

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 al, (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

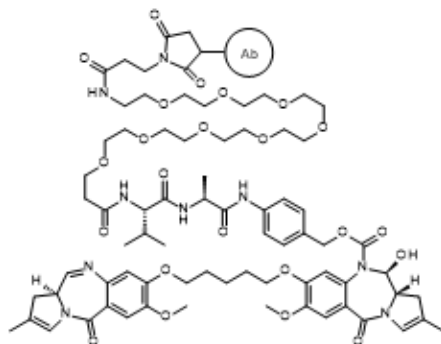
The efficacy of an Antibody Drug Conjugate comprising an anti-CD19 antibody (an anti-CD19-ADC) in the treatment of, for example, cancer has been established – see, for example, WO2014/057117 and WO2016/166298.

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 combination therapies in which an anti-CD19 ADC is administered in combination with at least one PI3K inhibitor or secondary agent.

SUMMARY

The present authors have determined that the administration of a combination of an anti-CD19 ADC and PI3K inhibitor or secondary agent to an individual leads to unexpected clinical advantages. The present authors have further determined that administration of an anti-CD19 ADC to an individual that has either been treated with, or is being treated with, a PI3K inhibitor or secondary agent leads to a synergistic increase in treatment efficacy.

In a first aspect, the present disclosure provides for a use of an anti-CD19 antibody drug conjugate (ADC) in the manufacture of a medicament for use in combination therapy for treating a cancer in an individual, wherein said medicament is to be administered in combination with a PI3K inhibitor or a PARP inhibitor; wherein the anti-CD19 ADC has



the chemical structure: , wherein Ab is the antibody that binds to CD19.

In another aspect, the present disclosure provides for a composition comprising an anti-CD19 ADC and a PI3K inhibitor or PARP inhibitor, wherein the anti-CD19 ADC and PI3K inhibitor or PARP inhibitor are as disclosed herein.

In a further aspect, the present disclosure provides for a use of the composition as disclosed herein in the preparation of a medicament for treating a cancer in an individual, wherein the treatment is as disclosed herein.

Accordingly, in a first example the present disclosure provides a method of selecting an individual as suitable for treatment with an anti-CD19 ADC, wherein the individual is selected for treatment with the anti-CD19 ADC if the individual has been treated, or is being treated, with a PI3K inhibitor or secondary agent. The individual may be selected for treatment if the individual is refractory to treatment, or further treatment, with the PI3K inhibitor or secondary agent.

In another example, the present disclosure provides a method for treating a disorder in an individual, the method comprising selecting an individual as suitable for treatment by a method of the first example, and then administering to the individual an effective amount of the anti-CD19 ADC. The method of treatment may further comprise administering a PI3K inhibitor or secondary agent in combination with the anti-CD19 ADC.

In another example the disclosure provides a method for treating a disorder in an individual, the method comprising administering to the individual an effective amount of an

anti-CD19 ADC and PI3K inhibitor or secondary agent. The individual may be selected for treatment according to a method according of the first example.

The disorder may be a proliferative disease, for example a cancer such as non-Hodgkin's Lymphoma, including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, (FL), Mantle Cell lymphoma (MCL), chronic lymphatic lymphoma (CLL), and Marginal Zone B-cell lymphoma (MZBL), and leukemias such as Hairy cell leukemia (HCL), Hairy cell leukemia variant (HCL-v), and Acute Lymphoblastic Leukaemia (ALL) such as Philadelphia chromosome-positive ALL (Ph+ALL) or Philadelphia chromosome-negative ALL (Ph-ALL).

The anti-CD19-ADC may be ADCX19 described herein.

The PI3K inhibitor may be idelalisib, copanlisib, duvelisib, Taselisib, Buparlisib, Alpelisib, Umbralisib, Dactolisib, and Voxtalisib. Preferably the PI3K inhibitor is idelalisib or copanlisib.

The secondary agent may be:

- (a) Bendamustine;
- (b) Lenalidomide;
- (c) a proteasome inhibitor such as bortezomib, carfilzomib, ixazomib, Oprozomib, and Salinosporamide A; or
- (d) a PARP inhibitor such as Olaparib, CEP-9722, BMN-673/talazoparib, Rucaparib, Iniparib/SAR24-550/BSI-201, Veliparib (ABT-888), Niraparib/MK-4827, BGB-290, 3-aminobenzamide, and E7016.

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

In the disclosed methods the anti-CD19 ADC may be administered before the PI3K inhibitor or secondary agent, simultaneous with the PI3K inhibitor or secondary agent, or after the PI3K inhibitor or secondary agent. The disclosed methods may comprise administering a further chemotherapeutic agent to the individual.

