tumor infiltrating lymphocytes (TILs), which may result in problems demonstrating CD25 tumor cells in these cases (Levi et al., Merz et al, 1995).

Expression of the target antigen has also been reported for several B- and T-cell-derived subtypes of non-Hodgkin-lymphomas, i.e. B-cell chronic lymphatic leukemia, hairy cell leukemia, small cell lymphocytic lymphoma/chronic lymphocytic leukemia as well as adult T-cell leukemia/lymphoma and anaplastic large cell lymphoma.

CD25 may be localised to the membrane, with some expression observed in the cytoplasm. Soluble CD25 may also be observed outside of cells, such as in serum.

Therapeutic uses of anti-CD25 ADCs

The efficacy of an Antibody Drug Conjugate comprising an anti-CD25 antibody (an anti-CD25-ADC) in the treatment of, for example, cancer has been established – see, for example, WO2014/057119, WO2016/083468, and WO2016/166341.

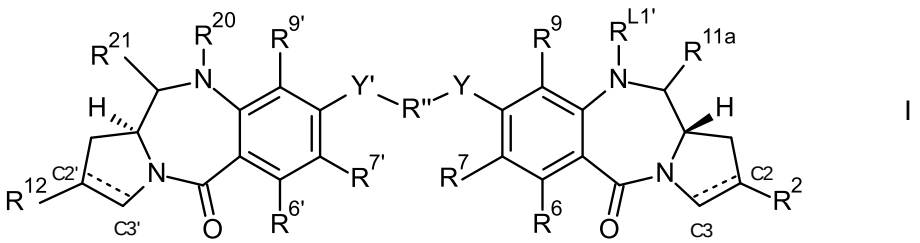
Research continues to further improve the efficacy, tolerability, and clinical utility of anti-CD25 ADCs. To this end, the present authors have identified clinically advantageous combination therapies in which an anti-CD25 ADC is administered in combination with Gemcitabine or 5-fluorouracil.

SUMMARY

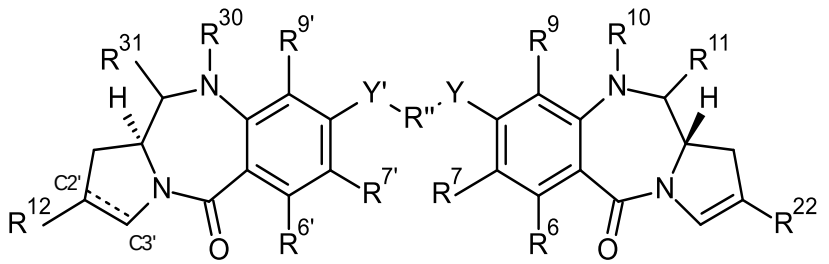
The present authors have determined that the administration of a combination of an ADC and Gemcitabine or 5-fluorouracil to an individual leads to unexpected clinical advantages.

In one aspect, the present disclosure refers to a use of an anti-CD25 ADC in the manufacture of a medicament for treating a proliferative disorder in an individual, wherein the anti-CD25 ADC is to be administered in combination with Gemcitabine to the individual in need thereof,

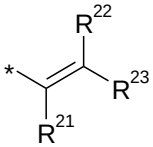
wherein the CD25-ADC comprise a conjugate of formula L - $(D^L)_p$, where D^L is of formula **I** or **II**:

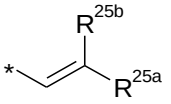


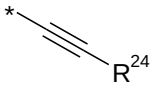
I

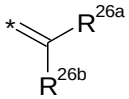


II

wherein:
L is an antibody (Ab) which is an antibody that binds to CD25;
when there is a double bond present between C2' and C3', R^{12} is selected from the group consisting of:
(ia) C_{5-10} aryl group, optionally substituted by one or more substituents selected from the group comprising: halo, nitro, cyano, ether, carboxy, ester, C_{1-7} alkyl, C_{3-7} heterocyclyl and bis-oxy-C_{1-3} alkylene;
(ib) C_{1-5} saturated aliphatic alkyl;
(ic) C_{3-6} saturated cycloalkyl;
(id) 

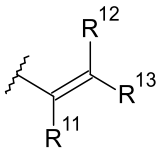
, wherein each of R^{21}, R^{22} and R^{23} are independently selected from H, C_{1-3} saturated alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl and cyclopropyl, where the total number of carbon atoms in the R^{12} group is no more than 5;
(ie) 

, 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) 

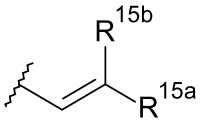
, where R^{24} is selected from: H; C_{1-3} saturated alkyl; C_{2-3} alkenyl; C_{2-3} alkynyl; cyclopropyl; phenyl, which phenyl is optionally substituted by a group selected from halo, methyl, methoxy; pyridyl; and thiophenyl;
when there is a single bond present between C2' and C3',
R^{12} is 

, where R^{26a} and R^{26b} are independently selected from H, F, C_{1-4} saturated alkyl, C_{2-3} alkenyl, which alkyl and alkenyl groups are optionally substituted by a group selected from C_{1-4} alkyl amido and C_{1-4} alkyl ester; or, when one of R^{26a} and R^{26b} is H, the other is selected from nitrile and a C_{1-4} alkyl ester;
R^6 and R^9 are independently selected from H, R, OH, OR, SH, SR, NH_2, NHR, NRR', nitro, Me_3Sn and halo;
where R and R' are independently selected from optionally substituted C_{1-12} alkyl, C_{3-20} heterocyclyl and C_{5-20} aryl groups;
R^7 is selected from H, R, OH, OR, SH, SR, NH_2, NHR, NHRR', nitro, Me_3Sn and halo;
R″ is a C_{3-12} alkylene group, which chain may be interrupted by one or more heteroatoms, e.g. O, S, NR^{N2} (where R^{N2} is H or C_{1-4} 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 R^6, R^7 and R^9 respectively;
[Formula I]
$R^{L1'}$ is a linker for connection to the antibody (Ab);
R^{11a} is selected from OH, OR^A, where R^A is C_{1-4} alkyl, and SO_zM, where z is 2 or 3 and M is a monovalent pharmaceutically acceptable cation;
R^{20} and R^{21} either together form a double bond between the nitrogen and carbon atoms to which they are bound or;
R^{20} is selected from H and R^C, where R^C is a capping group;
R^{21} is selected from OH, OR^A and SO_zM;
when there is a double bond present between C2 and C3, R^2 is selected from the group consisting of:

