dimer formation renders the new Cys unreactive for conjugation to a drug, ligand, or other label. Furthermore, if the protein oxidatively forms an intramolecular disulfide bond between the newly engineered Cys and an existing Cys residue, both Cys thiol groups are unavailable for active site participation and interactions. Furthermore, the protein may be rendered inactive or non-specific, by misfolding or loss of tertiary structure (Zhang et al (2002) Anal. Biochem. 311:1-9).

[0014] Cysteine-engineered antibodies have been designed as FAB antibody fragments (thioFab) and expressed as full-length, IgG monoclonal (thioMab) antibodies (Junutula, J.R. et al. (2008) J Immunol Methods 332:41-52; US 2007/0092940, the contents of which are incorporated by reference). ThioFab and ThioMab antibodies have been conjugated through linkers at the newly introduced cysteine thiols with thiol-reactive linker reagents and drug-linker reagents to prepare antibody drug conjugates (Thio ADC).

[0015] All references cited herein, including patent applications and publications, are incorporated by reference in their entirety.

Summary

[0016] We have now found out that the combination of an afucosylated anti-CD20 antibody with a CD79b antibody-drug conjugate showed significantly enhanced antiproliferative effects.

[0017] 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 CD79b antibody-drug conjugate.

[0018] The disclosure also relates to 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 CD79b antibody-drug conjugate.

[0019] 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 CD79b antibody-drug conjugate, to a patient in the need of such treatment.

[0020] 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.

[0021] 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 a humanized B-Ly1 antibody. In a specific embodiment, the anti-CD20 antibody is obinutuzumab (recommended INN, WHO Drug Information, Vol. 26, No. 4, 2012, p. 453). As used herein, obinutuzumab is synonymous for GA101. This replaces all previous versions (e.g. Vol. 25, No. 1, 2011, p.75-76), and is formerly known as afutuzumab (recommended INN, WHO Drug Information, Vol. 23, No. 2, 2009, p. 176;Vol. 22, No. 2, 2008, p. 124).

[0022] In one embodiment, the CD79b antibody in the CD79b antibody-drug conjugate disclosure is a humanized anti-CD79b antibody wherein the monovalent affinity (e.g affinity of the antibody as a Fab fragment to CD79b) or affinity in its bivalent form of the antibody to CD79b (e.g. affinity of the antibody as an IgG fragment to CD79b) is substantially the same as, lower than, or greater than, the monovalent affinity or affinity in its bivalent form, respectively, of a murine antibody (e.g. affinity of the murine antibody as a Fab fragment or as an IgG fragment to CD79b) or a chimeric antibody (e.g. affinity of the chimeric antibody as a Fab fragment or as an IgG fragment to CD79b), comprising, consisting or consisting essentially of a light chain and heavy chain variable domain sequence as as depicted in Figure 7 (SEQ ID NO: 26) and in Figure 8 (SEQ ID NO: 29).

[0023] In one embodiment, the CD79b antibody in the CD79b antibody-drug conjugate disclosure is a humanized anti-CD79b antibody wherein the affinity of the antibody in its bivalent form to CD79b (e.g., affinity of the antibody as an IgG to CD79b) is 0.4 nM, 0.2 nM or 0.5 nM.

[0024] In one embodiment, the CD79b antibody in the CD79b antibody-drug conjugate comprises at least one, two, three, four, five or six HVRs selected from the group consisting of:

(i) HVR-L1 comprising sequence A1-A15, wherein A1-A15 is KASQSVDYDGDSFLN (SEQ ID NO: 31)

(ii) HVR-L2 comprising sequence B1-B7, wherein B1-B7 is AASNLES (SEQ ID NO: 32)

(iii) HVR-L3 comprising sequence C1-C9, wherein C1-C9 is QQSNEDPLT (SEQ ID NO: 33)

(iv) HVR-H1 comprising sequence D1-D10, wherein D1-D10 is GYTFSSYWIE (SEQ ID NO: 34)

(v) HVR-H2 comprising sequence E1-E18, wherein E1-E18 is GEILPGGGDTNYNEIFKG (SEQ ID NO: 35) and

(vi) HVR-H3 comprising sequence F1-F10, wherein F1-F10 IS TRRVPVYFDY (SEQ ID NO: 36).

[0025] In one embodiment, an antibody that binds to CD79b in the CD79b antibody-drug conjugate according to the disclosure comprises at least one variant HVR wherein the variant HVR sequence comprises modification of at least one residue of the sequence depicted in SEQ ID NOs: 31, 32, 33, 34, 35 or 36.

