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(54) Title: DOSAGE REGIME

(57) Abstract: The present disclosure relates to the treatment of pathological conditions, such as cancer, with Antibody Drug Conjugates (ADCs). In particular, the present disclosure relates to particular dosage regimens for the administration of ADCs which bind to CD19 (CD19-ADCs).

DOSAGE REGIME

EARLIER APPLICATIONS

The present application claims priority from United States provisional application US62/772927 which was filed on 29 November 2018, United States provisional application US62/866982 which was filed on 26 June 2019, and United States provisional application US62/883867 which was filed on 7 August 2019. The disclosure of these three priority documents is incorporated by reference into the present application for all purposes.

FIELD

The present disclosure relates to the treatment of pathological conditions, such as cancer, with Antibody Drug Conjugates (ADCs). In particular, the present disclosure relates to particular dosage regimens for the administration of ADCs which bind to CD19 (CD19-ADCs).

BACKGROUND

Antibody Therapy

Antibody therapy has been established for the targeted treatment of subjects with cancer, immunological and angiogenic disorders (Carter, P. (2006) Nature Reviews Immunology 6:343-357). The use of antibody-drug conjugates (ADC), i.e. immunoconjugates, for the local delivery of cytotoxic or cytostatic agents, i.e. drugs to kill or inhibit tumour cells in the treatment of cancer, targets delivery of the drug moiety to tumours, and intracellular accumulation therein, whereas systemic administration of these unconjugated drug agents may result in unacceptable levels of toxicity to normal cells (Xie *et al* (2006) *Expert. Opin. Biol. Ther.* 6(3):281-291; Kovtun *et al* (2006) *Cancer Res.* 66(6):3214-3121; Law *et al* (2006) *Cancer Res.* 66(4):2328-2337; Wu *et al* (2005) *Nature Biotech.* 23(9):1137-1145; Lambert J. (2005) *Current Opin. in Pharmacol.* 5:543-549; Hamann P. (2005) *Expert Opin. Ther. Patents* 15(9):1087-1103; Payne, G. (2003) *Cancer Cell* 3:207-212; Trail *et al* (2003) *Cancer Immunol. Immunother.* 52:328-337; Syrigos and Epenetos (1999) *Anticancer Research* 19:605-614).

CD19

CD19 is a 95 kDa membrane receptor that is expressed early in B cell differentiation and continues to be expressed until the B cells are triggered to terminally differentiate (Pezzutto et al.(1987), J. Immunol 138:2793; Tedder et al (1994) Immunol Today 15:437). The CD19 extracellular domain contains two C2-type immunoglobulin (IG)-like domains separated by a smaller disulfide-linked domain. The CD19 cytoplasmic domain is structurally unique, but highly conserved between human, mouse, and guinea pig (Fujimoto et al., (1998) Semin Immunol.10:267). CD19 is part of a protein complex found on the cell surface of B-lymphocytes. The protein complex includes CD19, CD21 (complement receptor, type 2), CD81 (TAPA-1), and CD225 (Leu-13) (Fujimoto, supra).

CD19 is an important regulator of transmembrane signals in B cells. An increase or decrease in the cell surface density of CD19 affects B cell development and function,

resulting in diseases such as autoimmunity or hypogammaglobulinemia. The CD19 complex potentiates the response of B cells to antigen in vivo through cross-linking of two separate signal transduction complexes found on B cell membranes. The two signal transduction complexes, associated with membrane IgM and CD19, activate phospholipase C (PLC) by different mechanisms. CD19 and B cell receptor cross-linking reduces the number of IgM molecules required to activate PLC. CD19 also functions as a specialized adapter protein for the amplification of Arc family kinases (Hasegawa et ah, (2001) J Immunol 167:3190).

CD19 binding has been shown to both enhance and inhibit B-cell activation and proliferation, depending on the amount of cross-linking that occurs (Tedder, 1994, Immunol. Today 15:437). CD19 is expressed on greater than 90% of B-cell lymphomas and has been predicted to affect growth of lymphomas *in vitro* and *in vivo*.

Therapeutic uses of anti-CD19 ADCs

The efficacy of an Antibody Drug Conjugate comprising an anti-CD19 antibody (an anti-CD19-ADC) in the treatment of, for example, cancer has been disclosed – see, for example, WO2014/057117 and WO2016/166298.

Research continues to further improve the efficacy, tolerability, and clinical utility of anti-CD19 ADCs. To this end, the present authors have identified clinically advantageous dosage regimes for the administration of an anti-CD19 ADC.

SUMMARY

Through treatment of subjects with CD19-ADC, the present authors have developed dosage regimes that allow for improved efficacy, efficiency, and / or tolerability of CD19-ADC treatment. Interesting, it was found that the parameters required for optimal treatment efficacy, efficiency, and / or tolerability differed between indication subsets.

Lymphomas

During treatment of a cohort of subjects with Relapsed or Refractory B-cell Lineage Non-Hodgkin Lymphoma (B-NHL)' using a single dose of CD19-ADC per 3-week treatment cycle, the present authors noted that that repetitive dosing every three weeks is not well tolerated or necessary at doses of 120 µg/kg and higher:

- Of six responding patients treated at 120 µg/kg (four complete remissions , two partial remissions), four required at least one dose delay during treatment (3 to 7 treatment cycles) due to adverse events and two were discontinued from treatment.
- Of three patients treated at 150 µg/kg received 2 to 3 treatment cycles of CD19-ADC before side effects necessitated dose delay. The delay eventually led to removal from the study since the toxicities were slow to resolve.
- Of 6 patients treated at 200 µg/kg, five attained complete response and the other attained partial response. However, all patients had some evidence of toxicity at the end of the second or third treatment cycle.

In addition, pharmacokinetic studies indicate that CD19 ADC is not rapidly cleared from the bloodstream, with trough levels at the end of each 3-week treatment cycle maintained at a relatively high level, or even gradually increasing with each treatment cycle.

Accordingly, the present authors reasoned that tapering the dose of the CD19-ADC and/or increasing the length of each treatment cycle would allow for more effective long term treatment of lymphoma subjects by providing reasonable exposure to CD19-ADC to provide efficacy while maximizing long term tolerability through reducing CD19-ADC accumulation.

Accordingly, part of the subject-matter of the present disclosure concerns the use of CD19-ADCs in tapered and/or elongated dosage regimes for treating proliferative diseases. These tapered and/or elongated regimes are expected to be associated with a range of clinical benefits, including reduced toxicity and side-effects, and the consequent expansion of the population eligible to be treated to include subjects intolerant of the side effects of known dosage regimes.

Preferably, the tapered and/or elongated dosage regimes described here are employed when the proliferative disease is lymphoma. For example, the proliferative disease may be a non-Hodgkin's Lymphoma, such as diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, (FL), Mantle Cell lymphoma (MCL), chronic lymphatic lymphoma (CLL), Waldenstroms Microglobulinemia, Burkitt's lymphoma, and Marginal Zone B-cell lymphoma (MZBL).

In a first aspect the disclosure provides a method of treating a proliferative disease in a subject, said method comprising administering to a subject a CD19-ADC, wherein the CD19-ADC is administered to the subject in a tapered and/or elongated dosage regime.

The CD19-ADC may be ADCx19 as described herein.

The term "tapered dosage regime" is used herein to describe a dosage regime in which the total dose of CD19-ADC administered in the first treatment cycle (from hereon in termed the "starting dose") is greater than the total dose of CD19-ADC administered in one or more subsequent treatment cycle. A tapered dosage regime contrasts with a constant dosing regime in which the starting dose is the same as the total dose administered in each subsequent treatment cycle (see 'Constant' in Table 1, below).

In some cases, the administered dose is only reduced if the subject has attained at least Stable Disease [SD] at the end of the preceding treatment cycle (i.e. SD or better response, such as PR or CR).

Preferably the starting dose is reduced no more than once during the treatment of a subject. In these cases the total dose following dose reduction is from hereon in termed the “reduced dose”.

In some cases the dose is reduced following the first treatment cycle. That is, the starting dose is administered in the first treatment cycle and the reduced dose is administered in the second and subsequent treatment cycles. Dosing regime ‘Taper 6’ in Table 1 is an example of such a dosing regime.

In some cases the dose is reduced following the second treatment cycle. That is, the starting dose is administered in each of the first and second treatment cycles and the reduced dose is administered in each of the third and subsequent treatment cycles. Dosing regime ‘Taper 3’, ‘Taper 4, ‘Taper 5’, and ‘Taper 7’ in Table 1 are examples of such a dosing regime.

In some cases the starting dose is at least 120 µg/kg. In some cases the starting dose is at least 150 µg/kg, such as at least 200 µg/kg. In some cases the starting dose is about 120, 150, or 200 µg/kg. In some cases the reduced dose is about 50% of the starting dose. In some cases the reduced dose is about 60 µg/kg. In some cases the reduced dose is about 75 µg/kg. In some cases the starting dose is about 200 µg/kg and the reduced dose is about 60 µg/kg. In some cases the starting dose is about 140 to 160 µg/kg and the reduced dose is about 70 to 80 µg/kg. In some cases the starting dose is about 150 µg/kg and the reduced dose is about 75 µg/kg.

In some cases the length of each treatment cycle is 3 weeks.

In some cases the length of each treatment cycle is 6 weeks.

The term “elongated dosage regime” is used herein to describe a dosage regime in which the length of the first treatment cycle (from hereon in termed the “starting length”) is shorter than the length of one or more subsequent treatment cycles. An elongated dosage regime contrasts with a constant dosing regime in which the starting length is the same as the length of each subsequent treatment cycle (see ‘Constant’ in Table 2, below).

In some cases, the treatment cycle length is only increased if the subject has attained at least Stable Disease [SD] at the end of the preceding treatment cycle.

Preferably the treatment cycle length is increased no more than once during the treatment of a subject. In these cases the treatment cycle length following length increase is from hereon in termed the “increased length”.

In some cases the cycle length is increased following the first treatment cycle. That is, the first treatment cycle is the starting length, and each of the second and subsequent treatment

cycles is the increased length. Dosing regime 'Long 4' in Table 2 is an example of such a dosing regime.

In some cases the cycle length is increased following the second treatment cycle. That is, each of the first and second treatment cycles is the starting length, and each of the third and subsequent treatment cycles is the increased length. Dosing regime 'Long 3' in Table 2 is an example of such a dosing regime.

In some cases the starting length is 3 weeks. In some cases the increased length is 6 weeks.

Preferably, in a tapered and elongated dosage regime the starting dose is reduced no more than once and the treatment cycle length is increased no more than once during the treatment of a subject.

In some cases, the administered dose is only reduced and/or the cycle length increased if the subject has attained at least Stable Disease [SD] at the end of the preceding treatment cycle.

In some cases the dose reduction and the length increase is made following the second treatment cycle. That is, each of the first and second treatment cycles have the starting dose and the starting length, and each of the third and subsequent treatment cycles have the reduced dose and increased length.

In some cases the starting dose is at least 120 µg/kg. In some cases the starting dose is at least 150 µg/kg, such as at least 200 µg/kg. In some cases the starting dose is about 120, 150, or 200 µg/kg. In some cases the reduced dose is about 75 µg/kg. In some cases the reduced dose is about 60 µg/kg. In some cases the starting length is 3 weeks and the increased length is 6 weeks. In some cases the starting dose and starting length are respectively about 120 µg/kg and three weeks and the reduced dose and increased length are respectively about 60 µg/kg and six weeks. In some cases the starting dose and starting length are respectively about 150 µg/kg and three weeks and the reduced dose and increased length are respectively about 60 µg/kg and six weeks. In some cases the starting dose and starting length are respectively about 140 to 160 µg/kg and three weeks and the reduced dose and increased length are respectively about 70 to 80 µg/kg and three weeks. In some cases the starting dose and starting length are respectively about 150 µg/kg and three weeks and the reduced dose and increased length are respectively about 75 µg/kg and three weeks.

The subject may be human.

The subject may have cancer, or may have been determined to have cancer. The subject may have, or have been determined to have, a CD19+ cancer or CD19+ tumour-associated non-tumour cells, such as CD19+ infiltrating cells.

The tapered and/or elongated dosage regimes described here may be employed when the subject has, is suspected of having, or have been diagnosed with a lymphoma. For example, the subject may have, may be suspected or having, or may have been diagnosed with a non-Hodgkin's Lymphoma, such as diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, (FL), Mantle Cell lymphoma (MCL), chronic lymphatic lymphoma (CLL), Waldenstroms Microglobulinemia, Burkitt's lymphoma, and Marginal Zone B-cell lymphoma (MZBL).

Alternatively, the subject may have, may be suspected or having, or may have been diagnosed with a leukaemia such as Hairy cell leukaemia (HCL), Hairy cell leukaemia variant (HCL-v), 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 resistant, relapsed or refractory.

The subject may have, or have been determined to have Relapsed or Refractory B-cell Lineage Non-Hodgkin Lymphoma (B-NHL).

The subject may have, or have been determined to have B-Lineage Acute Lymphoblastic Leukaemia (B-ALL), which may be relapsed and/or refractory.

In some cases the subject has been diagnosed as having the proliferative disease prior to the start of treatment with the CD19-ADC.

In some cases the method further comprises administering a second anti-cancer compound in combination with the CD19-ADC.

Specifically envisioned combinations include: CD19-ADC with Ibrutinib, CD19-ADC with Durvalumab, CD19-ADC with rituximab, CD19-ADC with cytarabine, and CD19-ADC with rituximab and cytarabine.

In some cases the tapered and/or elongated dosage regime reduces the treatment toxicity or side-effects as compared to a constant dose level and cycle length regime.

In some cases the tapered and/or elongated dosage regime increases the treatment efficacy as compared to a constant dose level and cycle length regime.

In some cases the CD19-ADC is administered intravenously.

In a second aspect, the present disclosure provides a method of reducing the toxicity and/or side effects associated with administration of a CD19-ADC to a subject, the method comprising administering the CD19-ADC in a tapered and/or elongated dosage regime as defined herein.

In a third aspect, the present disclosure provides a method of increasing the treatment efficacy associated with administration of an CD19-ADC to a subject, the method comprising administering the CD19-ADC in tapered and/or elongated dosage regime as defined herein.

In a fourth aspect, the present disclosure provides a method of selecting a subject for treatment by a tapered and/or elongated dosage regime as described herein, which selection method comprises selecting for treatment subjects that express CD19 in a tissue of interest.

In a fifth aspect the present disclosure provides a packaged pharmaceutical product comprising a CD19-ADC as described herein in combination with a label or insert advising that the CD19-ADC should be administered in a tapered and/or elongated dosage regime.

The disclosure also provides a kit comprising:
a first medicament comprising a CD19-ADC; and, optionally,
a package insert or label comprising instructions for administration of the CD19-ADC in tapered and/or elongated dosage regime as described herein.

In a sixth aspect the present disclosure provides a CD19-ADC as defined herein for use in a method of treatment as described herein.

In a seventh aspect the present disclosure provides the use of a CD19-ADC as defined herein in the preparation of a medicament for use in a method of treatment as described herein.

Leukaemias

During treatment of a cohort of human subjects with relapsed or refractory Acute Lymphoblastic Leukemias (ALL) using a single dose of CD19-ADC per 3-week treatment cycle, the present authors noted that for most patients, plasma ADC concentrations when measured were near the lower limit of quantification and pharmokinetic (PK) parameters could not be discerned. In those patients, rapid drug clearance was apparent in the early time course. This observation was coupled with observation that a number of patients who attained complete recovery (CR) showed a slower clearance of ADC from the plasma was evident by treatment cycle 2.

Accordingly, the present authors sought an altered dosage regime to improve the efficacy of CD19-ADC treatment. Data collected from a number of different mouse xenograft models of CD19+ proliferative disease indicated that administration of CD19-ADC as a single dose on day 1 of the treatment cycle led to effective treatment, with administration of an identical total dose of AD19-ADC as a series of smaller partial doses resulting in higher mortality levels (see Figures 2 and 3).

Nonetheless, the present authors reasoned that fractionating the dose of the CD19-ADC and administering it at more regular intervals throughout the treatment cycle would allow for: (1) a more consistent, effective degree of ADC exposure to be maintained throughout the treatment cycle, and (2) the use of higher total doses but with decreased peak levels, thus reducing toxicity associated with peak exposure levels.

Without wishing to be bound by theory, the use of such fractionated dosage regimes is potentially especially advantageous in diseases such as acute leukaemia, where the rapid production of circulating myeloblasts acts as an antigenic sink for the CD19-ADC. This is consistent with the exploration or adoption of fractionated dosage regimes in some other treatments of subjects with leukaemia (Frey F, et al. Abstract 7002. Presented at: ASCO Annual Meeting; June 3-7, 2016; Chicago; Aue G, et al. Haematologica February 2010 95: 329-332; Taksin A, et al. Leukemias (2007) 21, 66–71. Published online 19 October 2006).

Accordingly, part of the subject-matter of the present disclosure concerns the use of CD19-ADCs in fractionated dosage regimes for treating proliferative diseases, in particular leukaemias. These fractionated regimes are expected to be associated with a range of clinical benefits, including improved efficacy, reduced toxicity and side-effects, and the consequent expansion of the population eligible to be treated to include subjects intolerant of the greater side effects of known dosage regimes.

Preferably, the fractionated dosage regimes described here are employed when the proliferative disease is leukaemia, such as Hairy cell leukaemia (HCL), Hairy cell leukaemia variant (HCL-v), and Acute Lymphoblastic Leukaemia (ALL) such as Philadelphia chromosome-positive ALL (Ph+ALL) or Philadelphia chromosome-negative ALL (Ph-ALL).

In an eighth aspect the disclosure provides a method of treating a proliferative disease in a subject, said method comprising administering to a subject a CD19-ADC, wherein the CD19-ADC is administered to the subject in a fractionated dosage regime.

The CD19-ADC may be ADCx19 as described herein.

The term “fractionated dosage regime” is used herein to describe a dosage regime in which the total dose of CD19-ADC administered during the treatment cycle is administered in a series of two or more partial doses during the treatment cycle. The term ‘partial dose’ is used herein to denote a dose of ADC that is a fraction of the total dose of ADC to be administered in the treatment cycle. The sum of all partial doses delivered in a treatment cycle equals the total dose. A fractionated dosage regime contrasts with a ‘single-dose’ dosing regime in which the total dose of CD19-ADC administered in the treatment cycle is administered as a single dose at the start of the treatment cycle.

Preferably the total dose of CD19-ADC is administered as partial doses of equal size regularly spaced throughout the treatment cycle. Administration to the subject once per week is particularly preferred. In some cases the total dose of CD19-ADC is administered over a three week treatment cycle in 3 equal partial doses, with a partial dose administered once a week. For example, with administration of a partial dose on days 1, 8, and 15 of a 3-week treatment cycle. Further features of fractionated dosage regimes are discussed herein.

The subject may be human. The subject may have cancer, or may have been determined to have cancer. The subject may have, or have been determined to have, a CD19+ cancer or CD19+ tumour-associated non-tumour cells, such as CD19+ infiltrating cells.

Preferably, the fractionated dosage regimes described here are employed when the subject has, is suspected of having, or have been diagnosed with leukaemia. For example, the subject may have, may be suspected or having, or may have been diagnosed with Hairy cell leukaemia (HCL), Hairy cell leukaemia variant (HCL-v), and Acute Lymphoblastic Leukaemia (ALL) such as Philadelphia chromosome-positive ALL (Ph+ALL) or Philadelphia chromosome-negative ALL (Ph-ALL).

In other, less-preferred embodiments, the subject may have, may be suspected or having, or may have been diagnosed with lymphoma. For example, with a non-Hodgkin’s Lymphoma, such as diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, (FL), Mantle Cell lymphoma (MCL), chronic lymphatic lymphoma (CLL), Waldenstroms Microglobulinemia, Burkitt’s lymphoma, and Marginal Zone B-cell lymphoma (MZBL).

The proliferative disease may be resistant, relapsed or refractory

The subject may have, or have been determined to have Relapsed or Refractory B-cell Lineage Acute Lymphoblastic Leukemias (B-ALL).

In some cases the subject has been diagnosed as having the proliferative disease prior to the start of treatment with the CD19-ADC.

In some cases the method further comprises administering a second anti-cancer compound in combination with the CD19-ADC.

In some cases the fractional dosage regime reduces the treatment toxicity or side-effects as compared to a single dose per treatment cycle regime.

In some cases the fractional dosage regime increases the treatment efficacy as compared to a single dose per treatment cycle regime.

In some cases the CD19-ADC is administered intravenously.

In a ninth aspect, the present disclosure provides a method of reducing the toxicity and/or side effects associated with administration of a CD19-ADC to a subject, the method comprising administering the CD19-ADC in a fractionated dosage regime as defined herein.

In a tenth aspect, the present disclosure provides a method of increasing the treatment efficacy associated with administration of an CD19-ADC to a subject, the method comprising administering the CD19-ADC in a fractionated dosage regime as defined herein.

In an eleventh aspect, the present disclosure provides a method of selecting a subject for treatment by a fractionated dosage regime as described herein, which selection method comprises selecting for treatment subjects that express CD19 in a tissue of interest.

In a twelfth aspect the present disclosure provides a packaged pharmaceutical product comprising a CD19-ADC as described herein in combination with a label or insert advising that the CD19-ADC should be administered in a fractionated dosage regime.

The disclosure also provides a kit comprising:

a first medicament comprising a CD19-ADC; and, optionally,

a package insert or label comprising instructions for administration of the CD19-ADC in a fractionated dosage regime as described herein.

In a thirteenth aspect the present disclosure provides a CD19ADC as defined herein for use in a method of treatment as described herein.

In a fourteenth aspect the present disclosure provides the use of a CD19-ADC as defined herein in the preparation of a medicament for use in a method of treatment as described herein.

DETAILED DISCLOSURE

As described in more detail below, the present authors have reasoned that CD19-ADCs as defined herein, when administered in tapered and/or elongated dosage regimes for the treatment of lymphomas, have improved efficacy and/or reduced toxicity as compared to that observed when an ADC is administered in a regime with constant dosage size and treatment cycle length.

Thus, in a first aspect the disclosure provides a method of treating a proliferative disease in a subject, said method comprising administering to a subject a CD19-ADC, wherein the CD19-ADC is administered to the subject in a tapered and/or elongated dosage regimes.

Further, the present authors have reasoned that CD19-ADCs as defined herein, when administered in a fractionated dosage regime for the treatment of leukaemia, have improved efficacy and/or reduced toxicity as compared to that observed when an equivalent amount of ADC is administered as a single dose.

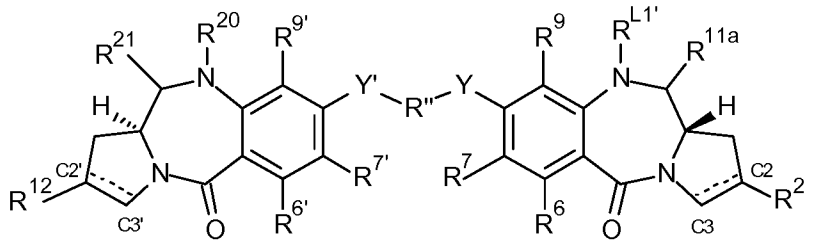
Thus, in an eighth aspect the disclosure provides a method of treating a proliferative disease in a subject, said method comprising administering to a subject a CD19-ADC, wherein the CD19-ADC is administered to the subject in a fractionated dosage regime.

These findings provides additional utilities for such CD19-ADCs, implying new therapeutic contexts for use, for example in relation to patient groups with heightened sensitivity to CD19-ADC toxicity, or in relation to patient groups requiring larger doses of CD19-ADC for effective treatment.

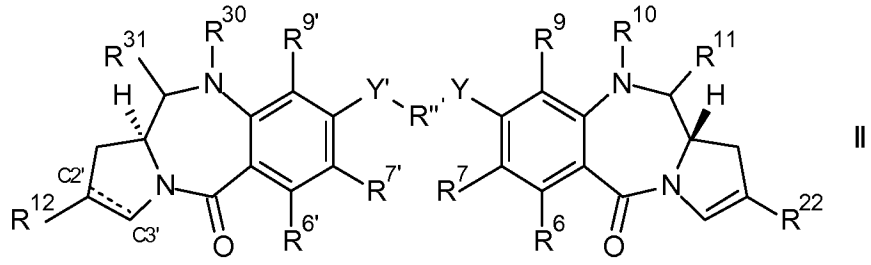
anti-CD19 ADCs

As used herein, the term “CD19-ADC” refers to an ADC in which the antibody component is an anti-CD19 antibody. The term “PBD-ADC” refers to an ADC in which the drug component is a pyrrolobenzodiazepine (PBD) warhead. The term “anti-CD19-ADC” refers to an ADC in which the antibody component is an anti-CD19 antibody, and the drug component is a PBD warhead.

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



I



II

wherein:

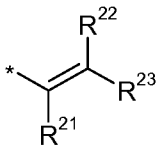
L is an antibody (Ab) which is an antibody that binds to CD19;

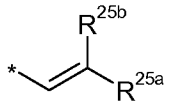
when there is a double bond present between C2' and C3', R^{12} is selected from the group consisting of:

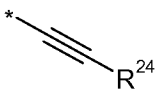
(ia) C_{5-10} aryl group, optionally substituted by one or more substituents selected from the group comprising: halo, nitro, cyano, ether, carboxy, ester, C_{1-7} alkyl, C_{3-7} heterocyclyl and bis-oxy-C_{1-3} alkylene;

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

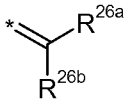
(ic) C_{3-6} saturated cycloalkyl;

(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;

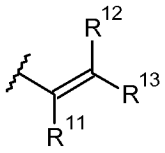
R^{21} is selected from OH, OR^A and SO_zM;

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

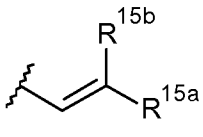
(ia) C_{5-10} aryl group, optionally substituted by one or more substituents selected from the group comprising: halo, nitro, cyano, ether, carboxy, ester, C_{1-7} alkyl, C_{3-7} heterocyclyl and bis-oxy-C_{1-3} alkylene;

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

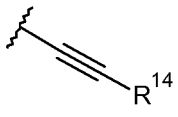
(ic) C_{3-6} saturated cycloalkyl;

(id) 

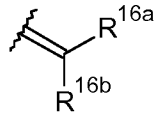
, wherein each of R^{11}, R^{12} and R^{13} are independently selected from H, C_{1-3} saturated alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl and cyclopropyl, where the total number of carbon atoms in the R^2 group is no more than 5;

(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

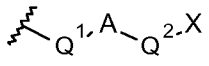
(if)  , where R^{14} is selected from: H; C_{1-3} saturated alkyl; C_{2-3} alkenyl; C_{2-3} alkynyl; cyclopropyl; phenyl, which phenyl is optionally substituted by a group selected from halo, methyl, methoxy; pyridyl; and thiophenyl;

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]

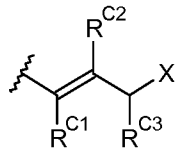
R^{22} is of formula IIIa, formula IIIb or formula IIIc:

(a)  IIIa

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

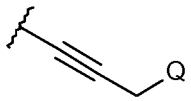
(i) Q^1 is a single bond, and Q^2 is selected from a single bond and -Z-$(CH_2)_n$-, where Z is selected from a single bond, O, S and NH and n is from 1 to 3; or

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

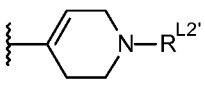
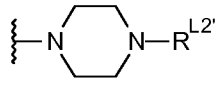
(b)  IIIb

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);

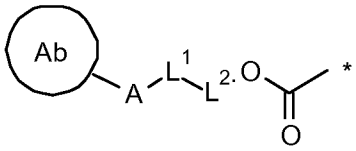
R^{10} and R^{11} either together form a double bond between the nitrogen and carbon atoms to which they are bound or;

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 some embodiments L-$R^{L1'}$ or L-$R^{L2'}$ is a group:

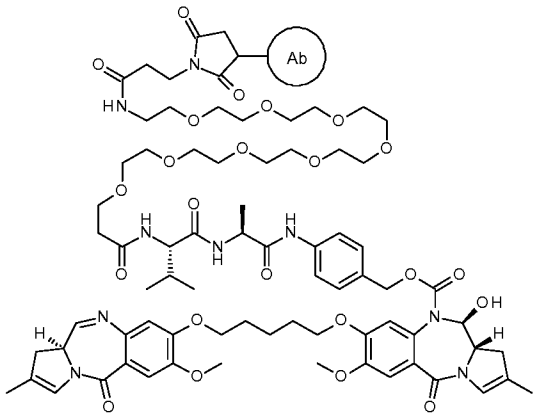


where the asterisk indicates the point of attachment to the PBD, Ab is the antibody, L^1 is a cleavable linker, A is a connecting group connecting L^1 to the antibody, L^2 is a covalent bond or together with -OC(=O)- forms a self-immolative linker.

In some of these embodiments, L^1 is enzyme cleavable.

It has previously been shown that such ADCs are useful in the treatment of CD19 expressing cancers (see, for example, WO2014/057117, which is incorporated by reference herein in its entirety).

The term anti-CD19-ADC may include any embodiment described in WO2014/057117. In particular, in preferred embodiments the ADC may have the chemical structure:



, where the Ab is a CD19 antibody, and the DAR is between 1 and 8.

The antibody may comprise a VH domain having the sequence according to any one of SEQ ID NOs. 1, 2, 3, 4, 5 or 6, optionally further comprising a VL domain having the sequence according to any one of SEQ ID NOs. 7, 8, 9, 10, 11 or 12.

In some aspects the antibody component of the anti-CD19-ADC is an antibody comprising: VH and VL domains respectively having the sequences of: SEQ ID NO. 1 and SEQ ID NO. 7, SEQ ID NO. 2 and SEQ ID NO. 8, SEQ ID NO. 3 and SEQ ID NO. 9, SEQ ID NO. 4 and SEQ ID NO. 10, SEQ ID NO. 5 and SEQ ID NO. 11, or SEQ ID NO. 6 and SEQ ID NO. 12.

In preferred embodiments the antibody comprises a VH domain having the sequence according to SEQ ID NO. 2. In preferred embodiments the antibody comprises a VL domain having the sequence according to SEQ ID NO. 8.

In preferred embodiments the antibody comprises a VH domain and a VL domain, the VH and domain having the sequence of SEQ ID NO. 2 and the VL domain having the sequences of SEQ ID NO. 8.

The VH and VL domain(s) may pair so as to form an antibody antigen binding site that binds CD19.

In some embodiments the antibody is an intact antibody comprising a VH domain and a VL domain, the VH and VL domains having sequences of SEQ ID NO. 2 and SEQ ID NO. 8.

In some embodiments the antibody is an antibody comprising a heavy chain having sequences of SEQ ID NO. 13 and a light chain having the sequences of SEQ ID NO. 14.

In some embodiments the antibody is a fully human monoclonal IgG1 antibody, preferably IgG1,κ.

In some embodiments the antibody is the RB4v1.2 antibody described in WO2014/057117.

In an aspect the antibody is an antibody as described herein which has been modified (or further modified) as described below. In some embodiments the antibody is a humanised, deimmunised or resurfaced version of an antibody disclosed herein.

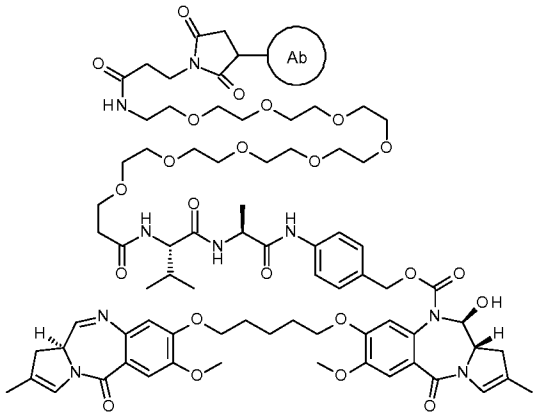
The most preferred anti-CD19-ADC for use with the aspects of the present disclosure is ADCX19, as described herein below.

Another particularly preferred anti-CD19-ADC for use with the aspects of the present disclosure is ADCT-402.

ADCx19

ADCX19 is an antibody drug conjugate composed of a humanized antibody against human CD19 attached to a pyrrolobenzodiazepine (PBD) warhead via a cleavable linker. The mechanism of action of ADCX19 depends on CD19 binding. The CD19 specific antibody targets the antibody drug conjugate (ADC) to cells expressing CD19. Upon binding, the ADC internalizes and is transported to the lysosome, where the protease sensitive linker is cleaved and free PBD dimer is released inside the target cell. The released PBD dimer inhibits transcription in a sequence-selective manner, due either to direct inhibition of RNA polymerase or inhibition of the interaction of associated transcription factors. The PBD dimer produces covalent crosslinks that do not distort the DNA double helix and which are not recognized by nucleotide excision repair factors, allowing for a longer effective period (Hartley 2011). These DNA crosslinks cause strand breaks when the DNA replication fork reaches them, leading to apoptosis induction.

It has the chemical structure:



Ab represents Antibody RB4v1.2 (antibody with the VH and VL sequences SEQ ID NO. 2 and SEQ ID NO. 8, respectively). It is synthesised as described in WO2014/057117 (RB4v1.2-E) and typically has a DAR (Drug to Antibody Ratio) of 2 +/- 0.3.

CD19 binding

As used herein, "binds CD19" is used to mean the antibody binds CD19 with a higher affinity than a non-specific partner such as Bovine Serum Albumin (BSA, Genbank accession no. CAA76847, version no. CAA76847.1 GI:3336842, record update date: Jan 7, 2011 02:30 PM). In some embodiments the antibody binds CD19 with an association constant (K_a) at least 2, 3, 4, 5, 10, 20, 50, 100, 200, 500, 1000, 2000, 5000, 10^4, 10^5 or 10^6-fold higher than the antibody's association constant for BSA, when measured at physiological conditions. The antibodies of the disclosure can bind CD19 with a high affinity. For example, in some embodiments the antibody can bind CD19 with a K_D equal to or less than about 10^{-6} M, such as 1 x 10^{-6}, 10^{-7}, 10^{-8}, 10^{-9},10^{-10}, 10^{-11}, 10^{-12}, 10^{-13} or 10^{-14}.

In some embodiments, CD19 polypeptide corresponds to Genbank accession no. NP_001171569, version no. NP_001171569.1 GI:296010921, record update date: Sep 10, 2012 12:43 AM. In one embodiment, the nucleic acid encoding CD19 polypeptide corresponds to Genbank accession no NM_001178098, version no. NM_001178098.1 GI:296010920, record update date: Sep 10, 2012 12:43 AM.In some embodiments, CD19 polypeptide corresponds to Uniprot/Swiss-Prot accession No. P15391.

Tapered and/or elongated dosage regimes

The term "tapered dosage regime" is used herein to describe a dosage regime in which the total dose of CD19-ADC administered in the first treatment cycle (from hereon in termed the "starting dose") is greater than the total dose of CD19-ADC administered in one or more subsequent treatment cycle. A tapered dosage regime contrasts with a constant dosing regime in which the starting dose is the same as the total dose administered in each subsequent treatment cycle (see 'Constant' in Table 1, below).

In embodiments where there is no step down in dosage, any stated “starting dose” indicates the total dose of CD19-ADC administered in the first treatment cycle and each subsequent treatment cycle.

As used herein, the term ‘total dose’ is used to mean the total amount of ADC administered during a single treatment cycle.

A subject’s tapered dosage regime may consist of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or more treatment cycles. In some cases, the dosage regime is ended once the subject attains CR. In some cases, the dosage regime is ended when the subject experiences a DLT. In some cases, the dosage regime is considered as ended if a dose delay exceeding the length of the preceding treatment cycle is required.