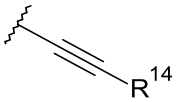
(ia) C_{5-10} aryl group, optionally substituted by one or more substituents selected from the group comprising: halo, nitro, cyano, ether, carboxy, ester, C_{1-7} alkyl, C_{3-7} heterocyclyl and bis-oxy-C_{1-3} alkylene;
(ib) C_{1-5} saturated aliphatic alkyl;
(ic) C_{3-6} saturated cycloalkyl;

(id) 

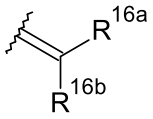
, wherein each of R^{11}, R^{12} and R^{13} are independently selected from H, C_{1-3} saturated alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl and cyclopropyl, where the total number of carbon atoms in the R^2 group is no more than 5;

(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) 

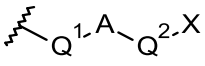
, where R^{14} is selected from: H; C_{1-3} saturated alkyl; C_{2-3} alkenyl; C_{2-3} alkynyl; cyclopropyl; phenyl, which phenyl is optionally substituted by a group selected from halo, methyl, methoxy; pyridyl; and thiophenyl;
when there is a single bond present between C2 and C3,

R^2 is 

, where R^{16a} and R^{16b} are independently selected from H, F, C_{1-4} saturated alkyl, C_{2-3} alkenyl, which alkyl and alkenyl groups are optionally substituted by a group selected from C_{1-4} alkyl amido and C_{1-4} alkyl ester; or, when one of R^{16a} and R^{16b} is H, the other is selected from nitrile and a C_{1-4} alkyl ester;

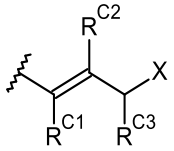
[Formula II]

R^{22} is of formula IIIa, formula IIIb or formula IIIc:

(a) 

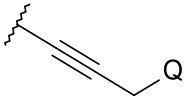
IIIa

where A is a C_{5-7} aryl group, and either
(i) Q^1 is a single bond, and Q^2 is selected from a single bond and -Z-$(CH_2)_n$-, where Z is selected from a single bond, O, S and NH and n is from 1 to 3; or
(ii) Q^1 is -CH=CH-, and Q^2 is a single bond;

(b) 

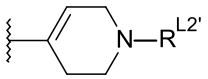
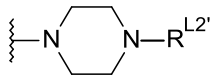
IIIb

where;
R^{C1}, R^{C2} and R^{C3} are independently selected from H and unsubstituted C_{1-2} alkyl;

(c) 

IIIc

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-$R^{L2'}$, CO_2-$R^{L2'}$, CO-$R^{L2'}$, NH-C(=O)-$R^{L2'}$, NHNH-$R^{L2'}$, CONHNH-$R^{L2'}$,  ,  , $NR^NR^{L2'}$, wherein R^N is selected from the group comprising H and C_{1-4} alkyl;
$R^{L2'}$ is a linker for connection to the antibody (Ab);
R^{10} and R^{11} either together form a double bond between the nitrogen and carbon atoms to which they are bound or;
R^{10} is H and R^{11} is selected from OH, OR^A and SO_zM;
R^{30} and R^{31} either together form a double bond between the nitrogen and carbon atoms to which they are bound or;
R^{30} is H and R^{31} is selected from OH, OR^A and SO_zM.

In another aspect, the present disclosure refers to a pharmaceutical composition comprising a CD25-ADC as disclosed herein and Gemcitabine.

In another aspect, the present disclosure refers to a use of the composition as disclosed herein in the manufacture of a medicament for treating a proliferative disorder in an individual, wherein said composition is to be administered to the individual.

Accordingly, in one example the disclosure provides a method for treating a disorder in an individual, the method comprising administering to the individual an effective amount of an ADC and Gemcitabine or 5-fluorouracil.

The disorder may be a proliferative disease, for example a cancer such as 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) and leukemias such as Hairy cell leukemia (HCL), Hairy cell leukemia variant (HCL-v), Acute Myeloid Leukaemia (AML), and Acute Lymphoblastic Leukaemia (ALL) such as Philadelphia chromosome-positive ALL (Ph+ALL) or Philadelphia chromosome-negative ALL (Ph-ALL).

The proliferative disease may be characterised by the presence of a neoplasm comprising both CD25+ve and CD25-ve cells.

The proliferative disease may be characterised by the presence of a neoplasm composed of CD25-ve neoplastic cells, optionally wherein the CD25-ve neoplastic cells are associated with CD25+ve non-neoplastic cells such as CD25+ve T-cells.

The target neoplasm or neoplastic cells may be all or part of a solid tumour.

"Solid tumor" herein will be understood to include solid haematological cancers such as lymphomas (Hodgkin's lymphoma or non-Hodgkin's lymphoma) which are discussed in more detail herein.

Solid tumors may be neoplasms, including non-haematological cancers, comprising or composed of CD25+ve neoplastic cells. Solid tumors may be neoplasms, including non-haematological cancers, infiltrated with CD25+ve cells, such as CD25+ve T-cells; such solid tumours may lack expression of CD25 (that is, comprise or be composed of CD25-ve neoplastic cells).