[0026] In one embodiment, the disclosure provides an antibody in the CD79b antibody-drug conjugate according to the disclosure comprising a heavy chain variable domain comprising the HVR1-HC, HVR2-HC and/or HVR3-HC sequence depicted in Figure 3B (SEQ ID NO: 50-52).

[0027] In one embodiment, the disclosure provides an antibody in the CD79b antibody-drug conjugate according to the disclosure comprising a light chain variable domain comprising HVR1-LC, HVR2-LC and/or HVR3-LC sequence depicted in Figure 3A (SEQ ID NO: 47-49).

[0028] In one embodiment, the disclosure provides an antibody in the CD79b antibody-drug conjugate according to the disclosure comprising a heavy chain variable domain comprising the HVR1-HC, HVR2-HC and/or HVR3-HC sequence depicted in Figure 4B (SEQ ID NO: 58-60).

[0029] In one embodiment, the disclosure provides an antibody in the CD79b antibody-drug conjugate according to the disclosure comprising a light chain variable domain comprising HVR1-LC, HVR2-LC and/or HVR3-LC sequence depicted in Figure 4A (SEQ ID NO: 55-57).

[0030] In one embodiment, the disclosure provides an antibody in the CD79b antibody-drug conjugate according to the disclosure comprising a heavy chain variable domain comprising the HVR1-HC, HVR2-HC and/or HVR3-HC sequence depicted in Figure 5B (SEQ ID NO: 66-68).

[0031] In one embodiment, the disclosure provides an antibody in the CD79b antibody-drug conjugate according to the disclosure comprising a light chain variable domain comprising HVR1-LC, HVR2-LC and/or HVR3-LC sequence depicted in Figure 5A (SEQ ID NO: 63-65).

[0032] In one embodiment, the disclosure provides an antibody in the CD79b antibody-drug conjugate according to the disclosure comprising a heavy chain variable domain comprising the HVR1-HC, HVR2-HC and/or HVR3-HC sequence depicted in Figure 6B (SEQ ID NO: 74-76).

[0033] In one embodiment, the disclosure provides an antibody in the CD79b antibody-drug conjugate according to the disclosure comprising a light chain variable domain comprising HVR1-LC, HVR2-LC and/or HVR3-LC sequence depicted in Figure 6A (SEQ ID NO: 71-73).

[0034]In one embodiment, the disclosure includes an anti-CD79b antibody in the CD79b antibody-drug conjugate according to the disclosure comprising a heavy chain variable domain selected from SEQ ID NOs: 54, 62, 70 or 78. In another aspect, the disclosure includes an anti-CD79b antibody in the CD79b antibody-drug

conjugate according to the disclosure comprising a light chain variable domain selected from SEQ ID NOs: 53, 61, 69 or 77.

[0035] In one embodiment, the disclosure includes a cysteine engineered anti-CD79b antibody in the CD79b antibody-drug conjugate according to the disclosure comprising one or more free cysteine amino acids and a sequence selected from SEQ ID NOs: 83-130. The cysteine engineered anti-CD79b antibody in the CD79b antibody-drug conjugate according to the disclosure may bind to a CD79b polypeptide. The cysteine engineered anti-CD79b antibody in the CD79b antibody-drug conjugate according to the disclosure may be prepared by a process comprising replacing one or more amino acid residues of a parent anti-CD79b antibody by cysteine.

[0036] In one embodiment, the disclosure includes a cysteine engineered anti-CD79b antibody in the CD79b antibody-drug conjugate according to the disclosure comprising one or more free cysteine amino acids wherein the cysteine engineered anti-CD79b antibody binds to a CD79b polypeptide and is prepared by a process comprising replacing one or more amino acid residues of a parent anti-CD79b antibody by cysteine wherein the parent antibody comprises at least one HVR sequence selected from:

(i) HVR-L1 comprising sequence A1-A15, wherein A1-A15 is KASQSVDYDGDSFLN (SEQ ID NO: 31) or KASQSVDYEGDSFLN (SEQ ID NO: 37);

(ii) HVR-L2 comprising sequence B1-B7, wherein B1-B7 is AASNLES (SEQ ID NO: 32);

(iii) HVR-L3 comprising sequence C1-C9, wherein C1-C9 is QQSNEDPLT (SEQ ID NO: 33);

(iv) HVR-H1 comprising sequence D1-D10, wherein D1-D10 is GYTFSSYWIE (SEQ ID NO: 34);

(v) HVR-H2 comprising sequence E1-E18, wherein E1-E18 is GEILPGGGDTNYNEIFKG (SEQ ID NO: 35) and

(vi) HVR-H3 comprising sequence F1-F10, wherein F1-F10 is TRRVPVYFDY (SEQ ID NO: 36) or TRRVPIRLDY (SEQ ID NO: 38).

