Summary

We have now found out that the combination of type I anti-CD20 antibody, or an afucosylated, type II anti-CD20 antibody with a Bcl-2 inhibitor and a MDM2 inhibitor showed significantly enhanced antiproliferative effects. Surprisingly, this combination is more than additive, i.e. highly synergistic.

The disclosure relates to an afucosylated anti-CD20 antibody with an amount of fucose of 60% or less of the total amount of oligosaccharides (sugars) at Asn297, for the treatment of cancer in combination with a Bcl-2 inhibitor and a MDM2 inhibitor.

The disclosure also relates to use of an afucosylated anti-CD20 antibody with an amount of fucose of 60% or less of the total amount of oligosaccharides (sugars) at Asn297, for the manufacture of a medicament for the treatment of cancer in combination with a Bcl-2 inhibitor and a MDM2 inhibitor.

In one aspect, there is provided a pharmaceutical composition comprising a combination of a humanized B-Ly1 antibody which is afucosylated with an amount of fucose of 60% or less of the total amount of oligosaccharides at Asn297, and 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-l-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide (GDC-0199, ABT199) and 4-{[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid (RG7388) or a salt thereof.

In another aspect, there is provided the pharmaceutical composition as defined herein for use in the treatment of cancer.

In another aspect, there is provided use of a humanized B-Ly1 antibody which is afucosylated with an amount of fucose of 60% or less of the total amount of oligosaccharides at Asn297, in the manufacture of a medicament for the treatment of cancer in combination with 4-(4-{[2-(4-

chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-l-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide (GDC-0199, ABT199) and 4-{[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid (RG7388) or a salt thereof.

The disclosure also relates to a method of treatment of patient suffering from cancer by administering an afucosylated anti-CD20 antibody with an amount of fucose of 60% or less of the total amount of oligosaccharides (sugars) at Asn297, in combination with a Bcl-2 inhibitor and a MDM2 inhibitor, to a patient in the need of such treatment.

In one embodiment, the amount of fucose is between 40% and 60% of the total amount of oligosaccharides (sugars) at Asn297. In another embodiment, the amount of fucose is 0% of the total amount of oligosaccharides (sugars) at Asn297.

In one embodiment, the type I anti-CD20 antibody is rituximab. In one embodiment, the afucosylated anti-CD20 antibody is an IgG1 antibody. In another embodiment, said cancer is a CD20 expressing cancer, preferably a lymphoma or lymphocytic leukemia. In one embodiment said afucosylated anti-CD20 antibody is humanized B-Ly1 antibody. In another embodiment, said afucosylated antibody is a type II anti-CD20 antibody. In a preferred embodiment, said afucosylated antibody is obinutuzumab.

In one embodiment, said Bcl-2 inhibitor is a compound selected from the compounds described in WO2010/138588. Methods of producing said Bcl-2 inhibitors are also disclosed in WO2010/138588.

Patent Claims

1. A pharmaceutical composition comprising a combination of a humanized B-Ly1 antibody which is afucosylated with an amount of fucose of 60% or less of the total amount of oligosaccharides at Asn297, and 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-l-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide (GDC-0199, ABT199) and 4-{[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid (RG7388) or a salt thereof.

2. The pharmaceutical composition according to claim 1, wherein said afucosylated anti-CD20 antibody is obinutuzumab.

3. The pharmaceutical composition according to claim 1 or 2, further comprising one or more additional other cytotoxic, chemotherapeutic or anti-cancer agents, or compounds or ionizing radiation enhancing the effects of such agents.

4. The pharmaceutical composition according to any one of claims 1 to 3 for use in the treatment of cancer.

5. The pharmaceutical composition for use according to claim 4, wherein said cancer is a CD20 expressing cancer.

6. The pharmaceutical composition for use according to claim 4 or 5, wherein said CD20 expressing cancer is a lymphoma or lymphocytic leukemia.

7. Use of a humanized B-Ly1 antibody which is afucosylated with an amount of fucose of 60% or less of the total amount of oligosaccharides at Asn297, in the manufacture of a medicament for the treatment of cancer in combination with 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-l-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide (GDC-0199, ABT199) and 4-{[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-cyano-5-(2,2-dimethyl-propyl)-pyrrolidine-2-carbonyl]-amino}-3-methoxy-benzoic acid (RG7388) or a salt thereof.

8. The use according to claim 7, wherein said cancer is a CD20 expressing cancer.

9. The use according to any one of claims 7 to 8, wherein said CD20 expressing cancer is a lymphoma or lymphocytic leukemia.

10. The use according to any one of claims 7 to 9, wherein said afucosylated anti-CD20 antibody is obinutuzumab.

11. The use according to any one of claims 7 to 10, wherein one or more additional other cytotoxic, chemotherapeutic or anti-cancer agents, or compounds or ionizing radiation enhancing the effects of such agents are to be administered.