In a tapered dosage regime, the starting dose may be reduced no more than once, no more than twice, or no more than three times during the dosage regime. In cases where there are two or more reductions to the starting dose, each reduction may be by the same or a different amount. A total dose may be held constant for one, two, three, or more than three treatment cycles before it is reduced (see Table 1, below, for examples).

Dosing Regime	Dose (µg/kg)						
	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7
Constant	100	100	100	100	100	100	100
Taper 1	100	90	80	70	60	50	40
Taper 2	100	90	70	65	60	40	40
Taper 3	120	120	60	60	60	60	60
Taper 4	150	150	60	60	60	60	60
Taper 5	200	200	60	60	60	60	60
Taper 6	200	60	60	60	60	60	60
Taper 7	150	150	75	75	75	75	75

Table 1

In some cases, the administered dose is only reduced if the subject has attained at least Stable Disease [SD] at the end of the preceding treatment cycle.

In some cases the starting dose is at least about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, or 200 µg/kg. In some cases the starting dose is at least 120 µg/kg. In some cases the starting dose is at least 150 µg/kg, such as at least 200 µg/kg.

In some cases the starting dose is about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 120, 150, 200, 250, 300, 350, 400, 450, 500, 550, or 600 µg/kg. In some cases the starting dose is 1 to 10 µg/kg, 11 to 20 µg/kg, 21 to 30 µg/kg, 31 to 40 µg/kg, 41 to 50 µg/kg, 51 to 60 µg/kg, 61 to 70 µg/kg, 71 to 80 µg/kg, 81 to 90 µg/kg, 91 to 100 µg/kg, 101 to 120 µg/kg, 121 to 140

µg/kg, 141 to 160 µg/kg, 161 to 180 µg/kg, 181 to 200 µg/kg, 201 to 220 µg/kg, 221 to 240 µg/kg, 241 to 260 µg/kg, 261 to 280 µg/kg, 281 to 300 µg/kg, 301 to 320 µg/kg, 321 to 340 µg/kg, 341 to 360 µg/kg, 361 to 380 µg/kg, 381 to 400 µg/kg, 401 to 420 µg/kg, 421 to 440 µg/kg, 441 to 460 µg/kg, 461 to 480 µg/kg, 481 to 500 µg/kg, 501 to 520 µg/kg, 521 to 540 µg/kg, 541 to 560 µg/kg, 561 to 580 µg/kg, or 581 to 600 µg/kg.

In some cases the starting dose is about 120, 150, or 200 µg/kg. In some cases the starting dose is about 140 to 160 µg/kg In some cases the starting dose is about 150 µg/kg.

In some cases, each dose reduction reduces the administered dose by at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or at least 95%. In some cases, each dose reduction reduces the administered dose by about 50%.

Preferably the starting dose is reduced no more than once during the treatment of a subject. In these cases the total dose following dose reduction is from hereon termed the “reduced dose”.

In some cases the dose is reduced following the first treatment cycle. That is, the starting dose is administered in the first treatment cycle and the reduced dose is administered in the second and subsequent treatment cycles. Dosing regime ‘Taper 6’ in Table 1 is an example of such a dosing regime.

In some cases the dose is reduced following the second treatment cycle. That is, the starting dose is administered in each of the first and second treatment cycles and the reduced dose is administered in each of the third and subsequent treatment cycles. Dosing regime ‘Taper 3’, ‘Taper 4, ‘Taper 5’, and ‘Taper 7’ in Table 1 are examples of such a dosing regime.

In some cases the reduced dose is about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 120, 150, 200, 250, or 300 µg/kg. In some cases the reduced dose is 1 to 10 µg/kg, 11 to 20 µg/kg, 21 to 30 µg/kg, 31 to 40 µg/kg, 41 to 50 µg/kg, 51 to 60 µg/kg, 61 to 70 µg/kg, 71 to 80 µg/kg, 81 to 90 µg/kg, 91 to 100 µg/kg, 101 to 120 µg/kg, 121 to 140 µg/kg, 141 to 160 µg/kg, 161 to 180 µg/kg, 181 to 200 µg/kg, 201 to 220 µg/kg, 221 to 240 µg/kg, 241 to 260 µg/kg, 261 to 280 µg/kg, or 281 to 300 µg/kg.

In some cases the reduced dose is 60 µg/kg.

In some cases the reduced dose is about 70 - 80 µg/kg. In some cases the reduced dose is 75 µg/kg.

In some cases the length of each treatment cycle is 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, or 9 weeks.

In some cases the length of each treatment cycle is 3 weeks. In some cases the length of each treatment cycle is 6 weeks.

The term “elongated dosage regime” is used herein to describe a dosage regime in which the length of the first treatment cycle (from hereon in termed the “starting length”) is shorter than the length of one or more subsequent treatment cycle. An elongated dosage regime contrasts with a constant dosing regime in which the starting length is the same the length of each subsequent treatment cycle (see ‘Constant’ in Table 2, below).

A subject’s tapered dosage regime may consist of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 treatment cycles. In some cases the dosage regime is ended once the subject attains CR. In some cases the dosage regime is ended when the subject experiences a DLT. In some cases the dosage regime is considered as ended if a dose delay exceeding the length of the preceding treatment cycle is required.

In an elongated dosage regime the treatment cycle length may be increased no more than once, no more than twice, or no more than three times during the dosage regime. In cases where there are two or more increases in length, each increase may be by the same or a different amount. The length of treatment cycle may be held constant for one, two, three, or more than three treatment cycles before it is increased (see Table 2, below, for examples).

Dosing Regime	Cycle length (weeks)						
	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7
Constant	3	3	3	3	3	3	3
Long 1	3	4	5	6	6	6	6
Long 2	3	3	4	5	5	5	5
Long 3	3	3	6	6	6	6	6
Long 4	3	6	6	6	6	6	6

Table 2

In some cases, the treatment cycle length is only increased if the subject has attained at least Stable Disease [SD] at the end of the preceding treatment cycle.

Preferably, the dose is administered as a single dose on Day 1 of the treatment cycle. So, for example, a subject starting the ‘constant’ dosing regime above may receive a dose on Day 1, Day 22, Day 43, and so on until the regime is halted.

Following this pattern, a subject starting the ‘Long 3’ dosing regime above may receive a dose on Day 1 –(+3 weeks)→ Day 22 –(+3 weeks)→ Day 43 –(+6 weeks)→ Day 85 –(+6 weeks)→ Day 127 and so on until the regime is halted. However, preferably the ‘Day 1’ of the first treatment cycle of increased length is delayed so that the time elapsed between ‘Day 1’ of the final shorter treatment cycle and ‘Day 1’ of the first treatment cycle of increased length is equal in length to the increased treatment cycle. Accordingly, in the

preferred administration pattern of the 'Long 3' dosing regime a subject receive a dose on Day 1 –(+3 weeks)→ Day 22 –(+3 weeks)→ –(+3 week delay)→ Day 64 –(+6 weeks)→ Day 106 –(+6 weeks)→ Day 148 and so on until the regime is halted.

In some cases the starting length is 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, or 9 weeks.

In some cases the starting length is 3 weeks.

In some cases each length increase increases the treatment cycle length by at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or at least 100%. In some cases each length increase increases the treatment cycle length by 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, or 6 weeks.

Preferably the treatment cycle length is increased no more than once during the treatment of a subject. In these cases the treatment cycle length following length increase is from hereon in termed the "increased length".

In some cases the cycle length is increased following the first treatment cycle. That is, the first treatment cycle is the starting length, and each of the second and subsequent treatment cycles is the increased length. Dosing regime 'Long 4' in Table 2 is an example of such a dosing regime.

In some cases the cycle length is increased following the second treatment cycle. That is, each of the first and second treatment cycles is the starting length, and each of the third and subsequent treatment cycles is the increased length. Dosing regime 'Long 3' in Table 2 is an example of such a dosing regime.

In some cases the increased length is 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, or 12 weeks.

In some cases the starting length is 3 weeks. In some cases the increased length is 6 weeks. In some cases the starting length is 3 weeks and the increased length is 6 weeks.

A dosing regime may be tapered, elongated, or both tapered and elongated.

Tapered and elongated dosing regimes incorporate both of those elements as described herein.

In some cases, the administered dose is only reduced and/or the treatment cycle length increased if the subject has attained at least Stable Disease [SD] at the end of the preceding treatment cycle.

Preferably, in a tapered and elongated dosage regime the starting dose is reduced no more than once and the treatment cycle length is increased no more than once during the treatment of a subject.

In some cases the dose reduction and the length increase is made following the first treatment cycle. That is, the first treatment cycle has the starting dose and the starting length, and each of the second and subsequent treatment cycles have the reduced dose and increased length.

In some cases the dose reduction and the length increase is made following the second treatment cycle. That is, each of the first and second treatment cycles have the starting dose and the starting length, and each of the third and subsequent treatment cycles have the reduced dose and increased length.

In some cases the starting dose is at least about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, or 200 µg/kg. In some cases the starting dose is at least 120 µg/kg. In some cases the starting dose is at least 150 µg/kg, such as at least 200 µg/kg.

In some cases the starting dose is about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 120, 150, 200, 250, 300, 350, 400, 450, 500, 550, or 600 µg/kg. In some cases the starting dose is 1 to 10 µg/kg, 11 to 20 µg/kg, 21 to 30 µg/kg, 31 to 40 µg/kg, 41 to 50 µg/kg, 51 to 60 µg/kg, 61 to 70 µg/kg, 71 to 80 µg/kg, 81 to 90 µg/kg, 91 to 100 µg/kg, 101 to 120 µg/kg, 121 to 140 µg/kg, 141 to 160 µg/kg, 161 to 180 µg/kg, 181 to 200 µg/kg, 201 to 220 µg/kg, 221 to 240 µg/kg, 241 to 260 µg/kg, 261 to 280 µg/kg, 281 to 300 µg/kg, 301 to 320 µg/kg, 321 to 340 µg/kg, 341 to 360 µg/kg, 361 to 380 µg/kg, 381 to 400 µg/kg, 401 to 420 µg/kg, 421 to 440 µg/kg, 441 to 460 µg/kg, 461 to 480 µg/kg, 481 to 500 µg/kg, 501 to 520 µg/kg, 521 to 540 µg/kg, 541 to 560 µg/kg, 561 to 580 µg/kg, or 581 to 600 µg/kg.

In some cases the reduced dose is about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 120, 150, 200, 250, or 300 µg/kg. In some cases the reduced dose is 1 to 10 µg/kg, 11 to 20 µg/kg, 21 to 30 µg/kg, 31 to 40 µg/kg, 41 to 50 µg/kg, 51 to 60 µg/kg, 61 to 70 µg/kg, 71 to 80 µg/kg, 81 to 90 µg/kg, 91 to 100 µg/kg, 101 to 120 µg/kg, 121 to 140 µg/kg, 141 to 160 µg/kg, 161 to 180 µg/kg, 181 to 200 µg/kg, 201 to 220 µg/kg, 221 to 240 µg/kg, 241 to 260 µg/kg, 261 to 280 µg/kg, or 281 to 300 µg/kg.

In some cases the starting length is 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, or 9 weeks.

In some cases the increased length is 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, or 12 weeks.

In some cases the starting dose is about 120, 150, or 200 µg/kg. . In some cases the starting dose is about 140 to 160 µg/kg. In some cases the starting dose is about 150 µg/kg. In some cases the reduced dose is about 60 µg/kg. In some cases the reduced dose is about 70 to 80 µg/kg. In some cases the reduced dose is about 75 µg/kg. In some cases the starting length is 3 weeks and the increased length is 6 weeks. In some cases the starting dose and starting length are respectively about 120 µg/kg and three weeks and the reduced dose and increased length are respectively about 60 µg/kg and six weeks. In some cases the starting dose and starting length are respectively about 150 µg/kg and three weeks and the reduced dose and increased length are respectively about 60 µg/kg and six weeks.

In some preferred cases the starting dose and starting length are respectively about 140 to 160 µg/kg and three weeks and the reduced dose and increased length are respectively about 7o to 80 µg/kg and three weeks (i.e. the regime is tapered but NOT elongated).

In some particularly preferred cases the starting dose and starting length are respectively about 150 µg/kg and three weeks and the reduced dose and increased length are respectively about 75 µg/kg and three weeks (i.e. the regime is tapered but NOT elongated).

In some particularly preferred cases, the dosing regime of the present disclosure is as shown in the table below, with [+21} indicating that the reduced 75 µg/kg dose may be repeated at three weekly intervals for as many treatment cycles as deemed appropriate by the medical professional administering the ADC.

Regimen Day	1	22	43	65	86	[+21]
ADC dose	150 ug/kg	150 ug/kg	75 ug/kg	75 ug/kg	75 ug/kg	[75 ug/kg]

Fractionated dosage regimes

The term “fractionated dosage regime” is used herein to describe a dosage regime in which the total dose of CD19-ADC administered during the treatment cycle is administered in a series of two or more partial doses during the treatment cycle. The term ‘partial dose’ is used herein to denote a dose of ADC that is a fraction of the total dose of ADC to be administered in the treatment cycle. The sum of all partial doses delivered in a treatment cycle equals the total dose. A fractionated dosage regime contrasts with a ‘single-dose’ dosing regime in which the total dose of CD19-ADC administered in the treatment cycle is administered as a single dose at the start of the treatment cycle.

For example, in an example single-dose dosing regime for a CD19-ADC, 100% of the total dose of CD19-ADC administered during the treatment cycle is administered on day 1 of a 3-week treatment cycle. The subject is then monitored throughout the cycle and the subject’s level of response used to decide if the treatment cycle should be repeated, stopped, or amended. In contrast, a fractionated dosage regime may involve administering only 33% of the total dose of ADC administered during the treatment cycle on day 1 of a 3-week

treatment cycle, with a further 33% administered on day 8, and the final 33% administered on day 15.

The total dose administered may be fractionated into any number of separate doses, with the number being determined according to the clinical requirements of the subject. For example, the total dose administered may be fractionated into 2, 3, 4, 5, 6, 7, 8, 9, 10 or more than 10 doses.

The amount of CD19-ADC administered in each partial dose may be the same or different. So, for example, a total dose of 100 units of ADC delivered in 3 partial doses may be delivered as (1 x 50 units, 1 x 30 units, and 1 x 20 units) or (3 x 33 1/3 units). Preferably all of the partial doses contain the same amount of CD19-ADC i.e. all of the partial doses are of equal size.

The time interval between one partial dose and the next partial dose may be the same as, or different to, the time interval between the one partial dose and the preceding partial dose. Preferably, the time interval between one partial dose and the next partial dose is the same as the time interval between the one partial dose and the preceding partial dose. That is, preferably the administration of the partial doses is regularly spaced throughout the treatment cycle. An example of such regular administration is the administration of 3 partial doses on days 1, 8, and 15 of a 3-week (i.e. 21 day) treatment cycle.

The length of the treatment cycle may vary depending upon the pharmokinetics (PK) of the CD19-ADC and the clinical requirements of the subject. The treatment cycle may be 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, or 9 weeks. Preferably the treatment cycle is 3 weeks or 6 weeks, with 3 weeks being particularly preferred.

The total dose of CD19-ADC administered during the treatment cycle may vary according to the clinical requirements of the subject. For example, the total dose may be about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 120, 150, 200, 250, 300, 350, 400, 450, 500, 550, or 600 µg/kg. In some cases the total dose is 1 to 10 µg/kg, 11 to 20 µg/kg, 21 to 30 µg/kg, 31 to 40 µg/kg, 41 to 50 µg/kg, 51 to 60 µg/kg, 61 to 70 µg/kg, 71 to 80 µg/kg, 81 to 90 µg/kg, 91 to 100 µg/kg, 101 to 120 µg/kg, 121 to 140 µg/kg, 141 to 160 µg/kg, 161 to 180 µg/kg, 181 to 200 µg/kg, 201 to 220 µg/kg, 221 to 240 µg/kg, 241 to 260 µg/kg, 261 to 280 µg/kg, 281 to 300 µg/kg, 301 to 320 µg/kg, 321 to 340 µg/kg, 341 to 360 µg/kg, 361 to 380 µg/kg, 381 to 400 µg/kg, 401 to 420 µg/kg, 421 to 440 µg/kg, 441 to 460 µg/kg, 461 to 480 µg/kg, 481 to 500 µg/kg, 501 to 520 µg/kg, 521 to 540 µg/kg, 541 to 560 µg/kg, 561 to 580 µg/kg, or 581 to 600 µg/kg.

The size of the partial dose will depend upon the total dose of CD19-ADC administered during the treatment cycle, and the number of partial doses into which the total dose it is divided, and the relative sizes of the partial doses. In some cases each partial dose is of equal size. In some cases the partial dose is about 3, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, or 200 µg/kg. In some the partial dose is 1 to

10 µg/kg, 11 to 20 µg/kg, 21 to 30 µg/kg, 31 to 40 µg/kg, 41 to 50 µg/kg, 51 to 60 µg/kg, 61 to 70 µg/kg, 71 to 80 µg/kg, 81 to 90 µg/kg, 91 to 100 µg/kg, 101 to 110 µg/kg, 111 to 120 µg/kg, 121 to 130 µg/kg, 131 to 140 µg/kg, 141 to 150 µg/kg, 151 to 160 µg/kg, 161 to 170 µg/kg, 171 to 180 µg/kg, 181 to 190 µg/kg, or 191 to 200 µg/kg.

Preferably the total dose of CD19-ADC is administered as partial doses of equal size regularly spaced throughout the treatment cycle. Administration to the subject once per week is particularly preferred. In preferred cases, each partial dose is 40 to 60 µg/kg, such as 45 to 55 µg/kg. In particularly preferred cases each partial dose is 50 µg/kg.

In some cases the total dose of CD19-ADC is administered over a three week treatment cycle in 3 equal partial doses, with a partial dose administered once a week. For example, with administration of a partial dose on days 1, 8, and 15 of a 3-week treatment cycle.

Treated disorders

The methods of therapy described herein include those with utility for anti-cancer therapy. In particular, in certain aspects the therapies include an antibody conjugated, i.e. covalently attached by a linker, to a PBD drug moiety, i.e. toxin. When the drug is not conjugated to an antibody, the PBD drug has a cytotoxic effect. The biological activity of the PBD drug moiety is thus modulated by conjugation to an antibody. The antibody-drug conjugates (ADC) of the disclosure selectively deliver an effective dose of a cytotoxic agent to tumor tissue whereby greater selectivity, i.e. a larger therapeutic window, may be achieved.

Thus, in one aspect, the present disclosure provides a method of therapy comprising administering an ADC which binds CD19 for use in therapy, wherein the method comprises selecting a subject based on expression of CD19.

In one aspect, the present disclosure provides a packaged ADC for use in therapy, wherein the packaged ADC is supplied with a label that specifies that the therapy is suitable for use with a subject determined to be suitable for such use. The label may specify that the therapy is suitable for use in a subject has expression of CD19, that is, is CD19+.

The label may specify that the ADC is administered in a tapered and/or elongated dosage regime as described herein. The label may specify that the subject has a particular type of cancer, such as lymphoma like a B-cell Lineage Non Hodgkin Lymphoma (B-NHL), optionally wherein the lymphoma is Relapsed or Refractory. Examples of NHL lymphoma include diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, (FL), Mantle Cell lymphoma (MCL), chronic lymphatic lymphoma (CLL), Waldenstroms Microglobulinemia, Burkitt's lymphoma, and Marginal Zone B-cell lymphoma (MZBL).

The label may specify that the ADC is administered in a fractionated dosage regime as described herein. The label may specify that the subject has a particular type of cancer, such as leukaemia, optionally wherein the B-ALL is Relapsed or Refractory. Examples of leukaemia include Hairy cell leukaemia (HCL), Hairy cell leukaemia variant (HCL-v), and

Acute Lymphoblastic Leukaemia (ALL) such as Philadelphia chromosome-positive ALL (Ph+ALL) or Philadelphia chromosome-negative ALL (Ph-ALL).B-cell Lineage Acute Lymphoblastic Leukemias (B-ALL).

The proliferative disease treated by the methods disclosed herein may be CD19+. However as explained herein, in the practice of the disclosure, in at least some of the cells in the target location (typically a neoplasm) the antigen may be absent, or present on the cell surface at an insignificant level. For example in the target neoplasm only e.g. less than 80, 70, 60, 50, 30, 20%, 10% or 5%of the cells may be CD19 positive. In some cases where the disease is a leukaemia, such as B-ALL, CD19+ may be defined as determination of CD19 expression by ≥5% of leukemic myeloblast cells within bone marrow (aspirate or biopsy), as assessed at an approved clinical laboratory.

In some cases the CD19+ve cell is a tumour infiltrating cell. In some cases the neoplasm or neoplastic cells are, or are present in, a haematological cancer. In some cases the neoplasm or neoplastic cells are, or are present in, a solid tumor. “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 below.

Other solid tumors may be neoplasms, including non-haematological cancers, infiltrated with CD-19 positive cells.

In some cases the neoplasm or neoplastic cells are malignant. In some cases the neoplasm or neoplastic cells are metastatic.

The therapies described herein may be used to treat a proliferative disease. The term “proliferative disease” pertains to an unwanted or uncontrolled cellular proliferation of excessive or abnormal cells which is undesired, such as, neoplastic or hyperplastic growth, whether *in vitro* or *in vivo*.

Any type of cell may be treated, including but not limited to, lung, gastrointestinal (including, e.g. bowel, colon), breast (mammary), ovarian, prostate, liver (hepatic), kidney (renal), bladder, pancreas, brain, and skin.

It is contemplated that the therapies of the present disclosure may be used to treat various diseases or disorders, e.g. characterized by the overexpression of a tumor antigen. Exemplary conditions of hyperproliferative disorders include benign or malignant tumors; leukaemia, haematological, and lymphoid malignancies. Others include neuronal, glial, astrocytal, hypothalamic, glandular, macrophagal, epithelial, stromal, blastocoelic, inflammatory, angiogenic and immunologic, including autoimmune disorders and graft-versus-host disease (GVHD).

Generally, the disease or disorder to be treated is a hyperproliferative disease such as cancer. Examples of cancer to be treated herein include, but are not limited to, carcinoma,

lymphoma, blastoma, sarcoma, and leukaemia or lymphoid malignancies. More particular examples of such cancers include squamous cell cancer (e.g. epithelial squamous cell cancer), lung cancer including small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung and squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer including gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, melanoma, sarcoma, osteosarcoma, as well as head and neck cancer.

Autoimmune diseases for which the combined therapies may be used in treatment include rheumatologic disorders (such as, for example, rheumatoid arthritis, Sjögren's syndrome, scleroderma, lupus such as SLE and lupus nephritis, polymyositis/dermatomyositis, cryoglobulinemia, anti-phospholipid antibody syndrome, and psoriatic arthritis), osteoarthritis, autoimmune gastrointestinal and liver disorders (such as, for example, inflammatory bowel diseases (e.g. ulcerative colitis and Crohn's disease), autoimmune gastritis and pernicious anemia, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, and celiac disease), vasculitis (such as, for example, ANCA-associated vasculitis, including Churg-Strauss vasculitis, Wegener's granulomatosis, and polyarteriitis), autoimmune neurological disorders (such as, for example, multiple sclerosis, opsoclonus myoclonus syndrome, myasthenia gravis, neuromyelitis optica, Parkinson’s disease, Alzheimer’s disease, and autoimmune polyneuropathies), renal disorders (such as, for example, glomerulonephritis, Goodpasture’s syndrome, and Berger’s disease), autoimmune dermatologic disorders (such as, for example, psoriasis, urticaria, hives, pemphigus vulgaris, bullous pemphigoid, and cutaneous lupus erythematosus), hematologic disorders (such as, for example, thrombocytopenic purpura, thrombotic thrombocytopenic purpura, post-transfusion purpura, and autoimmune hemolytic anemia), atherosclerosis, uveitis, autoimmune hearing diseases (such as, for example, inner ear disease and hearing loss), Behcet's disease, Raynaud's syndrome, organ transplant, graft-versus-host disease (GVHD), and autoimmune endocrine disorders (such as, for example, diabetic-related autoimmune diseases such as insulin-dependent diabetes mellitus (IDDM), Addison’s disease, and autoimmune thyroid disease (e.g. Graves’ disease and thyroiditis)). More preferred such diseases include, for example, rheumatoid arthritis, ulcerative colitis, ANCA-associated vasculitis, lupus, multiple sclerosis, Sjögren's syndrome, Graves’ disease, IDDM, pernicious anemia, thyroiditis, and glomerulonephritis.

Proliferative disorders of particular interest include, but are not limited to, non-Hodgkin’s Lymphoma, including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, (FL), Burkitt’s lymphoma (BL), Mantle Cell lymphoma (MCL), chronic lymphatic lymphoma (CLL), Waldenstroms Microglobulinemia, Burkitt’s lymphoma, and Marginal Zone B-cell lymphoma (MZBL), and leukemias such as Hairy cell leukaemia (HCL), Hairy cell leukaemia variant (HCL-v), and Acute Lymphoblastic Leukaemia (ALL) such as Philadelphia chromosome-

positive ALL (Ph+ALL) or Philadelphia chromosome-negative ALL (Ph-ALL). [Fielding A., Haematologica. 2010 Jan; 95(1): 8–12].

In certain aspects, the subject has diffuse large B cell lymphoma or peripheral T cell lymphoma, including the anaplastic large cell lymphoma and angioimmunoblastic T cell lymphoma subtypes.

The disease may be resistant, relapsed or refractory. As used herein, relapsed disease constitutes conditions in which a previously treated tumor which became undetectable by conventional imaging technology again becomes detectable; refractory disease a condition in which the cancer - despite anti-tumor therapy - continues to grow.

Preferably, the tapered and/or elongated dosage regimes described here are employed when the proliferative disease is lymphoma. For example, the proliferative disease may be non-Hodgkin's Lymphoma, such as diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, (FL), Mantle Cell lymphoma (MCL), chronic lymphatic lymphoma (CLL), Waldenstroms Microglobulinemia, Burkitt's lymphoma, and Marginal Zone B-cell lymphoma (MZBL). In some cases the proliferative disease is Relapsed or Refractory B-cell Lineage Non Hodgkin Lymphoma (B-NHL).

Preferably, the fractionated dosage regimes described here are employed when the proliferative disease is leukaemia, such as Hairy cell leukaemia (HCL), Hairy cell leukaemia variant (HCL-v), and Acute Lymphoblastic Leukaemia (ALL) such as Philadelphia chromosome-positive ALL (Ph+ALL) or Philadelphia chromosome-negative ALL (Ph-ALL). In some cases the proliferative disease is Relapsed or Refractory B-cell Lineage Acute Lymphoblastic Leukemias (B-ALL). In some cases the proliferative disease is CD19+ Acute Lymphoblastic Leukemias.

Reduced toxicity and improved efficacy

Lymphoma

The present disclosure provides a method of reducing the toxicity and/or side effects associated with administration of a CD19-ADC to a subject, the method comprising administering the CD19-ADC in a tapered and/or elongated dosage regime as defined herein.

In some cases the reduction in toxicity is measured relative to a dosage regime having constant dosage level and cycle length. The dosage level and cycle length of the constant comparator may be the same as the starting dose and starting length of the tapered and/or elongated regime.

In some cases the level of toxicity is measured as the incidence of Treatment Emergent Adverse Events (TEAE) occurring after one treatment cycle at a given total dose of CD19-ADC. A treatment-emergent AE (TEAE) is defined as any event not present before exposure

to the CD19-ADC or any event already present that worsens in either intensity or frequency after exposure to the CD19-ADC. The incidence of AE with the tapered and/or elongated dosage regime may be no more that 95%, such as no more than 90%, no more than 80%, no more than 70%, no more than 60%, no more than 50%, no more than 40%, no more than 30%, no more than 20%, no more than 10%, or no more than 5% of the incidence of AE in the corresponding constant dose level and cycle length regime. Adverse events will be graded according to CTCAE Version 4.0 (v4.03, published June 14, 2010; NIH Publication No. 09-5410).

For example, if a single treatment cycle of a single-dose regime in 100 subjects leads to 10 AEs and a single treatment cycle the corresponding tapered and/or elongated regime leads to 5 AEs, the incidence of AEs with the tapered and/or elongated regime is 50% of the incidence of AE in the corresponding constant dose level and cycle length regime.

In some cases the level of toxicity is measured as the incidence of Serious Adverse Events (SAE) occurring after one treatment cycle at a given total dose of CD19-ADC. A serious adverse event (SAE) is defined as any event that results in death, is immediately life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Hospitalization for elective procedures or for protocol compliance is not considered an SAE. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. The incidence of SAE with the tapered and/or elongated dosage regime may be no more that 95%, such as no more than 90%, no more than 80%, no more than 70%, no more than 60%, no more than 50%, no more than 40%, no more than 30%, no more than 20%, no more than 10%, or no more than 5% of the incidence of SAE in the corresponding constant dose level and cycle length regime. Adverse events will be graded according to CTCAE Version 4.0 (v4.03, published June 14, 2010; NIH Publication No. 09-5410).

In some cases the level of toxicity is measured as the incidence of Dose Limiting Toxicity (DLT) occurring after one treatment cycle at a given total dose of CD19-ADC. The incidence of DLT with the tapered and/or elongated dosage regime may be no more that 95%, such as no more than 90%, no more than 80%, no more than 70%, no more than 60%, no more than 50%, no more than 40%, no more than 30%, no more than 20%, no more than 10%, or no more than 5% of the incidence of DLT in the corresponding constant dose level and cycle length regime.

For example, if a single treatment cycle of a single-dose regime in 100 subjects leads to 10 DLTs and a single treatment cycle of the corresponding tapered and/or elongated regime

leads to 5 DLTs, the incidence of DLTs with the tapered and/or elongated regime is 50% of the incidence of DLT in the corresponding constant dose level and cycle length regime.

A DLT as used herein is defined as any of the following events, except those that are clearly due to underlying disease or extraneous causes:

- A hematologic DLT is defined as:
    - Grade 3 or 4 febrile neutropenia or neutropenic infection.
    - Grade 4 neutropenia lasting >7 days.
    - Grade 4 thrombocytopenia.
    - Grade 3 thrombocytopenia with clinically significant bleeding, or Grade 3 thrombocytopenia requiring a platelet transfusion
    - Grade 4 anemia.

- A non-hematologic DLT is defined as:
    - Grade 4 tumor lysis syndrome (Grade 3 TLS will not constitute DLT unless it leads to irreversible end-organ damage).
    - Grade 3 or higher AE (including nausea, vomiting, diarrhoea, and electrolyte imbalances lasting more than 48 hours despite optimal therapy; excluding all grade of alopecia).
    - Grade 3 or higher hypersensitivity reaction (regardless of premedication).
    - Grade 2 or higher skin ulceration.

The above adverse events will be graded according to CTCAE Version 4.0 (v4.03, published June 14, 2010; NIH Publication No. 09-5410).

The present disclosure also provides a method of increasing the treatment efficacy associated with administration of a CD19-ADC to a subject, the method comprising administering the CD19-ADC in a tapered and/or elongated dosage regime as defined herein.

In some cases the increase in efficacy is measured relative to a dosage regime having constant dosage level and cycle length. The dosage level and cycle length of the constant comparator may be the same as the starting dose and starting length of the tapered and/or elongated regime.

In some cases the level of efficacy is measured as the proportion of subjects achieving at least stable disease [SD] after one treatment cycle at a given total dose of ADC (i.e the proportion of subjects achieving either stable disease [SD], a partial response [PR], or a complete response [CR]. The proportion of subjects achieving at least SD may be at least 110%, such as at least 120%, at least 130%, at least 140%, at least 150%, at least 160%, at least 170%, at least 180%, at least 190%, or at least 200%, of the proportion of subjects

achieving at least stable disease [SD] in the corresponding constant dose level and cycle length regime.

For example, if a single-dose regime in 100 subjects leads to at least SD in 50 subjects and the corresponding tapered and/or elongated regime leads to at least SD in 80 subjects, the proportion of subjects achieving at least SD with the tapered and/or elongated regime is 160% of the proportion of subjects achieving at least a partial response [SD] in the corresponding constant dose level and cycle length regime.

Assessment of response to treatment with ADC may be based on bone marrow samples (aspirate or biopsy if aspirate unattainable) taken toward the end of each treatment cycle. For example, on day 19±3 days in a 21-day treatment cycle. The subject's response to ADC may be categorised as CR, PR, SD, or PD according to the 2014 Lugano Classification Criteria (using the New "Cheson" Criteria), in which:

- Complete response (CR) is defined as achieving each of the following:
    - Nodal Disease < 1.5 cm in LDi
    - Extranodal Disease: Absent
    - Spleen: regress to normal
    - No new lesions
    - Bone marrow: Normal by morphology; if indeterminate, IHC negative

- Partial response (PR) is defined as achieving each of the following:
    - Nodal Disease >= 50% decrease from baseline in SPD of all target lesions
    - No increase in non-target
    - Spleen: > 50% decrease from baseline in enlarged portion of spleen (value > 13 cm)
    - No new lesions

- Stable Disease (SD) is defined as achieving each of the following:
    - Nodal Disease < 50% decrease from baseline in SPD of all target lesions
    - No criteria for nodal PD are met
    - No progression in non-target
    - No progression in spleen enlargment
    - No new lesions

Nodal PD criteria:
An individual node/lesion must be abnormal with:

- LDi > 1.5 cm AND
- Increase by >= 50% from PPD nadir AND
- An increase in LDi or SDi from nadir
    - ≥ 0.5 cm for lesions ≤ 2 cm
    - ≥ 1.0 cm for lesions > 2 cm

Leukaemia

The present disclosure provides a method of reducing the toxicity and/or side effects associated with administration of a CD19-ADC to a subject, the method comprising administering the CD19-ADC in a fractionated dosage regime as defined herein.

In some cases the reduction in toxicity is measured relative to a single-dose dosage regime having the same total dose administered and length of treatment cycle. In such a single dose regime, the total dose of CD19-ADC is administered as a single dose at the start of the treatment cycle.

In some cases the level of toxicity is measured as the incidence of Treatment Emergent Adverse Events (TEAE) occurring after one treatment cycle at a given total dose of CD19-ADC. A treatment-emergent AE (TEAE) is defined as any event not present before exposure to the CD19-ADC or any event already present that worsens in either intensity or frequency after exposure to the CD19-ADC. The incidence of AE with the fractionated dosage regime may be no more that 95%, such as no more than 90%, no more than 80%, no more than 70%, no more than 60%, no more than 50%, no more than 40%, no more than 30%, no more than 20%, no more than 10%, or no more than 5% of the incidence of AE in the corresponding single dose regime. Adverse events will be graded according to CTCAE Version 4.0 (v4.03, published June 14, 2010; NIH Publication No. 09-5410).

For example, if a single treatment cycle of a single-dose regime in 100 subjects leads to 10 AEs and a single treatment cycle the corresponding fractionated regime leads to 5 AEs, the incidence of AEs with the fractionated regime is 50% of the incidence of AE in the corresponding single dose regime.

In some cases the level of toxicity is measured as the incidence of Serious Adverse Events (SAE) occurring after one treatment cycle at a given total dose of CD19-ADC. A serious adverse event (SAE) is defined as any event that results in death, is immediately life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Hospitalization for elective procedures or for protocol compliance is not considered an SAE. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. The incidence of SAE with the fractionated dosage regime may be no more that 95%, such as no more than 90%, no more than 80%, no more than 70%, no more than 60%, no more than 50%, no more than 40%, no more than 30%, no more than 20%, no more than 10%, or no more than 5% of the incidence of SAE in the corresponding single dose regime. Adverse events will be graded according to CTCAE Version 4.0 (v4.03, published June 14, 2010; NIH Publication No. 09-5410).

