

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.

In one aspect, there is provided an anti-CD20 antibody for the treatment of cancer in combination with a Bcl-2 inhibitor and a MDM2 inhibitor.

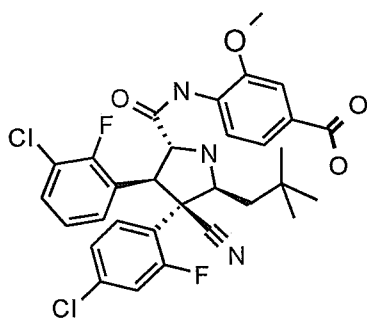
The disclosure also relates to use of an afucosylated anti-CD20 antibody with an amount of fucose of 60% or less of the total amount of oligosaccharides (sugars) at Asn297, for the manufacture of a medicament for the treatment of cancer in combination with a Bcl-2 inhibitor and a MDM2 inhibitor. In another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

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.

5 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.

10 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.



Molecular Weight =616.4973

Molecular Formula =C₃₁H₂₉Cl₂F₂N₃O₄

In one embodiment, said type I anti-CD20 antibody is rituximab, said afucosylated anti-CD20 antibody is humanized B-Ly1 antibody, preferably obinutuzumab, and Bcl-2 inhibitor, wherein the Bcl-2 inhibitor is selected from the compounds described in WO 2010/138588 and a MDM2 inhibitor selected from the compounds described in WO2011/098398. Said MDM2 inhibitor preferably is a compound according to formula I or according to formula I-1 as disclosed in the present specification above. Preferably, the MDM2 inhibitor is 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 or a salt thereof, and said cancer is a CD20 expressing cancer, in one embodiment a lymphoma or lymphocytic leukemia.

In one embodiment, the afucosylated anti-CD20 antibody binds CD20 with an KD of 10⁻⁸ M to 10⁻¹³ M.

One embodiment of the disclosure is a pharmaceutical composition comprising a combination of a type I anti-CD20 antibody (in one embodiment rituximab) or an afucosylated anti-CD20 antibody with an amount of fucose of 60% or less of the total amount of oligosaccharides (sugars) at Asn297, (in one embodiment an afucosylated humanized B-Ly1 antibody or preferably obinutuzumab), and a Bcl-2 inhibitor, wherein the Bcl-2 inhibitor is selected from the compounds described in WO 2010/138588 and a MDM2 inhibitor, wherein the MDM2 inhibitor is selected from the compounds described in WO2011/098398. Said MDM2 inhibitor preferably is a compound according to formula I or according to formula I-1 as disclosed in the present specification above. Preferably, the MDM2 inhibitor is 4-{[(2R,3S,4R,5S)-4-(4-Chloro-2-fluoro-phenyl)-3-(3-chloro-2-fluoro-phenyl)-4-

compounds or ionizing radiation enhancing the effects of such agents are administered.

11. A pharmaceutical composition comprising a combination of a type I anti-CD20 antibody or a humanized B-Ly1 antibody which afucosylated with an amount of fucose of 60% or less of the total amount of oligosaccharides (sugars) at Asn297, and 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl} sulfonyl)benzamide 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 or a salt thereof for the treatment of cancer.

12. Use of a type I anti-CD20 antibody or an afucosylated anti-CD20 antibody with an amount of fucose of 60% or less of the total amount of oligosaccharides (sugars) at Asn297, in the manufacture of a medicament for the treatment of cancer in combination with a Bcl-2 inhibitor and a MDM2 inhibitor.
13. The use according to claim 12, characterized in that said cancer is a CD20 expressing cancer.
14. The use according to any one of claims 12 to 13, characterized in that said CD20 expressing cancer is a lymphoma or lymphocytic leukemia.
15. The use according to any one of claims 12 to 14, characterized in that said afucosylated anti-CD20 antibody is a humanized B-Ly1 antibody.
16. The use according to any one of claims 12 to 15, characterized in that the Bcl-2 inhibitor is 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)-N-({4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]-3-[(trifluoromethyl)sulfonyl]phenyl}sulfonyl)benzamide or a salt or polymorph thereof.
17. The use according to any one of claims 12 to 16, characterized in that the MDM2 inhibitor is 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 or a salt or polymorph thereof.

18. The use according to any one of claims 12 to 17, characterized in that one or more additional other cytotoxic, chemotherapeutic or anti-cancer agents, or compounds or ionizing radiation enhancing the effects of such agents are administered.