For example, the solid tumour may be a tumour with high levels of infiltrating T-cells, such as infiltrating regulatory T-cells (Treg; Ménétrier-Caux, C., et al., Targ Oncol (2012) 7:15–28; Arce Vargas et al., 2017, Immunity 46, 1–10; Tanaka, A., et al., Cell Res. 2017

Jan;27(1):109-118). Accordingly, the solid tumour may be 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.

The ADC may be an anti-CD25-ADC, such as ADCX25 described herein.

The ADC may be anti-CD25-ADC, such as ADCT-301.

The individual may be human. The individual may have cancer, or may have been determined to have cancer. The individual may have, or have been determined to have, a CD25+ cancer or CD25+ tumour-associated non-tumour cells, such as CD25+ infiltrating T-cells.

The individual may have, or have been determined to have, a PD-L1+ cancer.

In the disclosed methods the ADC may be administered before the Gemcitabine or 5-fluorouracil, simultaneous with the Gemcitabine or 5-fluorouracil, or after the Gemcitabine or 5-fluorouracil. The disclosed methods may comprise administering a further chemotherapeutic agent to the individual.

In another example, the disclosure provides a first composition comprising an ADC for use in a method of treating a disorder in an individual, wherein the treatment comprises administration of the first composition in combination with a second composition comprising Gemcitabine or 5-fluorouracil.

Also provided by this example is a first composition comprising Gemcitabine or 5-fluorouracil for use in a method of treating a disorder in an individual, wherein the treatment comprises administration of the first composition in combination with a second composition comprising an ADC.

The disorder may be a proliferative disease, for example a cancer such as 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), and leukemias such as Hairy cell leukemia (HCL), Hairy cell leukemia variant (HCL-v), Acute Myeloid Leukaemia (AML), and Acute Lymphoblastic Leukaemia (ALL) such as Philadelphia chromosome-positive ALL (Ph+ALL) or Philadelphia chromosome-negative ALL (Ph-ALL).

The proliferative disease may be characterised by the presence of a neoplasm comprising both CD25+ve and CD25-ve cells.

The proliferative disease may be characterised by the presence of a neoplasm composed of CD25-ve neoplastic cells, optionally wherein the CD25-ve neoplastic cells are associated with CD25+ve non-neoplastic cells such as CD25+ve T-cells.

The target neoplasm or neoplastic cells may be all or part of a solid tumour.

"Solid tumor" herein will be understood to include solid haematological cancers such as lymphomas (Hodgkin's lymphoma or non-Hodgkin's lymphoma) which are discussed in more detail herein.

Solid tumors may be neoplasms, including non-haematological cancers, comprising or composed of CD25+ve neoplastic cells. Solid tumors may be neoplasms, including non-

haematological cancers, infiltrated with CD25+ve cells, such as CD25+ve T-cells; such solid tumours may lack expression of CD25 (that is, comprise or be composed of CD25-ve neoplastic cells).

For example, the solid tumour may be a tumour with high levels of infiltrating T-cells, such as infiltrating regulatory T-cells (Treg; Ménétrier-Caux, C., et al., Targ Oncol (2012) 7:15–28; Arce Vargas et al., 2017, Immunity 46, 1–10; Tanaka, A., et al., Cell Res. 2017 Jan;27(1):109-118). Accordingly, the solid tumour may be 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.

The ADC may be anti-CD25-ADC, such as ADCX25 described herein.

The ADC may be anti-CD25-ADC, such as ADCT-301.

The individual may be human. The individual may have cancer, or may have been determined to have cancer. The individual may have, or have been determined to have, a CD25+ cancer or CD25+ tumour-associated non-tumour cells, such as CD25+ infiltrating T-cells.

The individual may have, or have been determined to have, a PD-L1+ cancer.

The first composition may be administered before the second composition, simultaneous with the second composition, or after the second composition. The treatment may comprise administering a further chemotherapeutic agent to the individual.

In a further example, the disclosure provides the use of n ADC in the manufacture of a medicament for treating a disorder in an individual, wherein the medicament comprises an ADC, and wherein the treatment comprises administration of the medicament in combination with a composition comprising Gemcitabine or 5-fluorouracil.

Also provided by this example is the use of Gemcitabine or 5-fluorouracil in the manufacture of a medicament for treating a disorder in an individual, wherein the medicament comprises Gemcitabine or 5-fluorouracil, and wherein the treatment comprises administration of the medicament in combination with a composition comprising an ADC.

The disorder may be a proliferative disease, for example a cancer such as 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) and leukemias such as Hairy cell leukemia (HCL), Hairy cell leukemia variant (HCL-v), Acute Myeloid Leukaemia (AML), and Acute Lymphoblastic Leukaemia (ALL) such as Philadelphia chromosome-positive ALL (Ph+ALL) or Philadelphia chromosome-negative ALL (Ph-ALL).

The proliferative disease may be characterised by the presence of a neoplasm comprising both CD25+ve and CD25-ve cells.

The proliferative disease may be characterised by the presence of a neoplasm composed of CD25-ve neoplastic cells, optionally wherein the CD25-ve neoplastic cells are associated with CD25+ve non-neoplastic cells such as CD25+ve T-cells.

The target neoplasm or neoplastic cells may be all or part of a solid tumour.

“Solid tumor” herein will be understood to include solid haematological cancers such as lymphomas (Hodgkin’s lymphoma or non-Hodgkin’s lymphoma) which are discussed in more detail herein.

Solid tumors may be neoplasms, including non-haematological cancers, comprising or composed of CD25+ve neoplastic cells. Solid tumors may be neoplasms, including non-haematological cancers, infiltrated with CD25+ve cells, such as CD25+ve T-cells; such solid tumours may lack expression of CD25 (that is, comprise or be composed of CD25-ve neoplastic cells).