In some cases the level of toxicity is measured as the incidence of Dose Limiting Toxicity (DLT) occurring after one treatment cycle at a given total dose of CD19-ADC. The incidence of DLT with the fractionated dosage regime may be no more that 95%, such as no more than 90%, no more than 80%, no more than 70%, no more than 60%, no more than 50%, no more than 40%, no more than 30%, no more than 20%, no more than 10%, or no more than 5% of the incidence of DLT in the corresponding single dose regime.

For example, if a single treatment cycle of a single-dose regime in 100 subjects leads to 10 DLTs and a single treatment cycle of the corresponding fractionated regime leads to 5 DLTs, the incidence of DLTs with the fractionated regime is 50% of the incidence of DLT in the corresponding single dose regime.

A DLT as used herein is defined as any of the following events, except those that are clearly due to underlying disease or extraneous causes:

- A hematologic DLT is defined as:
    - Grade 3 or higher event of neutropenia or thrombocytopenia, or a Grade 4 anemia, with a hypocellular bone marrow lasting for 6 weeks or more after the start of a cycle, in the absence of residual leukaemia (i.e., with <5% myeloblasts). In case of a normocellular bone marrow with <5% myeloblasts, 8 weeks with ≥Grade 3 pancytopenia will be considered a DLT.

- A non-hematologic DLT is defined as:
    - Grade 4 tumor lysis syndrome (Grade 3 TLS will not constitute DLT unless it leads to irreversible end-organ damage).
    - Grade 3 or higher AE (including nausea, vomiting, diarrhoea, and electrolyte imbalances lasting more than 48 hours despite optimal therapy; excluding all grades of alopecia).
    - CTCAE Grade 3 or higher hypersensitivity reaction (regardless of premedication).
    - CTCAE Grade 3 or higher skin ulceration.

The above adverse events will be graded according to CTCAE Version 4.0 (v4.03, published June 14, 2010; NIH Publication No. 09-5410).

The present disclosure also provides a method of increasing the treatment efficacy associated with administration of a CD19-ADC to a subject, the method comprising administering the CD19-ADC in a fractionated dosage regime as defined herein.

In some cases the increase in efficacy is measured relative to a single-dose dosage regime having the same total dose administered and length of treatment cycle. In such a single dose

regime, the total dose of ADC is administered as a single dose at the start of the treatment cycle.

In some cases the level of efficacy is measured as the proportion of subjects achieving at least a partial response [PR] after one treatment cycle at a given total dose of ADC (i.e the proportion of subjects achieving either a partial response [PR], a complete response with incomplete blood count recovery [CRi], or a complete response [CR]. The proportion of subjects achieving at least PR may be at least 110%, such as at least 120%, at least 130%, at least 140%, at least 150%, at least 160%, at least 170%, at least 180%, at least 190%, or at least 200%, of the proportion of subjects achieving at least a partial response [PR] in the corresponding single dose regime.

For example, if a single-dose regime in 100 subjects leads to at least PR in 50 subjects and the corresponding fractionated regime leads to at least PR in 80 subjects, the proportion of subjects achieving at least PR with the fractionated regime is 160% of the proportion of subjects achieving at least a partial response [PR] in the corresponding single dose regime.

Assessment of response to treatment with ADC may be based on bone marrow samples (aspirate or biopsy if aspirate unattainable) taken toward the end of each treatment cycle. Assessment of response to treatment with ADC may be based on bone marrow samples (aspirate or biopsy if aspirate unattainable) taken toward the end of selected treatment cycles, for example, every other treatment cycle. For example, on day 19±3 days in a 21-day treatment cycle. The subject's response to ADC may be categorised as CR, CRi, PR, PD or NR according to the following criteria:

- Complete response (CR) is defined as achieving each of the following:
    - Bone marrow differential showing ≤5% blast cells,
    - Absolute neutrophil count ≥1.0 x 109/L and platelet count ≥100 x 109/L,
    - Absence of extra-medullary disease,
    - Patient is independent of red blood cell (RBC) transfusions.

- Complete response with incomplete blood count recovery (CRi) is defined as achieving all CR criteria except that values for ANC may be $<1.0 \times 10^9$/L and/or values for platelets may be $<100 \times 10^9$/L.

- Partial response (PR) is defined as achieving each of the following:
    - ANC ≥1.0 x 109/L and platelet count ≥100 x 109/L
    - Bone marrow differential showing a ≥50% decrease from baseline in the percentage of bone marrow blast cells to a level >5% and ≤25%.

- No response is defined as not achieving CR, CRi, or PR

- PD is defined as:

- For patients with CR or CRi, the first date of reappearance of blast cells in bone marrow and/or peripheral blood to a level ≥5%, or development of extramedullary disease.
- For patients with PR, the first date of an increase in blast cells in bone marrow and/or peripheral blood such that the patient does not continue to meet the criteria for PR.

Patient Selection

In certain cases, the subjects are selected as suitable for treatment with either, (a) the tapered and/or elongated dosage regime, or (b) the fractionated dosage regime, before the treatment is administered.

Preferably, subjects are selected for treatment with the tapered and/or elongated dosage regimes described if they have, are suspected of having, or have been diagnosed with lymphoma. For example, the lymphoma may be non-Hodgkin's Lymphoma, such as diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, (FL), Mantle Cell lymphoma (MCL), chronic lymphatic lymphoma (CLL), Waldenstroms Microglobulinemia, Burkitt's lymphoma, and Marginal Zone B-cell lymphoma (MZBL).

Preferably, subjects are selected for treatment with the fractionated dosage regimes described if they have, are suspected of having, or have been diagnosed with leukaemia, For example, the leukaemia may be Hairy cell leukaemia (HCL), Hairy cell leukaemia variant (HCL-v), and Acute Lymphoblastic Leukaemia (ALL) such as Philadelphia chromosome-positive ALL (Ph+ALL) or Philadelphia chromosome-negative ALL (Ph-ALL).

As used herein, subjects who are considered suitable for treatment are those subjects who are expected to benefit from, or respond to, the treatment. Subjects may have, or be suspected of having, or be at risk of having cancer. Subjects may have received a diagnosis of cancer. In particular, subjects may have, or be suspected of having, or be at risk of having, lymphoma or leukaemia. In some cases, subjects may have, or be suspected of having, or be at risk of having, a solid cancer that has tumour associated non-tumor cells that express a CD19, such as infiltrating cells that express CD19.

In some cases, subjects are selected on the basis of the amount or pattern of expression of CD19. In some cases, the selection is based on expression of CD19 at the cell surface.

In some cases, expression of CD19 in a particular tissue of interest is determined. For example, in a sample of lymphoid tissue or tumor tissue. In some cases, systemic expression of CD19 is determined. For example, in a sample of circulating fluid such as blood, plasma, serum or lymph.

In some cases, the subject is selected as suitable for treatment due to the presence of CD19 expression in a sample. In those cases, subjects without CD19 expression may be considered not suitable for treatment.

In other cases, the level of CD19 expression is used to select a subject as suitable for treatment. Where the level of expression of CD19 is above a threshold level, the subject is determined to be suitable for treatment.

In some cases, the presence of CD19+ in cells in the sample indicates that the subject is suitable for treatment with a combination comprising an ADC. In other cases, the amount of CD19 expression must be above a threshold level to indicate that the subject is suitable for treatment. In some cases, the observation that CD19 localisation is altered in the sample as compared to a control indicates that the subject is suitable for treatment.

In some cases, a subject is indicated as suitable for treatment if cells obtained from lymph node or extra nodal sites react with antibodies against CD19 as determined by IHC.

In some cases, a patient is determined to be suitable for treatment if at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or more of all cells in the sample express CD19. In some cases disclosed herein, a patient is determined to be suitable for treatment if at least at least 5% of the cells in the sample express CD19.

In some cases, a patient is determined to be suitable for treatment if they have had a DLT in a previous single-dose treatment cycle with the ADC.

In some cases, a patient is determined to be suitable for treatment if they are have exhibited any sign of ADC-induced toxicity in a previous single-dose treatment cycle with the ADC.

In some cases, a patient is determined to be suitable for if they have increased sensitivity to ADC-induced toxicity.

In some cases, a patient is determined to be suitable for treatment if their disease is relapsed or refractory.

In some cases, a subject undergoes a neurological examination prior to treatment with the ADC. Preferably the neurological examination includes tests of strength, sensation, and deep-tendon reflexes.

In some cases, a subject is determined to be not suitable for treatment with the ADC if they have, or have recently had, a neurologic disorder. Examples of such disorders include poliomyelitis and multiple sclerosis Generally, neurological disorders that are explained by the subject's previous medical history and known not to be related to, or a risk factor for, to treatment with ADC do not render a subject unsuitable for treatment with the ADC. An

example of such a disorder is a left-sided weakness known to be a result of a previous cerebral vascular accident, such as a stroke.

The neurologic disorder, as discussed herein, may be polyradiculopathy (including acute inflammatory demyelinating polyradiculoneuropathy (AIDP)), Guillain-Barré syndrome (GBS), myasthenia gravis, or neurologic disorder that is linked to or is an early indicator of polyradiculitis, GBS, or myasthenia gravis (e.g. ascending (bilateral) sensory loss and/or motor weakness).

In some cases, a subject undergoes a neurological examination after administration of the ADC. In some cases the results of the neurological examination of a subject after administration of the ADC are compared to the results from before administration of the ADC in order to assess any change in the tested neurological parameters. In some cases, treatment with the ADC is reduced, suspended, or permanently discontinued if the subject experiences a neurologic toxicity.

The neurologic toxicity, as discussed herein, may be polyradiculopathy (including acute inflammatory demyelinating polyradiculoneuropathy (AIDP)), Guillain-Barré syndrome (GBS), myasthenia gravis, or neurologic disorder that is linked to or is an early indicator of polyradiculitis, GBS, or myasthenia gravis (e.g. ascending (bilateral) sensory loss and/or motor weakness).

In some cases, a subject undergoes a neurological examination after each administration of the ADC. In some cases the results of the neurological examination of a subject after each administration of the ADC are compared to the results from before the most recent administration of the ADC in order to assess any change in the tested neurological parameters. In some cases the results of the neurological examination of a subject after each administration of the ADC are compared to the results from before the first administration of the ADC in order to assess any change in the tested neurological parameters.

In some cases, a subject undergoes a neurological examination if they experience a neurologic toxicity following administration of the ADC.

In some cases, treatment with the ADC is reduced, suspended, or permanently discontinued if the subject has a neurological disorder or experiences a neurologic toxicity. For example, if a subject experiences ≥ grade 1 neurologic toxicity, such as a grade 1 neurologic toxicity that is linked to or is an early indicator of polyradiculitis (e.g. ascending (bilateral) sensory loss and/or motor weakness) treatment with the ADC may be reduced or suspended. In some case, if the subject experiences a ≥ grade 2 neurologic toxicity (e.g. grade 2 polyradiculitis or GBS), treatment with the ADC may be permanently discontinued.

Adverse events will be graded according to CTCAE Version 4.0 (v4.03, published June 14, 2010; NIH Publication No. 09-5410).

In some cases, treatment with the ADC is reduced by reducing the dose of ADC that is administered to the subject in each subsequent treatment cycle. In some cases, treatment with the ADC is reduced by increasing the length of each subsequent treatment cycle for example, from a 3 week cycle to a 6 week cycle). In some cases, treatment with the ADC is reduced by reducing the dose of ADC that is administered to the subject in each subsequent treatments cycle and increasing the length of each subsequent treatment.

In some cases, treatment with the ADC is suspended by stopping treatment with the ADC until the toxicity is resolved. In some cases, treatment with the ADC is resumed after resolution of the toxicity to baseline. The subject may be monitored weekly until the neurologic toxicity is resolved. In some cases the treatment is suspended for up to 3 weeks (21 days).

For example, in some cases a subject undergoes a neurological examination if they experience ≥ grade 1 neurologic toxicity, such as a grade 1 neurologic toxicity that is linked to or is an early indicator of polyradiculitis (e.g. ascending (bilateral) sensory loss and/or motor weakness). In some cases, if a subject experiences a ≥ grade 1 neurologic toxicity (e.g. grade 1 polyradiculitis or GBS), treatment with the ADC is resumed after resolution of the toxicity to baseline. The subject may be monitored weekly until the neurologic toxicity is resolved.

In some cases, if a subject experiences a ≥ grade 2 neurologic toxicity (e.g. grade 2 polyradiculitis or GBS), treatment with the ADC is permanently discontinued.

In some cases, a subject is determined to be not suitable for treatment with the ADC if they have, have recently had, or historically had, an infection caused by a pathogen that may be associated with neurologic and/or immune-related disease. Examples of such pathogens include HSV1, HSV2, VZV, EBV, CMV, measles, Influenza A, Zika virus, Chikungunya virus, *Mycoplasma pneumonia*, *Campylobacter jejuni*, or enterovirus D68.

In some cases, treatment with the ADC is reduced, suspended, or permanently discontinued if the subject experiences has, or acquires, an infection caused by a pathogen that may be associated with neurologic and/or immune-related disease. Examples of such pathogens include HSV1, HSV2, VZV, EBV, CMV, measles, Influenza A, Zika virus, Chikungunya virus, Mycoplasma pneumonia, Campylobacter jejuni, or enterovirus D68. In some cases, treatment with the ADC is suspended until at least 4 weeks after symptoms of the infection are resolved.

Examples of immune-related diseases include rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, Sjögren's syndrome, autoimmune vasculitis [e.g., Wegener's granulomatosis].

In some cases, treatment with the ADC is reduced, suspended, or permanently discontinued if the subject experiences any ≥ grade 1 autoimmune toxicities (e.g. endocrinopathies,).

Samples

The sample may comprise or may be derived from: a quantity of blood; a quantity of serum derived from the subject's blood which may comprise the fluid portion of the blood obtained after removal of the fibrin clot and blood cells; a quantity of pancreatic juice or fluid from a spinal tap; a tissue sample or biopsy; or cells isolated from said subject.

A sample may be taken from any tissue or bodily fluid. In certain cases, the sample may include or may be derived from a tissue sample, biopsy, resection or isolated cells from said subject.

In certain cases, the sample is a tissue sample. The sample may be a sample of tumor tissue, such as cancerous tumor tissue. The sample may have been obtained by a tumor biopsy. In some cases, the sample is a lymphoid tissue sample, such as a lymphoid lesion sample or lymph node biopsy. In some cases, the sample is a skin biopsy.

In some cases the sample is taken from a bodily fluid, more preferably one that circulates through the body. Accordingly, the sample may be a blood sample or lymph sample. In some cases, the sample is a urine sample or a saliva sample.

In some cases, the sample is a blood sample or blood-derived sample. The blood derived sample may be a selected fraction of a subject's blood, e.g. a selected cell-containing fraction or a plasma or serum fraction.

A selected cell-containing fraction may contain cell types of interest which may include white blood cells (WBC), particularly peripheral blood mononuclear cells (PBC) and/or granulocytes, and/or red blood cells (RBC). Accordingly, methods according to the present disclosure may involve detection of a CD19 polypeptide or nucleic acid in the blood, in white blood cells, peripheral blood mononuclear cells, granulocytes and/or red blood cells.

The sample may be fresh or archival. For example, archival tissue may be from the first diagnosis of a subject, or a biopsy at a relapse. In certain cases, the sample is a fresh biopsy.

Subject status

The subject may be an animal, mammal, a placental mammal, a marsupial (e.g., kangaroo, wombat), a monotreme (e.g., duckbilled platypus), a rodent (e.g., a guinea pig, a hamster, a rat, a mouse), murine (e.g., a mouse), a lagomorph (e.g., a rabbit), avian (e.g., a bird), canine (e.g., a dog), feline (e.g., a cat), equine (e.g., a horse), porcine (e.g., a pig), ovine

(e.g., a sheep), bovine (e.g., a cow), a primate, simian (e.g., a monkey or ape), a monkey (e.g., marmoset, baboon), an ape (e.g., gorilla, chimpanzee, orangutang, gibbon), or a human.

Furthermore, the subject may be any of its forms of development, for example, a foetus. In one preferred embodiment, the subject is a human. The terms “subject”, “patient” and “individual” are used interchangeably herein.

In some cases disclosed herein, a subject has, or is suspected as having, or has been identified as being at risk of, cancer. In some cases disclosed herein, the subject has already received a diagnosis of cancer.

The subject may have, be suspected of having, been identified as being at risk of, or received a diagnosis of lymphoma like non-Hodgkin’s Lymphoma, including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, (FL), Mantle Cell lymphoma (MCL), chronic lymphatic lymphoma (CLL), Waldenstroms Microglobulinemia, Burkitt’s lymphoma, and Marginal Zone B-cell lymphoma (MZBL). Such subjects are preferably treated with a tapered and/or elongated dosage regime as disclosed herein.

The subject may have, be suspected of having, been identified as being at risk of, or received a diagnosis of leukaemia, such as Hairy cell leukaemia (HCL), Hairy cell leukaemia variant (HCL-v), and Acute Lymphoblastic Leukaemia (ALL) such as Philadelphia chromosome-positive ALL (Ph+ALL) or Philadelphia chromosome-negative ALL (Ph-ALL). [Fielding A., Haematologica. 2010 Jan; 95(1): 8–12]. Such subjects are preferably treated with a fractionated dosage regime as disclosed herein.

In some cases, the subject has received a diagnosis of a solid cancer containing CD19+ expressing infiltrating T-cells.

The Subject may be undergoing, or have undergone, a therapeutic treatment for that cancer. The subject may, or may not, have previously received ADCx19. In some cases the cancer is leukemia or lymphoma, including non-Hodgkin’s lymphoma.

Controls

In some cases, CD19 expression in the subject is compared to target expression in a control. Controls are useful to support the validity of staining, and to identify experimental artefacts.

In some cases, the control may be a reference sample or reference dataset. The reference may be a sample that has been previously obtained from a subject with a known degree of suitability. The reference may be a dataset obtained from analyzing a reference sample.

Controls may be positive controls in which the target molecule is known to be present, or expressed at high level, or negative controls in which the target molecule is known to be absent or expressed at low level.

Controls may be samples of tissue that are from subjects who are known to benefit from the treatment. The tissue may be of the same type as the sample being tested. For example, a sample of tumor tissue from a subject may be compared to a control sample of tumor tissue from a subject who is known to be suitable for the treatment, such as a subject who has previously responded to the treatment.

In some cases the control may be a sample obtained from the same subject as the test sample, but from a tissue known to be healthy. Thus, a sample of cancerous tissue from a subject may be compared to a non-cancerous tissue sample.

In some cases, the control is a cell culture sample.

In some cases, a test sample is analyzed prior to incubation with an antibody to determine the level of background staining inherent to that sample.

In some cases an isotype control is used. Isotype controls use an antibody of the same class as the target specific antibody, but are not immunoreactive with the sample. Such controls are useful for distinguishing non-specific interactions of the target specific antibody.

The methods may include hematopathologist interpretation of morphology and immunohistochemistry, to ensure accurate interpretation of test results. The method may involve confirmation that the pattern of expression correlates with the expected pattern. For example, where the amount of CD19 expression is analyzed, the method may involve confirmation that in the test sample the expression is observed as membrane staining, with a cytoplasmic component. The method may involve confirmation that the ratio of target signal to noise is above a threshold level, thereby allowing clear discrimination between specific and non-specific background signals.

Methods of Treatment

The term “treatment,” as used herein in the context of treating a condition, pertains generally to treatment and therapy, whether of a human or an animal (e.g., in veterinary applications), in which some desired therapeutic effect is achieved, for example, the inhibition of the progress of the condition, and includes a reduction in the rate of progress, a halt in the rate of progress, regression of the condition, amelioration of the condition, and cure of the condition. Treatment as a prophylactic measure (i.e., prophylaxis, prevention) is also included.

The term “therapeutically-effective amount” or “effective amount” as used herein, pertains to that amount of an active compound, or a material, composition or dosage from comprising an active compound, which is effective for producing some desired therapeutic effect,

commensurate with a reasonable benefit/risk ratio, when administered in accordance with a desired treatment regimen. Generally, when a method of treatment describes the use of an ADC, it is intended that the ADC is used in a therapeutically-effective amount.

The actual amount administered, and rate and time-course of administration, will depend on the nature and severity of what is being treated. Prescription of treatment, e.g. decisions on dosage, is within the responsibility of general practitioners and other medical doctors. The subject may have been tested to determine their eligibility to receive the treatment according to the methods disclosed herein. The method of treatment may comprise a step of determining whether a subject is eligible for treatment, using a method disclosed herein.

Similarly, the term "prophylactically-effective amount," as used herein, pertains to that amount of an active compound, or a material, composition or dosage from comprising an active compound, which is effective for producing some desired prophylactic effect, commensurate with a reasonable benefit/risk ratio, when administered in accordance with a desired treatment regimen.

Disclosed herein are methods of therapy. Also provided is a method of treatment, comprising administering to a subject in need of treatment a therapeutically-effective amount of an ADC in a tapered and/or elongated dosage regime.

The ADC may comprise an anti-CD19 antibody. The anti-CD19 antibody may be RB4v1.2 antibody. The ADC may comprise a drug which is a PBD dimer. The ADC may be an anti-CD19-ADC, and in particular, ADCX19. The ADC may be an ADC disclosed in WO2014/057117.

The treatment may involve administration of the ADC alone or in further combination with other treatments, either simultaneously or sequentially dependent upon the condition to be treated. In sequential administration, for some cases the ADC is administered before the other treatment; for other cases the ADC is administered after the other treatment. Examples of treatments and therapies include, but are not limited to, chemotherapy (the administration of active agents, including, e.g. drugs, such as chemotherapeutics); immunotherapy; surgery; and radiation therapy.

A "chemotherapeutic agent" is a chemical compound useful in the treatment of cancer, regardless of mechanism of action. Classes of chemotherapeutic agents include, but are not limited to: alkylating agents, antimetabolites, spindle poison plant alkaloids, cytotoxic/antitumor antibiotics, topoisomerase inhibitors, antibodies, photosensitizers, and kinase inhibitors. Chemotherapeutic agents include compounds used in "targeted therapy", Immuno-oncology drugs such as checkpoint inhibitors, and conventional chemotherapy.

Examples of chemotherapeutic agents include: Lenalidomide (REVLIMID®, Celgene), Vorinostat (ZOLINZA®, Merck), Panobinostat (FARYDAK®, Novartis), Mocetinostat (MGCD0103), Everolimus (ZORTRESS®, CERTICAN®, Novartis), Bendamustine

(TREAKISYM®, RIBOMUSTIN®, LEVACT®, TREANDA®, Mundipharma International), erlotinib (TARCEVA®, Genentech/OSI Pharm.), docetaxel (TAXOTERE®, Sanofi-Aventis), 5-FU (fluorouracil, 5-fluorouracil, CAS No. 51-21-8), gemcitabine (GEMZAR®, Lilly), PD-0325901 (CAS No. 391210-10-9, Pfizer), cisplatin (cis-diamine, dichloroplatinum(II), CAS No. 15663-27-1), carboplatin (CAS No. 41575-94-4), paclitaxel (TAXOL®, Bristol-Myers Squibb Oncology, Princeton, N.J.), trastuzumab (HERCEPTIN®, Genentech), temozolomide (4-methyl-5-oxo- 2,3,4,6,8-pentazabicyclo [4.3.0] nona-2,7,9-triene- 9-carboxamide, CAS No. 85622-93-1, TEMODAR®, TEMODAL®, Schering Plough), tamoxifen ((*Z*)-2-[4-(1,2-diphenylbut-1-enyl)phenoxy]-*N*,*N*-dimethylethanamine, NOLVADEX®, ISTUBAL®, VALODEX®), and doxorubicin (ADRIAMYCIN®), Akti-1/2, HPPD, and rapamycin.

More examples of chemotherapeutic agents include: oxaliplatin (ELOXATIN®, Sanofi), bortezomib (VELCADE®, Millennium Pharm.), sutent (SUNITINIB®, SU11248, Pfizer), letrozole (FEMARA®, Novartis), imatinib mesylate (GLEEVEC®, Novartis), XL-518 (Mek inhibitor, Exelixis, WO 2007/044515), ARRY-886 (Mek inhibitor, AZD6244, Array BioPharma, Astra Zeneca), SF-1126 (PI3K inhibitor, Semafore Pharmaceuticals), BEZ-235 (PI3K inhibitor, Novartis), XL-147 (PI3K inhibitor, Exelixis), PTK787/ZK 222584 (Novartis), fulvestrant (FASLODEX®, AstraZeneca), leucovorin (folinic acid), rapamycin (sirolimus, RAPAMUNE®, Wyeth), lapatinib (TYKERB®, GSK572016, Glaxo Smith Kline), lonafarnib (SARASAR™, SCH 66336, Schering Plough), sorafenib (NEXAVAR®, BAY43-9006, Bayer Labs), gefitinib (IRESSA®, AstraZeneca), irinotecan (CAMPTOSAR®, CPT-11, Pfizer), tipifarnib (ZARNESTRA™, Johnson & Johnson), ABRAXANE™ (Cremophor-free), albumin-engineered nanoparticle formulations of paclitaxel (American Pharmaceutical Partners, Schaumberg, Il), vandetanib (rINN, ZD6474, ZACTIMA®, AstraZeneca), chloranmbucil, AG1478, AG1571 (SU 5271; Sugen), temsirolimus (TORISEL®, Wyeth), pazopanib (GlaxoSmithKline), canfosfamide (TELCYTA®, Telik), thiotepa and cyclosphosphamide (CYTOXAN®, NEOSAR®); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide and trimethylomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analog topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogs); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogs, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, chlorophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosoureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimnustine; antibiotics such as the enediyne antibiotics (e.g. calicheamicin, calicheamicin gamma1I, calicheamicin omegaI1 (*Angew Chem. Intl. Ed. Engl.* (1994) 33:183-186); dynemicin, dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, carminomycin, carzinophilin, chromomycinis, dactinomycin,

daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, nemorubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, porfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogs such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfornithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, OR); razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; vinorelbine (NAVELBINE®); novantrone; teniposide; edatrexate; daunomycin; aminopterin; capecitabine (XELODA®, Roche); ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; and pharmaceutically acceptable salts, acids and derivatives of any of the above. Combinations of agents may be used, such as CHP (doxorubicin, prednisone, cyclophosphamide), or CHOP (doxorubicin, prednisone, cyclophopsphamide, vincristine).

Also included in the definition of "chemotherapeutic agent" are: (i) anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens and selective estrogen receptor modulators (SERMs), including, for example, tamoxifen (including NOLVADEX®; tamoxifen citrate), raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and FARESTON® (toremifine citrate); (ii) aromatase inhibitors that inhibit the enzyme aromatase, which regulates estrogen production in the adrenal glands, such as, for example, 4(5)-imidazoles, aminoglutethimide, MEGASE® (megestrol acetate), AROMASIN® (exemestane; Pfizer), formestanie, fadrozole, RIVISOR® (vorozole), FEMARA® (letrozole; Novartis), and ARIMIDEX® (anastrozole; AstraZeneca); (iii) anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; as well as troxacitabine (a 1,3-dioxolane nucleoside cytosine analog); (iv) protein kinase inhibitors such as MEK inhibitors (WO 2007/044515); (v) lipid kinase inhibitors; (vi) antisense oligonucleotides, particularly those which inhibit expression of genes in signaling pathways

implicated in aberrant cell proliferation, for example, PKC-alpha, Raf and H-Ras, such as oblimersen (GENASENSE®, Genta Inc.); (vii) ribozymes such as VEGF expression inhibitors (e.g., ANGIOZYME®) and HER2 expression inhibitors; (viii) vaccines such as gene therapy vaccines, for example, ALLOVECTIN®, LEUVECTIN®, and VAXID®; PROLEUKIN® rIL-2; topoisomerase 1 inhibitors such as LURTOTECAN®; ABARELIX® rmRH; (ix) anti-angiogenic agents such as bevacizumab (AVASTIN®, Genentech); and pharmaceutically acceptable salts, acids and derivatives of any of the above.

Also included in the definition of "chemotherapeutic agent" are therapeutic antibodies such as alemtuzumab (Campath), bevacizumab (AVASTIN®, Genentech); cetuximab (ERBITUX®, Imclone); panitumumab (VECTIBIX®, Amgen), rituximab (RITUXAN®, Genentech/Biogen Idec), ofatumumab (ARZERRA®, GSK), pertuzumab (PERJETA™, OMNITARG™, 2C4, Genentech), trastuzumab (HERCEPTIN®, Genentech), tositumomab (Bexxar, Corixia), MDX-060 (Medarex) and the antibody drug conjugate, gemtuzumab ozogamicin (MYLOTARG®, Wyeth).

Humanized monoclonal antibodies with therapeutic potential as chemotherapeutic agents in combination with the conjugates of the disclosure include: alemtuzumab, apolizumab, aselizumab, atlizumab, bapineuzumab, bevacizumab, bivatuzumab mertansine, cantuzumab mertansine, cedelizumab, certolizumab pegol, cidfusituzumab, cidtuzumab, daclizumab, eculizumab, efalizumab, epratuzumab, erlizumab, felvizumab, fontolizumab, gemtuzumab ozogamicin, inotuzumab ozogamicin, ipilimumab, labetuzumab, lintuzumab, matuzumab, mepolizumab, motavizumab, motovizumab, natalizumab, nimotuzumab, nolovizumab, numavizumab, ocrelizumab, omalizumab, palivizumab, pascolizumab, pecfusituzumab, pectuzumab, pertuzumab, pexelizumab, ralivizumab, ranibizumab, reslivizumab, reslizumab, resyvizumab, rovelizumab, ruplizumab, sibrotuzumab, siplizumab, sontuzumab, tacatuzumab tetraxetan, tadocizumab, talizumab, tefibazumab, tocilizumab, toralizumab, trastuzumab, tucotuzumab celmoleukin, tucusituzumab, umavizumab, urtoxazumab, nivolumab, pembrolizumab, durvalumab, and visilizumab.

In some cases in particular, the ADC is administered to subjects in combination with a steroid, Ibrutnib, Durvulamab, rituximab, and/or cytarabine.

Combination with steroids

In developing the ADC dosage regimes described herein, it was observed that administration of steroids such as dexamethasone reduced the frequency and/or severity of toxicity symptom reported by subjects.

Accordingly, in preferred embodiments the ADC is administered in combination with a steroid, such as dexamethasone.

Preferably, the steroid is dexamethasone. Other suitable steroid are found in the classes of corticosteroids, such as glucocorticoids. Example glucocorticoids are Cortisol

(hydrocortisone), Cortisone, Prednisone, Prednisolone, Methylprednisolone, Dexamethasone, Betamethasone, Triamcinolone, Fludrocortisone acetate, and Deoxycorticosterone acetate.

Specifically envisaged are embodiments where the CD19-ADC is administered in combination with a steroid, such as dexamethasone. Preferably the first dose of the steroid is given before the CD19-ADC is administered, for example at least 2 hours before the ADC is administered. A further dose of steroid such as dexamethasone may be administered to the subject the day after the ADC is administered. Optionally, a yet further dose of steroid such as dexamethasone may be administered to the subject the day before the ADC is administered.

The steroid may be administered before the ADC is administered, for example at least 2 hours, at least 6 hours, at least 12 hours, or the day before the ADC is administered.

In some embodiments, a first dose of steroid is administered the day before the ADC is administered. A second dose of steroid may then be administered on the day the ADC is administered, preferably before the ADC is administered, such as at least 2 hours before the ADC is administered. A third dose of steroid may then be administered on the day after the ADC is administered. In dosing regimes comprising more than one administration of ADC per treatment cycle (e.g. fractionated dosage regimes), the steroid is preferably administered only in conjunction with the first administration of ADC in each treatment cycle.

In some embodiments, a first dose of steroid is administered the day the ADC is administered, preferably before the ADC is administered, such as at least 2 hours before the ADC is administered. A second dose of steroid may then be administered on the day after the ADC is administered. In dosing regimes comprising more than one administration of ADC per treatment cycle (e.g. fractionated dosage regimes), the steroid is preferably administered only in conjunction with the first administration of ADC in each treatment cycle.

The steroid may be administered in any method known in the art, such as orally, parenterally (e.g. injection intravenously, intramuscularly, or intrathecally) , inhalation, or topically. Preferably the steroid is administered orally.

The steroid may be administered in a range of dosage regimes. For example, the dose of steroid to be administered in a day may be administered as a single dose, two partial doses, three partial doses, or more than three partial doses. Preferably partial doses are of equal size. Preferably, the dose of steroid to be administered in a day is administered as two equal, partial doses.

Each dose of steroid may be 1mg, 2mg, 3mg, 4mg, 5mg, 6mg, 7mg, 8mg, 9mg, 10mg, 11mg, 12mg, 14mg, 16mg, 18mg, 20mg, 22mg, 24mg, 26mg, 28mg, or 30mg.

Each partial dose of steroid may be 1mg, 2mg, 3mg, 4mg, 5mg, 6mg, 7mg, 8mg, 9mg, 10mg, 11mg, 12mg, 13mg, 14mg, or 15mg..

In some embodiments Dexamethasone is administered orally as 4mg twice daily: (i) the day before ADC administration, (ii) the day of ADC administration, and (iii) the day after ADC administration. The steroid is administered in conjunction with the ADC administered on Week 1, Day 1 of each cycle only, regardless of ADC treatment schedule.

In some embodiments Dexamethasone is administered orally as 4mg twice daily: (i) the day of ADC administration, at least 2 hours before the ADC, and (ii) the day after ADC administration. The steroid is administered in conjunction with the ADC administered on Week 1, Day 1 of each cycle only, regardless of ADC treatment schedule.

In some embodiments Dexamethasone is administered orally as 8mg twice daily: (i) the day before ADC administration, (ii) the day of ADC administration, preferably at least 2 hours before the ADC, and (iii) the day after ADC administration. The steroid is administered in conjunction with the ADC administered on Week 1, Day 1 of each cycle only, regardless of ADC treatment schedule.

In some embodiments Dexamethasone is administered orally as 8mg twice daily: (i) the day of ADC administration, preferably at least 2 hours before the ADC, and (ii) the day after ADC administration. The steroid is administered in conjunction with the ADC administered on Week 1, Day 1 of each cycle only, regardless of ADC treatment schedule.

Dexamethasone:

(i) CAS Number → 50-02-2
(see http://www.cas.org/content/chemical-substances/faqs)

(ii) Unique Ingredient Identifier (UNII) → 7S5I7G3JQL
(see http://www.fda.gov/ForIndustry/DataStandards/SubstanceRegistrationSystem-UniqueIngredientIdentifierUNII/default.htm)

(iii) IUPAC name →
(8S,9R,10S,11S,13S,14S,16R,17R)-9- Fluoro-11,17-dihydroxy-17-(2-hydroxyacetyl)-10,13,16-trimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-3-one

(iv) Structure →

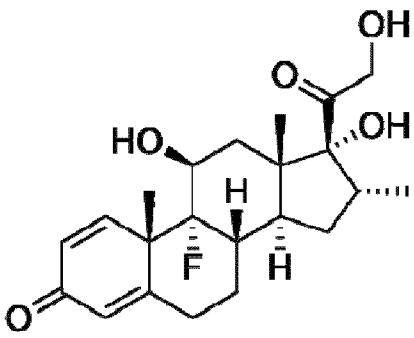
Combination with Ibrutinib

Administration of the CD19-ADC in combination with Ibrutinib is contemplated, particularly in embodiments where the proliferative disorder is lymphoma.

The Ibrutinib may be administered to the subject before, concurrently with, or after the CD19-ADC. Preferably, the CD19-ADC and Ibrutinib are administered concurrently. For example, in some cases administration of Ibrutinib begins on day 1 of treatment cycle 1 of the CD19-ADC dosage regime described herein.

When administered in combination with Ibrutinib, the CD19-ADC is preferably administered in a dosage regime consisting of two Q3W (one dose every 3 weeks) treatment cycles. Preferably, the dose administered in each of the two treatment cycles is the same. Alternatively, the second dose may be a reduced dose; that is, the dosage regime may be a tapered dosing regime as defined herein.

