

BTK is activated upstream by Src-family kinases Blk, Lyn and Fyn and leads to downstream activation of essential cell survival pathways such as NF- κ B and MAP kinase. BTK contains a pleckstrin-homology (PH) domain that binds phosphatidylinositol (3,4,5)-trisphosphate (PI(3,4,5)P₃). PI(3,4,5)P₃ binding induces Btk to phosphorylate phospholipase C γ (PLC γ), which in turn hydrolyzes PI(4,5)P₂, a phosphatidylinositol, into two second messengers, inositol triphosphate (IP₃) and diacylglycerol (DAG), which then go on to modulate the activity of downstream proteins during B-cell signalling. Subsequently, Ca²⁺ is mobilized and NF- κ B and MAP kinase pathways are activated.

An exemplary BTK inhibitor described in the art is ibrutinib (PCI-32765; Advani et al.; J Clin Oncol. 2013: Jan 1; 31(1), page 88-94) which is a small molecule irreversible BTK inhibitor.

Summary of the Invention

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

One aspect of the ~~invention~~ disclosure is an anti-CD20 antibody for use in the treatment of cancer in combination with a BTK inhibitor. The disclosure relates to ~~is~~ 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 BTK inhibitor.

Another aspect of the ~~invention~~ disclosure is the 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, for the manufacture of a medicament for the treatment of cancer in combination with a BTK inhibitor. The disclosure relates to ~~is~~ the 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 BTK inhibitor.

The disclosure also relates to ~~Another aspect of the invention is~~ 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 BTK inhibitor, to a
5 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 one embodiment, said BTK inhibitor is a compound selected from the compounds described in WO2011/152351 and WO2013/081016. Said BTK inhibitor preferably is a compound according to formula I or according to formula I-1 as disclosed herein. Preferably, the BTK inhibitor is 6-amino-9-[(3R)-1-(2-butynoyl)-3-pyrrolidinyl]-7-(4-phenoxyphenyl)-7,9-dihydro-8H-purin-8-one or a salt thereof.

In one embodiment, said type I anti-CD20 antibody is rituximab, said afucosylated anti-CD20 antibody is humanized B-Ly1 antibody and said BTK inhibitor is selected from the group consisting of: the compounds described in WO2011/152351 and WO2013/081016. Said BTK inhibitor preferably is a compound according to formula I or according to formula I-1 as disclosed herein. Preferably, the BTK inhibitor is 6-amino-9-[(3R)-1-(2-butynoyl)-3-pyrrolidinyl]-7-(4-phenoxyphenyl)-7,9-dihydro-8H-purin-8-one 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.

Another aspect of the disclosure is 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 a BTK inhibitor which is selected from the group consisting of 6-amino-9-[(3R)-1-(2-butynoyl)-3-pyrrolidinyl]-7-(4-phenoxyphenyl)-7,9-dihydro-8H-purin-8-one or a salt thereof for use in the treatment of cancer.

One embodiment of the ~~disclosure invention~~ 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), and a BTK inhibitor (in one embodiment, the BTK inhibitor is selected from the group consisting of: the compounds described in WO2011/152351 and WO2013/081016. Said BTK inhibitor preferably is a compound according to formula I or according to formula I-1 as disclosed herein. Preferably, the BTK inhibitor is 6-amino-9-[(3R)-1-(2-

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Patent Claims

1. An anti-CD20 antibody for use in the treatment of cancer in combination with a BTK inhibitor.
- 5 2. The antibody according to claim 1, characterized in that said anti-CD20 antibody is 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.
3. The antibody according to any one of claims 1 to 2, characterized in that said cancer is a CD20 expressing cancer.
- 10 4. The antibody according to any one of claims 1 to 3, characterized in that said CD20 expressing cancer is a lymphoma or lymphocytic leukemia.
5. The antibody according to any one of claims 1 to 4, characterized in that said afucosylated anti-CD20 antibody is a humanized B-Ly1 antibody.
- 15 6. The antibody according to any one of claims 1 to 5, characterized in that said afucosylated anti-CD20 antibody is obinutuzumab.
7. The antibody according to any one of claims 1 to 4, characterized in that said type I anti-CD20 antibody is rituximab.
8. The antibody according to any one of claims 1 to 7, characterized in that said BTK inhibitor is 6-amino-9-[(3R)-1-(2-butynoyl)-3-pyrrolidinyl]-7-(4-
20 phenoxyphenyl)-7,9-dihydro-8H-purin-8-one or a salt thereof.
9. The antibody according to any one of claims 1 to 8, 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.
- 25 10. 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 a BTK inhibitor which is selected from the group consisting of 6-amino-9-[(3R)-1-(2-butynoyl)-3-pyrrolidinyl]-7-(4-

phenoxyphenyl)-7,9-dihydro-8H-purin-8-one or a salt thereof for use in the treatment of cancer.

- 5 ~~11. A method of treatment of patient suffering from cancer by administering 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 combination with a BTK inhibitor, to a patient in the need of such treatment.~~
- ~~12. The method according to claim 11, characterized in that said cancer is a CD20-expressing cancer.~~
- 10 ~~13. The method according to any one of claims 11 to 12, characterized in that said CD20-expressing cancer is a lymphoma or lymphocytic leukemia.~~
- ~~14. The method according to any one of claims 11 to 13, characterized in that said afucosylated anti-CD20 antibody is a humanized B-Ly1 antibody.~~
- 15 ~~15. The method according to any one of claims 11 to 13, characterized in that said type I anti-CD20 antibody is rituximab.~~
- ~~16. The method according to any one of claim 11 to 15, characterized in that said BTK inhibitor is selected from the group consisting of 6-amino-9-[(3R)-1-(2-butynoyl)-3-pyrrolidinyl]-7-(4-phenoxyphenyl)-7,9-dihydro-8H-purin-8-one or a salt thereof.~~
- 20 ~~17. The method according to any one of claims 9 to 16, 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.~~
- 25 ~~18~~11. 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, for the manufacture of a medicament for the treatment of cancer in combination with a BTK inhibitor.

~~19~~12. The use according to claim ~~18~~11, characterized in that said cancer is a CD20 expressing cancer.

~~20~~13. The use according to any one of claims ~~18~~11 to ~~19~~12, characterized in that said CD20 expressing cancer is a lymphoma or lymphocytic leukemia.

5 ~~21~~14. The use according to any one of claims ~~18~~11 to ~~20~~13, characterized in that said afucosylated anti-CD20 antibody is a humanized B-Ly1 antibody.

15. The use according to any one of claims 11 to 14, characterized in that said afucosylated anti-CD20 antibody is obinutuzumab.

10 16. The use according to any one of claims 11 to 13, characterized in that said type I anti-CD20 antibody is rituximab.

~~22~~17. The use according to any one of claims ~~18~~11 to ~~21~~16, characterized in that said BTK inhibitor is 6-amino-9-[(3R)-1-(2-butynoyl)-3-pyrrolidinyl]-7-(4-phenoxyphenyl)-7,9-dihydro-8H-purin-8-one or a salt thereof.

15 ~~23~~18. The use according to any one of claims ~~18~~11 to ~~22~~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.