For example, the solid tumour may be a tumour with high levels of infiltrating T-cells, such as infiltrating regulatory T-cells (Treg; Ménétrier-Caux, C., et al., Targ Oncol (2012) 7:15–28; Arce Vargas et al., 2017, Immunity 46, 1–10; Tanaka, A., et al., Cell Res. 2017 Jan;27(1):109-118). Accordingly, the solid tumour may be 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.

The ADC may be anti-CD25-ADC, such as ADCX25 described herein.

The ADC may be anti-CD25-ADC, such as ADCT-301.

The individual may be human. The individual may have cancer, or may have been determined to have cancer. The individual may have, or have been determined to have, a CD25+ cancer or CD25+ tumour-associated non-tumour cells, such as CD25+ infiltrating T-cells.

The individual may have, or have been determined to have, a PD-L1+ cancer.

The medicament may be administered before the composition, simultaneous with the composition, or after the composition. The treatment may comprise administering a further chemotherapeutic agent to the individual.

Another example of the disclosure provides a kit comprising:

a first medicament comprising an ADC;

a second medicament comprising Gemcitabine or 5-fluorouracil; and, optionally,

a package insert comprising instructions for administration of the first medicament to an individual in combination with the second medicament for the treatment of a disorder.

Also provided by this example is a kit comprising a medicament comprising an ADC and a package insert comprising instructions for administration of the medicament to an individual in combination with a composition comprising Gemcitabine or 5-fluorouracil for the treatment of a disorder.

Further provided by this example is a kit comprising a medicament comprising Gemcitabine or 5-fluorouracil and a package insert comprising instructions for administration of the medicament to an individual in combination with a composition comprising an ADC for the treatment of a disorder.

The disorder may be a proliferative disease, for example a cancer such as 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) and leukemias such as Hairy cell leukemia (HCL), Hairy cell leukemia variant (HCL-v), Acute Myeloid Leukaemia (AML), and Acute Lymphoblastic Leukaemia (ALL) such as Philadelphia chromosome-positive ALL (Ph+ALL) or Philadelphia chromosome-negative ALL (Ph-ALL).

The proliferative disease may be characterised by the presence of a neoplasm comprising both CD25+ve and CD25-ve cells.

The proliferative disease may be characterised by the presence of a neoplasm composed of CD25-ve neoplastic cells, optionally wherein the CD25-ve neoplastic cells are associated with CD25+ve non-neoplastic cells such as CD25+ve T-cells.

The target neoplasm or neoplastic cells may be all or part of a solid tumour.

"Solid tumor" herein will be understood to include solid haematological cancers such as lymphomas (Hodgkin's lymphoma or non-Hodgkin's lymphoma) which are discussed in more detail herein.

Solid tumors may be neoplasms, including non-haematological cancers, comprising or composed of CD25+ve neoplastic cells. Solid tumors may be neoplasms, including non-haematological cancers, infiltrated with CD25+ve cells, such as CD25+ve T-cells; such solid tumours may lack expression of CD25 (that is, comprise or be composed of CD25-ve neoplastic cells).

For example, the solid tumour may be a tumour with high levels of infiltrating T-cells, such as infiltrating regulatory T-cells (Treg; Ménétrier-Caux, C., et al., Targ Oncol (2012) 7:15–28; Arce Vargas et al., 2017, Immunity 46, 1–10; Tanaka, A., et al., Cell Res. 2017 Jan;27(1):109-118). Accordingly, the solid tumour may be 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.

The ADC may be anti-CD25-ADC, such as ADCX25 described herein.

The ADC may be anti-CD25-ADC, such as ADCT-301.

The individual may be human. The individual may have cancer, or may have been determined to have cancer. The individual may have, or have been determined to have, a CD25+ cancer or CD25+ tumour-associated non-tumour cells, such as CD25+ infiltrating T-cells.

The individual may have, or have been determined to have, a PD-L1+ cancer.

The medicament or composition comprising the ADC may be administered before the medicament or composition comprising Gemcitabine or 5-fluorouracil, simultaneous with the medicament or composition comprising Gemcitabine or 5-fluorouracil, or after the medicament or composition comprising Gemcitabine or 5-fluorouracil. The treatment may comprise administering a further chemotherapeutic agent to the individual.

In a yet further example, the disclosure provides a composition comprising an ADC and Gemcitabine or 5-fluorouracil.

Also provided in this example of the disclosure is a method of treating a disorder in an individual, the method comprising administering to the individual an effective amount of the composition comprising an ADC and Gemcitabine or 5-fluorouracil.

Also provided in this example of the disclosure is a composition comprising an ADC and Gemcitabine or 5-fluorouracil for use in a method of treating a disorder in an individual.

Also provided in this example of the disclosure is the use of a composition comprising an ADC and Gemcitabine or 5-fluorouracil in the manufacture of a medicament for treating a disorder in an individual.

Also provided in this example of the disclosure is a kit comprising composition comprising an ADC and Gemcitabine or 5-fluorouracil and a set of instructions for administration of the medicament to an individual for the treatment of a disorder.

The disorder may be a proliferative disease, for example a cancer such as 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), and leukemias such as Hairy cell leukemia (HCL), Hairy cell leukemia variant (HCL-v), Acute Myeloid Leukaemia (AML), and Acute Lymphoblastic Leukaemia (ALL) such as Philadelphia chromosome-positive ALL (Ph+ALL) or Philadelphia chromosome-negative ALL (Ph-ALL).

The proliferative disease may be characterised by the presence of a neoplasm comprising both CD25+ve and CD25-ve cells.

The proliferative disease may be characterised by the presence of a neoplasm composed of CD25-ve neoplastic cells, optionally wherein the CD25-ve neoplastic cells are associated with CD25+ve non-neoplastic cells such as CD25+ve T-cells.

The target neoplasm or neoplastic cells may be all or part of a solid tumour.

"Solid tumor" herein will be understood to include solid haematological cancers such as lymphomas (Hodgkin's lymphoma or non-Hodgkin's lymphoma) which are discussed in more detail herein.