When administered in combination with Ibrutinib, the starting dose may be about 60 µg/kg, about 90 µg/kg, about 120 µg/kg, or about 150 µg/kg. In some embodiments when administered in combination with Ibrutinib, the starting dose of CD19-ADC may be about 140 to 160 µg/kg.



In some cases, the CD19-ADC and Ibrutinib are administered sequentially. For example, in some cases administration of Ibrutinib begins after the completion of CD19-ADC treatment.

In some cases, the administration of Ibrutinib is discontinued on the completion of CD19-ADC treatment. However, typically administration of Ibrutinib continues after the completion of CD19-ADC treatment. In some cases, Ibrutinib administration continues for up to 1 year after the completion of CD19-ADC treatment.

In cases where the subject achieves CR following initial treatment with the CD19-ADC and Ibrutinib combination, typically no further CD19-ADC is administered to the subject. In these cases, Ibrutinib administration typically continues for up to 1 year after the completion of CD19-ADC treatment.

In cases where the subject achieves SD or PR following initial treatment with the CD19-ADC and Ibrutinib combination, further CD19-ADC may be administered to the subject. In these cases, Ibrutinib administration typically continues after the initial treatment with the CD19-ADC and Ibrutinib combination. If the subject has not achieved CR within 3 months after the completion of initial CD19-ADC treatment, further CD19-ADC may be administered to the subject.

The further CD19-ADC may be administered in a dosage regime consisting of two Q3W treatment cycles. Preferably the dose administered in each of the two treatment cycles is the same. Alternatively, the second dose may be a reduced dose; that is, the dosage regime may be a tapered dosing regime as defined herein. Typically the further CD19-ADC is administered in combination with Ibrutinib treatment.

The Ibrutinib may be administered in a QD (one dose per day) dosage regime; that is, the Ibrutinib may be administered once a day. Preferably the dose of Ibrutinib administered is about 550 to 570 mg/day, such as about 560mg/day. Reduced daily doses are about 420mg/day and about 280 mg/day; reduced doses may be administered if, for example, the subject exhibits a treatment-related toxicity.

In some cases where the CD19-ADC is administered in combination with Ibrutinib, the subject has, or is suspected as having, or has been identified as being at risk of, or has received a diagnosis of cancer of a non-Hodgkin's Lymphoma, such as diffuse large B-cell lymphoma (DLBCL) or Mantle Cell lymphoma (MCL).

Ibrutinib (Imbruvica):

(i) CAS Number → 936563-96-1
(see http://www.cas.org/content/chemical-substances/faqs)

(ii) Unique Ingredient Identifier (UNII) → 1X70OSD4VX (see http://www.fda.gov/ForIndustry/DataStandards/SubstanceRegistrationSystem-UniqueIngredientIdentifierUNII/default.htm)

(iii) IUPAC name → 1-[(3R)-3-[4-Amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d] pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one

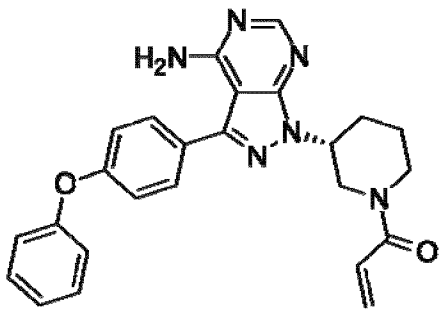
(iv) Structure →

Combination with Durvalumab

Administration of the CD19-ADC in combination with Durvalumab is contemplated, particularly in embodiments where the proliferative disorder is lymphoma.

The Durvalumab may be administered to the subject before, concurrently with, or after the CD19-ADC. Preferably, the CD19-ADC and Durvalumab are administered concurrently; that is the CD19-ADC and the Durvalumab are administered as part of the same treatment cycle. In some cases the CD19-ADC and Durvalumab are not administered on the same day of the treatment cycle. For example, in some cases the CD19-ADC is administered on day 1 of the treatment cycle and Durvalumab is administered on day 8 of the treatment cycle.

When administered in combination with Durvalumab, the CD19-ADC may be administered in a dosage regime consisting of two Q3W treatment cycles. Preferably, the dose of CD19-ADC administered in each of the two treatment cycles is the same. Alternatively, the second dose may be a reduced dose; that is, the dosage regime may be a tapered dosing regime as defined herein.



When administered in combination with the CD19-ADC, the Durvalumab may be administered in a Q3W dosage regime. However, preferably, the Durvalumab is administered in a Q4W dosage regime. In some embodiments the dose of Durvalumab administered is about 1400 to 1600 mg. The dose of Durvalumab administered is preferably 1500 mg.

In some cases where the CD19-ADC is administered in combination with Durvalumab, the starting dose is about 90 µg/kg, about 120 µg/kg, or about 150 µg/kg. In some embodiments when administered in combination with Durvalumab, the starting dose of CD19-ADC may be about 140 to 160 µg/kg.

In some cases, the CD19-ADC and Durvalumab are administered sequentially. For example, in some cases administration of Durvalumab begins after the completion of CD19-ADC treatment.

In some cases, the administration of Durvalumab is discontinued on the completion of CD19-ADC treatment. However, typically administration of Durvalumab continues after the completion of CD19-ADC treatment. In some cases, Durvalumab administration continues for up to 1 year after the completion of CD19-ADC treatment.

When administered after the completion of CD19-ADC treatment, the Durvalumab is preferably administered in a Q4W dosage regime. In some embodiments the dose of Durvalumab administered is about 1400 to 1600 mg. The dose of Durvalumab administered is preferably 1500 mg.

In cases where the subject achieves CR following initial treatment with the CD19-ADC and Durvalumab combination, typically no further CD19-ADC is administered to the subject. In these cases, Durvalumab administration typically continues for up to 1 year after the completion of CD19-ADC treatment.

In cases where the subject achieves SD or PR following initial treatment with the CD19-ADC and Durvalumab combination, further CD19-ADC may be administered to the subject. In these cases, Durvalumab administration typically continues after the initial treatment with the CD19-ADC and Durvalumab combination. If the subject has not achieved CR within 3 months after the completion of initial CD19-ADC treatment, further CD19-ADC may be administered to the subject. For example, in some embodiments further CD19-ADC is administered to the subject if the subject has attained SD or PR response after the completion of initial CD19-ADC treatment. The assessment of response is typically made between 12 to 16 weeks after the first dose of CD19-ADC is administered. For example, at 13, 14 or 15 weeks after the first dose of CD19-ADC is administered.

The further CD19-ADC may be administered in a dosage regime consisting of two Q3W treatment cycles. Preferably the dose administered in each of the two treatment cycles is the same. Alternatively, the second dose may be a reduced dose; that is, the dosage regime may be a tapered dosing regime as defined herein. Typically the further CD19-ADC is administered in combination with Durvalumab treatment.

In some cases where the CD19-ADC is administered in combination with Durvalumab, the subject has, or is suspected as having, or has been identified as being at risk of, or has received a diagnosis of cancer of a non-Hodgkin's Lymphoma, such as diffuse large B-cell lymphoma (DLBCL), Mantle Cell lymphoma (MCL), or Follicular Lymphoma (FL).

Durvalumab/MEDI4736:

(i) CAS Number → 1428935-60-7
(see http://www.cas.org/content/chemical-substances/faqs)

(ii) Unique Ingredient Identifier (UNII) → 28X28X9OKV (see http://www.fda.gov/ForIndustry/DataStandards/SubstanceRegistrationSystem-UniqueIngredientIdentifierUNII/default.htm)

(iii) VH sequence
EVQLVESGGGLVQPGGSLRLSCAASGFTFSRYWMSWVRQAPGKGLEWVA
NIKQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREG
GWFGELAFDYWGQGTLVTVSS

(iv) VL sequence
EIVLTQSPGTLSLSPGERATLSCRASQRVSSSYLAWYQQKPGQAPRLLIYDA
SSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSLPWTFGQGT
KVEIK

Combination with Rituximab

Administration of the CD19-ADC in combination with Rituximab is contemplated, particularly in embodiments where the proliferative disorder is lymphoma.

The Rituximab may be administered to the subject before, concurrently with, or after the CD19-ADC. Preferably, the CD19-ADC and Rituximab are administered concurrently. For example, in some cases administration of Rituximab and CD19-ADC begin on day 1 of treatment cycle 1 of the CD19-ADC dosage regime described.

In some cases, the CD19-ADC and Rituximab are administered sequentially. For example, in some cases administration of Rituximab begins after the completion of CD19-ADC treatment.

The Rituximab may be administered in a Q3W dosage regime. In some embodiments, the dose of Rituximab administered is 325 to 425 mg/m2. Preferably the dose of Rituximab administered is 375 mg/m^2.

Preferably, in cases where the CD19-ADC is administered in combination with Rituximab, the starting dose is about 90 µg/kg, about 120 µg/kg, or about 150 µg/kg. In some embodiments when administered in combination with Rituximab, the starting dose of CD19-ADC may be about 140 to 160 µg/kg.

In some cases where the CD19-ADC is administered in combination with Rituximab, the subject has, or is suspected as having, or has been identified as being at risk of, or has received a diagnosis of cancer of a non-Hodgkin's Lymphoma, such as diffuse large B-cell lymphoma (DLBCL).

In some cases where the CD19-ADC is administered in combination with Rituximab, the subject may be undergoing, or have undergone, treatment with Rituximab. In some cases the individual may be refractory to treatment (or further treatment) with Rituximab. In embodiments where the individual is undergoing, or has undergone, treatment with Rituximab, the anti CD19 ADC may be administered in combination with Rituximab, or without continued administration of Rituximab.

Rituximab:

(i) CAS Number → 174722-31-7
(see http://www.cas.org/content/chemical-substances/faqs)

(ii) Drugbank reference → DB00073
(see https://www.drugbank.ca/)

(iii) Unique Ingredient Identifier (UNII) → 4F4X42SYQ6 (see http://www.fda.gov/ForIndustry/DataStandards/SubstanceRegistrationSystem-UniqueIngredientIdentifierUNII/default.htm)

(iv) Heavy chain sequence:
QVQLQQPGAELVKPGASVKMSCKASGYTFTSYNMHWVKQTPGRGLEWIG
AIYPGNGDTSYNQKFKGKATLTADKSSSTAYMQLSSLTSEDSAVYYCARST
YYGGDWYFNVWGAGTTVTVSAASTKGPSVFPLAPSSKSTSGGTAALGCLV
KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQT
YICNVNHKPSNTKVDKKAEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYT
LPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD
GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

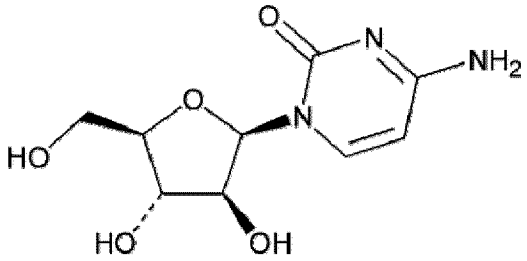
Light chain sequence:
QIVLSQSPAILSASPGEKVTMTCRASSSVSYIHWFQQKPGSSPKPWIYATSN
LASGVPVRFSGSGSGTSYSLTISRVEAEDAATYYCQQWTSNPPTFGGGTKL
EIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS
GNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTK
SFNRGEC

Combination with Cytarabine

Administration of the CD19-ADC in combination with Cytarabine is contemplated, particularly in embodiments where the proliferative disorder is lymphoma.

The Cytarabine may be administered to the subject before, concurrently with, or after the CD19-ADC. Preferably, the CD19-ADC and Cytarabine are administered concurrently.

In preferred embodiments the CD19-ADC is administered in a Q3W regime, preferably on day 2 of the treatment cycle. Preferably the CD19-ADC is administered at a starting dose for 2 treatment cycles and at a reduced dose of 50% of the starting dose in subsequent cycles. In some emboduiments the starting dose is about 140 to 160 µg/kg and the reduced dose is about 70 to 80 µg/kg. Preferably the starting dose is about 150 µg/kg and the reduced dose is about 75 µg/kg.



In preferred embodiments, the Cytarabine is administered in a Q3W regime, preferably as 5 partial doses spread one partial dose per day on days 1 to 5 of each cycle. Preferably, the Cytarabine is administered as 5 equal partial doses. The partial dose may be about 100 mg/m^2, about 200 mg/m^2, about 300 mg/m^2, or about 400 mg/m^2.

In some cases where the CD19-ADC is administered in combination with cytarabine, the subject has, or is suspected as having, or has been identified as being at risk of, or has received a diagnosis of cancer of a non-Hodgkin's Lymphoma, such as diffuse large B-cell lymphoma (DLBCL).

Cytarabine:

(i) CAS Number → 147-94-4 (see http://www.cas.org/content/chemical-substances/faqs)

(ii) Unique Ingredient Identifier (UNII) → 04079A1RDZ (see http://www.fda.gov/ForIndustry/DataStandards/SubstanceRegistrationSystem-UniqueIngredientIdentifierUNII/default.htm)

(iii) IUPAC name: 4-amino-1-[(2R,3S,4R,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl] pyrimidin-2-one

(iv) Structure →

Combination with Cytarabine and Rituximab

Administration of the CD19-ADC in combination with Cytarabine and Rituximab is contemplated, particularly in embodiments where the proliferative disorder is lymphoma.

The Cytarabine and Rituximab may be administered to the subject before, concurrently with, or after the CD19-ADC. Preferably, the CD19-ADC, Cytarabine and Rituximab are administered concurrently. For example, in some cases administration of Cytarabine, Rituximab, and CD19-ADC begin on day 1 of treatment cycle 1 of the CD19-ADC dosage regime described.

In preferred embodiments the Rituximab is administered in a Q3W regime, preferably on day 1 of the treatment cycle. In some embodiments the dose of Rituximab administered is 325 to 425 mg/m2. Preferably the dose of Rituximab administered is 375 mg/m^2.

In preferred embodiments the CD19-ADC is administered in a Q3W regime, preferably on day 2 of the treatment cycle. Preferably the CD19-ADC is administered at a starting dose for 2 treatment cycles and at a reduced dose of 50% of the starting dose in subsequent cycles. In some embodiments the starting dose is about 140 to 160 µg/kg and the reduced dose is about 70 to 80 µg/kg. Preferably the starting dose is about 150 µg/kg and the reduced dose is about 75 µg/kg.

In preferred embodiments, the Cytarabine is administered in a Q3W regime, preferably as 5 partial doses spread one partial dose per day on days 1 to 5 of each cycle. Preferably, the Cytarabine is administered as 5 equal partial doses. The partial dose may be about 100 mg/m^2, about 200 mg/m^2, about 300 mg/m^2, or about 400 mg/m^2.

In some cases where the CD19-ADC is administered in combination with Rituximab and cytarabine, the subject has, or is suspected as having, or has been identified as being at risk of, or has received a diagnosis of cancer of a non-Hodgkin's Lymphoma, such as diffuse large B-cell lymphoma (DLBCL).

In some cases where the CD19-ADC is administered in combination with cytarabine and Rituximab, the subject may be undergoing, or have undergone, treatment with Rituximab. In

some cases the individual may be refractory to treatment (or further treatment) with Rituximab. In embodiments where the individual is undergoing, or has undergone, treatment with Rituximab, the anti CD19 ADC may be administered in combination with Rituximab, or without continued administration of Rituximab.

Specifically envisaged are embodiments where the CD19-ADC is administered in combination with a diuretic, such as spironolactone. The diuretic may be administered to subjects receiving CD19-ADC that are exhibiting an increase in weight, oedema or pleural effusion.

Specifically envisaged are embodiments where the CD19-ADC is administered in combination with intrathecal medication for CNS prophylaxis.

Compositions according to the present disclosure are preferably pharmaceutical compositions. Pharmaceutical compositions according to the present disclosure, and for use in accordance with the present disclosure, may comprise, in addition to the active ingredient, i.e. a conjugate compound, a pharmaceutically acceptable excipient, carrier, buffer, stabiliser or other materials well known to those skilled in the art. Such materials should be non-toxic and should not interfere with the efficacy of the active ingredient. The precise nature of the carrier or other material will depend on the route of administration, which may be oral, or by injection, e.g. cutaneous, subcutaneous, or intravenous.

Pharmaceutical compositions for oral administration may be in tablet, capsule, powder or liquid form. A tablet may comprise a solid carrier or an adjuvant. Liquid pharmaceutical compositions generally comprise a liquid carrier such as water, petroleum, animal or vegetable oils, mineral oil or synthetic oil. Physiological saline solution, dextrose or other saccharide solution or glycols such as ethylene glycol, propylene glycol or polyethylene glycol may be included. A capsule may comprise a solid carrier such a gelatin.

For intravenous, cutaneous or subcutaneous injection, or injection at the site of affliction, the active ingredient will be in the form of a parenterally acceptable aqueous solution which is pyrogen-free and has suitable pH, isotonicity and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles such as Sodium Chloride Injection, Ringer's Injection, Lactated Ringer's Injection. Preservatives, stabilisers, buffers, antioxidants and/or other additives may be included, as required.

Dosage

It will be appreciated by one of skill in the art that appropriate dosages of the ADC and compositions comprising these active elements, can vary from subject to subject. Determining the optimal dosage will generally involve the balancing of the level of therapeutic benefit against any risk or deleterious side effects. The selected dosage level will depend on a variety of factors including, but not limited to, the activity of the particular

compound, the route of administration, the time of administration, the rate of excretion of the compound, the duration of the treatment, other drugs, compounds, and/or materials used in combination, the severity of the condition, and the species, sex, age, weight, condition, general health, and prior medical history of the subject. The amount of compound and route of administration will ultimately be at the discretion of the physician, veterinarian, or clinician, although generally the dosage will be selected to achieve local concentrations at the site of action which achieve the desired effect without causing substantial harmful or deleterious side-effects.

In certain aspects, the dosage of ADC is determined by the expression of CD19 in a sample obtained from the subject. Thus, the level or localisation of expression of CD19 in the sample may be indicative that a higher or lower dose of ADC is required. For example, a high expression level CD19 may indicate that a higher dose of ADC would be suitable. In some cases, a high expression level of CD19 may indicate the need for administration of another agent in addition to the ADC. For example, administration of the ADC in conjunction with a chemotherapeutic agent. A high expression level of the CD19 may indicate a more aggressive therapy.

In general, a suitable dose of each active compound is in the range of about 100 ng to about 25 mg (more typically about 1 µg to about 10 mg) per kilogram body weight of the subject per day. Where the active compound is a salt, an ester, an amide, a prodrug, or the like, the amount administered is calculated on the basis of the parent compound and so the actual weight to be used is increased proportionately.

In some situations dosage normalization based on body size parameters such as Body Surface Area (BSA) better accounts for intersubject variability in ADC pharmacokinetics such as clearance rate than normalization based on body weight. In these situations, calculation of dosage levels using body size parameters allows for more precise dosing,

Accordingly, in some aspects the dose of the ADC administered to the subject is normalised to the subject body size (i.e. not subject body weight). In some cases, the dose of the ADC administered to the subject is normalised to the subject body surface area (BSA). Preferably, the ADC dosage is normalised to BSA using the DuBois formula (as disclosed in, for example, Japanese Journal of Clinical Oncology, Volume 33, Issue 6, 1 June 2003, Pages 309–313, https://doi.org/10.1093/jjco/hyg062).

Antibodies

The term “antibody” herein is used in the broadest sense and specifically covers monoclonal antibodies, polyclonal antibodies, dimers, multimers, multispecific antibodies (*e.g.,* bispecific antibodies), intact antibodies (also described as “full-length” antibodies) and antibody fragments, so long as they exhibit the desired biological activity, for example, the ability to bind a first target protein (Miller *et al* (2003) *Jour. of Immunology* 170:4854-4861). Antibodies may be murine, human, humanized, chimeric, or derived from other species such as rabbit, goat, sheep, horse or camel.

An antibody is a protein generated by the immune system that is capable of recognizing and binding to a specific antigen. (Janeway, C., Travers, P., Walport, M., Shlomchik (2001) *Immuno Biology, 5th Ed.*, Garland Publishing, New York). A target antigen generally has numerous binding sites, also called epitopes, recognized by Complementarity Determining Regions (CDRs) on multiple antibodies. Each antibody that specifically binds to a different epitope has a different structure. Thus, one antigen may have more than one corresponding antibody. An antibody may comprise a full-length immunoglobulin molecule or an immunologically active portion of a full-length immunoglobulin molecule, *i.e.*, a molecule that contains an antigen binding site that immunospecifically binds an antigen of a target of interest or part thereof, such targets including but not limited to, cancer cell or cells that produce autoimmune antibodies associated with an autoimmune disease. The immunoglobulin can be of any type (e.g. IgG, IgE, IgM, IgD, and IgA), class (e.g. IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass, or allotype (e.g. human G1m1, G1m2, G1m3, non-G1m1 [that, is any allotype other than G1m1], G1m17, G2m23, G3m21, G3m28, G3m11, G3m5, G3m13, G3m14, G3m10, G3m15, G3m16, G3m6, G3m24, G3m26, G3m27, A2m1, A2m2, Km1, Km2 and Km3) of immunoglobulin molecule. The immunoglobulins can be derived from any species, including human, murine, or rabbit origin.

"Antibody fragments" comprise a portion of a full length antibody, generally the antigen binding or variable region thereof. Examples of antibody fragments include Fab, Fab', $F(ab')_2$, and scFv fragments; diabodies; linear antibodies; fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies, CDR (complementary determining region), and epitope-binding fragments of any of the above which immunospecifically bind to cancer cell antigens, viral antigens or microbial antigens, single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

The term “monoclonal antibody” as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e. the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to polyclonal antibody preparations which include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they may be synthesized uncontaminated by other antibodies. The modifier “monoclonal” indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present disclosure may be made by the hybridoma method first described by Kohler *et al* (1975) *Nature* 256:495, or may be made by recombinant DNA methods (see, US 4816567). The monoclonal antibodies may also be isolated from phage antibody libraries using the techniques described in Clackson et al (1991) Nature, 352:624-628; Marks et al (1991) J.

Mol. Biol., 222:581-597 or from transgenic mice carrying a fully human immunoglobulin system (Lonberg (2008) Curr. Opinion 20(4):450-459).

The monoclonal antibodies herein specifically include "chimeric" antibodies in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (US 4816567; and Morrison *et al* (1984) *Proc. Natl. Acad. Sci.* USA, 81:6851-6855). Chimeric antibodies include "primatized" antibodies comprising variable domain antigen-binding sequences derived from a non-human primate (e.g. Old World Monkey or Ape) and human constant region sequences.

An "intact antibody" herein is one comprising VL and VH domains, as well as a light chain constant domain (CL) and heavy chain constant domains, CH1, CH2 and CH3. The constant domains may be native sequence constant domains (e.g. human native sequence constant domains) or amino acid sequence variant thereof. The intact antibody may have one or more "effector functions" which refer to those biological activities attributable to the Fc region (a native sequence Fc region or amino acid sequence variant Fc region) of an antibody. Examples of antibody effector functions include C1q binding; complement dependent cytotoxicity; Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; and down regulation of cell surface receptors such as B cell receptor and BCR.

Depending on the amino acid sequence of the constant domain of their heavy chains, intact antibodies can be assigned to different "classes." There are five major classes of intact antibodies: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into "subclasses" (isotypes), *e.g.,* IgG1, IgG2, IgG3, IgG4, IgA, and IgA2. The heavy-chain constant domains that correspond to the different classes of antibodies are called α, δ, ε, γ, and μ, respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

Brief Description of the Figures

Embodiments and experiments illustrating the principles of the disclosure will now be discussed with reference to the accompanying figures in which:

Figure 1.

Sequences

Figure 2.

Subcutaneous Ramos-e222 model – murine xenograft

Figure 3.

NALM-6 tumour cell inoculation model – murine xenograft

Figure 4.

Total antibody and ADCx19 concentrations versus time by patient and dose (Cycle 1)

The disclosure includes the combination of the cases and preferred features described except where such a combination is clearly impermissible or expressly avoided.

The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

Cases and embodiments of the present disclosure will now be illustrated, by way of example, with reference to the accompanying figures. Further cases and embodiments will be apparent to those skilled in the art. All documents mentioned in this text are incorporated herein by reference.

Throughout this specification, including the claims which follow, unless the context requires otherwise, the word “comprise,” and variations such as “comprises” and “comprising,” will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

It must be noted that, as used in the specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. Ranges may be expressed herein as from “about” one particular value, and/or to “about” another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by the use of the antecedent “about,” it will be understood that the particular value forms another embodiment.

SOME EMBODIMENTS

Lymphoma

The disclosure provides a method of treating a proliferative disease in a subject, said method comprising administering to a subject a CD19-ADC, wherein the CD19-ADC is administered to the subject in a tapered and/or elongated dosage regimes.

In some cases the dosage regime comprises dosing about 120 µg/kg every 3 weeks for 2 cycles, then continuing treatment with the third and subsequent cycles at a reduced dose of about 60 µg/kg every 6 weeks, beginning 6 weeks after cycle 2 administration. Preferably only subjects who have attained at least SD after the second cycle will continue with the reduced dose and increased cycle length.

In some cases the dosage regime comprises dosing about 150 µg/kg every 3 weeks for 2 cycles, then continuing treatment with the third and subsequent cycles at a reduced dose of about 60 µg/kg every 6 weeks, beginning 6 weeks after cycle 2 administration. Preferably only subjects who have attained at least SD after the second cycle will continue with the reduced dose and increased cycle length.

In some preferred cases the dosage regime comprises dosing about 140 to 160 µg/kg every 3 weeks for 2 cycles, then continuing treatment with the third and subsequent cycles at a reduced dose of about 7o to 80 µg/kg every 3 weeks, beginning 3 weeks after cycle 2 administration. Preferably only subjects who have attained at least SD after the second cycle will continue with the reduced dose.

In some particularly preferred cases the dosage regime comprises dosing about 150 µg/kg every 3 weeks for 2 cycles, then continuing treatment with the third and subsequent cycles at a reduced dose of about 75 µg/kg every 3 weeks, beginning 3 weeks after cycle 2 administration. Preferably only subjects who have attained at least SD after the second cycle will continue with the reduced dose.

In some particularly preferred cases the dosage regime comprises dosing about 150 µg/kg every 3 weeks for 2 cycles (Q3W x 2), then continuing treatment with the third and subsequent cycles at a reduced dose of about 75 µg/kg every 3 weeks (Q3W), beginning 3 weeks after cycle 2 administration. Preferably, only subjects who have attained at least SD after the second cycle will continue with the reduced dose. In some cases, treatment may continue for up to one year or until disease progression, unacceptable toxicity, or other discontinuation criteria, whichever occurs first. In some preferred cases the proliferative disorder treated with this regime is DLBCL.

In some cases the dosage regime comprises dosing about 200 µg/kg every 6 weeks for 2 cycles, then continuing treatment with the third and subsequent cycles at a reduced dose of about 60 µg/kg every 6 weeks, beginning 6 weeks after cycle 2 administration. Preferably

only subjects who have attained at least SD after the second cycle will continue with the reduced dose.

In some cases the dosage regime comprises dosing about 200 µg/kg every 6 weeks for 1 cycle, then continuing treatment with the second and subsequent cycles at a reduced dose of about 60 µg/kg every 6 weeks, beginning 6 weeks after cycle 1 administration. Preferably only subjects who have attained at least SD after the first cycle will continue with the reduced dose.

In some cases the dosage regime comprises dosing about 45 µg/kg every 3 weeks for up to 4 treatment cycles, then continuing treatment every 3 weeks at a reduced dose of about 30 µg/kg or about 20 µg/kg (such as 20 to 30 µg/kg). In some cases, the starting dose of 45 µg/kg is administered for only 1 treatment cycle before the dose is reduced. In some cases, the starting dose of 45 µg/kg is administered for only 2 treatment cycles before the dose is reduced. In some cases, the starting dose of 45 µg/kg is administered for only 3 treatment cycles before the dose is reduced. In some cases, the starting dose of 45 µg/kg is administered for 4 treatment cycles before the dose is reduced.

Preferably the CD19-ADC is administered as single dose on Day 1 of each cycle, unless otherwise specified.

Preferably the CD19-ADC is ADCx19 as described herein, or ADCT-402.

Preferably the proliferative disease is a B-cell Lineage Non Hodgkin Lymphoma (B-NHL), such as diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, (FL), Mantle Cell lymphoma (MCL), chronic lymphatic lymphoma (CLL), Waldenstroms Microglobulinemia, Burkitt's lymphoma, and Marginal Zone B-cell lymphoma (MZBL). The disease may be relapsed or refractory.

Preferably the subject is human.

Preferably the CD19-ADC is administered in combination with dexamethasone, as described herein.

Combination with Ibrutinib

In embodiments where the CD19-ADC is administered in combination with Ibrutinib, the CD19-ADC is preferably administered in a dosage regime consisting of two, equal, Q3W treatment cycles.

Preferably, the starting dose of CD19-ADC is about 60 µg/kg, about 90 µg/kg, about 120 µg/kg, or about 150 µg/kg.

The Ibrutinib is preferably administered concurrently with the CD19-ADC in a QD regime. The dose of Ibrutinib is preferably about 560mg/day.

Preferably, the administration of Ibrutinib continues after the completion of CD19-ADC treatment.

In cases where the subject achieves CR following initial treatment with the CD19-ADC and Ibrutinib combination, preferably no further CD19-ADC is administered to the subject.

In cases where the subject achieves SD or PR following initial treatment with the CD19-ADC and Ibrutinib combination, preferably, the administration of Ibrutinib continues after the completion of CD19-ADC treatment. Further CD19-ADC may be administered to the subject For example, in some embodiments if the subject has not achieved CR within 3 months after the completion of initial CD19-ADC treatment, preferably further CD19-ADC is administered to the subject. For example, in some embodiments further CD19-ADC is administered to the subject if the subject has attained SD or PR response after the completion of initial CD19-ADC treatment. The assessment of response is typically made between 12 to 16 weeks after the first dose of CD19-ADC is administered. For example, at 13, 14 or 15 weeks after the first dose of CD19-ADC is administered.

Preferably, the further CD19-ADC is administered in a dosage regime consisting of two, equal, Q3W treatment cycles in combination with Ibrutinib, as described above.

In some preferred cases the proliferative disorder treated with this regime is DLBCL.

In some other preferred cases the proliferative disorder treated with this regime is MCL.

Combination with Durvalumab

In embodiments where the CD19-ADC is administered in combination with Durvalumab, the CD19-ADC is preferably administered in a dosage regime consisting of two, equal, Q3W treatment cycles.

Preferably, the starting dose of CD19-ADC is about 90 µg/kg, about 120 µg/kg, or about 150 µg/kg.

The Durvalumab may be administered concurrently with the CD19-ADC in a Q3W regime. However, preferably the Durvalumab is administered in a Q4W regime. The dose of Durvalumab is preferably about 1500 mg.

When administered concurrently in a Q3W regime, preferably the CD19-ADC is administered on day 1 of the Q3W cycle and the Durvalumab is administered on day 8 of the Q3W cycle.

When the Durvalumab is administered in a Q4W regime and the CD19-ADC in a Q3W regime, the regimes may be timed so that day 1 of the first Durvalumab Q4W cycle falls on day 8 of the first CD19-ADC Q3W cycle.

Preferably, the administration of Durvalumab continues after the completion of CD19-ADC treatment. When administered after the completion of CD19-ADC treatment, the Durvalumab is preferably administered in a Q4W dosage regime. The dose of Durvalumab administered is preferably about 1500 mg.

In cases where the subject achieves CR following initial treatment with the CD19-ADC and Durvalumab combination, preferably no further CD19-ADC is administered to the subject.

In cases where the subject achieves SD or PR following initial treatment with the CD19-ADC and Durvalumab combination, preferably the administration of Durvalumab continues after the completion of CD19-ADC treatment. Further CD19-ADC may be administered to the subject For example, in some embodiments if the subject has not achieved CR within 3 months after the completion of initial CD19-ADC treatment, preferably further CD19-ADC is administered to the subject. For example, in some embodiments further CD19-ADC is administered to the subject if the subject has attained SD or PR response after the completion of initial CD19-ADC treatment. The assessment of response is typically made between 12 to 16 weeks after the first dose of CD19-ADC is administered. For example, at 13, 14 or 15 weeks after the first dose of CD19-ADC is administered.

Preferably, the further CD19-ADC is administered in a dosage regime consisting of two, equal, Q3W treatment cycles in combination with Durvalumab, as described above.

In some preferred cases the proliferative disorder treated with this regime is DLBCL.

In some other preferred cases the proliferative disorder treated with this regime is MCL.

In some other preferred cases the proliferative disorder treated with this regime is FL.

Combination with Rituximab

In some embodiments where the CD19-ADC is administered in combination with Rituximab, the CD19-ADC is administered in a dosing regime comprising dosing about 140 to 160 µg/kg every 3 weeks for 2 cycles, then continuing treatment with the third and subsequent cycles at a reduced dose of about 7o to 80 µg/kg every 3 weeks, beginning 3 weeks after cycle 2 administration.

In some preferred embodiments where the CD19-ADC is administered in combination with Rituximab, the CD19-ADC is preferably administered in a dosing regime comprising dosing about 150 µg/kg every 3 weeks for 2 cycles, then continuing treatment with the third and

subsequent cycles at a reduced dose of about 75 µg/kg every 3 weeks, beginning 3 weeks after cycle 2 administration.

The Rituximab is preferably administered concurrently with the CD19-ADC in a Q3W regime; for example, both on day 1 of each treatment cycle. In some embodiments the dose of Rituximab is about 325 to 425 mg/m^2. The dose of Rituximab is preferably about 375 mg/m^2.

Combination with Cytarabine

In some embodiments where the CD19-ADC is administered in combination with Cytarabine, the CD19-ADC is administered in a dosing regime comprising dosing about 140 to 160 µg/kg every 3 weeks for 2 cycles, then continuing treatment with the third and subsequent cycles at a reduced dose of about 7o to 80 µg/kg every 3 weeks, beginning 3 weeks after cycle 2 administration.

In some preferred embodiments where the CD19-ADC is administered in combination with Cytarabine, the CD19-ADC is preferably administered in a dosing regime comprising dosing about 150 µg/kg every 3 weeks for 2 cycles, then continuing treatment with the third and subsequent cycles at a reduced dose of about 75 µg/kg every 3 weeks, beginning 3 weeks after cycle 2 administration.

Preferably the CD19-ADC is administered on day 2 of each Q3W treatment cycle.

The cytarabine is preferably administered concurrently with the CD19-ADC in a Q3W regime. Preferably the cytarabine is administered as 5 equal, partial doses spread one partial dose per day on days 1 to 5 of each cycle. The partial dose level may be about 100 mg/m^2, about 200 mg/m^2, about 300 mg/m^2, or about 400 mg/m^2 per partial dose.

Combination with Cytarabine and Rituximab

In some embodiments where the CD19-ADC is administered in combination with Cytarabine and Rituximab, the CD19-ADC is administered in a dosing regime comprising dosing about 140 to 160 µg/kg every 3 weeks for 2 cycles, then continuing treatment with the third and subsequent cycles at a reduced dose of about 7o to 80 µg/kg every 3 weeks, beginning 3 weeks after cycle 2 administration.

In some preferred embodiments where the CD19-ADC is administered in combination with Cytarabine and Rituximab, the CD19-ADC is preferably administered in a dosing regime comprising dosing about 150 µg/kg every 3 weeks for 2 cycles, then continuing treatment with the third and subsequent cycles at a reduced dose of about 75 µg/kg every 3 weeks, beginning 3 weeks after cycle 2 administration.

Preferably the CD19-ADC is administered on day 2 of each Q3W treatment cycle.