In another example, the present disclosure provides an anti-CD19 ADC, or a composition comprising an anti-CD19 ADC, for use in a method of treatment as described herein.

In one example, the present disclosure provides a PI3K inhibitor or secondary agent, or a composition comprising a PI3K inhibitor or secondary agent, for use in a method of treatment as described herein.

In a further example, the present disclosure provides for the use of an anti-CD19 ADC, a PI3K inhibitor, or a secondary agent in the manufacture of a medicament for treating a

disorder in an individual, wherein the treatment comprises a method of treatment as described herein.

In another example, the disclosure provides a first composition comprising an anti-CD19 ADC for use in a method of treating a disorder in an individual, wherein the treatment comprises administration of the first composition in combination with a second composition comprising a PI3K inhibitor or secondary agent.

Also provided by this example is a first composition comprising a PI3K inhibitor or secondary agent for use in a method of treating a disorder in an individual, wherein the treatment comprises administration of the first composition in combination with a second composition comprising an anti-CD19 ADC.

The disorder may be a proliferative disease, for example a cancer such as non-Hodgkin's Lymphoma, including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, (FL), Mantle Cell lymphoma (MCL), chronic lymphatic lymphoma (CLL), and Marginal Zone B-cell lymphoma (MZBL), and leukemias such as Hairy cell leukemia (HCL), Hairy cell leukemia variant (HCL-v), and Acute Lymphoblastic Leukaemia (ALL) such as Philadelphia chromosome-positive ALL (Ph+ALL) or Philadelphia chromosome-negative ALL (Ph-ALL).

The anti-CD19-ADC may be ADCX19 described herein.

The PI3K inhibitor may be idelalisib, copanlisib, duvelisib, Taselisib, Buparlisib, Alpelisib, Umbralisib, Dactolisib, and Voxtalisib. Preferably the PI3K inhibitor is idelalisib or copanlisib.

The secondary agent may be:

- (a) Bendamustine;
- (b) Lenalidomide;
- (c) a proteasome inhibitor such as bortezomib, carfilzomib, Ixazomib, Oprozomib, and Salinosporamide A; or
- (d) a PARP inhibitor such as Olaparib, CEP-9722, BMN-673/talazoparib, Rucaparib, Iniparib/SAR24-550/BSI-201, Veliparib (ABT-888), Niraparib/MK-4827, BGB-290, 3-aminobenzamide, and E7016.

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

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

In a further example, the disclosure provides the use of an anti-CD19 ADC in the manufacture of a medicament for treating a disorder in an individual, wherein the medicament comprises an anti-CD19 ADC, and wherein the treatment comprises administration of the medicament in combination with a composition comprising a PI3K inhibitor or secondary agent.

Also provided by this example is the use of a PI3K inhibitor or secondary agent in the manufacture of a medicament for treating a disorder in an individual, wherein the medicament comprises a PI3K inhibitor or secondary agent, and wherein the treatment comprises administration of the medicament in combination with a composition comprising an anti-CD19 ADC.

The disorder may be a proliferative disease, for example a cancer such as non-Hodgkin's Lymphoma, including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, (FL), Mantle Cell lymphoma (MCL), chronic lymphatic lymphoma (CLL), and Marginal Zone B-cell lymphoma (MZBL), and leukemias such as Hairy cell leukemia (HCL), Hairy cell leukemia variant (HCL-v), and Acute Lymphoblastic Leukaemia (ALL) such as Philadelphia chromosome-positive ALL (Ph+ALL) or Philadelphia chromosome-negative ALL (Ph-ALL).

The anti-CD19 ADC may be ADCX19 as described herein.

The PI3K inhibitor may be idelalisib, copanlisib, duvelisib, Taselisib, Buparlisib, Alpelisib, Umbralisib, Dactolisib, and Voxtalisib. Preferably the PI3K inhibitor is idelalisib or copanlisib.

The secondary agent may be:

- (a) Bendamustine;
- (b) Lenalidomide;
- (c) a proteasome inhibitor such as bortezomib, carfilzomib, Ixazomib, Oprozomib, and Salinosporamide A; or
- (d) a PARP inhibitor such as Olaparib, CEP-9722, BMN-673/talazoparib, Rucaparib, Iniparib/SAR24-550/BSI-201, Veliparib (ABT-888), Niraparib/MK-4827, BGB-290, 3-aminobenzamide, and E7016.

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

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

Another example of the disclosure provides a kit comprising:

- a first medicament comprising an anti-CD19 ADC;
- a package insert comprising instructions for administration of the first medicament according to a method of treatment as disclosed herein. The kit may further comprise a second medicament comprising a PI3K inhibitor or secondary agent.

