

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

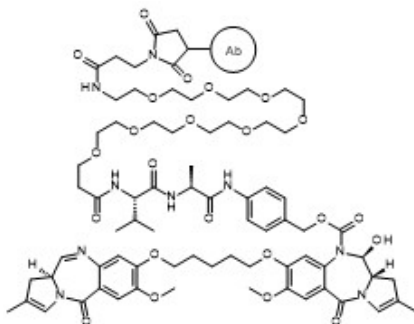
The efficacy of an Antibody Drug Conjugate comprising an anti-CD19 antibody (an anti-CD19-ADC) in the treatment of, for example, cancer has been established – see, for example, WO2014/057117 and WO2016/166298.

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

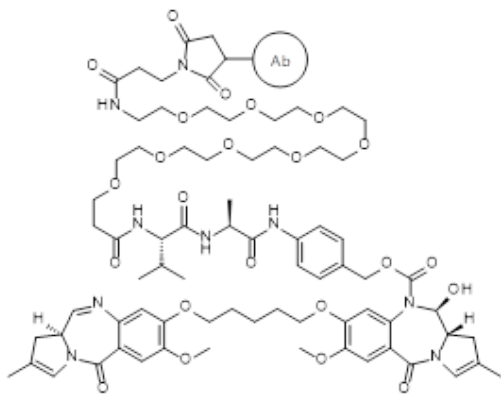


the chemical structure: , wherein Ab is the antibody that binds to CD19, and which comprises: a VH domain having the sequence according to SEQ ID NO 2; and, a VL domain having the sequence according to SEQ ID NO 8; wherein the PI3K inhibitor is idelalisib or copanlisib; wherein the PARP inhibitor is olaparib; and wherein the cancer is a cancer which expresses CD19 or has tumour-associated non-tumour cells that express CD19.

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, and which comprises: 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;

wherein the PI3K inhibitor is idelalisib or copanlisib;

wherein the PARP inhibitor is olaparib; and

wherein the cancer is a cancer which expresses CD19 or has tumour-associated non-tumour cells that express CD19.

2. The use according to claim 1 wherein the cancer is a lymphoma.

3. The use according to claim 1 wherein the cancer is a non-Hodgkin's Lymphoma.

4. The use according to any one of claims 1 to 3, 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 been determined to have a cancer;

(ii) 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 one of claims 1 and 4 to 6, 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. 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 1-7.

9. Use of the composition of claim 8 in the preparation of a medicament for treating a cancer in an individual, wherein the treatment is as defined in any one of claims 1-7.