The Rituximab is preferably administered concurrently with the CD19-ADC in a Q3W regime. In some embodiments the dose of Rituximab is about 325 to 425 mg/m^2. The dose of Rituximab is preferably about 375 mg/m^2.

Preferably the Rituximab is administered on day 1 of each Q3W treatment cycle.

The cytarabine is preferably administered concurrently with the CD19-ADC in a Q3W regime. Preferably the cytarabine is administered as 5 equal, partial doses spread one partial dose per day on days 1 to 5 of each cycle. The partial dose level may be about 100 mg/m^2, about 200 mg/m^2, about 300 mg/m^2, or about 400 mg/m^2 per partial dose.

Leukaemia

Fractionated dosage regimes in which a partial dose is administered to the subject once per week are specifically contemplated. For example, on days 1, 8, and 15 of a 21 day (3-week) treatment cycle.

Preferably each partial dose is of equal size, that is, each partial dose delivers the same amount of CD19-ADC to the subject.

Preferably, each partial dose is 40 to 60 µg/kg, such as 45 to 55 µg/kg. In particularly preferred cases each partial dose is 50 µg/kg.

Preferably the CD19-ADC is ADCx19 as described herein.

Preferably the subject is human.

Preferably the proliferative disease is a leukaemia, such as Hairy cell leukaemia (HCL), Hairy cell leukaemia variant (HCL-v), and Acute Lymphoblastic Leukaemia (ALL) such as Philadelphia chromosome-positive ALL (Ph+ALL) or Philadelphia chromosome-negative ALL (Ph-ALL). The disease may be relapsed or refractory.

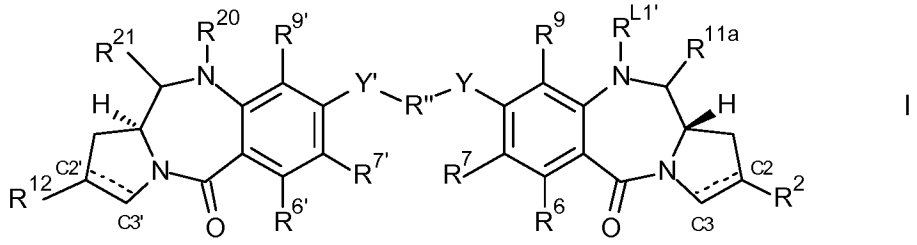
The use of this type of fractionated dosage regime to treat haematological cancers such as ALL are embodiments of particular interest. Preferably the ALL is CD19+, and may be relapsed or refractory types.

Preferably the CD19-ADC is administered in combination with dexamethasone, as described herein.

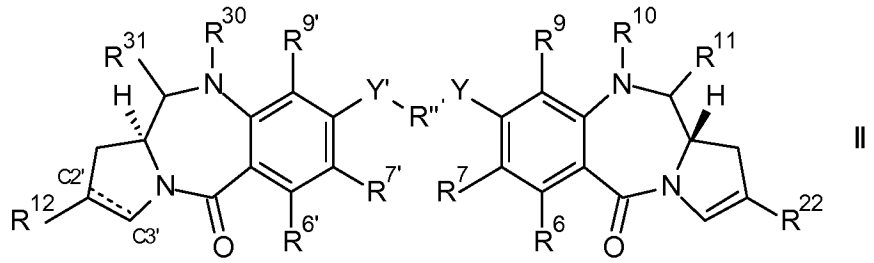
STATEMENTS OF DISCLOSURE

Lymphoma or Leukaemia

1. A method of treating a proliferative disease in a subject, said method comprising administering to a subject a CD19-ADC, wherein the CD19-ADC comprises a conjugate of formula L - $(D^L)_p$, where D^L is of formula **I** or **II**:



I



II

wherein:

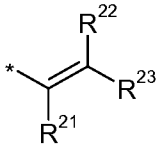
L is an antibody (Ab) which is an antibody that binds to CD19;

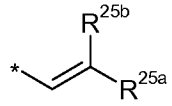
when there is a double bond present between C2' and C3', R^{12} is selected from the group consisting of:

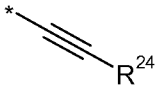
(ia) C_{5-10} aryl group, optionally substituted by one or more substituents selected from the group comprising: halo, nitro, cyano, ether, carboxy, ester, C_{1-7} alkyl, C_{3-7} heterocyclyl and bis-oxy-C_{1-3} alkylene;

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

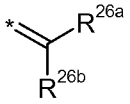
(ic) C_{3-6} saturated cycloalkyl;

(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;

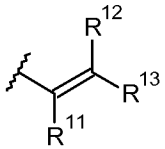
R^{21} is selected from OH, OR^A and SO_zM;

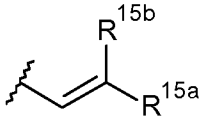
when there is a double bond present between C2 and C3, R^2 is selected from the group consisting of:

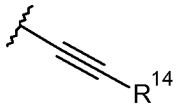
(ia) C_{5-10} aryl group, optionally substituted by one or more substituents selected from the group comprising: halo, nitro, cyano, ether, carboxy, ester, C_{1-7} alkyl, C_{3-7} heterocyclyl and bis-oxy-C_{1-3} alkylene;

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

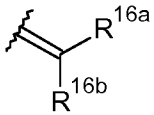
(ic) C_{3-6} saturated cycloalkyl;

(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

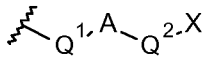
(if)  , where R^{14} is selected from: H; C_{1-3} saturated alkyl; C_{2-3} alkenyl; C_{2-3} alkynyl; cyclopropyl; phenyl, which phenyl is optionally substituted by a group selected from halo, methyl, methoxy; pyridyl; and thiophenyl;

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]

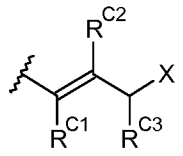
R^{22} is of formula IIIa, formula IIIb or formula IIIc:

(a)  IIIa

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

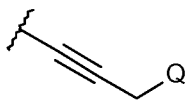
(i) Q^1 is a single bond, and Q^2 is selected from a single bond and -Z-$(CH_2)_n$-, where Z is selected from a single bond, O, S and NH and n is from 1 to 3; or

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

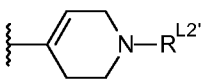
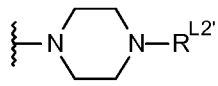
(b)  IIIb

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

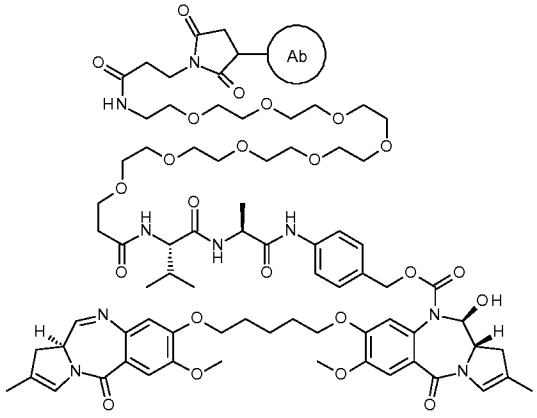
X is selected from the group comprising: O-$R^{L2'}$, S-$R^{L2'}$, CO_2-$R^{L2'}$, CO-$R^{L2'}$, NH-C(=O)-$R^{L2'}$, NHNH-$R^{L2'}$, CONHNH-$R^{L2'}$,  ,  , $NR^NR^{L2'}$, wherein R^N is selected from the group comprising H and C_{1-4} alkyl;

$R^{L2'}$ 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 method according to statement 1 wherein the CD19-ADC is administered to the subject in a tapered and/or elongated dosage regime.

3. The method according to either one of statements 1 or 2 wherein the CD19-ADC has the chemical structure:



, where the Ab is a CD19 antibody, and the DAR is between 1 and 8.

4. The method according to any one of statements 1 to 3 wherein Ab comprises a VH domain having the sequence of SEQ ID NO. 2 and a VL domain having the sequence of SEQ ID NO. 8.

5. The method according to any one of statements 1 to 4 wherein Ab comprises a heavy chain having sequences of SEQ ID NO. 13 and a light chain having the sequences of SEQ ID NO. 14.

6. The method according to any one of statements 1 to 5 wherein the CD19-ADC is ADCx19 or ADCT-402.

7. The method according to any preceding statement wherein the starting dose of CD19-ADC is reduced no more than twice during the dosage regime.

8. The method according to any preceding statement wherein the starting dose of CD19-ADC is reduced no more than once during the dosage regime.

9. The method according to any preceding statement wherein the dose is reduced following the first treatment cycle.

10. The method according to any preceding statement wherein the dose is reduced following the second treatment cycle.

11. The method according to any preceding statement wherein the dose is reduced following the third treatment cycle.

12. The method according to any preceding statement wherein the dose is reduced following the fourth treatment cycle.

13. The method according to any preceding statement wherein the dose is reduced only if the subject has attained at least Stable Disease [SD] at the end of the preceding treatment cycle.

13a. The method according to any preceding statement wherein the starting dose is 20 to 40 µg/kg, such as about 30 µg/kg.

14. The method according to any preceding statement wherein the starting dose is 40 to 50 µg/kg, such as about 45 µg/kg.

15. The method according to any preceding statement wherein the starting dose is at least 60 µg/kg.

16. The method according to any preceding statement wherein the starting dose is about 60 µg/kg.

17. The method according to any preceding statement wherein the starting dose is at least 90 µg/kg.

18. The method according to any preceding statement wherein the starting dose is about 90 µg/kg.

19. The method according to any preceding statement wherein the starting dose is at least 120 µg/kg.

20. The method according to any preceding statement wherein the starting dose is about 120 µg/kg.

21. The method according to any preceding statement wherein the starting dose is at least 150 µg/kg.

22. The method according to any preceding statement wherein the starting dose is about 140 to 160 µg/kg, such as 150 µg/kg.

23. The method according to any preceding statement wherein the starting dose is at least 200 µg/kg.

24. The method according to any preceding statement wherein the starting dose is about 200 µg/kg.

25. The method according to any preceding statement wherein the reduced dose is about 50% of the starting dose.

26. The method according to any preceding statement wherein the reduced dose is about 60 µg/kg.

27. The method according to any preceding statement wherein the reduced dose is about 70 to 80 µg/kg, optionally wherein the reduced dose is 75 µg/kg.

28. The method according to any preceding statement wherein the reduced dose is 15 to 35 µg/kg, such as about 20 µg/kg or about 30 µg/kg.

29. The method according to any preceding statement wherein each treatment cycle is the same length.

30. The method according to statement 29, wherein each treatment cycle is 3 weeks.

31. The method according to statement 29, wherein each treatment cycle is 6 weeks.

32. The method according to statement 31, wherein about 200 µg/kg of CD19-ADC are administered for two, 6-week treatment cycles,

followed by subsequent 6-week cycles of 60 µg/kg beginning 6 weeks after the cycle 2 administration.

33. The method according to statement 31, wherein about 200 µg/kg of CD19-ADC are administered for one, 6-week treatment cycle,

followed by subsequent 6-week cycles of 60 µg/kg beginning 6 weeks after the cycle 1 administration.

34. The method according to statement 30, wherein about 140 to 160 µg/kg of CD19-ADC are administered for two, 3-week treatment cycles,

followed by subsequent 3-week cycles of 70 to 80 µg/kg beginning 3 weeks after the cycle 2 administration;

optionally wherein about 150 µg/kg of CD19-ADC are administered for two, 3-week treatment cycles,

followed by subsequent 3-week cycles of 75 µg/kg beginning 3 weeks after the cycle 2 administration

35. The method according to any one of statements 1 to 27, wherein the treatment cycle length is increased no more than twice during the dosage regime.

36. The method according to any one of statements 1 to 27 or 31, wherein the treatment cycle length is increased no more than once during the dosage regime.

37. The method according to any one of statements 1 to 27 or 35 to 36, wherein the treatment cycle length is increased following the first treatment cycle.

38. The method according to any one of statements 1 to 27 or 35 to 37, wherein the treatment cycle length is increased following the second treatment cycle.

39. The method according to any one of statements 1 to 27 or 35 to 38, wherein the cycle length is increased only if the subject has attained at least Stable Disease [SD] at the end of the preceding treatment cycle.

40. The method according to any one of statements 1 to 27 or 35 to 39, wherein 'Day 1' of the first treatment cycle of increased length is delayed so that the time elapsed between 'Day 1' of the final shorter treatment cycle and 'Day 1' of the first treatment cycle of increased length is equal in length to the increased treatment cycle.

41. The method according to any one of statements 1 to 27 or 35 to 40, wherein the starting length is 3 weeks.

42. The method according to any one of statements 1 to 27 or 35 to 41, wherein the increased length is 6 weeks.

43. The method according to statement 42, wherein about 150 µg/kg of CD19-ADC are administered for two, 3-week treatment cycles,

followed by subsequent 6-week cycles of 60 µg/kg beginning 6 weeks after the cycle 2 administration.

44. The method according to statement 42, wherein about 120 µg/kg of CD19-ADC are administered for two, 3-week treatment cycles,

followed by subsequent 6-week cycles of 60 µg/kg beginning 6 weeks after the cycle 2 administration.

45. The method according to any preceding statement, wherein the CD19-ADC is administered as a single dose.

46. The method according to any preceding statement, wherein the dose of CD19-ADC is administered on Day 1 of the treatment cycle.

46a. The method according to any preceding statement, wherein the course of treatment consists of 2 treatment cycles.

46b. The method according to any preceding statement, wherein the course of treatment consists of 3 treatment cycles.

46c. The method according to any preceding statement, wherein the course of treatment consists of 4 treatment cycles.

46d. The method according to any preceding statement, wherein the course of treatment consists of 5 treatment cycles.

46e. The method according to any preceding statement, wherein the course of treatment consists of 6 treatment cycles.

47. The method according to any preceding statement wherein the proliferative disease is characterised by the presence of a neoplasm comprising CD19+ve cells

48. The method according to any preceding statement wherein the subject has been diagnosed as having the proliferative disease prior to the start of treatment with the CD19-ADC.

49. The method according to any preceding statement wherein the method comprises the step of selecting a subject for treatment based on expression of CD19.

50. The method according to statement 49, wherein a subject is selected if at least 5% of neoplasm cells express CD19.

51. The method according to any preceding statement wherein the proliferative disease is non-Hodgkin's Lymphoma, including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, (FL), Mantle Cell lymphoma (MCL), chronic lymphatic lymphoma (CLL), Waldenstroms Microglobulinemia, Burkitt's lymphoma, and Marginal Zone B-cell lymphoma (MZBL), and leukemias such as Hairy cell leukaemia (HCL), Hairy cell leukaemia variant (HCL-v), and Acute Lymphoblastic Leukaemia (ALL) such as Philadelphia chromosome-positive ALL (Ph+ALL) or Philadelphia chromosome-negative ALL (Ph-ALL).

52. The method according to any preceding statement wherein the proliferative disease is B-cell Lineage Non-Hodgkin Lymphoma (B-NHL).

53. The method according to any one of statements 1 to 51, wherein the proliferative disease is B-Lineage Acute Lymphoblastic Leukaemia (B-ALL), optionally wherein the disease is relapsed and/or refractory.

53a. The method according to any one of statements 1 to 51, wherein the proliferative disease is DLBCL, optionally wherein the disease is relapsed and/or refractory.

54. The method according to any preceding statement wherein the proliferative disease is resistant, relapsed or refractory.

55. The method according to any preceding statement wherein the subject is human.

56. The method according to any preceding statement wherein the CD19-ADC is administered intravenously.

57. The method according to any preceding claim further comprising administering a chemotherapeutic agent in combination with the CD19-ADC.

58. The method according to statement 57, wherein the chemotherapeutic agent is a checkpoint inhibitor.

59. The method according to statement 57, wherein the chemotherapeutic agent is ibrutinib.

60. The method according to statement 59, wherein the ibrutinib is administered concurrently with the CD19-ADC.

61. The method according to either one of statements 59 or 60, wherein the ibrutinib is administered in a QD dosage regime.

62. The method according to any one of statements 59 to 61, wherein the dose of ibrutinib administered is 560mg/day, 420mg/day, or 280 mg/day.

63. The method according to any one of statements 59 to 61, wherein the dose of ibrutinib administered is 560mg/day.

64. The method according to any one of statements 59 to 63, wherein the CD19-ADC is administered to the subject for two Q3W cycles.

65. The method according to statement 64, wherein the dose of CD19-ADC administered in each of the two, 3-week treatment cycles is the same.

66. The method according to any one of statements 59 to 65, wherein the dose of CD19-ADC is about 60 µg/kg, about 90 µg/kg, about 120 µg/kg, about 140 to 160 µg/kg, or about 150 µg/kg.

67. The method according to any one of statements 59 to 66, wherein the administration of Ibrutinib continues after the completion of CD19-ADC treatment.

68. The method according to any one of statements 64 to 67, wherein the CD19-ADC is administered to the subject for a further two, 3-week treatment cycles.

69. The method according to statements 68, wherein the further two CD19-ADC treatment cycles are administered If the subject has not achieved CR within 3 months after the completion of initial two, 3-week treatment cycles.

70. The method according to any one of statements 59 to 69, wherein the subject has, or is suspected as having, or has been identified as being at risk of, or has received a diagnosis of a non-Hodgkin's Lymphoma, such as diffuse large B-cell lymphoma (DLBCL) or Mantle Cell lymphoma (MCL).

71. The method according to statement 57, wherein the chemotherapeutic agent is Durvalumab.

72. The method according to statement 71, wherein the Durvalumab is administered concurrently with the CD19-ADC.

73. The method according to either one of statements 71 or 72, wherein the Durvalumab is administered in a Q3W dosage regime.

73a. The method according to statement 71, wherein the Durvalumab is administered in a Q4W dosage regime.

73b. The method according to either one of statements 71 or 73a, wherein day 1 of the first Durvalumab treatment cycle falls on day 8 of the first CD19-ADC treatment cycle.

74. The method according to any one of statements 71 to 73b, wherein the dose of Durvalumab is 1500 mg.

75. The method according to any one of statements 71 to 74, wherein the CD19-ADC is administered to the subject for two, 3-week treatment cycles.

76. The method according to statement 75, wherein the dose of CD19-ADC administered in each of the two, 3-week treatment cycles is the same.

77. The method according to any one of statements 71 to 76, wherein the dose of CD19-ADC is about 90 µg/kg, about 120 µg/kg, about 140 to 160 µg/kg, or about 150 µg/kg.

78. The method according to any one of statements 71 to 77, wherein the administration of Durvalumab continues after the completion of CD19-ADC treatment.

79. The method according to statement 78, wherein after the completion of CD19-ADC treatment the Durvalumab is administered in a Q4W dosage regime.

80. The method according to any one of statements 75 to 79, wherein the CD19-ADC is administered to the subject for a further two, 3-week treatment cycles.

81. The method according to statements 80, wherein the further two CD19-ADC treatment cycles are administered If the subject has not achieved CR within 3 months after the completion of initial two, 3-week treatment cycles.

82. The method according to any one of statements 59 to 69, wherein the subject has, or is suspected as having, or has been identified as being at risk of, or has received a diagnosis of a non-Hodgkin's Lymphoma, such as diffuse large B-cell lymphoma (DLBCL), Follicular Lymphoma (FL), or Mantle Cell lymphoma (MCL).

83. The method according to statement 57, wherein the chemotherapeutic agent is Rituximab.

84. The method according to statement 83, wherein the Rituximab is administered concurrently with the CD19-ADC.

85. The method according to either one of statements 83 or 84, wherein the Rituximab is administered in a Q3W dosage regime.

86. The method according to any one of statements 83 to 85, wherein the dose of Rituximab administered is 325 to 425 mg/m^2;
Optionally wherein the dose of Rituximab administered is 375 mg/m^2.

87. The method according to any one of statements 83 to 86, wherein the dose of CD19-ADC is about 90 µg/kg, about 120 µg/kg, about 140 to 160 µg/kg, or about 150 µg/kg.

88. The method according to any one of statements 83 to 87, wherein the subject has, or is suspected as having, or has been identified as being at risk of, or has received a diagnosis of a non-Hodgkin's Lymphoma, such as diffuse large B-cell lymphoma (DLBCL).

89. The method according to statement 57, wherein the chemotherapeutic agent is Cytarabine.

90. The method according to statement 89, wherein the Cytarabine is administered concurrently with the CD19-ADC.

91. The method according to either one of statements 89 or 90, wherein the CD19-ADC is administered on day 2 of each Q3W treatment cycle.

92. The method according to any one of statements 89 to 91, wherein the cytarabine is administered in a Q3W dosage regime.

93. The method according to statement 92, wherein the cytarabine is administered as 5 partial doses spread one partial dose per day on days 1 to 5 of each cycle.

94. The method according to statement 93, wherein each partial dose of cytarabine is 100 mg/m^2, 200 mg/m^2, 300 mg/m^2, or 400 mg/m^2.

95. The method according to any one of statements 89 to 94, wherein the subject has, or is suspected as having, or has been identified as being at risk of, or has received a diagnosis of a non-Hodgkin's Lymphoma, such as diffuse large B-cell lymphoma (DLBCL).

96. The method according to any one of statements 89 to 95, wherein the cytarabine is administered in further combination with rituximab as described in any one of statements 84 to 88.

97. The method according to statement 57 or statement 58, wherein the chemotherapeutic agent is administered to the subject before, at the same time, or after the CD19-ADC.

98. The method according to any preceding statement, wherein the CD19-ADC is administered in combination with a steroid.

99 The method according to statement 98, wherein a first dose of steroid is administered on the same day as the ADC.

100. The method according to statement 99, wherein the first dose of steroid is administered at least 2 hours before the ADC.

101. The method according to either one of statements 98 or 99, wherein a second dose of steroid is administered the day after the ADC.

102. The method according to statement 98, wherein a first dose of steroid is administered the day before the ADC.

103. The method according to statement 102, wherein a second dose of steroid is administered on the same day as the ADC.

104. The method according to statement 103, wherein the second dose of steroid is administered at least 2 hours before the ADC.

105. The method according to either one of statements 103 or 104 wherein a third dose of steroid is administered the day after the ADC.

106. The method according to any one of statements 98 to 105, wherein the steroid or steroid doses are administered only in conjunction with the first administration of ADC in each treatment cycle.

107. The method according to any one of statements 98 to 106, wherein the steroid is administered orally.

108. The method according to any one of statements 98 to 107, wherein each dose of steroid is 8 mg.

109. The method according to any one of statements 98 to 108, wherein each dose of steroid is 16 mg.

110. The method according to any one of statements 98 to 109, wherein each dose of steroid is administered as two equal, partial doses.

111. The method according to any one of statements 98 to 110, wherein each partial dose is 4 mg.

112. The method according to any one of statements 96 to 111, wherein each partial dose is 8 mg.

113. The method according to any one of statements 96 to 112, wherein the steroid is dexamethasone.

114. The method according to statement 98, wherein 4mg or 8mg dexamethasone is administered orally twice daily: (i) the day before ADC administration on week 1, day 1 of the treatment cycle, (ii) the day of ADC administration on week 1, day 1 of the treatment cycle, and (iii) the day after ADC administration on week 1, day 1 of the treatment cycle.

115. The method according to statement 98, wherein 4mg or 8mg dexamethasone is administered orally twice daily: (i) the day of ADC administration on week 1, day 1 of the treatment cycle, and (ii) the day after ADC administration on week 1, day 1 of the treatment cycle.

116. The method according to either one of statements 114 and 115, wherein the dexamethasone administered on the same day as the ADC is administered at least two hours before the ADC.

117. The method according to any one of statements 114 to 115, wherein the dexamethasone is administered only in conjunction with the first administration of ADC in each treatment cycle.

118. The method according to any preceding statement wherein the tapered and/or elongated dosage regime has lower toxicity than a single-dose dosage regime a dosage regime having constant dosage level and cycle length, optionally wherein the constant dose level and cycle length of the comparator regime is the same as the starting dose and starting length of the tapered and/or elongated regime.

119. The method according to statement 98, wherein the incidence of TEAE with the tapered and/or elongated dosage regime is no more than 50% of the incidence of TEAE in the constant dose level and cycle length regime.

120. The method according to statement 119, wherein the incidence of SAE with the tapered and/or elongated dosage regime is no more than 50% of the incidence of SAE in the constant dose level and cycle length regime.

121 The method according to statement 98, wherein the incidence of DLT with the tapered and/or elongated dosage regime is no more than 50% of the incidence of DLT in the constant dose level and cycle length regime.

122. The method according to any preceding statement wherein the tapered and/or elongated dosage regime has greater efficacy than a dosage regime having constant dosage level and cycle length, optionally wherein the constant dose level and cycle length of the comparator regime is the same as the starting dose and starting length of the tapered and/or elongated regime.

123. The method according to statement 122, wherein the proportion of subjects achieving at least PR with the tapered and/or elongated dosage regime is at least 150% of the proportion of subjects achieving at least a partial response [PR] in the constant dose level and cycle length regime.

124. The method according to any preceding statement, wherein the subject undergoes a neurological examination prior to treatment with the ADC.

125. The method according to any preceding statement, wherein the subject undergoes a neurological examination after administration of the ADC.

126. The method according to any preceding statement, wherein the subject undergoes a neurological examination after each administration of the ADC.

127. The method according to any preceding statement, wherein the subject undergoes a neurological examination if they experience a neurologic toxicity following administration of the ADC.

128. The method according to any one of statements 124 to 127, wherein the neurological examination includes tests of strength, sensation, and/or deep-tendon reflexes.

129. The method according to any preceding statement, wherein treatment with the ADC is reduced, suspended, or permanently discontinued if the subject has a neurological disorder or experiences a neurologic toxicity.

130. The method according to any preceding statement, wherein treatment with the ADC is reduced or suspended if the subject experiences a grade 1 neurologic toxicity.

131. The method according to any preceding statement, wherein treatment with the ADC is permanently discontinued if the subject experiences a grade 2 neurologic toxicity.

132. The method according to any one of statements 129 to 131, wherein treatment with the ADC is reduced by reducing the dose of ADC that is administered to the subject in each subsequent treatment cycle, and/or by increasing the length of each subsequent treatment cycle.

133. A method of selecting a subject for treatment by a method according to any one of statements 1 to 129, which method comprises determining if the subject has, or recently had, a neurologic disorder, wherein the subject is determined to be not suitable for treatment with the ADC if they have, or have recently had, a neurologic disorder.

134. A method of selecting a subject for treatment by a method according to any one of statements 1 to 132, which method comprises determining if the subject has, or recently had, an infection caused by a pathogen that may be associated with neurologic and/or immune-related disease; wherein the subject is determined to be not suitable for treatment with the ADC if they have, or have recently had, such an infection and/or immune-related disease.

135. The method according to any one of statements 127 to 134, wherein the neurologic disorder or neurological toxicity is polyradiculopathy, acute inflammatory demyelinating (AIDP), Guillain-Barré syndrome (GBS), myasthenia gravis, or a neurologic disorder that is linked to or is an early indicator of polyradiculitis, GBS, or myasthenia gravis, such as ascending sensory loss and/or motor weakness.

136. The method according to any one of statements 125 to 132, wherein the neurologic disorder or neurological toxicity is Guillain-Barré syndrome (GBS).

137. A method of reducing the toxicity and/or side effects associated with administration of a CD19-ADC to a subject, the method comprising administering the CD19-ADC according to the method of any preceding statement.

138. A method of increasing the treatment efficacy associated with administration of a CD19-ADC to a subject, the method comprising administering the CD19-ADC according to the method of any preceding statement.

139. A method of selecting a subject for treatment by a method according to any one of statements 1 to 138, which method comprises selecting for treatment subjects that express CD19 in a tissue of interest.

140. The method according to statement 139 wherein subjects are selected if at least 5% of cells in a sample of the tissue of interest express CD19.

141. The method according to either one of statements 139 and 140 wherein the tissue of interest is lymphoid tissue or tumour tissue.

142. The method according to any one of statements 139 to 141, wherein the subject has experienced a DLT in a constant dose and or constant cycle length dosage regime of a CD19-ADC.

143. A packaged pharmaceutical product comprising a CD19-ADC as defined in any one of statements 1 to 5, in combination with a label or insert advising that the CD19-ADC should be administered according to the method of any one of statements 1 to 92.

144. A kit comprising:
a first medicament comprising a CD19-ADC as defined in any one of statements 1 to 6; and, optionally,
a package insert or label comprising instructions for administration of the CD19-ADC according to the method of any one of statements 1 to 136.

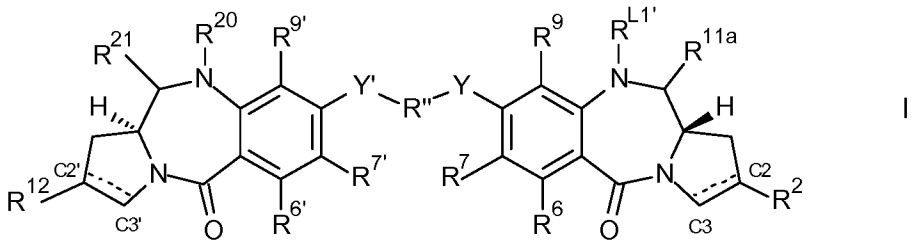
145. A CD19-ADC as defined in any one of statements 1 to 6 for use in a method of any one of statements 1 to 136.

146. A pharmaceutical composition comprising a CD19-ADC as defined in any one of statements 1 to 6, optionally in combination with a pharmaceutically acceptable excipient, for use in a method of any one of statements 1 to 136.

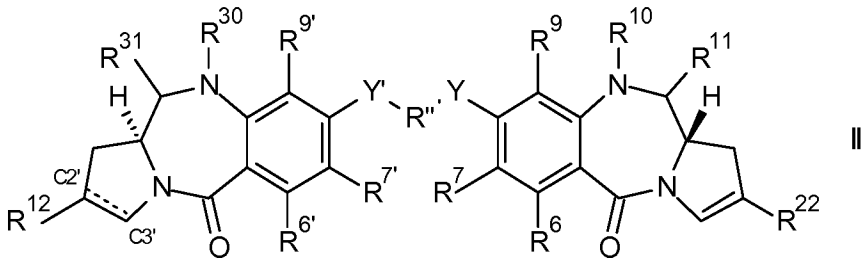
147. Use of a CD19-ADC as defined in any one of statements 1 to 6 in the preparation of a medicament for use in a method of any one of statements 1 to 136.

Leukaemia

1. A method of treating a proliferative disease in a subject, said method comprising administering to a subject a CD19-ADC, wherein the CD19-ADC is administered to the subject in a fractionated dosage regime, and;
wherein the CD19-ADC comprises a conjugate of formula L - $(D^L)_p$, where D^L is of formula **I** or **II**:



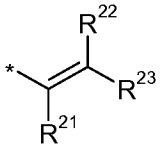
I



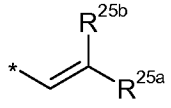
II

wherein:
L is an antibody (Ab) which is an antibody that binds to CD19;

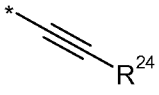
when there is a double bond present between C2' and C3', R^{12} is selected from the group consisting of:
(ia) C_{5-10} aryl group, optionally substituted by one or more substituents selected from the group comprising: halo, nitro, cyano, ether, carboxy, ester, C_{1-7} alkyl, C_{3-7} heterocyclyl and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



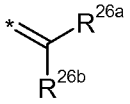
(id) , wherein each of R^{21}, R^{22} and R^{23} are independently selected from H, C_{1-3} saturated alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl and cyclopropyl, where the total number of carbon atoms in the R^{12} group is no more than 5;



(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;

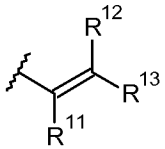
R^{21} is selected from OH, OR^A and SO_zM;

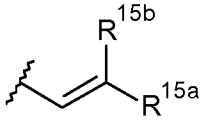
when there is a double bond present between C2 and C3, R^2 is selected from the group consisting of:

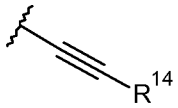
(ia) C_{5-10} aryl group, optionally substituted by one or more substituents selected from the group comprising: halo, nitro, cyano, ether, carboxy, ester, C_{1-7} alkyl, C_{3-7} heterocyclyl and bis-oxy-C_{1-3} alkylene;

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

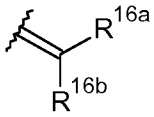
(ic) C_{3-6} saturated cycloalkyl;

(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

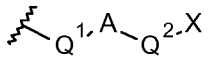
(if)  , where R^{14} is selected from: H; C_{1-3} saturated alkyl; C_{2-3} alkenyl; C_{2-3} alkynyl; cyclopropyl; phenyl, which phenyl is optionally substituted by a group selected from halo, methyl, methoxy; pyridyl; and thiophenyl;

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]

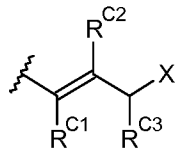
R^{22} is of formula IIIa, formula IIIb or formula IIIc:

(a)  IIIa

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

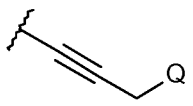
(i) Q^1 is a single bond, and Q^2 is selected from a single bond and -Z-$(CH_2)_n$-, where Z is selected from a single bond, O, S and NH and n is from 1 to 3; or

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

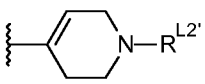
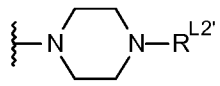
(b)  IIIb

where;

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

(c)  IIIc

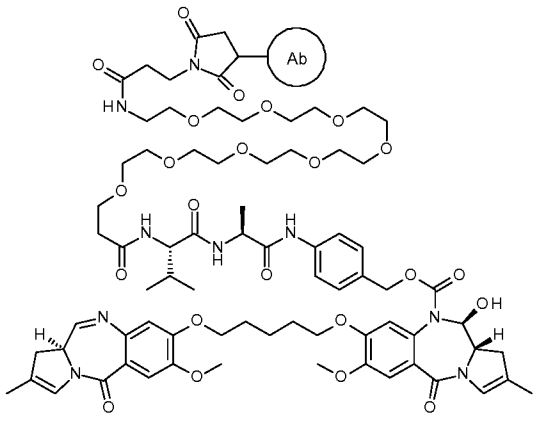
where Q is selected from O-$R^{L2'}$, S-$R^{L2'}$ and NR^N-$R^{L2'}$, and R^N is selected from H, methyl and ethyl

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 method according to statement 1 wherein the CD19-ADC has the chemical structure:



, where the Ab is a CD19 antibody, and the DAR is between 1 and 8.

3. The method according to either one of statements 1 and 2 wherein Ab comprises a VH domain having the sequence of SEQ ID NO. 2 and a VL domain having the sequence of SEQ ID NO. 8.

4. The method according to any one of statements 1 to 3 wherein Ab comprises a heavy chain having sequences of SEQ ID NO. 13 and a light chain having the sequences of SEQ ID NO. 14.

5. The method according to any one of statements 1 to 4 wherein the CD19-ADC is ADCx19 or ADCT-402.

6. The method according to any preceding statement wherein the total dose of CD19-ADC administered during the treatment cycle is administered as a series of two or more partial doses during a treatment cycle.

7. The method according to any preceding statement wherein the partial doses of CD19 ADC are administered at regularly spaced intervals throughout the treatment cycle.

8. The method according to any preceding statement wherein a partial dose of CD19-ADC is administered to the subject once per week.

9. The method according to any preceding statement wherein the length of the treatment cycle is 3 weeks.

10. The method according to any preceding statement wherein the length of the treatment cycle is 6 weeks.

11. The method according to any preceding statement wherein a partial dose of the CD19-ADC is administered once a week in a 3-week treatment cycle.

12. The method according to any preceding statement wherein a partial dose of the CD19-ADC is administered on days 1, 8, and 15 of a 3-week treatment cycle.