Solid tumors may be neoplasms, including non-haematological cancers, comprising or composed of CD25+ve neoplastic cells. Solid tumors may be neoplasms, including non-haematological cancers, infiltrated with CD25+ve cells, such as CD25+ve T-cells; such solid tumours may lack expression of CD25 (that is, comprise or be composed of CD25-ve neoplastic cells).

For example, the solid tumour may be a tumour with high levels of infiltrating T-cells, such as infiltrating regulatory T-cells (Treg; Ménétrier-Caux, C., et al., Targ Oncol (2012) 7:15–28; Arce Vargas et al., 2017, Immunity 46, 1–10; Tanaka, A., et al., Cell Res. 2017 Jan;27(1):109-118). Accordingly, the solid tumour may be 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.

The ADC may be anti-CD25-ADC, such as ADCX25 described herein.

The ADC may be anti-CD25-ADC, such as ADCT-301.

The individual may be human. The individual may have cancer, or may have been determined to have cancer. The individual may have, or have been determined to have, a CD25+ cancer or CD25+ tumour-associated non-tumour cells, such as CD25+ infiltrating T-cells.

The individual may have, or have been determined to have, a PD-L1+ cancer.

The treatment may comprise administering a further chemotherapeutic agent to the individual.

DETAILED DESCRIPTION

Antibody Drug Conjugates (ADCs)

The present disclosure relates to the improved efficacy of combinations of an ADC and Gemcitabine or 5-fluorouracil.

The ADC can deliver a drug to a target location. The target location is preferably a proliferative cell population. The antibody is an antibody for an antigen present on a proliferative cell population. In one aspect the antigen is absent or present at a reduced level in a non-proliferative cell population compared to the amount of antigen present in the proliferative cell population, for example a tumour cell population.

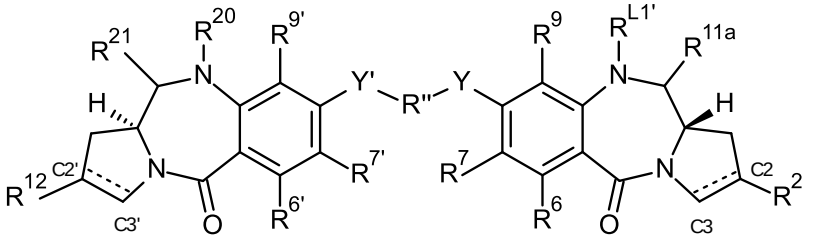
The ADC may comprise a linker which may be cleaved so as to release the drug at the target location. The drug may be a compound selected from RelA, RelB, RelC, RelD or RelE. Thus, the conjugate may be used to selectively provide a compound RelA, RelB, Rel C, RelD or RelE to the target location.

The linker may be cleaved by an enzyme present at the target location.

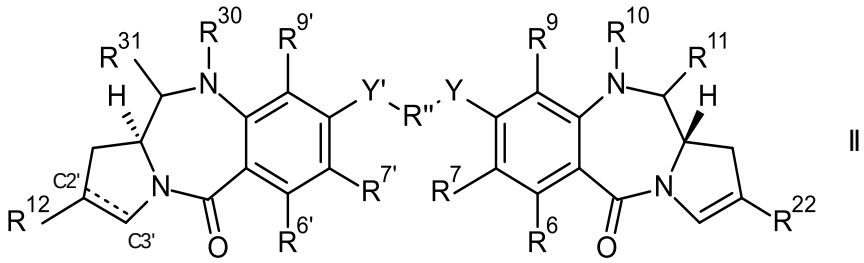
CLAIMS

1. Use of an anti-CD25 ADC in the manufacture of a medicament for treating a proliferative disorder in an individual, wherein the anti-CD25 ADC is to be administered in combination with Gemcitabine to the individual in need thereof,

wherein the CD25-ADC comprise a conjugate of formula L - $(D^L)_p$, where D^L is of formula **I** or **II**:



I



II

wherein:

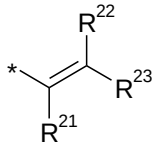
L is an antibody (Ab) which is an antibody that binds to CD25;

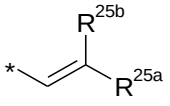
when there is a double bond present between C2' and C3', R^{12} is selected from the group consisting of:

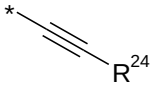
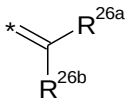
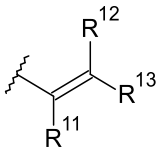
(ia) C_{5-10} aryl group, optionally substituted by one or more substituents selected from the group comprising: halo, nitro, cyano, ether, carboxy, ester, C_{1-7} alkyl, C_{3-7} heterocyclyl and bis-oxy-C_{1-3} alkylene;

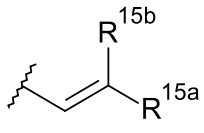
(ib) C_{1-5} saturated aliphatic alkyl;

(ic) C_{3-6} saturated cycloalkyl;

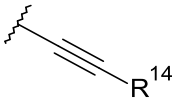
(id) , wherein each of R^{21}, R^{22} and R^{23} are independently selected from H, C_{1-3} saturated alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl and cyclopropyl, where the total number of carbon atoms in the R^{12} group is no more than 5;

