

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 combination comprising 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-1-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 obinutuzumab, in the manufacture of a medicament for the treatment of a CD20 expressing cancer, wherein the obinutuzumab is to be administered in combination with 4-(4-{[2-(4-

chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-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,

wherein said obinutuzumab is to be administered intraperitoneally at a dose of 0.5 mg/kg or 10 mg/kg once weekly for 3 weeks, said 4-(4-{{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl}piperazin-1-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) is to be administered orally at a dose of 100 mg/kg once daily for 17 days or 19 days and said 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) is to be administered orally at a dose of 30 mg/kg once daily for 13 days or at a dose of 100 mg/kg once daily for 5 days followed by a dose of 80 mg/kg once daily for 12 days.

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 combination comprising 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, 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-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 combination according to claim 1, wherein said afucosylated anti-CD20 antibody is obinutuzumab.
3. The combination 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 combination according to any one of claims 1 to 3 for use in the treatment of cancer.
5. The combination for use according to claim 4, wherein said cancer is a CD20 expressing cancer.
6. The combination for use according to claim 4 or 5, wherein said CD20 expressing cancer is a lymphoma or lymphocytic leukemia.

7. Use of obinutuzumab in the manufacture of a medicament for the treatment of a CD20 expressing cancer, wherein the obinutuzumab is to be administered in combination with 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-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,

wherein said obinutuzumab is to be administered intraperitoneally at a dose of 0.5 mg/kg or 10 mg/kg once weekly for 3 weeks, said 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-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) is to be administered orally at a dose of 100 mg/kg once daily for 17 days or 19 days and said 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) is to be administered orally at a dose of 30 mg/kg once daily for 13 days or at a dose of 100 mg/kg once daily for 5 days followed by a dose of 80 mg/kg once daily for 12 days.

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

9. The use according to claim 7 or 8, further comprising one or more additional other cytotoxic, chemotherapeutic or anti-cancer agents, or compounds or ionizing radiation enhancing the effects of such agents to be administered.