13. The method according to any preceding statement wherein a total dose of about 10 µg/kg CD19-ADC is administered during the treatment cycle.

14. The method according to any preceding statement wherein a total dose of about 20 µg/kg CD19-ADC is administered during the treatment cycle.

15. The method according to any preceding statement wherein a total dose of about 30 µg/kg CD19-ADC is administered during the treatment cycle.

16. The method according to any preceding statement wherein a total dose of about 40 µg/kg CD19-ADC is administered during the treatment cycle.

17. The method according to any preceding statement wherein a total dose of about 50 µg/kg CD19-ADC is administered during the treatment cycle.

18. The method according to any preceding statement wherein a total dose of about 60 µg/kg CD19-ADC is administered during the treatment cycle.

19. The method according to any preceding statement wherein a total dose of about 70 µg/kg CD19-ADC is administered during the treatment cycle.

20. The method according to any preceding statement wherein a total dose of about 80 µg/kg CD19-ADC is administered during the treatment cycle.

21. The method according to any preceding statement wherein a total dose of about 90 µg/kg CD19-ADC is administered during the treatment cycle.

22. The method according to any preceding statement wherein a total dose of about 100 µg/kg CD19-ADC is administered during the treatment cycle.

23. The method according to any preceding statement wherein a total dose of about 120 µg/kg CD19-ADC is administered during the treatment cycle.

24. The method according to any preceding statement wherein a total dose of about 140 to 160 µg/kg, such as about 150 µg/kg CD19-ADC is administered during the treatment cycle.

25. The method according to any preceding statement wherein a total dose of about 200 µg/kg CD19-ADC is administered during the treatment cycle.

26. The method according to any preceding statement wherein a total dose of about 250 µg/kg CD19-ADC is administered during the treatment cycle.

27. The method according to any preceding statement wherein a total dose of about 300 µg/kg CD19-ADC is administered during the treatment cycle.

28. The method according to any preceding statement wherein a total dose of about 350 µg/kg CD19-ADC is administered during the treatment cycle.

29. The method according to any preceding statement wherein a total dose of about 400 µg/kg CD19-ADC is administered during the treatment cycle.

30. The method according to any preceding statement wherein a total dose of about 450 µg/kg CD19-ADC is administered during the treatment cycle.

31. The method according to any preceding statement wherein a total dose of about 500 µg/kg CD19-ADC is administered during the treatment cycle.

32. The method according to any preceding statement wherein a total dose of about 550 µg/kg CD19-ADC is administered during the treatment cycle.

33. The method according to any preceding statement wherein a total dose of about 600 µg/kg CD19-ADC is administered during the treatment cycle.

34. The method according to any preceding statement wherein a total dose of 1 to 10 µg/kg CD19-ADC is administered during the treatment cycle.

35. The method according to any preceding statement wherein a total dose of 11 to 20 µg/kg CD19-ADC is administered during the treatment cycle.

36. The method according to any preceding statement wherein a total dose of 21 to 30 µg/kg CD19-ADC is administered during the treatment cycle.

37. The method according to any preceding statement wherein a total dose of 31 to 40 µg/kg CD19-ADC is administered during the treatment cycle.

38. The method according to any preceding statement wherein a total dose of 41 to 50 µg/kg CD19-ADC is administered during the treatment cycle.

39. The method according to any preceding statement wherein a total dose of 51 to 60 µg/kg CD19-ADC is administered during the treatment cycle.

40. The method according to any preceding statement wherein a total dose of 61 to 70 µg/kg CD19-ADC is administered during the treatment cycle.

41. The method according to any preceding statement wherein a total dose of 71 to 80 µg/kg CD19-ADC is administered during the treatment cycle.

42. The method according to any preceding statement wherein a total dose of 81 to 90 µg/kg CD19-ADC is administered during the treatment cycle.

43. The method according to any preceding statement wherein a total dose of 91 to 100 µg/kg CD19-ADC is administered during the treatment cycle.

44. The method according to any preceding statement wherein a total dose of 101 to 120 µg/kg CD19-ADC is administered during the treatment cycle.

45. The method according to any preceding statement wherein a total dose of 121 to 140 µg/kg CD19-ADC is administered during the treatment cycle.

46. The method according to any preceding statement wherein a total dose of 141 to 160 µg/kg CD19-ADC is administered during the treatment cycle.

47. The method according to any preceding statement wherein a total dose of 161 to 180 µg/kg CD19-ADC is administered during the treatment cycle.

48. The method according to any preceding statement wherein a total dose of 181 to 200 µg/kg CD19-ADC is administered during the treatment cycle.

49. The method according to any preceding statement wherein a total dose of 201 to 220 µg/kg CD19-ADC is administered during the treatment cycle.

50. The method according to any preceding statement wherein a total dose of 221 to 240 µg/kg CD19-ADC is administered during the treatment cycle.

51. The method according to any preceding statement wherein a total dose of 241 to 260 µg/kg CD19-ADC is administered during the treatment cycle.

52. The method according to any preceding statement wherein a total dose of 261 to 280 µg/kg CD19-ADC is administered during the treatment cycle.

53. The method according to any preceding statement wherein a total dose of 281 to 300 µg/kg CD19-ADC is administered during the treatment cycle.

54. The method according to any preceding statement wherein a total dose of 301 to 320 µg/kg CD19-ADC is administered during the treatment cycle.

55. The method according to any preceding statement wherein a total dose of 321 to 340 µg/kg CD19-ADC is administered during the treatment cycle.

56. The method according to any preceding statement wherein a total dose of 341 to 360 µg/kg CD19-ADC is administered during the treatment cycle.

57. The method according to any preceding statement wherein a total dose of 361 to 380 µg/kg CD19-ADC is administered during the treatment cycle.

58. The method according to any preceding statement wherein a total dose of 381 to 400 µg/kg CD19-ADC is administered during the treatment cycle.

59. The method according to any preceding statement wherein a total dose of 401 to 420 µg/kg CD19-ADC is administered during the treatment cycle.

60. The method according to any preceding statement wherein a total dose of 421 to 440 µg/kg CD19-ADC is administered during the treatment cycle.

61. The method according to any preceding statement wherein a total dose of 441 to 460 µg/kg CD19-ADC is administered during the treatment cycle.

62. The method according to any preceding statement wherein a total dose of 461 to 480 µg/kg CD19-ADC is administered during the treatment cycle.

63. The method according to any preceding statement wherein a total dose of 481 to 500 µg/kg CD19-ADC is administered during the treatment cycle.

64. The method according to any preceding statement wherein a total dose of 501 to 520 µg/kg CD19-ADC is administered during the treatment cycle.

65. The method according to any preceding statement wherein a total dose of 521 to 540 µg/kg CD19-ADC is administered during the treatment cycle.

66. The method according to any preceding statement wherein a total dose of 541 to 560 µg/kg CD19-ADC is administered during the treatment cycle.

67. The method according to any preceding statement wherein a total dose of 561 to 580 µg/kg CD19-ADC is administered during the treatment cycle.

68. The method according to any preceding statement wherein a total dose of 581 to 600 µg/kg CD19-ADC is administered during the treatment cycle.

69. The method according to any preceding statement wherein the partial dose is about 10 µg/kg.

70. The method according to any preceding statement wherein the partial dose is about 20 µg/kg.

71. The method according to any preceding statement wherein the partial dose is about 30 µg/kg.

72. The method according to any preceding statement wherein the partial dose is about 40 µg/kg.

73 The method according to any preceding statement wherein the partial dose is about 50 µg/kg.

74. The method according to any preceding statement wherein the partial dose is about 60 µg/kg.

75. The method according to any preceding statement wherein the partial dose is about 70 µg/kg.

76. The method according to any preceding statement wherein the partial dose is about 80 µg/kg.

77. The method according to any preceding statement wherein the partial dose is about 90 µg/kg.

78. The method according to any preceding statement wherein the partial dose is about 100 µg/kg.

79. The method according to any preceding statement wherein the partial dose is about 110 µg/kg.

80. The method according to any preceding statement wherein the partial dose is about 120 µg/kg.

81. The method according to any preceding statement wherein the partial dose is about 130 µg/kg.

82. The method according to any preceding statement wherein the partial dose is about 140 µg/kg.

83 The method according to any preceding statement wherein the partial dose is about 150 µg/kg.

84. The method according to any preceding statement wherein the partial dose is about 160 µg/kg.

85. The method according to any preceding statement wherein the partial dose is about 170 µg/kg.

86. The method according to any preceding statement wherein the partial dose is about 180 µg/kg.

87. The method according to any preceding statement wherein the partial dose is about 190 µg/kg.

88. The method according to any preceding statement wherein the partial dose is about 200 µg/kg.

89. The method according to any preceding statement wherein the partial dose is 1 to 10 µg/kg.

90. The method according to any preceding statement wherein the partial dose is 11 to 20 µg/kg.

91. The method according to any preceding statement wherein the partial dose is 21 to 30 µg/kg.

92. The method according to any preceding statement wherein the partial dose is 31 to 40 µg/kg.

93. The method according to any preceding statement wherein the partial dose is 41 to 50 µg/kg.

94. The method according to any preceding statement wherein the partial dose is 51 to 60 µg/kg.

95. The method according to any preceding statement wherein the partial dose is 61 to 70 µg/kg.

95a. The method according to any preceding statement wherein the partial dose is about 40 to 60 μg/kg, such as about 45 to 55 μg/kg.

96 The method according to any preceding statement wherein the partial dose is 71 to 80 μg/kg.

97. The method according to any preceding statement wherein the partial dose is 81 to 90 μg/kg.

98. The method according to any preceding statement wherein the partial dose is 91 to 100 μg/kg.

99. The method according to any preceding statement wherein the partial dose is 101 to 110 μg/kg.

100. The method according to any preceding statement wherein the partial dose is 111 to 120 μg/kg.

101. The method according to any preceding statement wherein the partial dose is 121 to 130 μg/kg.

102. The method according to any preceding statement wherein the partial dose is 131 to 140 μg/kg.

103. The method according to any preceding statement wherein the partial dose is 141 to 150 μg/kg.

104. The method according to any preceding statement wherein the partial dose is 151 to 160 μg/kg.

105. The method according to any preceding statement wherein the partial dose is 161 to 170 μg/kg.

106 The method according to any preceding statement wherein the partial dose is 171 to 180 μg/kg.

107. The method according to any preceding statement wherein the partial dose is 181 to 190 μg/kg.

108. The method according to any preceding statement wherein the partial dose is 191 to 200 μg/kg.

109. The method according to any preceding statement wherein the amount of CD19-ADC in each partial dose is the same.

110. The method according to any preceding statement wherein the proliferative disease is characterised by the presence of a neoplasm comprising CD19+ve cells

111. The method according to any preceding statement wherein the subject has been diagnosed as having the proliferative disease prior to the start of treatment with the CD19-ADC.

112. The method according to statement 111, wherein the disease is CD19+ALL.

113. The method according to any preceding statement wherein the method comprises the step of selecting a subject for treatment based on expression of CD19.

114. The method according to statement 113, wherein a subject is selected if at least 5% of neoplasm cells express CD19.

115. The method according to any preceding statement wherein the proliferative disease is non-Hodgkin's Lymphoma, including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, (FL), Mantle Cell lymphoma (MCL), chronic lymphatic lymphoma (CLL), Waldenstroms Microglobulinemia, Burkitt's lymphoma, and Marginal Zone B-cell lymphoma (MZBL), and leukemias such as Hairy cell leukaemia (HCL), Hairy cell leukaemia variant (HCL-v), and Acute Lymphoblastic Leukaemia (ALL) such as Philadelphia chromosome-positive ALL (Ph+ALL) or Philadelphia chromosome-negative ALL (Ph-ALL).

115a. The method according to any one of statements 1 to 115, wherein the proliferative disease is B-Lineage Acute Lymphoblastic Leukaemia (B-ALL), optionally wherein the disease is relapsed and/or refractory.

116. The method according to any preceding statement wherein the proliferative disease is CD19+ ALL.

117. The method according to any preceding statement wherein the proliferative disease is resistant, relapsed or refractory.

118. The method according to any preceding statement wherein the subject is human.

119. The method according to any preceding statement wherein the CD19-ADC is administered intravenously.

120. The method according to any preceding claim further comprising administering a chemotherapeutic agent in combination with the CD19-ADC.

121. The method according to statement 120, wherein the chemotherapeutic agent is administered to the subject before, at the same time, or after the CD19-ADC.

122. The method according to any preceding statement, wherein the CD19-ADC is administered in combination with a steroid.

123. The method according to statement 122, wherein a first dose of steroid is administered on the same day as the ADC.

124. The method according to statement 123, wherein the first dose of steroid is administered at least 2 hours before the ADC.

125. The method according to either one of statements 123 or 124, wherein a second dose of steroid is administered the day after the ADC.

126. The method according to statement 122, wherein a first dose of steroid is administered the day before the ADC.

127. The method according to statement 126, wherein a second dose of steroid is administered on the same day as the ADC.

128. The method according to statement 127, wherein the second dose of steroid is administered at least 2 hours before the ADC.

129. The method according to either one of statements 127 or 128, wherein a third dose of steroid is administered the day after the ADC.

130. The method according to any one of statements 122 to 129, wherein the steroid or steroid doses are administered only in conjunction with the first administration of ADC in each treatment cycle.

131. The method according to any one of statements 122 to 130, wherein the steroid is administered orally.

132. The method according to any one of statements 122 to 131, wherein each dose of steroid is 8 mg.

133. The method according to any one of statements 122 to 132, wherein each dose of steroid is 16 mg.

134. The method according to any one of statements 122 to 133, wherein each dose of steroid is administered as two equal, partial doses.

135. The method according to any one of statements 122 to 134, wherein each partial dose is 4 mg.

136. The method according to any one of statements 122 to 135 wherein each partial dose is 8 mg.

137. The method according to any one of statements 122 to 136, wherein the steroid is dexamethasone.

138 The method according to statement 122, wherein 4mg dexamethasone is administered orally twice daily: (i) the day before ADC administration on week 1, day 1 of the treatment cycle, (ii) the day of ADC administration on week 1, day 1 of the treatment cycle, and (iii) the day after ADC administration on week 1, day 1 of the treatment cycle.

139. The method according to statement 122, wherein 4mg dexamethasone is administered orally twice daily: (i) the day of ADC administration on week 1, day 1 of the treatment cycle, and (ii) the day after ADC administration on week 1, day 1 of the treatment cycle.

140. The method according to either one of statements 138 and 139, wherein the dexamethasone administered on the same day as the ADC is administered at least two hours before the ADC.

141 The method according to any one of statements 138 to 140, wherein the dexamethasone is administered only in conjunction with the first administration of ADC in each treatment cycle.

142. The method according to any preceding statement wherein the fractionated dosage regime has lower toxicity than a single-dose dosage regime having the same total dose administered and length of treatment cycle.

143. The method according to statement 142, wherein the incidence of TEAE with the fractionated dosage regime is no more than 50% of the incidence of TEAE in the single-dose regime.

144. The method according to statement 142, wherein the incidence of SAE with the fractionated dosage regime is no more than 50% of the incidence of SAE in the single-dose regime.

145 The method according to statement 142, wherein the incidence of DLT with the fractionated dosage regime is no more than 50% of the incidence of DLT in the single-dose regime.

146. The method according to any preceding statement wherein the fractionated dosage regime has greater efficacy than a single-dose dosage regime having the same total dose administered and length of treatment cycle.

147. The method according to statement 146, wherein the proportion of subjects achieving at least PR with the fractionated dosage regime is at least 150% of the proportion of subjects achieving at least a partial response [PR] in the single dose regime.

148. A method of reducing the toxicity and/or side effects associated with administration of a CD19-ADC to a subject, the method comprising administering the CD19-ADC according to the method of any preceding statement.

149. A method of increasing the treatment efficacy associated with administration of a CD19-ADC to a subject, the method comprising administering the CD19-ADC according to the method of any preceding statement.

150. A method of selecting a subject for treatment by a method according to any one of statements 1 to 141, which method comprises selecting for treatment subjects that express CD19 in a tissue of interest.

151. The method according to statement 150 wherein subjects are selected if at least 5% of cells in a sample of the tissue of interest express CD19.

152. The method according to either one of statements 150 and 151 wherein the tissue of interest is lymphoid tissue or tumour tissue.

153. The method according to any one of statements 150 to 152, wherein the subject has experienced a DLT in a single-dose dosage regime of a CD19-ADC.

154. A packaged pharmaceutical product comprising a CD19-ADC as defined in any one of statements 1 to 5, in combination with a label or insert advising that the CD19-ADC should be administered according to the method of any one of statements 1 to 151.

155. A kit comprising:

a first medicament comprising a CD19-ADC as defined in any one of statements 1 to 5; and, optionally,

a package insert or label comprising instructions for administration of the CD19-ADC according to the method of any one of statements 1 to 151.

156. A CD19-ADC as defined in any one of statements 1 to 5 for use in a method of any one of statements 1 to 151.

157. A pharmaceutical composition comprising a CD19-ADC as defined in any one of statements 1 to 5, optionally in combination with a pharmaceutically acceptable excipient, for use in a method of any one of statements 1 to 151.

158. Use of a CD19-ADC as defined in any one of statements 1 to 5 in the preparation of a medicament for use in a method of any one of statements 1 to 151.

EXAMPLES

Example 1: pharmokinetics of ADCx19 in ALL patients

At least one dose of ADCx19 was administered to 48 patients with Relapsed or Refractory B-cell Lineage Non Hodgkin Lymphoma (B-NHL) (4 at 15 µg/kg, 4 at 30 µg/kg, 4 at 60 µg/kg, 5 at 90µg/kg, 12 at 120 µg/kg, 3 at 150 µg/kg and 17 at 200 µg/kg). Cohorts at 120 µg/kg and 200 µg/kg were expanded to further explore the early efficacy signals seen at those dose levels.

Emerging safety, pharmacokinetic and efficacy data suggest that repetitive dosing every three weeks is not well tolerated or necessary at doses of 120 µg/kg and higher. Twelve patients have been treated at 120 µg/kg (10 DLBCL, 1 FL and 1 MCL) with 4 patients attaining complete remission (CR) and 2 partial remission (PR). The 6 responding patients have received 3-7 infusions of ADCx19 with 4 of these patients having at least one dose delay due to adverse events (fatigue (2), oedema (3), muscle pain (2), rash (1), Elevated GGT and alkaline phosphatase (1)). Two patients were discontinued from treatment due to adverse events in this cohort (both had attained CR).

At 150 µg/kg, the three initial patients received either 2 or 3 cycles of ADCTx19 before side effects necessitated dose delay which eventually led to removal from the study since the toxicities were slow to resolve.

The first six evaluable patients treated on the 200 µg/kg cohort with dose administered every three weeks attained CR(5) or PR(1) on first restaging scans at the end of Cycle 2 (after second dose). However, all patients had some evidence of toxicity at the end of Cycle 2 (4 patients) or cycle 3 (1 patient). The pharmacokinetic profiles for the first two cycles for the initial 3 patients treated on the 200 µg/kg cohort indicated that the AUC and Cmax at the 200 µg/kg dose level are significantly higher than seen at lower doses. The trough levels at the end of Cycle 1 appear to be in the range of 500-1000 ng/ml.

In view of the emerging safety profile, it is proposed to modify the dosage regimes for future subjects at doses of 120 µg/kg or higher so that they are tapered and/or elongated dosage regimes as described herein. In particular, the following tapered and elongated dosage regimes will be utilised:

A. **120 µg/kg:** Dosing every 3 weeks for 2 cycles. Patients with at least SD after the second cycle continue treatment at a reduced dose of 60 µg/kg q6weeks, beginning 6 weeks after Cycle 2 infusion.

B. **150 µg/kg:** Dosing every 3 weeks for 2 cycles. Patients with at least SD after the second cycle continue treatment at a reduced dose of 60 µg/kg q6weeks, beginning 6 weeks after Cycle 2 infusion.

C. **200 µg/kg:** Dosing every 6 weeks for 2 cycles. For patients with at least SD 6 weeks after Cycle 2, continue treatment at a reduced dose of 60 µg/kg q6weeks, beginning 6 weeks after Cycle 2 infusion.

D. **200 µg/kg:** Dosing every 6 weeks. For patients with at least SD 6 weeks after Cycle 1, continue treatment at a reduced dose of 60 µg/kg every 6 weeks beginning 6 weeks after Cycle 1 infusion.

E. **150 µg/kg:** Dosing every 3 weeks for 2 cycles. Patients with at least SD after the second cycle continue treatment at a reduced dose of 75 µg/kg q3weeks, beginning 3 weeks after Cycle 2 infusion.

The full clinical study protocol for the 3-week treatment cycle with a single-dose administered on day 1 is publically available at www.clinical trials.gov, having the ClinicalTrials.gov unique identifier: NCT02669017 (25 April 2017 update).

Example 2: Synopsis of tapered and/or elongated dosage protocol

Indication

Patients with relapsed or refractory B-cell lineage non-Hodgkin Lymphoma (B-NHL) who have failed, or are intolerant to, any established therapy; or for whom no other treatment options are available, in the opinion of the Investigator.

The Dose Escalation Steering Committee (DESC) will determine which histologic sub-types will be investigated in Part 2 of the study based on the emerging efficacy and tolerability profile from part 1.

B-cell NHL defined as:

- Diffuse large B-cell lymphoma (DLBCL)
- Follicular lymphoma (FL)
- Chronic lymphocytic leukaemia (CLL)
- Mantle cell lymphoma (MCL)
- Marginal Zone B-cell Lymphoma (MZBCL)
- Burkitt's lymphoma (BL)
- Lymphoplasmacytic lymphoma (Waldenstrom macroglobulinemia [WM]).

Objectives

Primary objectives:

- Evaluate the safety and tolerability, and determine, as appropriate, the maximum tolerated dose (MTD) of ADCx19 in patients with relapsed or refractory B-cell lineage NHL (Part 1).
- Determine the recommended dose(s) of ADCx19 for Part 2 (expansion).
- Evaluate the safety and tolerability of ADCx19 in Part 2 (expansion) at the dose level(s) recommended in Part 1.

Secondary objectives:

- Evaluate the clinical activity of ADCx19 as measured by overall response rate (ORR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS).
- Characterize the pharmacokinetic (PK) profile of ADCx19 (total antibody; drug to-antibody ratio [DAR] ≥0), PBD-conjugated antibody (DAR ≥1), and free warhead.
- Evaluate anti-drug antibodies (ADAs) in blood before, during, and after treatment with ADCx19.

Efficacy assessment

Disease assessments will be conducted within 6 days prior to Day 1 of Cycles 3 and 5 and thereafter every third cycle (i.e., Cycles 8, 11, 14, etc.), until disease progression, or more frequently, if clinically indicated. The same methods used at Screening which identify sites of disease should be used uniformly for all subsequent assessments. If PET-CT is positive, subsequent diagnostic CT and MRI are not needed unless clinically indicated. PET-CT is not required if a PET-CT examination at Screening was negative.

For patients who have reduced dosing frequency and are following a 6 week schedule, disease assessments should occur approximately 6 weeks and 12 weeks after Cycle 1 Day 1, and thereafter at least every 12 weeks. It is understood that there will be a ± 6 day window for restaging of these patients.

The patient's response to treatment will be determined by the Investigator as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD), based on the 2014 Lugano Classification Criteria.

PK assessment

The PK profile of ADCT-402 (total antibody; DAR ≥0), PBD-conjugated antibody (DAR ≥1), and free warhead SG3199 will be assessed using measures from validated bioanalytical methods. The PK profile will include determination of standard PK parameters (e.g., maximum concentration [Cmax], time to Cmax [Tmax]).

The following pharmacodynamic and other exploratory assessments will be performed at various time points in the study:

- Immunohistochemistry (archival tumor tissue or pre-treatment tumor biopsies in consenting patients) for CD19 protein expression
- Level of ADAs against ADCx19 in serum.
- Analysis of peripheral WBC populations and CD marker panel expression (CD19, CD20, CD21, CD22), before, during, and after treatment with ADCx19 (US only).
- Serum concentrations of ADCx19 and free warhead will be determined. The QTc interval will also be measured.

Safety assessment

Safety will be assessed based on the evaluation of adverse events (AEs), serious AEs (SAEs), treatment discontinuations due to AEs, dose limiting toxicity(s) (DLTs), periodic 12-lead electrocardiogram (ECG) recordings, physical examinations, vital signs measurements, ECOG performance status, and haematology, coagulation panel and pregnancy testing (for women of child-bearing potential), biochemistry, and urinalysis test results obtained at various timepoints during the study. Adverse events will be graded according to CTCAE Version 4.0 (v4.03, published June 14, 2010; NIH Publication No. 09-5410).

Product dosage and mode of administration

ADCx19 is a sterile formulation containing PBD-conjugated humanized monoclonal IgG1 antibody (DAR ≥1), humanized monoclonal IgG1 antibody (DAR = 0), and SG3249. It is provided pre-formulated in 10 mL single-use, glass vials containing approximately 16 mg ADCx19 per vial (deliverable volume 3.2 mL, with an additional 0.3 mL overfill at 5 mg/mL). Patients will receive a 1-hour intravenous (IV) infusion of ADCx19on Day 1 of Cycle 1. If ADCx19 is well tolerated after the first infusion, the infusion duration may be shortened to 30 minutes for subsequent cycles for that patient, at the Investigator's discretion.

Dose escalation design

In Part 1, patients will be assigned to treatment with ADCT-402 at escalating doses according to a 3+3 study design. The initial dose of ADCT-402 will be 15 µg/kg (Dose Level 1), and the highest allowed dose will be 300 µg/kg.

Further dose levels and schedules evaluated include the following:

A. **120 µg/kg:** Dosing every 3 weeks for 2 cycles. Patients with at least SD after the second cycle continue treatment at a reduced dose of 60 µg/kg q6weeks, beginning 6 weeks after Cycle 2 infusion.

B. **150 µg/kg:** Dosing every 3 weeks for 2 cycles. Patients with at least SD after the second cycle continue treatment at a reduced dose of 60 µg/kg q6weeks, beginning 6 weeks after Cycle 2 infusion.

C. **200 µg/kg:** Dosing every 6 weeks for 2 cycles. For patients with at least SD 6 weeks after Cycle 2, continue treatment at a reduced dose of 60 µg/kg q6weeks, beginning 6 weeks after Cycle 2 infusion.

D. **200 µg/kg:** Dosing every 6 weeks. For patients with at least SD 6 weeks after Cycle 1, continue treatment at a reduced dose of 60 µg/kg every 6 weeks beginning 6 weeks after Cycle 1 infusion.
E. **150 µg/kg:** Dosing every 3 weeks for 2 cycles. Patients with at least SD after the second cycle continue treatment at a reduced dose of 60 µg/kg q6weeks, beginning 6 weeks after Cycle 2 infusion.

The first patient enrolled into the study at 15 µg/kg (Dose Level 1) must be observed for 7 days for occurrence of AEs prior to treating the second patient in the study. The DLT observation period for dose escalation is 1 cycle.

For each dose level, if none of the first 3 patients at that level experiences a DLT, new patients may be entered at the next higher dose level. If 1 of 3 patients experiences a DLT, up to 3 more patients are to be treated at that same dose level. If none of the additional 3 patients at that dose level experiences a DLT, new patients may then be entered at the next higher dose level. However, if 1 or more of the additional 3 patients experiences a DLT, then no further patients are to be started at that dose level and the preceding dose is identified as the MTD. The MTD is therefore defined as the highest dose level at which none of the first 3 treated patients, or no more than 1 of the first 6 treated patients, experiences a DLT.

The study will be continuously monitored for safety and early stopping for successful identification of the MTD.

Dose expansion design

In Part 2, (expansion), patients will be assigned to dose level(s) and/or schedule(s) of ADCT-402 identified in Part 1 based on evolving safety, efficacy and pharmacokinetic data.

The population in Part 2 expansion may be restricted to specific histologies based on both signals of activity and the safety observed in Part 1.

Further, dose levels and schedules evaluated in Part 2 may include the regimes A, B, C. and D as described for Part 1, above.

Example 3: Summary of ADCx19 treatment safety and efficacy studies

Study design

Concentrations of PBD-conjugated Ab in serum were determined using a validated electrochemiluminescence immunoassay. Data were analyzed by population PK methodology using NONMEM (version 7.3, first-order conditional estimation).

The base PK analysis employed the log-transformed both sides approach with a 2-compartment open model and zero-order infusion rate. Area under the curve (AUC) values were estimated from individual patient Bayesian post hoc predictions.

The influence of various covariate factors on PK variability was assessed and included age, gender, race, body surface area (BSA), body mass index, weight, albumin, alanine aminotransferase, aspartate aminotransferase, bilirubin, creatinine clearance, and haemoglobin (Hb).

PK exposure trends with maximum severity of early (Cycle 1) and later (all cycles) TEAEs for any grade TEAEs, anemia, platelets, neutrophils, Hb, fatigue, oedema, and pleural effusion were graphically explored.

Apparent trends were quantitatively assessed with logistic regression relating the probability of the following binary outcome variables with AUC and demographic factors (age, sex, weight, BSA, and maximum Eastern Cooperative Oncology Group status):

- Grade ≥3 maximum severity TEAE
- Grade ≥3 platelet decrease
- Grade ≥1 oedema or pleural effusion.

Associations of dose and PK with maximum change from baseline tumor size were determined to identify potential relationships between exposure and activity (at least 50% reduction; complete response and partial response).

RESULTS

Patient characteristics

Data for 77 patients (53 men, 24 women), comprising 1138 observations, were included in the population PK model.

Final population PK model

Final population PK model parameters are provided in the table below.

There was a strong correlation between observed and estimated serum drug concentrations. Exposure and associated magnitude of intersubject variability increased with dose. Apparent terminal half-life values were long but moderately variable

Modest drug accumulation was seen with repeated dosing.

BSA significantly affected volume of distribution.

No other significant covariates were identified.

Parameter (units)	Typical value	SE (CV%)
CL (L/hr)	0.0155	15.5
Vc (L)	4.37	2.1
Q (L/hr)	0.0322	36
Vp (L)	5.41	37
Residual error (CV%)	41.8	0.5
SHARE	0.102	31
Effect of BSA on Vc	1.69	5.2
Effect of BSA on Vp	7.86	21.4
IIV CL	81.9	17.6
IIV Q1	177	11.4
IIV Vp	144	12.6

BSA, body surface area; CL, systemic clearance; CV, coefficient of variation; IIV, interindividual variability of respective pharmacokinetic term; Q1, intercompartmental clearance; SE, standard error; Vc, central volume of distribution; Vp, peripheral volume of distribution.

Relationship between exposure and safety

Increased exposure (AUC) of PBD-conjugated Ab was associated with probability of Grade ≥3 platelet decrease in Cycle 1 (p=0.0067) and any TEAE Grade ≥3 during Cycle 1 and all cycles (both; p=0.031) (see Table below). For any TEAEs Grade ≥3, men appeared to be more sensitive than women. A visual trend of increased AUC with probability of Grade ≥1 oedema or pleural effusion was apparent.

		Dose cohort (µg/kg)	15	30	60	90	120	200
		Median predicted AUC (µg*h/L)[a]	14820	31850	68060	124100	245400	517000
Potential relationships identified	Model parameters	p-value[b]	Mean predicted probability					
Platelet decrease Grade ≥3 Cycle 1[c]	AUC Cycle 1	0.0067	0.006	0.006	0.007	0.011	0.023	0.11
Platelet decrease Grade ≥3 all cycles	Mean AUC	0.068	0.086	0.089	0.093	0.10	0.12	0.18
Edema/pleural effusion Grade ≥1 all cycles	Mean AUC	0.18	0.18	0.18	0.19	0.21	0.24	0.33
TEAE Grade ≥3 Cycle 1[c]	AUC Cycle 1	0.031	0.074	0.078	0.086	0.10	0.14	0.26
TEAE Grade ≥3 all cycles	Mean AUC, gender=M	0.031	0.49	0.49	0.50	0.53	0.57	0.66
TEAE Grade ≥3 all cycles	Mean AUC, gender=F	0.031	0.25	0.26	0.27	0.28	0.32	0.41

Relationship between exposure and efficacy

Increased dose of ADCx19 was significantly associated with increased probability of objective response (p=0.0439).

Increased exposure (AUC) of PBD-conjugated Ab was significantly associated with increased probability of objective response (p=0.0292).

CONCLUSIONS
The PK profile of PBD-conjugated Ab after administration of ADCx19 was described using a linear 2-compartment model.

BSA was a significant covariate of volume of distribution

Significant positive correlations were observed between PBD-conjugated Ab exposure (AUC) and incidence of Grade ≥3 TEAEs (Cycle 1 and all cycles), and Grade ≥3 platelet decrease in Cycle 1:

Frequency of Grade ≥3 TEAEs were higher with protracted doses; limiting the number of cycles administered will control the rate of severe adverse events

For severe adverse events, men may be more sensitive than women

A relevant trend was apparent between AUC and Grade ≥1 oedema or pleural effusion.

Interim efficacy assessment indicated significant dose-response and exposure-response relationships for ADCx19 when administered with a q3w schedule.

Example 4: efficacy of ADCx19 treatment in mouse xenograft *in vivo* model
Subcutaneous Ramos-e222 model
Female severe combined immunodeficient mice (Fox Chase SCID®, C.B-17/Icr-Prkdcscid, Charles River) were eight weeks old, with a body weight (BW) range of 17.5 to 25.6 grams on Day 1 of the study.

On the day of implant, Ramos cells were harvested during log phase growth and resuspended in phosphate buffered saline. Xenografts were initiated by subcutaneously implanting 1 x 107 Ramos cells (0.1 mL suspension) into the right flank of each test animal and tumors were monitored as their volumes approached the target range of 100 to 150 mm3. Tumors were measured in two dimensions using callipers, and volume was calculated using the formula:

Tumor Volume (mm3) = w2 x l/2

where w = width and l = length, in mm, of the tumor. Tumor weight may be estimated with the assumption that 1 mg is equivalent to 1 mm3 of tumor volume.

Thirteen days after tumor implantation, designated as Day 1 of the study, the animals were sorted into groups each consisting of ten mice with individual tumor volumes ranging from 108 to 172 mm^3 and group mean tumor volumes of 120 mm^3. All agents were administered intravenously (i.v.) via tail vein injection once on Day 1 in a dosing volume of 0.2 mL per 20 grams of body weight (10 mL/kg), scaled to the body weight of each individual animal. Tumors were measured using callipers twice per week, and each animal was euthanized

when its tumor reached the endpoint volume of 2000 mm3 or at the end of the study, whichever came first.

In one group of animals, 1mg/kg ADCx19 was administered as a single dose on day 1 (qd x 1).

In two other groups, the same dose of ADCx19 was administered as 3 fractionated doses i.e. 3 doses each of 0.33mg/kg. In one group the doses were administered at 1 week intervals (qwk x 3), in the second group the doses were administered at 4-day intervals (q4d x 3).

It was observed that in both groups receiving the fractionated dose, tumour size grew steadily from ~day 20. In contrast, the group receiving the single dose on day 1 showed no significant tumour mass through to the end of the study (see Figure 2).

NALM-6 tumour cell inoculation model

The human B-cell leukaemia NALM-6 was used as iv-xenotransplantation model. NALM-6 culture at passage 12 was used for tumor cell inoculation. Viability of inoculated cells was 90%.

Adult female NOG mice were 5-8 weeks of age and had a mean body weight of 17.2 g at the start of the experiment. After an acclimatization time of 7 days, 1x10^7 tumor cells from in vitro passage were iv inoculated into each female NOG mouse (day 0).

Treatment was started at day three after NALM-6 inoculation. Body weights were measured three times/week and all animals were checked daily for general health status.

Individual mice were sacrificed and autopsy was done, when hind leg paralysis occurred and/or body weight decreased ≥20%. The study was finished at day 90.