[0037] In one embodiment, the CD79b antibody in the CD79b antibody-drug conjugate comprises a variable light chain sequence selected from the group consisting of light chain human kappa I consensus sequence (labeled as "huKI"; SEQ ID NO: 25) with VL-FR1, VL-FR2, VL-FR3, VL-FR4 (SEQ ID NOs: 39-42, respectively), murine anti-CD79b antibody (labeled as "MA79b"; SEQ ID NO: 26), MA79b-grafted "humanized" antibody (labeled as "huMA79b graft"; SEQ ID NO: 27), MA79b-grated "humanized" antibody variant 17 (labeled as "huMA79b.v17"; SEQ ID NO: 53), MA79b-grafted "humanized" antibody variant 18 (labeled as "huMA79b.v18"; SEQ ID NO: 61), MA79b-grafted "humanized" antibody variant 28 (labeled as "huMA79b.v28"; SEQ ID NO: 69) and MA79b-grafted "humanized" antibody variant 32 (labeled as "huMA79b.v32"; SEQ ID NO: 77).

[0038] In one embodiment, the CD79b antibody in the CD79b antibody-drug conjugate disclosure comprises a variable heavy chain sequence selected from the group consisting of: heavy chain human subgroup III consensus sequence (labeled as "humIII"; SEQ ID NO: 28) with VH-FR1, VH-FR2, VH-FR3, and VH-FR4 (SEQ ID NOs: 43-46), murine anti-CD79b antibody (labeled as "MA79b"; SEQ ID NO: 29), MA79b-grafted "humanized" antibody (labeled as "huMA79b graft"; SEQ ID NO: 30) (containing 71A, 73T and 78A), MA79b-grated "humanized" antibody variant 17 (labeled as "huMA79b.v17"; SEQ ID NO: 54) (containing 71A, 73T and 78A), MA79b-grafted "humanized" antibody variant 18 (labeled as "huMA79b.v18"; SEQ ID NO: 62) (containing 71A, 73T and 78A), MA79b-grafted "humanized" antibody variant 28 (labeled as "huMA79b.v28"; SEQ ID NO: 70) (containing 71A, 73T and 78A) and MA79b-grafted "humanized" antibody variant 32 (labeled as "huMA79b.v32"; SEQ ID NO: 78) (containing 71A, 73T and 78A).

[0039] In one embodiment, the CD79b antibody in the CD79b antibody-drug conjugate comprises a cysteine engineered anti-CD79b antibody comprising one or more free cysteine amino acids wherein the cysteine engineered anti-CD79b antibody binds to a CD79b polypeptide and is prepared by a process comprising replacing one or more amino acid residues of a parent anti-CD79b antibody by

cysteine wherein the parent antibody comprises at least one HVR sequence selected from:

(a) HVR-L1 comprising sequence A1-A15, wherein A1-A15 is KASQSVDYDGDSFLN (SEQ ID NO: 31) or KASQSVDYEGDSFLN (SEQ ID NO: 37);

(b) HVR-L2 comprising sequence B1-B7, wherein B1-B7 is AASNLES (SEQ ID NO: 32)

(c) HVR-L3 comprising sequence C1-C9, wherein C1-C9 is QQSNEDPLT (SEQ ID NO: 33)

(d) HVR-H1 comprising sequence D1-D10, wherein D1-D10 is GYTFSSYWIE (SEQ ID NO: 34)

(e) HVR-H2 comprising sequence E1-E18, wherein E1-E18 is GEILPGGGDTNYNEIFKG (SEQ ID NO: 35) and

(f) HVR-H3 comprising sequence F1-F10, wherein F1-F10 is TRRVPVYFDY (SEQ ID NO: 36) or TRRVPIRLDY (SEQ ID NO: 38).

[0040] In one embodiment, the CD79b antibody-drug conjugate having the formula Ab-(L-D)p (Formula I), wherein

(a) Ab is the CD79b antibody as defined herein;

(b) L is a linker;

(c) D is a drug moiety.

[0041] Accordingly, the antibody may be conjugated to the drug either directly or via a linker. In Formula I, p is the average number of drug moieties per antibody, which can range, e.g., from about 1 to about 20 drug moieties per antibody, and in certain embodiments, from 1 to about 8 drug moieties per antibody. The disclosure includes a composition comprising a mixture of antibody-drug compounds of Formula I where the average drug loading per antibody is about 2 to about 5, or about 3 to about 4.