Another example of the disclosure provides a kit comprising:

- a first medicament comprising an anti-CD19 ADC;
- a second medicament comprising a PI3K inhibitor or secondary agent; and,
- optionally,
a package insert comprising instructions for administration of the first medicament to an individual in combination with the second medicament for the treatment of a disorder.

Also provided by this example is a kit comprising a medicament comprising an anti-CD19 ADC and a package insert comprising instructions for administration of the medicament to an individual in combination with a composition comprising a PI3K inhibitor or secondary agent for the treatment of a disorder.

Further provided by this example is a kit comprising a medicament comprising a PI3K inhibitor or secondary agent and a package insert comprising instructions for administration of the medicament to an individual in combination with a composition comprising an anti-CD19 ADC for the treatment of a disorder.

The disorder may be a proliferative disease, for example a cancer such as non-Hodgkin's Lymphoma, including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, (FL), Mantle Cell lymphoma (MCL), chronic lymphatic lymphoma (CLL), and Marginal Zone B-cell lymphoma (MZBL), and leukemias such as Hairy cell leukemia (HCL), Hairy cell leukemia variant (HCL-v), and Acute Lymphoblastic Leukaemia (ALL) such as Philadelphia chromosome-positive ALL (Ph+ALL) or Philadelphia chromosome-negative ALL (Ph-ALL).

The anti-CD19 ADC may be ADCX19 as described herein.

The PI3K inhibitor may be idelalisib, copanlisib, duvelisib, Taselisib, Buparlisib, Alpelisib, Umbralisib, Dactolisib, and Voxtalisib. Preferably the PI3K inhibitor is idelalisib or copanlisib.

The secondary agent may be:

- (a) Bendamustine;
- (b) Lenalidomide;
- (c) a proteasome inhibitor such as bortezomib, carfilzomib, Ixazomib, Oprozomib, and Salinosporamide A; or

(d) a PARP inhibitor such as Olaparib, CEP-9722, BMN-673/talazoparib, Rucaparib, Iniparib/SAR24-550/BSI-201, Veliparib (ABT-888), Niraparib/MK-4827, BGB-290, 3-aminobenzamide, and E7016.

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

The medicament or composition comprising the anti-CD19 ADC may be administered before the medicament or composition comprising the PI3K inhibitor or secondary agent, simultaneous with the medicament or composition comprising the PI3K inhibitor or secondary agent, or after the medicament or composition comprising the PI3K inhibitor or secondary agent. The treatment may comprise administering a further chemotherapeutic agent to the individual.

In a yet further example, the disclosure provides a composition comprising an anti-CD19 ADC and a PI3K inhibitor or secondary agent.

Also provided in this example of the disclosure is a method of treating a disorder in an individual, the method comprising administering to the individual an effective amount of the composition comprising an anti-CD19 ADC and a PI3K inhibitor or secondary agent.

Also provided in this example of the disclosure is a composition comprising an anti-CD19 ADC and a PI3K inhibitor or secondary agent for use in a method of treating a disorder in an individual.

Also provided in this example of the disclosure is the use of a composition comprising an anti-CD19 ADC and a PI3K inhibitor or secondary agent in the manufacture of a medicament for treating a disorder in an individual.

Also provided in this example of the disclosure is a kit comprising composition comprising an anti-CD19 ADC and a PI3K inhibitor or secondary agent and a set of instructions for administration of the medicament to an individual for the treatment of a disorder.

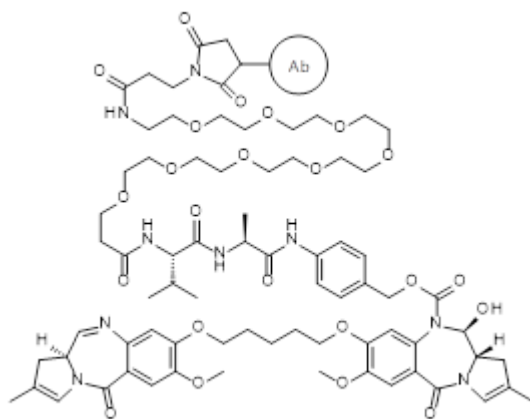
The disorder may be a proliferative disease, for example a cancer such as non-Hodgkin's Lymphoma, including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, (FL), Mantle Cell lymphoma (MCL), chronic lymphatic lymphoma (CLL), and Marginal Zone B-cell lymphoma (MZBL), and leukemias such as Hairy cell leukemia (HCL), Hairy cell leukemia variant (HCL-v), and Acute Lymphoblastic Leukaemia (ALL) such as Philadelphia chromosome-positive ALL (Ph+ALL) or Philadelphia chromosome-negative ALL (Ph-ALL).