In one group of animals, 1mg/kg ADCx19 was administered as a single dose on day 1 (qd x 1).

In the other group, the same dose of ADCx19 was administered as 3 fractionated doses i.e. 3 doses each of 0.33mg/kg, administered at 4-day intervals (q4d x 3).

It was observed that in the group receiving the fractionated dose, mortality occurred in some individuals toward the end of the study. In contrast, the group receiving the single dose on day 1 showed no mortality through to the end of the study (see Figure 3).

Example 5: pharmokinetics of ADCx19 in ALL patients

ADCx19 was administered to 19 patients with Relapsed or Refractory B-cell Lineage Acute Lymphoblastic Leukemias (B-ALL) comprising 3 dose cohorts (15, 30, and 60 µg/kg), using a 3-week treatment cycle with a single-dose administered on day 1.

Preliminary pharmacokinetic (PK) information from 7 patients (n=4 at 15 µg/kg; n=2 at 30 µg/kg; n=1 at 60 µg/kg) indicate inter-patient variability. For most patients, concentrations were near the lower limit of quantification and PK parameters could not be discerned. In those patients, rapid drug clearance was apparent in the early time course. In patients who exhibited a CR, a slower clearance compared to others was evident by Cycle 2.

The full clinical study protocol for the 3-week treatment cycle with a single-dose administered on day 1 is publically available at www.clinical trials.gov, having the ClinicalTrials.gov unique identifier: NCT02669264 (21 February 2017 update).

Example 6: Synopsis of fractionated dosage protocol

Indication

Patients with relapsed or refractory B-cell lineage acute lymphoblastic leukaemia (B-ALL) who have failed, or are intolerant to, any established therapy; or for whom no other treatment options are available.

Objectives

Primary objectives:

- Evaluate the safety and tolerability and determine the maximum tolerated dose (MTD) of ADCx19 in patients with relapsed or refractory B-ALL (Part 1).
- Determine the recommended dose of ADCx19for Part 2 (expansion).
- Evaluate the safety and tolerability of ADCx19in Part 2 (expansion) at the dose level recommended in Part 1.

Secondary objectives:

The secondary objectives for Part 1 and Part 2 of the study are:

- Evaluate the clinical activity of ADCx19, based on the patient's response to treatment (complete response [CR], CR with incomplete blood count recovery [CRi], partial response [PR], progressive disease [PD], no response [NR]) and determination of the overall response rate (ORR), duration of response (DOR), overall survival (OS), and progression-free survival (PFS).
- Characterize the pharmacokinetic (PK) profile of ADCx19 (total antibody, drug-to-antibody ratio [DAR] ≥0), PBD-conjugated antibody (DAR ≥1), and free warhead.
- Evaluate anti-drug antibodies (ADAs) against ADCx19in serum before, during, and after treatment with ADCx19.

Efficacy assessment

Assessment of response to treatment with ADCx19 will be based on bone marrow samples (aspirate or biopsy, if aspirate unattainable). The activity of ADCx19 will be evaluated based on the Investigator's evaluation of the patient's response to ADCx19 as CR, CRi, PR, PD, or NR as defined herein.

PK assessment

The PK profile of ADCx19 (total antibody; DAR ≥0), PBD-conjugated antibody (DAR ≥1), and free warhead will be assessed centrally in Cycles 1 and 2. The PK profile will include determination of standard PK parameters (e.g., maximum concentration [Cmax], time to Cmax [Tmax]). The following PD and other exploratory assessments will be performed at various time points in the study:

- Flow cytometric assessment of CD19 and other CD marker expression in mononuclear cells (MNCs) isolated from bone marrow aspirate and whole blood (WB), tested retrospectively by a central laboratory in samples obtained before treatment with ADCx19.
- Level of ADAs against ADCx19 in serum before, during, and after treatment with ADCx19.
- Analysis of peripheral WBC populations and CD marker panel expression (e.g., CD19, CD20, CD21, CD22) before, during, and after treatment with ADCx19 (Cycles 1 and 2) by flow cytometry in WB.
- Serum concentrations of ADCx19 and free warhead, QTc interval.
- Measurement of MRD by flow cytometry in bone marrow.

Safety assessment

Safety will be assessed based on AEs, serious AEs (SAEs), treatment discontinuations due to AEs, DLTs (as defined herein) measurements of cytokines in serum, periodic 12-lead electrocardiogram (ECG) recordings, physical examinations, vital signs measurements, ECOG performance status, and haematology, biochemistry, coagulation panel, pregnancy testing (for women of child-bearing potential) and urinalysis test results. Adverse events will be graded according to CTCAE Version 4.0 (v4.03, published June 14, 2010; NIH Publication No. 09-5410).

Product dosage and mode of administration

ADCx19 is a sterile formulation containing PBD-conjugated humanized monoclonal IgG1 antibody (DAR ≥1), humanized monoclonal IgG1 antibody (DAR = 0), and SG3249. It is provided pre-formulated in 10 mL single-use, glass vials containing approximately 16 mg ADCx19 per vial (deliverable volume 3.2 mL, with an additional 0.3 mL overfill at 5 mg/mL). Patients will receive a 1-hour intravenous (IV) infusion of ADCx19on Day 1 of Cycle 1. If ADCx19 is well tolerated after the first infusion, the infusion duration may be shortened to 30 minutes for subsequent cycles for that patient, at the Investigator's discretion.

The investigational product administration schedule is as follows:

Patients will be given ADCx19 (weekly [QW]) on Days 1, 8, and 15 of each 3-week (21-day) treatment cycle.

A patient will maintain the same treatment schedule throughout the duration of the trial.

Once a patient achieves CR/CRi, frequency or dose may be adjusted by the DESC based on emerging safety, efficacy, and PK profile.

The trial will be continuously monitored for emerging safety, efficacy and/or PK profile, and the DESC will determine if it is appropriate to maintain a QW schedule, revert to an every 3-week (Q3W) schedule, or test other dosing regimens.

Dose escalation design

Dose-escalation (Part 1) will be conducted according to a 3+3 design. The initial dose of ADCx19 will be 15 µg/kg (Dose Level 1), and the highest allowed dose will be 600 µg/kg.

The DLT observation period for dose-escalation will be 1 cycle. Patients will be entered sequentially to each dose level.

For each dose level, if none of the first 3 patients at that level experiences a DLT, new patients may be entered at the next higher dose level. If 1 of 3 patients experiences a DLT, up to 3 more patients are to be treated at that same dose level. If none of the additional 3 patients at that dose level experiences a DLT, new patients may then be entered at the next higher dose level. However, if 1 or more of the additional 3 patients experiences a DLT, then no further patients are to be started at that dose level and the preceding dose is identified as the MTD. The MTD; therefore, is defined as the highest dose level at which none of the first 3 treated patients, or no more than 1 of the first 6 treated patients, experiences a DLT.

During Part 1, the dose escalation steering committee (DESC) may expand enrolment at doses below the current dose level as part of the dose-escalation process. Additional patients may only be added at a lower dose level provided there is at least one patient who has achieved a PR (or better). No more than 10 patients in total can be treated at any dose level unless ≥3 of the 10 patients have achieved a PR or better.

During dose expansion, patients will be monitored for safety using the same DLT criteria employed during dose-escalation. If during the treatment period, >30% of patients experience safety events that would meet the criteria that define a DLT in the dose-escalation phase of the study, enrolment in the expansion cohort(s) may be paused and the study data reviewed to determine whether additional monitoring or other action (such as alternate dose levels) should be evaluated prior to further enrolment.

Example 7: Summary of ADCx19 treatment safety and efficacy studies

Study design

A Phase 1, open-label, dose-escalation (part 1) and dose-expansion (part 2), multicenter, US study is enrolling patients with R/R B-ALL.

In part 1, patients are assigned to treatment according to a 3+3 dose-escalation design to determine the maximum tolerated dose (MTD). The initial dose of ADCx19 was 15 µg/kg (dose level 1). ADCx19 is given intravenously on Day 1 of each 21-day cycle for patients

treated every 3 weeks, and on Days 1, 8, and 15 for patients assigned to a weekly dosing regimen.

Part 2 will further evaluate the safety, tolerability, PK, and clinical activity of ADCx19 at the dose recommended from part 1. Complete response is defined as achieving each of the following:

- Bone marrow differential showing ≤5% blast cells
- Absolute neutrophil count ≥1.0 x 109/L and platelet count ≥100 x 109/L
- Absence of extramedullary disease
- Patient is independent of red blood cell transfusions.

Key patient inclusion criteria	**Key patient exclusion criteria**
Patients aged 12 years and older with R/R B-ALL who have failed, or are intolerant to, any established therapy; or for whom no other treatment options are available	Known active central nervous system leukaemia or Burkitt's leukaemia/lymphoma
Eastern Cooperative Oncology Group performance status 0–2	Autologous or allogenic transplant within 60 days prior to screening or active graft-versus-host disease
White blood cell count <15,000 cells/μL prior to Day 1	Major surgery, chemotherapy, systemic therapy, or radiotherapy within 14 days prior to Day 1 treatment
	Active autoimmune disease

RESULTS

Patient characteristics

As of October 30, 2017, 29 patients (18 male, 11 female) with B-ALL have been treated with ADCx19.

Patients had received a median (min, max) of 2 (1, 12) previous chemotherapies. Eleven (37.9%) patients had received prior allogeneic stem cell transplantation. No dose-limiting toxicities (DLTs) have been observed up to the highest evaluated dose of 150 μg/kg once every 3 weeks (q3w). The most recently treated cohort received ADCx19 at a dose of 50 μg/kg once weekly.

PK data

PK data show PBD-conjugated antibody and total antibody concentrations below quantifiable levels of 5.0 and 20 ng/L, respectively, well before end of the 21-day treatment cycle (see Figure 4). PBD dimer concentrations were largely below measurable levels throughout the time course, justifying a change to weekly dosing.

Safety data

No DLTs were observed Treatment-emergent adverse events (TEAEs) were reported by 28/29 (96.6%) patients with 265 TEAEs reported in total. Twelve (41.4%) patients reported adverse events deemed to be possibly or probably related to ADCx19. The most common TEAEs were:

- Nausea (n=9)
- Fatigue (n=7)
- Febrile neutropenia (n=7)
- Headache (n=7).

Grade ≥3 TEAEs were reported in 24/29 (82.8%) patients, of which febrile neutropenia (n=7) and neutrophil count decrease (n=4) were the most common (see table below).
Two patients experienced TEAEs with fatal outcomes (lung infection and sepsis), both from the 120 µg/kg q3w dosing group. Four patients experienced TEAEs leading to a dose delay or reduction, but no TEAEs led to treatment withdrawal. Liver toxicity events were recorded in 7 patients, leading to dose delay in 1 patient (owing to hyperbilirubinemia) Four patients experienced Grade 3 liver toxicity events, including during Cycle 1; all were reversible (median [range] duration: 11.5 [5–36] days) and not related to veno-occlusive disease. There were 3 infusion-related reactions, including 1 case each of Grade 2 infusion-related reaction and cytokine release syndrome, and 1 case of Grade 1 tachycardia.

The MTD has not yet been reached.

Grade ≥3 TEAEs by preferred term (safety analysis set; dose in ug/kg):

TEAEs (Grade ≥3)	q3w						qw	Total
	15 (n=5)	30 (n=7)	60 (n=3)	90 (n=4)	120 (n=5)	150 (n=4)	50 (n=1)	(N=29)
Grade ≥3 TEAE reported by ≥10% of patients, n (%)	5 (100)	4 (57.1)	3 (100)	3 (75.0)	5 (100)	4 (100)	0	24 (82.8)
Febrile neutropenia	0	1 (14.3)	1 (33.3)	2 (50.0)	1 (20.0)	2 (50.0)	0	7 (24.1)
Neutrophil count decreased	1 (20.0)	2 (28.6)	0	0	1 (20.0)	0	0	4 (13.8)
Abdominal pain	0	1 (14.3)	0	1 (25.0)	0	1 (25.0)	0	3 (10.3)
Bacteremia	0	0	0	2 (50.0)	1 (20.0)	0	0	3 (10.3)
Lung infection	0	1 (14.3)	1 (33.3)	0	1 (20.0)	0	0	3 (10.3)
Sepsis	0	2 (28.6)	0	0	1 (20.0)	0	0	3 (10.3)

Efficacy data

Two patients achieved a complete response with no minimal residual disease (MRD), at a dose of 30 µg/kg and 120 µg/kg q3w after 5 and 2 treatment cycles, respectively.

Both responders had previously received blinatumomab.

A third patient achieved a complete response with positive MRD at a dose of 150 µg/kg q3w.

A fourth patient achieved a complete marrow response with an incomplete blood count response and progression of extramedullary disease at a dose of 150 µg/kg q3w.

Conclusions

In this Phase 1 study in patients with R/R B-ALL, single-agent ADCx19 was well tolerated with no DLTs and showed 2 MRD-negative complete remissions in a heavily pretreated population.

Dose escalation will continue to find the MTD for a weekly regimen.

A dose-expansion phase in part 2 of the study is planned to further evaluate the tolerability, safety, PK, and activity of ADCx19.

Example 8: Demonstration of acceptable safety, tolerability profile, and efficacy of ADCx19 in adults with R/R B-cell ALL

Methods

This was a study in adult patients with R/R B-ALL (clinicaltrials.gov: NCT02669264). The study was performed in accordance with the International Council for Harmonization (ICH) good clinical practice guidelines and the ethical principles of the Declaration of Helsinki. All patients provided written informed consent.

The primary objectives of the study were to evaluate the safety and tolerability of ADCx19 and to determine the MTD and recommended dose for expansion in patients with R/R B-ALL. Secondary objectives were to evaluate the preliminary clinical activity and PK profile of ADCx19 in R/R B-ALL, and to evaluate induction of anti-drug antibodies (ADA) to ADCx19.

Study population

Patients aged ≥12 years with R/R B-ALL who had failed or were intolerant to standard therapies, or for whom no other treatment options were available, were eligible for the study. Other key inclusion criteria included Eastern Cooperative Oncology Group (ECOG) performance status 0–2 and white blood cell count <15,000 cells/µl prior to Day 1.

Key exclusion criteria were known active central nervous system leukemia, Burkitt leukemia/lymphoma, active autoimmune disease, allogeneic stem cell transplant within 60 days, active graft-versus-host disease, and major surgery or anti-cancer treatment within 14 days prior to Day 1 treatment.

Study design and treatment

ADCx19 was given intravenously over 60 minutes once every three weeks (Q3W; Day 1 of each 21-day cycle), or once weekly (QW; Days 1, 8 and 15 of each 21-day cycle). If the first infusion was well tolerated, the infusion duration for subsequent doses could be shortened to 30 minutes. Patients were assigned to treatment according to a 3+3 dose escalation design and overseen by a Dose Escalation Steering Committee (DESC).

A hematologic dose-limiting toxicity (DLT) was defined as a Grade ≥3 event of neutropenia or thrombocytopenia, or a Grade 4 anemia, with a hypocellular bone marrow lasting for ≥6 weeks, in the absence of residual leukemia (i.e., with <5% blasts in the bone marrow). In the case of a normocellular bone marrow with <5% blasts, 8 weeks with ≥Grade 3 pancytopenia was considered a DLT. A non-hematologic DLT was defined as: Grade 4 tumor lysis syndrome, or Grade ≥3 adverse event (including nausea, vomiting, diarrhea, and electrolyte imbalances lasting more than 48 hours despite optimal therapy; excluding all grades of alopecia), or Grade ≥3 hypersensitivity reaction, or Grade ≥3 skin ulceration. The protocol-defined DLT observation period for dose-escalation was the duration of cycle 1. No intra-patient dose escalation was permitted. The MTD was defined as the highest dose level at which none of the first three treated patients, or no more than one of the first six treated

patients, experienced a DLT. The DESC determined if it was appropriate to maintain a QW schedule, revert to a Q3W schedule or test other dosing regimens based on safety and tolerability and/ or PK profile in patients treated Q3W. In QW dosing, patients were given a cumulative dose each cycle comparable to the highest dose tested Q3W without a DLT.

The trial was continuously monitored for safety, efficacy and PK profile. Additional patients could be added to a dose level, provided there was at least one patient who had achieved a partial response (PR) or better.

Patients were treated until disease progression, initiation of new anticancer treatment, or significant toxicity. Patients who discontinued treatment for any reason other than disease progression were followed until disease progression or start of new anti-cancer treatment. All patients were followed by telephone or chart review for up to 12 months after documentation of disease progression or start of new anti-cancer treatment.

Study endpoints
Safety endpoints included AEs graded according to NCI CTCAE Version 4.0, serious AEs (SAEs), DLTs, as assessed by periodic 12-lead electrocardiogram recordings, physical examinations, vital signs measurements, ECOG performance status, and laboratory abnormalities.

According to NCCN guidelines, preliminary assessments of clinical activity were based on the Investigator's assessment of response to treatment using bone marrow samples and included complete response (CR), complete response with incomplete blood count recovery (CRi), PR, no response (NR) or progressive disease (PD).

PK concentrations of total antibody, PBD-conjugated antibody and free SG3199 in serum were measured using validated bioanalytical methods. PK parameters (i.e., maximum concentration [Cmax] and area under the concentration time curve [AUC]) were determined by non-compartmental analysis (NCA). ADA levels in serum before, during, and after treatment were measured using validated bioanalytical methods.

Statistical analysis
Descriptive statistics and listings were used to report safety, efficacy, and PK parameters. Patients were evaluable for efficacy and toxicity if they had received at least one dose of ADCx19. The population for PK analysis comprised all treated patients with sufficient concentration data available for PK analysis.

Results
Patient characteristics
A total of 35 patients were treated during the dose escalation part of the study. The study was terminated by the study sponsor during the dose escalation phase. After study termination, patients were to be followed for 30 days after the last dose of study medication

or until initiation of new treatment initiation. Baseline demographics and clinical characteristics of the study population are reported in Table 2, below.

Table 2. Patient baseline characteristics.

Characteristic	All patients (N=35)
Age, years, median (range)	55 (20-80)
Sex, n (%)	
Male	19 (54)
Female	16 (46)
ECOG score, median (range)	1 (0-3)
ALL cytogenetic characteristics, n (%)	
Philadelphia chromosome	4 (11)
MLL rearrangement	0
E2A-PBX1	1 (3)
TEL-AML1	0
IL3-IGH	1 (3)
Hyperdiploid >50	1 (3)
Hypodiploid	3 (9)
Others (Mixed/Unknown)	25 (71)
Disease status at enrolment, n (%)	
Primary refractory	6 (17)
Relapsed	29 (83)
Extramedullary involvement, n (%)	
Yes	2 (6)
No	33 (94)
Number of prior systemic therapies*, Median (range) n (%)	3 (1–15)
1	4 (11)
2	8 (23)
3	8 (23)
≥4	15 (43)
Prior CD19 directed therapies	
Blinatumomab	16 (46)
Prior HSCT, n (%)	
Allogeneic	11 (31)
Autologous	3 (9)

* Prior stem cell transplant is included. For patients who received an autologous transplant, the mobilization regimen was considered a line of therapy if it was chemotherapy based and distinct from the other previous lines of treatment.

ECOG, Eastern Cooperative Oncology Group; HSCT, hematopoietic stem cell transplantation; MLL, mixed lineage leukemia.

All patients received at least one infusion of ADCx19. The majority of patients (30/35) received ADCx19 Q3W at doses ranging from 15 to 150 µg/kg; five patients received 50 µg/kg ADCx19 QW. Patients received a median of two infusions (range, 1–10) of ADCx19, with a median overall cumulative dose of 120.2 µg/kg (range, 15.0–741.2 µg/kg). The median treatment duration was 3.1 weeks (range, 0.1–35.4 weeks).

Safety

All patients experienced at least one treatment-emergent adverse event (TEAE). TEAEs reported in at least 20% of patients are summarized in Table 3, and the most common included nausea, febrile neutropenia, and liver test abnormalities (aspartate aminotransferase [AST] increased, gamma-glutamyl transferase [GGT] increased, alanine aminotransferase increased, blood alkaline phosphatase increased). Two patients (2/35 [5.7%]) had effusion-related TEAEs; one patient had Grade 1 ascites and one patient had Grade 2 ascites, pericardial effusion and pleural effusion; both were able to continue with study drug. Four patients (11.4%) experienced infusion related reactions, all of which were Grade 2 and resolved on the same day or the next day and all affected patients continued to receive the study drug.

Table 3. Any grade TEAEs reported by ≥20% of patients (safety analysis set).

TEAE, n (%)	Dose (µg/kg)							
	Q3W						QW	
	15	30	60	90	120	150	50	Total
	(n=5)	(n=7)	(n=3)	(n=4)	(n=5)	(n=6)	(n=5)	(N=35)
Any TEAE	5 (100)	7 (100)	3 (100)	4 (100)	5 (100)	6 (100)	5 (100)	35 (100)
Nausea	1 (20.0)	2 (28.6)	1 (33.3)	2 (50.0)	3 (60.0)	5 (83.3)	1 (20.0)	15 (42.9)
Febrile neutropenia	0	1 (14.3)	1 (33.3)	2 (50.0)	3 (60.0)	4 (66.7)	2 (40.0)	13 (37.1)
AST increased	0	0	2 (66.7)	2 (50.0)	2 (40.0)	4 (66.7)	1 (20.0)	11 (31.4)
GGT increased	1 (20.0)	0	0	2 (50.0)	3 (60.0)	3 (50.0)	1 (20.0)	10 (28.6)
Ala-AT up	0	0	1 (33.3)	2 (50.0)	2 (40.0)	2 (33.3)	2 (40.0)	9 (25.7)
Blood alk-Phos up	0	0	2 (66.7)	1 (25.0)	1 (20.0)	3 (50.0)	2 (40.0)	9 (25.7)
Fatigue	0	3 (42.9)	1 (33.3)	3 (75.0)	2 (40.0)	0	0	9 (25.7)
Headache	1 (20.0)	2 (28.6)	1 (33.3)	0	2 (40.0)	2 (33.3)	1 (20.0)	9 (25.7)
Rash maculopapular	0	1 (14.3)	1 (33.3)	1 (25.0)	2 (40.0)	2 (33.3)	2 (40.0)	9 (25.7)
Vomiting	0	1 (14.3)	0	1 (25.0)	3 (60.0)	3 (50.0)	1 (20.0)	9 (25.7)
Abdominal pain	0	1 (14.3)	1 (33.3)	1 (25.0)	0	3 (50.0)	2 (40.0)	8 (22.9)
Dizziness	0	0	1 (33.3)	1 (25.0)	2 (40.0)	2 (33.3)	2 (40.0)	8 (22.9)
Diarrhea	1 (20.0)	1 (14.3)	1 (33.3)	2 (50.0)	0	1 (16.7)	1 (20.0)	7 (20.0)
Dyspnea	0	1 (14.3)	1 (33.3)	3 (75.0)	0	1 (16.7)	1 (20.0)	7 (20.0)

Overall, 85.7% (30/35) patients experienced a TEAE of Grade 3 or higher. Grade ≥3 TEAEs reported in at least 10% of patients are presented in Table 4, and most commonly included febrile neutropenia and reversible liver test abnormalities (AST increased, blood bilirubin increased and GGT increased). There was a trend for more Grade ≥3 TEAEs with increasing dose.

Table 4. Grade ≥3 TEAEs reported by ≥10% of patients (safety analysis set).

TEAE, n (%)	Dose (µg/kg)							
	Q3W						QW	
	15 (n=5)	30 (n=7)	60 (n=3)	90 (n=4)	120 (n=5)	150 (n=6)	50 (n=5)	Total (N=35)
Any TEAE	5 (100)	4 (57.1)	3 (100)	3 (75.0)	5 (100)	6 (100)	4 (80.0)	30 (85.7)
Febrile neutropenia	0	1 (14.3)	1 (33.3)	2 (50.0)	2 (40.0)	3 (50.0)	1 (20.0)	10 (28.6)
AST increased	0	0	0	2 (50.0)	1 (20.0)	2 (33.3)	1 (20.0)	6 (17.1)
Blood bilirubin up	0	0	1 (33.3)	0	1 (20.0)	2 (33.3)	1 (20.0)	5 (14.3)
GGT increased	0	0	0	0	3 (60.0)	1 (16.7)	1 (20.0)	5 (14.3)
Abdominal pain	0	1 (14.3)	0	1 (25.0)	0	1 (16.7)	1 (20.0)	4 (11.4)
Anemia	0	1 (14.3)	1 (33.3)	1 (25.0)	0	0	1 (20.0)	4 (11.4)
Bacteremia	0	0	0	2 (50.0)	0	1 (16.7)	1 (20.0)	4 (11.4)
Neutrophils down	0	2 (28.6)	0	0	1 (20.0)	1 (16.7)	0	4 (11.4)
Sepsis	0	2 (28.6)	0	0	1 (20.0)	0	1 (20.0)	4 (11.4)

A total of 80% (28/35) of patients experienced a serious TEAE of any grade and 20% (7/35) of patients had a TEAE with a fatal outcome; a fatal event of worsening ALL was also reported as a TEAE but was considered as disease progression. TEAEs resulting in death were infections (6/28 [21.4%]: sepsis [n=3], lung infection [n=2], bacteremia [n=1]), and subarachnoid hemorrhage (1/28 [3.5%]). Disease progression was the most common reason for death (18/28 [64.3%] patients). No deaths were considered related to the study drug by investigators.

Approximately half of the patients (19/35 [54.3%]) experienced TEAEs considered by the investigator to be at least possibly related to the study treatment. The most common were gastrointestinal disorders (12/35 [34.3%] patients) and laboratory investigations (9/35 [25.7%] patients), including liver test and hematological abnormalities. There was a trend toward more study treatment-related AEs at higher dose levels, with 11/16 (68.7%) patients in the higher-dose groups (120 and 150 µg/kg Q3W and 50 µg/kg QW) and 8/19 (42.1%) patients in the lower dose groups (≤90 µg/kg) experiencing AEs related to study treatment.

TEAEs that led to dose delay or treatment interruption occurred in 7/35 (20%) patients; six had dose delays and one had a dose interruption due to an infusion related reaction.

One patient experienced a DLT. This patient was in the 150 µg/kg Q3W group and had worsening Grade 3 blood bilirubin increased, considered by the investigator to be possibly related to study treatment. The event resolved after six days without requiring further action. The patient had concurrent AST increased in laboratory tests. One patient in the 50 µg/kg QW dose group had a TEAE of GGT increased that led to treatment discontinuation, but it was considered unrelated to study treatment. The MTD was not reached.

Pharmacokinetics and Pharmacodynamics
Measurable PK data of cycle 1 were available for PBD-conjugated antibody, total antibody and SG3199 in 28, 26 and 13 patients, respectively, on the Q3W dosing schedule. For cycle 2, measurable PK data were available for PBD-conjugated antibody, total antibody and SG3199 in 18, 18 and 8 patients on the Q3W dosing schedule, respectively. Due to the low number of patients, limited PK data were available for the QW dosing schedule. Patients with insufficient data or levels of SG3199 below the LLOQ were excluded from the PK analysis.

Serum concentrations of PBD conjugated antibody and total antibody appeared to increase with dose and displayed significant degrees of variability. There was a sharp decline in serum concentration of PBD-conjugated and total antibody observed in the 150 ug/kg compared to the 120 ug/kg. This was possibly due to shorter half-life of PBD-conjugated and total antibody observed in the 150 ug/kg group compared with the 120 ug/kg dose group, in addition to target mediated drug disposition (TMDD), fewer patients than in 120 ug/kg and high individual target variation (Figure 1). Similar observations were apparent for the associated PK metrics of Cmax and AUClast (Table 5 and Table S1). For SG3199, PK profiles for the majority of patients were found largely below the lower limit of quantification immediately after dosing (LLOQ; 25 pg/mL) and decreased rapidly.10 However, one patient had a half-life of 0.5 day for SG3199.

Despite limited data and highly variable apparent PK parameters of CL and Vdβ estimations, the apparent half-life of total antibody and conjugated antibody at higher doses (≥90 µg/kg, Q3W) appeared similar, indicating good stability of ADCx19 in the circulation (Table 5). However, the apparent half life of ADCx19 conjugated and total antibody (less than one day) at the first dose cycle in B-ALL patients was much shorter than the known serum half-life of IgG1 and much shorter than observed in the B-cell NHL population (cycle 1: 7.2 days for conjugated antibody and 9.1 days for total antibody). This difference may be due to high clearance in association with the TMDD.

Table 5

Q3W	Cohort (µg/kg)	Cycle 1 CL	Cycle 1 $V_{d\beta}$	Cycle 1 T_{half}	Cycle 2 CL_{ss}	Cycle 2 $V_{d\beta}$	Cycle 2 T_{half}
		(L/d)	(L)	(d)	(L/d)	(L)	(d)
Conj Ab	90	80.8 (131) [3]	10.5 (121) [3]	0.355 (141) [3]	9.63 (130) [2]	5.61 (-) [1]	4.96 (-) [1]
	120	84.3 (121) [2]	6.89 (45.5) [2]	0.156 (105) [2]	31.1 (119) [4]	8.33 (65.1) [3]	7.55 (136) [3]
	150	27.4 (45.2) [5]	34.2 (104) [5]	0.713 (83.6) [5]	1.57 (46.2) [4]	9.45 (55.7) [4]	3.99 (18.1) [4]
Total Ab	90	3.98 (-) [1]	4.50 (-) [1]	0.784 (-) [1]	0.831 (-) [1]	6.71 (-) [1]	5.59 (-) [1]
	120	-	-	-	10.3 (162) [4]	11.4 (0.891) [2]	14.5 (113) [2]
	150	18.9 (115) [2]	2.68 (11.5) [2]	0.275 (111) [2]	1.37 (47.9) [4]	9.14 (65.2) [3]	4.67 (35.9) [3]
SG3199	90	-	-	-	-	-	-
	120	-	-	-	838 (-) [1]	614 (-) [1]	0.508 (-) [1]
	150	-	-	-	-	-	-

Data presented as arithmetic mean (CV%) [n].

Ab, antibody; Conj, conjugated; CL, clearance; CL_{ss}, clearance at steady-state; CV%, percent coefficient of variation; PK, pharmacokinetic; T_{half}, apparent terminal half-life; $V_{d\beta}$, volume of distribution at terminal phase; Q3W, every 3-weeks; d, day; L, liter; µg, micrograms; -, not available.

Exploratory analysis of the correlation between the AUC of ADCx19 conjugated antibody during cycle 1 and the baseline peripheral CD19+ cell count displayed a potential inverse relationship, suggesting lower baseline CD19+ cell count is associated with higher exposure of ADCx19. However, the AUC of conjugated antibody is influenced by dose and might be affected by baseline peripheral CD19+ cell levels.

By cycle 2, there was a decrease in apparent clearance, and an increase in apparent half-life of conjugated antibody to approximately four to eight days (Table 5). The highest mean accumulation of PBD conjugated and total antibody in cycle 2 relative to cycle 1 was approximately 30% and 67%, respectively. Overall, the PK of PBD conjugated and total antibody appeared to be time- and dose dependent in patients with B ALL.

Samples from all 35 patients were tested for ADA to ADCx19, with 111 sample measures available overall. Only one patient had a confirmed positive ADA titer, which occurred at pre-

dose only. No other patients exhibited confirmed positive ADA responses. There was no evidence of immunogenicity (i.e., no clinically relevant ADA induction effect).

Clinical activity
Formal assessment of potential anti-leukemic effect of ADCx19 was not performed due to early termination of the study. Three patients had a response to ADCx19, all achieving CR; one patient in each of the 30, 120 and 150 µg/kg Q3W dose groups. Two of the three patients had received previous CD19-directed therapy.

One patient treated at 30 µg/kg Q3W schedule had a total of 10 cycles of treatment, with no response at cycle 2 but a CR at cycle 4 and remained in CR at all subsequent assessments. This patient had previously received two lines of chemotherapy and a further line of CD19-directed therapy (blinatumomab) with best outcome as PR to all prior therapies. Blinatumomab was discontinued due to toxicity. Prior to receiving ADCx19, this patient had blast count of ≤5% in the bone marrow.

One patient in the 120 µg/kg Q3W schedule had a CR at cycle 2 and during the follow-up period after end of treatment. However, this patient later discontinued the treatment to have a stem cell transplant, but later died due to anoxic brain injury 80 days after receiving the last dose. This patient had previously received two lines of chemotherapy and a further line of CD19 directed therapy (blinatumomab) with no response to any prior therapy. Blinatumomab was discontinued due to toxicity. Prior to receiving ADCx19, this patient had blast counts between 5%–25% in the marrow.

One patient in the 150 µg/kg Q3W schedule had a PR at cycle 2, improving to CR at cycle 5. This patient had five cycles in total before discontinuing the treatment after having a dose delay of more than 30 days due to fluid overload and hypoxia, both of which resolved. The patient died 70 days after receiving the last dose of ADCx19 due to unknown cause. This patient had previously received two lines of chemotherapy in combination with the tyrosine kinase inhibitor dasatinib, achieving CRi with second-line therapy, followed by third-line chemotherapy resulting in progressive disease. This patient had blast count of >50% prior to ADCx19 treatment.

Five patients received 50 µg/kg ADCx19 QW, but no responses were seen on this schedule.

Example 9: Interim Futility Analysis of a Phase II Study of ADCT-402 in subjects with R/R DLBCL

Introduction
Subjects with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) after stem cell transplant or chimeric antigen receptor T-cell therapy or who are ineligible for such therapies need more treatment options. ADCT-402's provides such an option.

Preliminary data from a Phase 1 dose-escalation and dose-expansion trial of Lonca in R/R B-cell non-Hodgkin lymphoma (B-NHL) showed significant clinical activity in DLBCL, with an acceptable safety profile, and the recommended Phase 2 dose (RP2D) of 150 µg/kg was identified. Here is presented the planned interim analysis for futility on the first 52 pts with R/R DLBCL treated with ADCT-402 in Phase 2.

Methods

This single-arm, multi-centre, open-label, two-stage, Phase 2 trial is currently enrolling pts ≥18 years of age with R/R DLBCL following ≥2 multi-agent systemic treatment regimens (NCT03589469). The primary objective is to evaluate the efficacy of single-agent ADCT-402 by overall response rate (ORR). The secondary objectives are to further evaluate efficacy (including duration of response [DOR], progression-free survival [PFS], and overall survival [OS]), to characterize the safety, pharmacokinetics and immunogenecity profile of ADCT-402, and to evaluate the impact of ADCT-402 on health-related quality-of-life.

Subjects receive 30-minute intravenous infusions of ADCT-402 once every 3 weeks (Q3W; 1 cycle) at a dose of 150 µg/kg for the first 2 cycles, then 75 µg/kg for subsequent cycles, for up to 1 year or until disease progression, unacceptable toxicity, or other discontinuation criteria, whichever occurs first.

An interim analysis for futility was conducted when the 52nd subject had 2 tumor assessments (approximately 12 weeks after the start of study drug), with the study planned to proceed to full enrollment if ≥10 of the first 52 pts respond to ADCT-402. ORR (complete response [CR] + partial response [PR]) was determined by an independent reviewer.