(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 R^{24} is selected from: H; C_{1-3} saturated alkyl; C_{2-3} alkenyl; C_{2-3} 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',
R^{12} is , where R^{26a} and R^{26b} are independently selected from H, F, C_{1-4} saturated alkyl, C_{2-3} alkenyl, which alkyl and alkenyl groups are optionally substituted by a group selected from C_{1-4} alkyl amido and C_{1-4} alkyl ester; or, when one of R^{26a} and R^{26b} is H, the other is selected from nitrile and a C_{1-4} alkyl ester;
R^6 and R^9 are independently selected from H, R, OH, OR, SH, SR, NH_2, NHR, NRR', nitro, Me_3Sn and halo;
where R and R' are independently selected from optionally substituted C_{1-12} alkyl, C_{3-20} heterocyclyl and C_{5-20} aryl groups;
R^7 is selected from H, R, OH, OR, SH, SR, NH_2, NHR, NHRR', nitro, Me_3Sn and halo;
R″ is a C_{3-12} alkylene group, which chain may be interrupted by one or more heteroatoms, e.g. O, S, NR^{N2} (where R^{N2} is H or C_{1-4} 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 R^6, R^7 and R^9 respectively;
[Formula I]
$R^{L1'}$ is a linker for connection to the antibody (Ab);
R^{11a} is selected from OH, OR^A, where R^A is C_{1-4} alkyl, and SO_zM, where z is 2 or 3 and M is a monovalent pharmaceutically acceptable cation;
R^{20} and R^{21} either together form a double bond between the nitrogen and carbon atoms to which they are bound or;
R^{20} is selected from H and R^C, where R^C is a capping group;
R^{21} is selected from OH, OR^A and SO_zM;
when there is a double bond present between C2 and C3, R^2 is selected from the group consisting of:
(ia) C_{5-10} aryl group, optionally substituted by one or more substituents selected from the group comprising: halo, nitro, cyano, ether, carboxy, ester, C_{1-7} alkyl, C_{3-7} heterocyclyl and bis-oxy-C_{1-3} alkylene;
(ib) C_{1-5} saturated aliphatic alkyl;
(ic) C_{3-6} saturated cycloalkyl;
(id) , wherein each of R^{11}, R^{12} and R^{13} are independently selected from H, C_{1-3} saturated alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl and cyclopropyl, where the total number of carbon atoms in the R^2 group is no more than 5;

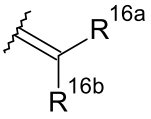
(ie) 

, 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 R^{14} is selected from: H; C_{1-3} saturated alkyl; C_{2-3} alkenyl; C_{2-3} alkynyl; cyclopropyl; phenyl, which phenyl is optionally substituted by a group selected from halo, methyl, methoxy; pyridyl; and thiophenyl;

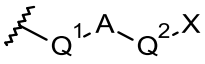
when there is a single bond present between C2 and C3,

R^2 is 

, where R^{16a} and R^{16b} are independently selected from H, F, C_{1-4} saturated alkyl, C_{2-3} alkenyl, which alkyl and alkenyl groups are optionally substituted by a group selected from C_{1-4} alkyl amido and C_{1-4} alkyl ester; or, when one of R^{16a} and R^{16b} is H, the other is selected from nitrile and a C_{1-4} alkyl ester;

[Formula II]

R^{22} is of formula IIIa, formula IIIb or formula IIIc:

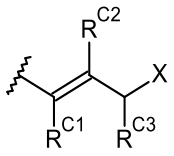
(a) 

IIIa

where A is a C_{5-7} aryl group, and either

(i) Q^1 is a single bond, and Q^2 is selected from a single bond and -Z-$(CH_2)_n$-, where Z is selected from a single bond, O, S and NH and n is from 1 to 3; or

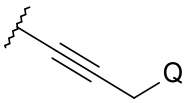
(ii) Q^1 is -CH=CH-, and Q^2 is a single bond;

(b) 

IIIb

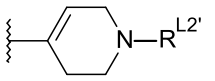
where;

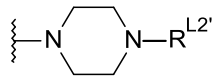
R^{C1}, R^{C2} and R^{C3} are independently selected from H and unsubstituted C_{1-2} alkyl;

(c) 

IIIc

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-$R^{L2'}$, CO_2-$R^{L2'}$, CO-$R^{L2'}$, NH-C(=O)-$R^{L2'}$, NHNH-$R^{L2'}$, CONHNH-$R^{L2'}$, 

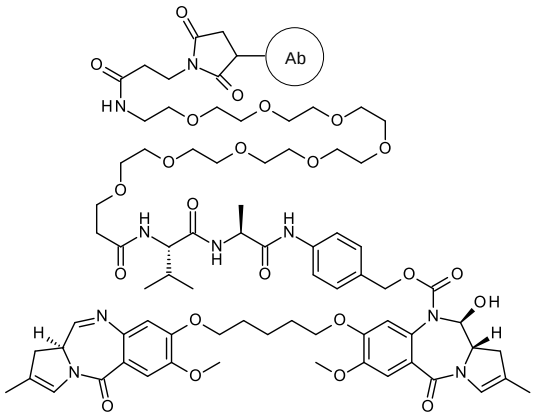
, 

, $NR^NR^{L2'}$, wherein R^N is selected from the group comprising H and C_{1-4} alkyl;

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

R^{10} and R^{11} either together form a double bond between the nitrogen and carbon atoms to which they are bound or;
R^{10} is H and R^{11} is selected from OH, OR^A and SO_zM;
R^{30} and R^{31} either together form a double bond between the nitrogen and carbon atoms to which they are bound or;
R^{30} is H and R^{31} is selected from OH, OR^A and SO_zM.

2. The use according to claim 1, wherein the ADC has the chemical structure:



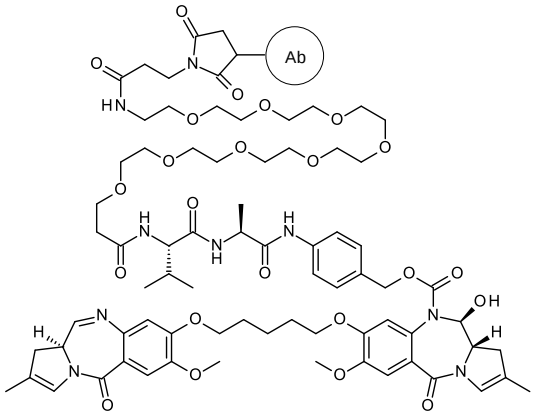
, where the Ab is an antibody that binds to CD25, and the DAR is between 1 and 8.