The anti-CD19-ADC may be ADCX19 as described herein.

CLAIMS

1. Use of an anti-CD19 antibody drug conjugate (ADC) in the manufacture of a medicament for use in combination therapy for treating a cancer in an individual, wherein said medicament is to be administered in combination with a PI3K inhibitor or a PARP inhibitor;

wherein the anti-CD19 ADC has the chemical structure:



, wherein Ab is the antibody that binds to CD19.

2. The use according to claim 1, wherein the PI3K inhibitor is idelalisib or copanlisib, or the PARP inhibitor is olaparib.

3. The use according to any one of claims 1 or 2, wherein the anti-CD19 ADC comprises an antibody having:

(i) a VH domain having the sequence according to any one of SEQ ID NOs. 1, 2, 3, 4, 5 or 6, and a VL domain having the sequence according to any one of SEQ ID NOs. 7, 8, 9, 10, 11 or 12;

(ii) a VH domain having the sequence according to SEQ ID NO. 1 and a VL domain having the sequence according to SEQ ID NO. 7;

(iii) a VH domain having the sequence according to SEQ ID NO. 2 and a VL domain having the sequence according to SEQ ID NO. 8;

(iv) a VH domain having the sequence according to SEQ ID NO. 3 and a VL domain having the sequence according to SEQ ID NO. 9;

(v) a VH domain having the sequence according to SEQ ID NO. 4 and a VL domain having the sequence according to SEQ ID NO. 10;

(vi) a VH domain having the sequence according to SEQ ID NO. 5 and a VL domain having the sequence according to SEQ ID NO. 11; or

(vii) a VH domain having the sequence according to SEQ ID NO. 6 and a VL domain having the sequence according to SEQ ID NO. 12.

4. The use according to any one of claims 1 or 2, wherein the anti-CD19 ADC is ADCT-402.

5. The use according to any preceding claim, wherein the anti-CD19 ADC is to be administered before the PI3K inhibitor or PARP inhibitor, simultaneously with the PI3K inhibitor or PARP inhibitor, or after the PI3K inhibitor or PARP inhibitor.
6. The use according to any preceding claim, wherein the individual:
 - (i) has a cancer or has been determined to have a cancer;
 - (ii) has, or has been determined to have, a cancer which expresses CD19 or CD19+ tumour-associated non-tumour cells, such as CD19+ infiltrating cells;
 - (iii) is undergoing treatment with a PI3K inhibitor or PARP inhibitor;
 - (iv) has undergone treatment with a PI3K inhibitor or PARP inhibitor; and / or
 - (v) is refractory to treatment, or further treatment, with the PI3K inhibitor or PARP inhibitor.
7. The use according to any preceding claim, wherein the cancer is selected from the group comprising: non-Hodgkin's Lymphoma, including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, (FL), Mantle Cell lymphoma (MCL), chronic lymphatic lymphoma (CLL), and Marginal Zone B-cell lymphoma (MZBL), and leukemias such as Hairy cell leukemia (HCL), Hairy cell leukemia variant (HCL-v), and Acute Lymphoblastic Leukaemia (ALL) such as Philadelphia chromosome-positive ALL (Ph+ALL) or Philadelphia chromosome-negative ALL (Ph-ALL); or wherein the cancer is diffuse large B-cell lymphoma (DLBCL); optionally wherein the DLBCL is relapsed or refractory.
8. The use according to any one of claims 1 or 3 to 7, wherein the PI3K inhibitor is idelalisib, copanlisib, duvelisib, Taselisib, Buparlisib, Alpelisib, Umbralisib, Dactolisib, or Voxtalisisb.
9. The use according to any preceding claim, wherein the PI3K inhibitor is idelalisib.
10. The use according to any preceding claim, wherein the PI3K inhibitor is copanlisib.
11. The use according to any one of claims 1 or 3 to 7 wherein the PARP inhibitor is selected from Olaparib, CEP-9722, BMN-673/talazoparib, Rucaparib, Iniparib/SAR24-550/BSI-201, Veliparib (ABT-888), Niraparib/MK-4827, BGB-290, 3-aminobenzamide, and E7016.
12. The use according to any one of claims 1 to 7 or 11 wherein the PARP inhibitor is Olaparib.
13. A composition comprising an anti-CD19 ADC and a PI3K inhibitor or PARP inhibitor, wherein the anti-CD19 ADC and PI3K inhibitor or PARP inhibitor are defined according to any one of claims 1-12.
14. Use of the composition of claim 13 in the preparation of a medicament for treating a cancer in an individual, wherein the treatment is as defined in any one of claims 1-12.