Results

As of May 01, 2019, 52 subjects with DLBCL (73.1% male, 26.9% female) had been enrolled on the study. Subjects had a median age of 62.5 years [range 24–84] and had received a median of 3 previous therapies (range 2–7; Table 6). Subjects had received a median of 2.5 (range 1–9) cycles of Lonca. All (100%) subjects had at least 1 treatment-emergent adverse event (TEAE), and 37 (71.2%) pts had grade ≥3 TEAEs. The most common all-grade non-hematological TEAEs, regardless of relationship to study treatment, were gamma-glutamyltransferase (GGT) increased (24 [46.2%]), pyrexia (18 [34.6%]) and hypokalemia (15 [28.8%]), and the most common grade ≥3 TEAEs were GGT increased (11 [21.2%]), hypercalcemia (4 [7.7%]) and hypokalemia (3 [5.8%]). The most common all-grade hematological TEAEs were neutropenia (18 [34.6%], thrombocytopenia (16 [30.8%] and anaemia (14 [26.9%]), and the most common grade ≥3 hematological TEAEs were neutropenia (11 [21.2%], thrombocytopenia (9 [17.3%]) and anaemia (6 [11.5%]). Overall, 26 (50%) subjects had TEAEs leading to dose reductions/delays and 10 (19.2%) subjects had TEAEs leading to treatment discontinuation. Overall, among all treated subjects (52), ORR was 44.2%, with 10/52 (19.2%) and 13/52 (25.0%) subjects attaining CR and PR, respectively. In addition, 11 subjects (21.2%) had stable disease.

Table 6

Characteristic	Total (N=52)
Sex, n (%)	
Female	14 (26.9)
Male	38 (73.1)
Race, n (%)	
White	48 (92.3)
Black or African American	2 (3.8)
Asian	1 (1.9)
Other	1 (1.9)
Age, years, median (min, max)	62.5 (24, 84)
Histology	
Diffuse large B-cell lymphoma, NOS	44 (84.6)
High-grade B-cell lymphoma	5 (9.6)
Primary mediastinal B-cell lymphoma	3 (5.8)
Double-hit (myc and bcl-2), n (%)	3 (5.8)
Triple-hit (myc, bcl-2 and bcl-6), n (%)	0 (0)
Transformed disease, n (%)	
Follicular	3 (5.8)
Richter's	0 (0)
Disease stage, n (%)	
I	8 (15.4)
II	7 (13.5)
III	1 (1.9)
IV	5 (9.6)
First-line prior chemotherapy response, n (%)	
Relapsed	9 (17.3)
Refractory	8 (15.4)
Other	30 (57.7)
Last-line prior chemotherapy response group, n (%)	
Relapsed	32 (61.5)
Refractory	16 (30.8)
Other	4 (7.7)
Number of prior systemic therapies, median (min, max)	3 (2, 7)
Prior stem cell transplantation, n (%)	
Allogeneic	16 (30.8)
Autologous	27 (51.9)
Both	9 (17.3)
	9 (17.3)
	0 (0.0)
	8 (15.4)
	1 (1.9)

NOS, not otherwise specified.

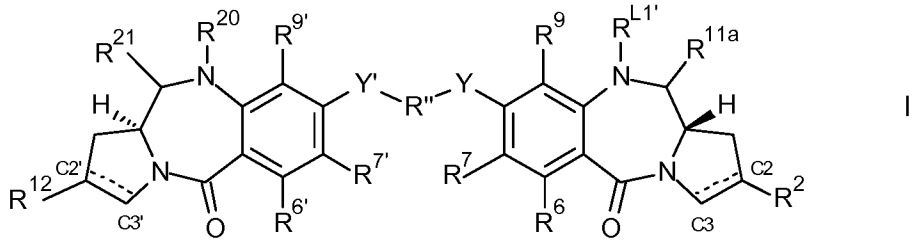
Conclusions

ADCT-402 demonstrated significant single-agent anti-tumor activity and manageable toxicity in subjects with R/R DLBCL. Futility requirements were met.

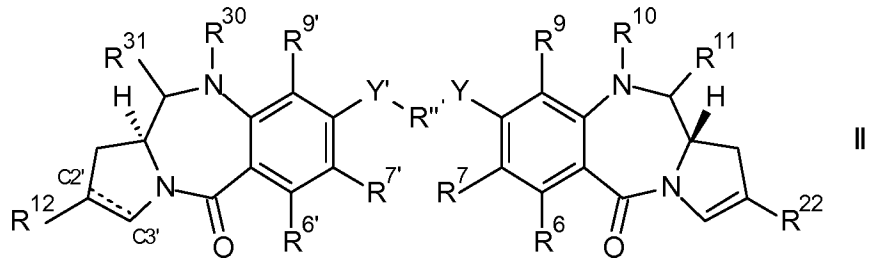
CLAIMS

1. A method of treating a proliferative disease in a subject, said method comprising administering to a subject a CD19-ADC, wherein the CD19-ADC is administered to the subject in a tapered and/or elongated dosage regime;

wherein the CD19-ADC comprises a conjugate of formula L - $(D^L)_p$, where D^L is of formula **I** or **II**:



I



II

wherein:

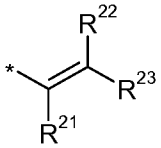
L is an antibody (Ab) which is an antibody that binds to CD19;

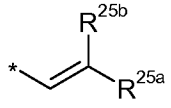
when there is a double bond present between C2' and C3', R^{12} is selected from the group consisting of:

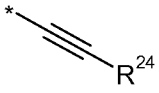
(ia) C_{5-10} aryl group, optionally substituted by one or more substituents selected from the group comprising: halo, nitro, cyano, ether, carboxy, ester, C_{1-7} alkyl, C_{3-7} heterocyclyl and bis-oxy-C_{1-3} alkylene;

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

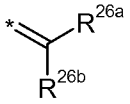
(ic) C_{3-6} saturated cycloalkyl;

(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;

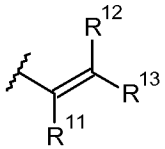
R^{21} is selected from OH, OR^A and SO_zM;

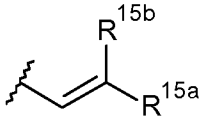
when there is a double bond present between C2 and C3, R^2 is selected from the group consisting of:

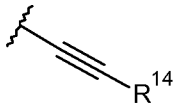
(ia) C_{5-10} aryl group, optionally substituted by one or more substituents selected from the group comprising: halo, nitro, cyano, ether, carboxy, ester, C_{1-7} alkyl, C_{3-7} heterocyclyl and bis-oxy-C_{1-3} alkylene;

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

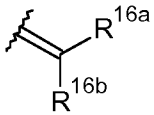
(ic) C_{3-6} saturated cycloalkyl;

(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

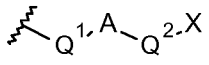
(if)  , where R^{14} is selected from: H; C_{1-3} saturated alkyl; C_{2-3} alkenyl; C_{2-3} alkynyl; cyclopropyl; phenyl, which phenyl is optionally substituted by a group selected from halo, methyl, methoxy; pyridyl; and thiophenyl;

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]

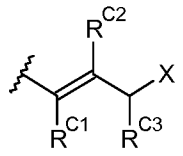
R^{22} is of formula IIIa, formula IIIb or formula IIIc:

(a)  IIIa

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

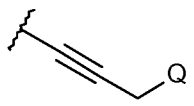
(i) Q^1 is a single bond, and Q^2 is selected from a single bond and -Z-$(CH_2)_n$-, where Z is selected from a single bond, O, S and NH and n is from 1 to 3; or

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

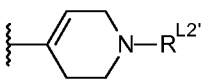
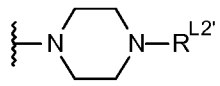
(b)  IIIb

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

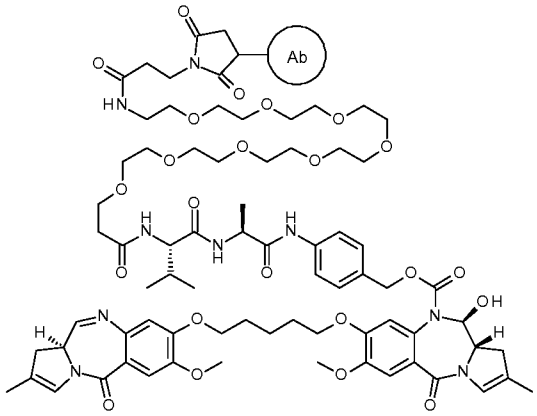
X is selected from the group comprising: O-$R^{L2'}$, S-$R^{L2'}$, CO_2-$R^{L2'}$, CO-$R^{L2'}$, NH-C(=O)-$R^{L2'}$, NHNH-$R^{L2'}$, CONHNH-$R^{L2'}$,  ,  , $NR^NR^{L2'}$, wherein R^N is selected from the group comprising H and C_{1-4} alkyl;

$R^{L2'}$ 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 method according to claim 1, wherein the proliferative disease is lymphoma.

3. The method according to either one of claims 1 or 2 wherein the CD19-ADC has the chemical structure:



, where the Ab is a CD19 antibody, and the DAR is between 1 and 8.

4. The method according to any one of claims 1 to 3 wherein Ab comprises a VH domain having the sequence of SEQ ID NO. 2 and a VL domain having the sequence of SEQ ID NO. 8.

5. The method according to any one of claims 1 to 4 wherein Ab comprises a heavy chain having sequences of SEQ ID NO. 13 and a light chain having the sequences of SEQ ID NO. 14.

6. The method according to any one of claims 1 to 5 wherein the CD19-ADC is ADCx19.

7. The method according to any preceding claim, wherein the starting dose of CD19-ADC is reduced no more than twice during the dosage regime.

8. The method according to any preceding claim, wherein the starting dose of CD19-ADC is reduced no more than once during the dosage regime.

9. The method according to any preceding claim wherein the dose is reduced following the first treatment cycle.

10. The method according to any preceding claim wherein the dose is reduced following the second treatment cycle.

11. The method according to any preceding claim wherein the dose is reduced only if the subject has attained at least Stable Disease [SD] at the end of the preceding treatment cycle.

12. The method according to any preceding claim the starting dose is at least 120 µg/kg, such as about 120 µg/kg.

13. The method according to any preceding claim wherein the starting dose is at least 150 µg/kg.

14. The method according to any preceding claim wherein the starting dose is about 150 µg/kg.

15. The method according to any preceding claim wherein the starting dose is at least 200 µg/kg, such as about 200 µg/kg.

16. The method according to any preceding claim wherein the reduced dose is about 50% of the starting dose.

17. The method according to any preceding claim wherein the reduced dose is about 60 µg/kg.

18. The method according to any preceding claim wherein the reduced dose is about 70 to 80 µg/kg..

19. The method according to any preceding claim wherein the reduced dose is about 75 µg/kg.

20. The method according to any preceding claim wherein each treatment cycle is the same length.

21. The method according to claim 20, wherein each treatment cycle is 3 weeks.

22. The method according to claim 21, wherein about 140 to 160 µg/kg of CD19-ADC are administered for two, 3-week treatment cycles,

followed by subsequent 3-week cycles of 70 to 80 µg/kg beginning 3 weeks after the cycle 2 administration.

23. The method according to claim 21, wherein about 150 µg/kg of CD19-ADC are administered for two, 3-week treatment cycles,

followed by subsequent 3-week cycles of 75 µg/kg beginning 3 weeks after the cycle 2 administration

24. The method according to any preceding claim, wherein the CD19-ADC is administered as a single dose.

25. The method according to any preceding claim, wherein the dose of CD19-ADC is administered on Day 1 of the treatment cycle.

26. The method according to any preceding claim wherein the proliferative disease is characterised by the presence of a neoplasm comprising CD19+ve cells

27. The method according to any preceding claim wherein the subject has been diagnosed as having the proliferative disease prior to the start of treatment with the CD19-ADC.

28. The method according to any preceding claim wherein the method comprises the step of selecting a subject for treatment based on expression of CD19.

29. The method according to claim 28, wherein a subject is selected if at least 5% of neoplasm cells express CD19.

30. The method according to any preceding claim wherein the proliferative disease is a non-Hodgkin's Lymphoma, such as diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, (FL), Mantle Cell lymphoma (MCL), chronic lymphatic lymphoma (CLL), Waldenstrom macroglobulinemia, and Marginal Zone B-cell lymphoma (MZBL).

31. The method according to any preceding claim wherein the proliferative disease is B-cell Lineage Non-Hodgkin Lymphoma (B-NHL).

32. The method according to any preceding claim wherein the proliferative disease is resistant, relapsed or refractory.

33. The method according to any preceding claim wherein the subject is human.

34. The method according to any preceding claim wherein the CD19-ADC is administered intravenously.

35. The method according to any preceding claim further comprising administering a chemotherapeutic agent in combination with the CD19-ADC.

36. The method according to claim 35, wherein the chemotherapeutic agent is a checkpoint inhibitor.

37. The method according to claim 35, wherein the chemotherapeutic agent is ibrutinib.

38. The method according to claim 37, wherein the ibrutinib is administered concurrently with the CD19-ADC.

39. The method according to either one of claims 37 or 38, wherein the ibrutinib is administered in a QD dosage regime.

40. The method according to any one of claims 37 to 39, wherein the dose of ibrutinib administered is about 560mg/day, 420mg/day, or 280 mg/day.

41. The method according to any one of claims 37 to 39, wherein the dose of ibrutinib administered is about 560mg/day.

42. The method according to any one of claims 37 to 41, wherein the CD19-ADC is administered to the subject for two Q3W cycles.

43. The method according to claim 42, wherein the dose of CD19-ADC administered in each of the two, 3-week treatment cycles is the same.

44. The method according to any one of claims 37 to 43, wherein the dose of CD19-ADC is about 60 µg/kg, about 90 µg/kg, about 120 µg/kg, or about 150 µg/kg.

45. The method according to any one of claims 37 to 44, wherein the administration of Ibrutinib continues after the completion of CD19-ADC treatment.

46. The method according to any one of claims 42 to 45, wherein the CD19-ADC is administered to the subject for a further two, 3-week treatment cycles.

47. The method according to claim 46, wherein the further two CD19-ADC treatment cycles are administered If the subject has not achieved CR within 3 months after the completion of initial two, 3-week treatment cycles.

48. The method according to any one of claims 37 to 47, wherein the subject has, or is suspected as having, or has been identified as being at risk of, or has received a diagnosis of a non-Hodgkin's Lymphoma, such as diffuse large B-cell lymphoma (DLBCL) or Mantle Cell lymphoma (MCL).

49. The method according to claim 35, wherein the chemotherapeutic agent is Durvalumab.

50. The method according to claim 49, wherein the Durvalumab is administered concurrently with the CD19-ADC.

51. The method according to either one of claims 49 or 50, wherein the Durvalumab is administered in a Q3W dosage regime.

52. The method according to statement 50, wherein the Durvalumab is administered in a Q4W dosage regime.

53. The method according to either one of statements 50 or 52, wherein day 1 of the first Durvalumab treatment cycle falls on day 8 of the first CD19-ADC treatment cycle.

54. The method according to any one of claims 49 to 53, wherein the dose of Durvalumab is about 1500 mg.

55. The method according to any one of claims 49 to 54, wherein the CD19-ADC is administered to the subject for two, 3-week treatment cycles.

56. The method according to claim 55, wherein the dose of CD19-ADC administered in each of the two, 3-week treatment cycles is the same.

57. The method according to any one of claims 49 to 56, wherein the dose of CD19-ADC is about 90 µg/kg, about 120 µg/kg, or about 150 µg/kg.

58. The method according to any one of claims 49 to 57, wherein the administration of Durvalumab continues after the completion of CD19-ADC treatment.

59. The method according to claim 58, wherein after the completion of CD19-ADC treatment the Durvalumab is administered in a Q4W dosage regime.

60. The method according to any one of claims 55 to 59, wherein the CD19-ADC is administered to the subject for a further two, 3-week treatment cycles.

61. The method according to claims 60, wherein the further two CD19-ADC treatment cycles are administered If the subject has not achieved CR within 3 months after the completion of initial two, 3-week treatment cycles.

62. The method according to any one of claims 37 to 49, wherein the subject has, or is suspected as having, or has been identified as being at risk of, or has received a diagnosis of a non-Hodgkin's Lymphoma, such as diffuse large B-cell lymphoma (DLBCL), Follicular Lymphoma (FL), or Mantle Cell lymphoma (MCL).

63. The method according to claim 35, wherein the chemotherapeutic agent is Rituximab.

64 The method according to claim 63, wherein the Rituximab is administered concurrently with the CD19-ADC.

65. The method according to either one of claims 63 or 64, wherein the Rituximab is administered in a Q3W dosage regime.

66. The method according to any one of claims 63 to 65, wherein the dose of Rituximab administered is about 375 mg/m^2.

67. The method according to any one of claims 63 to 66, wherein the dose of CD19-ADC is about 90 µg/kg, about 120 µg/kg, or about 150 µg/kg.

68. The method according to any one of claims 63 to 67, wherein the subject has, or is suspected as having, or has been identified as being at risk of, or has received a diagnosis of a non-Hodgkin's Lymphoma, such as diffuse large B-cell lymphoma (DLBCL).

69. The method according to claim 35, wherein the chemotherapeutic agent is Cytarabine.

70. The method according to claim 69, wherein the Cytarabine is administered concurrently with the CD19-ADC.

70. The method according to either one of claims 69 or 70, wherein the CD19-ADC is administered on day 2 of each Q3W treatment cycle.

72. The method according to any one of claims 69 to 71, wherein the cytarabine is administered in a Q3W dosage regime.

73. The method according to claim 72, wherein the cytarabine is administered as 5 partial doses spread one partial dose per day on days 1 to 5 of each cycle.

74. The method according to claim 73, wherein each partial dose of cytarabine is about 100 mg/m^2, about 200 mg/m^2, about 300 mg/m^2, or about 400 mg/m^2.

75. The method according to any one of claims 69 to 74, wherein the subject has, or is suspected as having, or has been identified as being at risk of, or has received a diagnosis of a non-Hodgkin's Lymphoma, such as diffuse large B-cell lymphoma (DLBCL).

76. The method according to any one of claims 69 to 75, wherein the cytarabine is administered in further combination with rituximab as described in any one of claims 62 to 66.

77. The method according to claim 35 or claim 36, wherein the chemotherapeutic agent is administered to the subject before, at the same time, or after the CD19-ADC.

78. The method according to any preceding claim, wherein the CD19-ADC is administered in combination with a steroid.

79. The method according to claim 78, wherein a first dose of steroid is administered on the same day as the ADC.

80. The method according to claim 79, wherein the first dose of steroid is administered at least 2 hours before the ADC.

81. The method according to either one of claims 78 or 79, wherein a second dose of steroid is administered the day after the ADC.

82. The method according to claim 78, wherein a first dose of steroid is administered the day before the ADC.

83. The method according to claim 82, wherein a second dose of steroid is administered on the same day as the ADC.

84. The method according to claim 83, wherein the second dose of steroid is administered at least 2 hours before the ADC.

85. The method according to either one of claims 83 or 84 wherein a third dose of steroid is administered the day after the ADC.

86. The method according to any one of claims 78 to 85, wherein the steroid or steroid doses are administered only in conjunction with the first administration of ADC in each treatment cycle.

87. The method according to any one of claims 78 to 86, wherein the steroid is administered orally.

88. The method according to any one of claims 78 to 87, wherein each dose of steroid is 8 mg.

89. The method according to any one of claims 78 to 88, wherein each dose of steroid is 16 mg.

90. The method according to any one of claims 78 to 89, wherein each dose of steroid is administered as two equal, partial doses.

91. The method according to any one of claims 78 to 90, wherein each partial dose is 4 mg.

92. The method according to any one of claims 90 to 891, wherein each partial dose is 8 mg.

93. The method according to any one of claims 78 to 92, wherein the steroid is dexamethasone.

94. The method according to claim 78, wherein 4mg or 8mg dexamethasone is administered orally twice daily: (i) the day before ADC administration on week 1, day 1 of the treatment cycle, (ii) the day of ADC administration on week 1, day 1 of the treatment cycle, and (iii) the day after ADC administration on week 1, day 1 of the treatment cycle.

95. The method according to claim 78, wherein 4mg or 8mg dexamethasone is administered orally twice daily: (i) the day of ADC administration on week 1, day 1 of the treatment cycle, and (ii) the day after ADC administration on week 1, day 1 of the treatment cycle.

96. The method according to either one of claims 94 and 95, wherein the dexamethasone administered on the same day as the ADC is administered at least two hours before the ADC.

97. The method according to any one of claims 94 to 95, wherein the dexamethasone is administered only in conjunction with the first administration of ADC in each treatment cycle.

98. A packaged pharmaceutical product comprising a CD19-ADC as defined in any one of claims 1 to 5, in combination with a label or insert advising that the CD19-ADC should be administered according to the method of any one of claims 1 to 94.

99. A CD19-ADC as defined in any one of claims 1 to 6 for use in a method of any one of claims 1 to 97.

100. A pharmaceutical composition comprising a CD19-ADC as defined in any one of claims 1 to 6, optionally in combination with a pharmaceutically acceptable excipient, for use in a method of any one of claims 1 to 97.

101. Use of a CD19-ADC as defined in any one of claims 1 to 6 in the preparation of a medicament for use in a method of any one of claims 1 to 97.

SEQUENCES

SEQ ID NO. 1 (RB4v1.0 VH):
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SEQ ID NO. 3 (B43 VH):
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SEQ ID NO. 4 (HD37 VH):
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SEQ ID NO. 6 (FMC63 VH):
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SEQ ID NO.7 (RB4v1.0 VK):
EIVLTQSPAIMSASPGERVTMTCSASSGVNYMHWYQQKPGTSPRRWIYDTSKLASGVPAR
FSGSGSGTSYSLTISSMEPEDAATYYCHQRGSYTFGGGTKLEIK

Figure 1A

SEQ ID NO. 8 (RB4v1.2 VK):
EIVLTQSPAIMSASPGERVTMTCSASSGVNYMHWYQQKPGTSPRRWIYDTSKLASGVPAR
FSGSGSGTSYSLTISSMEPEDAATYYCHQRGSYTFGGGTKLEIK

SEQ ID NO. 9 (B43 VK):
ELVLTQSPASLAVSLGQRATISCKASQSVDYDGDSYLNWYQQIPGQPPKLLIYDASNLVSGI
PPRFSGSGSGTDFTLNIHPVEKVDAATYHCQQSTEDPWTFGGGTKLEIK

SEQ ID NO. 10 (HD37 VK):
DILLTQTPASLAVSLGQRATISCKASQSVDYDGDSYLNWYQQIPGQPPKLLIYDASNLVSGIP
PRFSGSGSGTDFTLNIHPVEKVDAATYHCQQSTEDPWTFGGGTKLEIK

SEQ ID NO. 11 (4G7 VK):
DIVMTQAAPSIPVTPGESVSISCRSSKSLLNSNGNTYLYWFLQRPGQSPQLLIYRMSNLASG
VPDRFSGSGSGTAFTLRISRVEAEDVGVYYCMQHLEYPFTFGAGTKLELK

SEQ ID NO. 12 (FMC63 VK):
DIQMTQTTSSLSASLGDRVTISCRASQDISKYLNWYQQKPDGTVKLLIYHTSRLHSGVPSRF
SGSGSGTDYSLTISNLEQEDIATYFCQQGNTLPYTFGGGTKLEIT

SEQ ID NO. 13 (RB4v1.2-HC):
QVQLVQPGAEVVKPGASVKLSCKTSGYTFTSNWMHWVKQAPGQGLEWIGEIDPSDSYTN
YNQNFQGKAKLTVDKSTSTAYMEVSSLRSDDTAVYYCARGSNPYYYAMDYWGQGTSVTV
SSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS
SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGG
PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS
TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ
GNVFSCSVMHEALHNHYTQKSLSLSPG

SEQ ID NO. 14 (RB4v1.2-LC):
EIVLTQSPAIMSASPGERVTMTCSASSGVNYMHWYQQKPGTSPRRWIYDTSKLASGVPAR
FSGSGSGTSYSLTISSMEPEDAATYYCHQRGSYTFGGGTKLEIKRTVAAPSVFIFPPSDEQL
KSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKAD
YEKHKVYACEVTHQGLSSPVTKSFNRGEC

Figure 1B

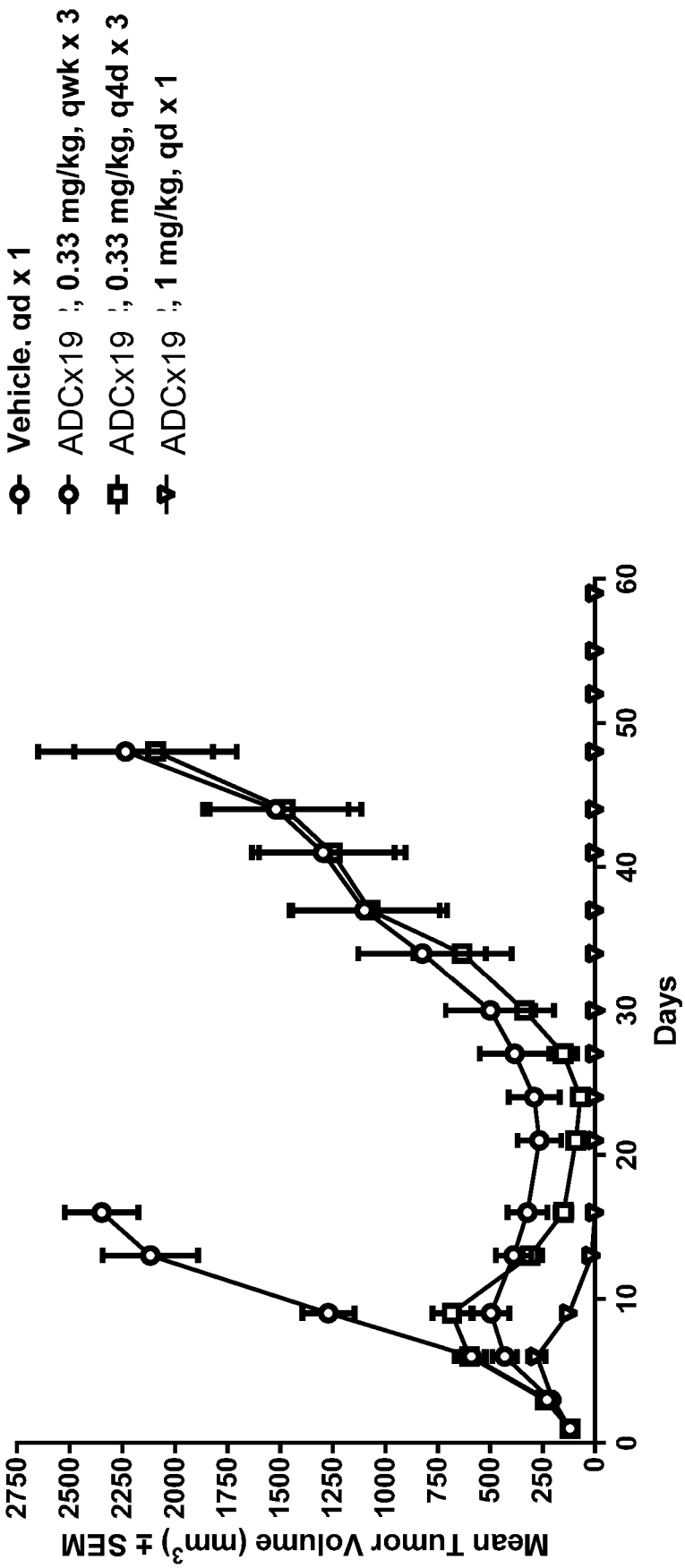
Vehicle. qd x 1
ADCx19 ; 0.33 mg/kg, qwk x 3
ADCx19 ; 0.33 mg/kg, q4d x 3
ADCx19 ; 1 mg/kg, qd x 1
Mean Tumor Volume (mm3) ± SEM
2750
2500
2250
2000
1750
1500
1250
1000
750
500
250
0
0
10
20
30
40
50
60
Days

Figure 2

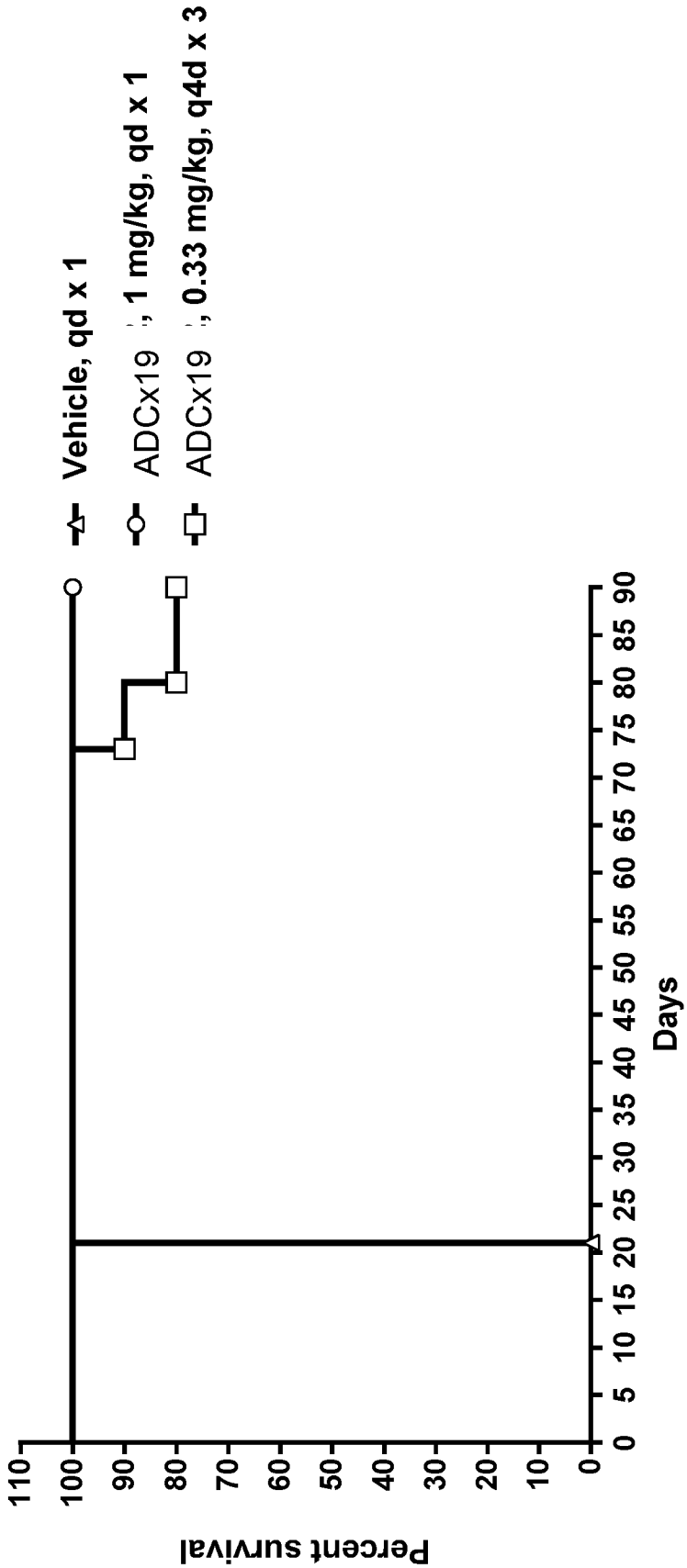
Vehicle, qd x 1
ADCx19 , 1 mg/kg, qd x 1
ADCx19 , 0.33 mg/kg, q4d x 3
Percent survival
110
100
90
80
70
60
50
40
30
20
10
0
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90
Days

Figure 3

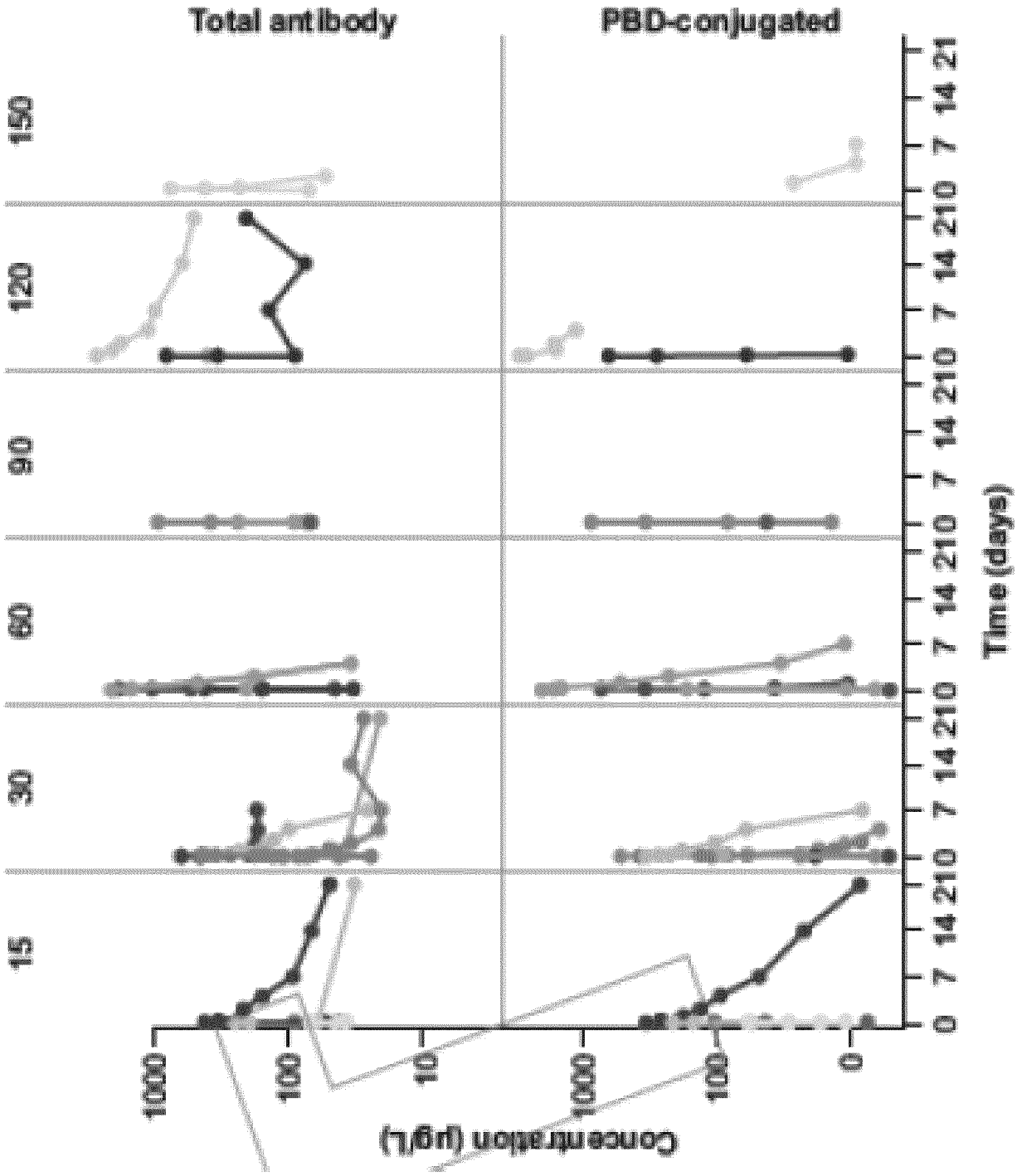
Total antibody
PBD-conjugated
150
120
90
60
30
15
1000
100
10
1000
100
0
Concentration (µg/L)
0 7 14 21 0 7 14 21 0 7 14 21 0 7 14 21 0 7 14 21 0 7 14 21
Time (days)

Figure 4

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/082464

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K47/50 A61P35/00 A61K45/06
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2018/250417 A1 (VAN BERKEL PATRICIUS HENDRIKUS CORNELIS [CH] ET AL) 6 September 2018 (2018-09-06) claims 130-141 paragraph [0701] -----	1-101
X	WO 2018/193105 A1 (ADC THERAPEUTICS SA [CH]; MEDIMMUNE LTD [GB]) 25 October 2018 (2018-10-25)	1-101
Y	page 12, line 26 - page 18, line 13 figure 1A page 17, lines 30-35 claims 1-49 page 61, last paragraph example 4 ----- -/--	1-101

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 January 2020	29/01/2020

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Hörtner, Michael

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2019/082464

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