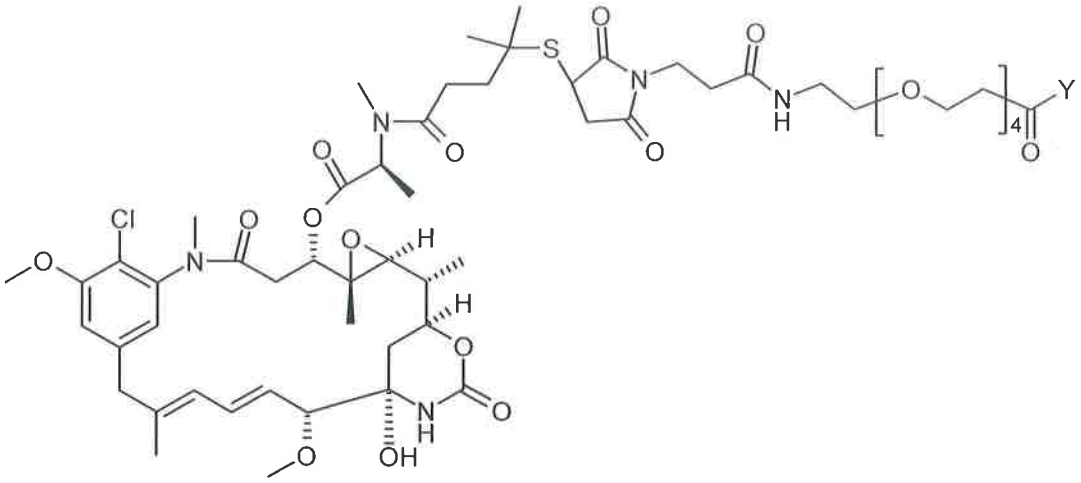
the compound of formula (XVII):



(XVII)

wherein Y is N-succinimidyloxy, N-sulfosuccinimidyloxy, N-phthalimidyloxy, N-sulfophthalimidyloxy, 2-nitrophenyloxy, 4-nitrophenyloxy, 2,4-dinitrophenyloxy, 3-sulfonyl-4-nitrophenyloxy, 3-carboxy-4-nitrophenyloxy, imidazolyl, or halogen atom; and

the compound of formula (XVIII):



(XVIII)

wherein Y is N-succinimidyloxy, N-sulfosuccinimidyloxy, N-phthalimidyloxy, N-sulfophthalimidyloxy, 2-nitrophenyloxy, 4-nitrophenyloxy, 2,4-dinitrophenyloxy, 3-sulfonyl-4-nitrophenyloxy, 3-carboxy-4-nitrophenyloxy, imidazolyl, or halogen atom; and

14. A pharmaceutical composition containing an antibody or epitope-binding fragment thereof according to any of claims 1-6, or a conjugate according to any of claims 7-12, and a pharmaceutically acceptable carrier or excipient.

15. An antibody or epitope-binding fragment thereof according to any of claims 1-6, or a conjugate according to any of claims 7-12, for use as a medicament.

16. The use of an antibody or epitope-binding fragment thereof according to any of claims 1-6, or a conjugate according to any of claims 7-12, to make a medicament to treat cancer.

17. The use of claim 16 wherein the cancer is chosen between carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, ovary, pancreas, stomach, cervix, thyroid and skin; including squamous cell carcinoma ; hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Burkitt's lymphoma ; hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias and promyelocytic leukemia; tumors of mesenchymal origin, including fibrosarcoma and rhabdomyoscarcoma; other tumors, including melanoma, seminoma, tetratocarcinoma, neuroblastoma and glioma; tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma, and schwannomas; tumors of

mesenchymal origin, including fibrosarcoma, rhabdomyoscarama, and osteosarcoma; and other tumors, including melanoma, xeroderma pigmentosum, keratoactanthoma, seminoma, thyroid follicular cancer and teratocarcinoma.

18. An antibody or an epitope-binding fragment thereof according to claims 1-6, wherein the paratope of said monoclonal antibody or epitope-binding fragment thereof comprises in the light chain: Arg35 of Loop L1, Tyr54, Arg58 and Asp60 of L2.

19. An antibody or an epitope-binding fragment thereof according to claims 1-6, wherein the paratope of said monoclonal antibody or epitope-binding fragment thereof comprises in the heavy chain: Thr30, Ala31, Tyr32 and Tyr33 of Loop H1, Asn52, Tyr54, Asn55 and Phe57 of H2 and Glu99, Phe100, Tyr101, Gly102, Tyr103 and Tyr105 of H3.

20. An antibody or an epitope-binding fragment thereof according to claims 1-6, wherein said monoclonal antibody or epitope-binding fragment thereof comprises mutation at the position: Thr H28.

21. An antibody or an epitope-binding fragment thereof according to claims 1-6, wherein said monoclonal antibody or epitope-binding fragment thereof comprises mutation at one of few of the following positions on the light chain: 26 to 31, 34 to 37, 55, 56, 57, 59 and 94 to 102.

22. An antibody or an epitope-binding fragment thereof according to claims 1-6, wherein said monoclonal antibody or epitope-binding fragment thereof comprises mutation at one of few of the following positions on the heavy chain: 28, 54 and 57.

23. An antibody or an epitope-binding fragment thereof according to claims 1-6, which specifically binds to an epitope of human EphA2 receptor comprising residues Gly49, Lys50, Gly51, Asp53, Cys70, Asn71, Val72, Met73, Ser74, Gly75, Gln77, Phe108, Pro109, Gly110, Gly111, Ser113 and Ser114.of the LBD from the extra-cellular domain of EphA2 receptor , or a conservatively substituted form thereof.

24. A conjugate according to any of claims 7-12 having an average DAR above 4, the DAR being measured with a UV spectrophotometer and determined by the following equation $DAR = c_D / c_A$

With :

$$c_D = [(\varepsilon_{A280} \times A_{252}) - (\varepsilon_{A252} \times A_{280})] / [(\varepsilon_{D252} \times \varepsilon_{A280}) - (\varepsilon_{A252} \times \varepsilon_{D280})]$$

$$c_A = [A_{280} - (c_D \times \varepsilon_{D280})] / \varepsilon_{A280}$$

$\varepsilon_{D252} = 26,159\ M^{-1}cm^{-1}$

$\varepsilon_{D280} = 5,180\ M^{-1}cm^{-1}$

$\varepsilon_{A280} = 224,000\ M^{-1}\ cm^{-1}$

$\varepsilon_{A252} = 82,880\ M^{-1}cm^{-1}$

A_{252} and A_{280} being the absorbances of the conjugate measured on the UV spectrophotometer at respectively 252 and 280 nm

25. , A conjugate according to claim 24 having an average DAR comprised between 4 and 10 or 5 and 8.

26. A conjugate according to claim 24 having an average DAR comprised between 5.9 and 7.5.

27. An article of manufacture comprising:

- a) a packaging material
- b) an antibody or epitope-binding fragment thereof according to any of claims 1-6, or a conjugate according to any of claims 7-12 and 24 to 26, and
- c) a label or package insert contained within said packaging material indicting that said antibody or epitope-binding fragment thereof is effective for treating cancer.