3. The use according to either on of claims 1 or 2, wherein the antibody comprises:
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; and
a VL domain comprising 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.

4. The use according to any one of claims 1 to 3, wherein the antibody comprises:
a VH domain having the sequence of SEQ ID NO. 1; and
a VL domain having the sequence of SEQ ID NO.2.

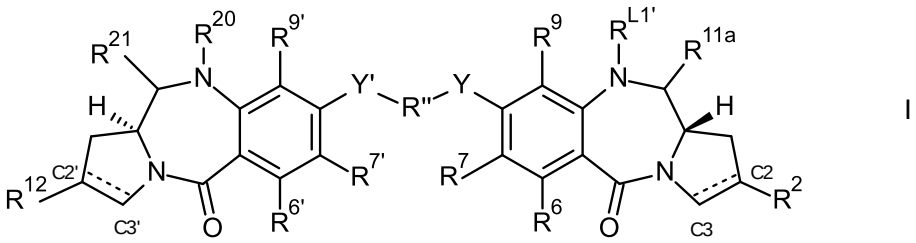
5. The use according to any one of claims 1 to 4, wherein the antibody is an intact antibody.

6. The use according to any one of claims 1 to 5, wherein the anti-CD25 ADC has the structure:

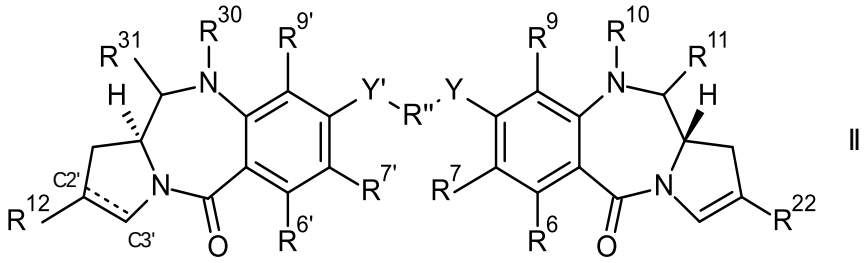


, where Ab is an antibody that binds to CD25 and has the VH sequence of SEQ ID NO. 1 and the VL sequence of SEQ ID NO. 2.

7. A pharmaceutical composition comprising a CD25-ADC and Gemcitabine wherein the CD25-ADC comprise a conjugate of formula L - $(D^L)_p$, where D^L is of formula **I** or **II**:



I



II

wherein:

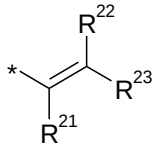
L is an antibody (Ab) which is an antibody that binds to CD25;

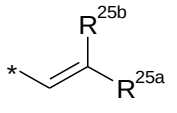
when there is a double bond present between C2' and C3', R^{12} is selected from the group consisting of:

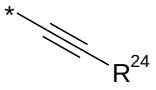
(ia) C_{5-10} aryl group, optionally substituted by one or more substituents selected from the group comprising: halo, nitro, cyano, ether, carboxy, ester, C_{1-7} alkyl, C_{3-7} heterocyclyl and bis-oxy-C_{1-3} alkylene;

(ib) C_{1-5} saturated aliphatic alkyl;

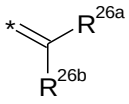
(ic) C_{3-6} saturated cycloalkyl;

(id) , wherein each of R^{21}, R^{22} and R^{23} are independently selected from H, C_{1-3} saturated alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl and cyclopropyl, where the total number of carbon atoms in the R^{12} 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 R^{24} is selected from: H; C_{1-3} saturated alkyl; C_{2-3} alkenyl; C_{2-3} 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',

R^{12} is  , where R^{26a} and R^{26b} are independently selected from H, F, C_{1-4} saturated alkyl, C_{2-3} alkenyl, which alkyl and alkenyl groups are optionally substituted by a group selected from C_{1-4} alkyl amido and C_{1-4} alkyl ester; or, when one of R^{26a} and R^{26b} is H, the other is selected from nitrile and a C_{1-4} alkyl ester;

R^6 and R^9 are independently selected from H, R, OH, OR, SH, SR, NH_2, NHR, NRR', nitro, Me_3Sn and halo;

where R and R' are independently selected from optionally substituted C_{1-12} alkyl, C_{3-20} heterocyclyl and C_{5-20} aryl groups;

R^7 is selected from H, R, OH, OR, SH, SR, NH_2, NHR, NHRR', nitro, Me_3Sn and halo;

R″ is a C_{3-12} alkylene group, which chain may be interrupted by one or more heteroatoms, e.g. O, S, NR^{N2} (where R^{N2} is H or C_{1-4} 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 R^6, R^7 and R^9 respectively;

[Formula I]

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

R^{11a} is selected from OH, OR^A, where R^A is C_{1-4} alkyl, and SO_zM, where z is 2 or 3 and M is a monovalent pharmaceutically acceptable cation;

R^{20} and R^{21} either together form a double bond between the nitrogen and carbon atoms to which they are bound or;

R^{20} is selected from H and R^C, where R^C is a capping group;

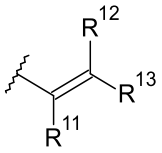
R^{21} is selected from OH, OR^A and SO_zM;

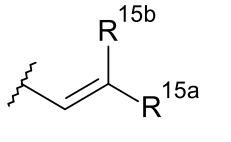
when there is a double bond present between C2 and C3, R^2 is selected from the group consisting of:

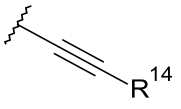
(ia) C_{5-10} aryl group, optionally substituted by one or more substituents selected from the group comprising: halo, nitro, cyano, ether, carboxy, ester, C_{1-7} alkyl, C_{3-7} heterocyclyl and bis-oxy-C_{1-3} alkylene;

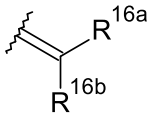
(ib) C_{1-5} saturated aliphatic alkyl;

(ic) C_{3-6} saturated cycloalkyl;

(id)  , wherein each of R^{11}, R^{12} and R^{13} are independently selected from H, C_{1-3} saturated alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl and cyclopropyl, where the total number of carbon atoms in the R^2 group is no more than 5;

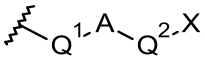
(ie)  , wherein one of R^{15a} and R^{15b} is H and the other is selected from: phenyl, which phenyl is optionally substituted by a group selected from halo, methyl, methoxy; pyridyl; and thiophenyl; and

(if)  , where R^{14} is selected from: H; C_{1-3} saturated alkyl; C_{2-3} alkenyl; C_{2-3} 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,

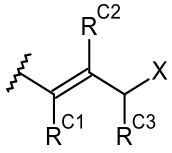
R^2 is  , where R^{16a} and R^{16b} are independently selected from H, F, C_{1-4} saturated alkyl, C_{2-3} alkenyl, which alkyl and alkenyl groups are optionally substituted by a group selected from C_{1-4} alkyl amido and C_{1-4} alkyl ester; or, when one of R^{16a} and R^{16b} is H, the other is selected from nitrile and a C_{1-4} alkyl ester;

[Formula II]

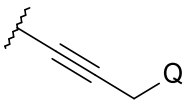
R^{22} is of formula IIIa, formula IIIb or formula IIIc:

(a)  IIIa

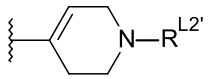
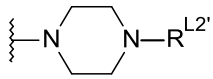
where A is a C_{5-7} aryl group, and either
(i) Q^1 is a single bond, and Q^2 is selected from a single bond and -Z-$(CH_2)_n$-, where Z is selected from a single bond, O, S and NH and n is from 1 to 3; or
(ii) Q^1 is -CH=CH-, and Q^2 is a single bond;

(b)  IIIb

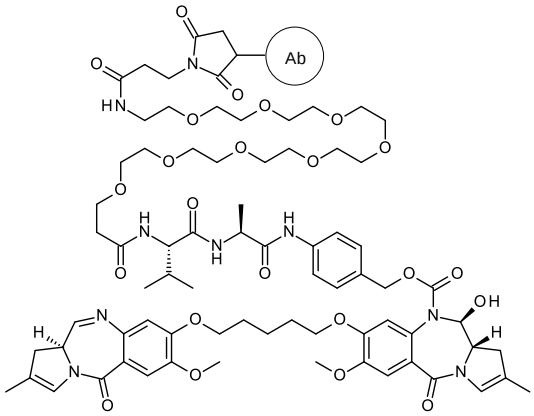
where;
R^{C1}, R^{C2} and R^{C3} are independently selected from H and unsubstituted C_{1-2} alkyl;

(c)  IIIc

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-$R^{L2'}$, CO_2-$R^{L2'}$, CO-$R^{L2'}$, NH-C(=O)-$R^{L2'}$, NHNH-$R^{L2'}$, CONHNH-$R^{L2'}$,  ,  , $NR^NR^{L2'}$, wherein R^N is selected from the group comprising H and C_{1-4} alkyl;
$R^{L2'}$ is a linker for connection to the antibody (Ab);
R^{10} and R^{11} either together form a double bond between the nitrogen and carbon atoms to which they are bound or;
R^{10} is H and R^{11} is selected from OH, OR^A and SO_zM;
R^{30} and R^{31} either together form a double bond between the nitrogen and carbon atoms to which they are bound or;
R^{30} is H and R^{31} is selected from OH, OR^A and SO_zM.

8. The composition of claim 7, wherein the anti-CD25 ADC has the structure:



, where Ab is an antibody that binds to CD25 and has the VH sequence of SEQ ID NO. 1 and the VL sequence of SEQ ID NO. 2.

9. Use of the composition of either one of claims 7 or 8 in the manufacture of a medicament for treating a proliferative disorder in an individual, wherein said composition is to be administered to the individual.

10. The use according to any one of claims 1 to 6 and 9, wherein the treatment comprises the anti-CD25-ADC to be administered before Gemcitabine, simultaneous with Gemcitabine, or after Gemcitabine.

11. The use according to any one of claims 1 to 6 and 10, wherein a chemotherapeutic agent is to be further administered.

12. The use according to any one of claims 1 to 6 and 9 to 11 wherein the individual is human.

13. The use according to any one of claims 1 to 6 and 9 to 12, wherein the individual has, or has been determined to have, a proliferative disorder.

14. The use according to any one of claims 1 to 6 and 9 to 13, wherein the individual has, or has been determined to have, a proliferative disorder characterised by the presence of a neoplasm comprising both CD25+ve and CD25-ve cells.

15. The use according to any one of claims 1 to 6 and 9 to 14, wherein the individual has, or has been determined to have, a proliferative disorder characterised by the presence of a neoplasm comprising, or composed of, CD25-ve neoplastic cells.

16. The use according to any one of claims 1 to 6 and 9 to 15, wherein the neoplasm is all or part of a solid tumour.

17. The use according to any one of claims 1 to 6 and 9 to 16, wherein the individual has, or has been determined to have, a cancer which expresses CD25 or CD25+ tumour-associated non-tumour cells, such as CD25+ infiltrating T-cells.

18. The use according to any one of claims 1 to 6 and 9 to 17, wherein the individual has, or has been determined to have, a cancer with high levels of infiltrating regulatory T-cells.

19. The use according to claim 18, wherein the individual has, or has been determined to have, 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, or head and neck cancer.

20. The use according to any one of claims 1 to 6 and 9 to 18, wherein the proliferative 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), 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.