[0042] In one embodiment of the CD79b antibody-drug conjugate having the formula Ab-(L-D)p, L is selected from 6-maleimidocaproyl (MC), maleimidopropanoyl (MP), valine-citrulline (val-cit), alanine-phenylalanine (ala-phe), p-aminobenzyloxycarbonyl (PAB), N-Succinimidyl 4-(2-pyridylthio) pentanoate (SPP), N-succinimidyl 4-(N-maleimidomethyl) cyclohexane-1 carboxylate (SMCC), and N-Succinimidyl (4-iodo-acetyl) aminobenzoate (SIAB).

[0043] In one embodiment of the CD79b antibody-drug conjugate having the formula Ab-(L-D)p, D is selected from the group consisting of auristatin, dolostantin, DM1, DM3, DM4, MMAE and MMAF.

[0044] In one embodiment, said CD79b antibody-drug conjugate is anti-CD79b-MC-vc-PAB-MMAE. In a specific embodiment, the anti-CD79b antibody in said conjugate is huMA79b.v28.

[0045] In one embodiment, the afucosylated anti-CD20 antibody binds CD20 with an KD of 10^{-8} M to 10^{-13} M.

[0046] One embodiment of the disclosure is a composition comprising 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 CD79b antibody-drug conjugate. In one embodiment of the composition according to the disclosure, said anti-CD20 antibody is obinutuzumab.

[0047] In one embodiment of the composition according to the disclosure, said CD79b antibody in the CD79b antibody-drug conjugate comprises at least one, two, three, four, five or six HVRs selected from the group consisting of:

(i) HVR-L1 comprising sequence A1-A15, wherein A1-A15 is KASQSVDYDGDSFLN (SEQ ID NO: 31)

(ii) HVR-L2 comprising sequence B1-B7, wherein B1-B7 is AASNLES (SEQ ID NO: 32)

(iii) HVR-L3 comprising sequence C1-C9, wherein C1-C9 is QQSNEDPLT (SEQ ID NO: 33)

(iv) HVR-H1 comprising sequence D1-D10, wherein D1-D10 is GYTFSSYWIE (SEQ ID NO: 34)

(v) HVR-H2 comprising sequence E1-E18, wherein E1-E18 is GEILPGGGDTNYNEIFKG (SEQ ID NO: 35) and

(vi) HVR-H3 comprising sequence F1-F10, wherein F1-F10 IS TRRVPVYFDY (SEQ ID NO: 36).

[0048] In one embodiment of the composition according to the disclosure, the CD79b antibody in the CD79b antibody-drug conjugate comprises a variable light chain sequence selected from the group consisting of light chain human kappa I consensus sequence (labeled as "huKI"; SEQ ID NO: 25) with VL-FR1, VL-FR2, VL-FR3, VL-FR4 (SEQ ID NOs: 39-42, respectively), murine anti-CD79b antibody (labeled as "MA79b"; SEQ ID NO: 26), MA79b-grafted "humanized" antibody (labeled as "huMA79b graft"; SEQ ID NO: 27), MA79b-grated "humanized" antibody variant 17 (labeled as "huMA79b.v17"; SEQ ID NO: 53), MA79b-grafted "humanized" antibody variant 18 (labeled as "huMA79b.v18"; SEQ ID NO: 61), MA79b-grafted "humanized" antibody variant 28 (labeled as "huMA79b.v28"; SEQ ID NO: 69) and MA79b-grafted "humanized" antibody variant 32 (labeled as "huMA79b.v32"; SEQ ID NO: 77).

[0049] In one embodiment of the composition according to the disclosure, the CD79b antibody in the CD79b antibody-drug conjugate comprises a variable heavy chain sequence selected from the group consisting of: heavy chain human subgroup III consensus sequence (labeled as "humIII"; SEQ ID NO: 28) with VH-FR1, VH-FR2, VH-FR3, and VH-FR4 (SEQ ID NOs: 43-46), murine anti-CD79b antibody (labeled as "MA79b"; SEQ ID NO: 29), MA79b-grafted "humanized" antibody (labeled as "huMA79b graft"; SEQ ID NO: 30) (containing 71A, 73T and 78A), MA79b-grated "humanized" antibody variant 17 (labeled as "huMA79b.v17"; SEQ ID NO: 54) (containing 71A, 73T and 78A), MA79b-grafted "humanized" antibody variant 18 (labeled as "huMA79b.v18"; SEQ ID NO: 62) (containing 71A, 73T and 78A), MA79b-grafted "humanized" antibody variant 28 (labeled as "huMA79b.v28"; SEQ ID NO: 70) (containing 71A, 73T and 78A) and MA79b-grafted "humanized" antibody variant 32 (labeled as "huMA79b.v32"; SEQ ID NO: 78) (containing 71A, 73T and 78A).

[0050] In one embodiment of the composition according to the disclosure, one or more additional other cytotoxic, chemotherapeutic or anti-cancer agents, or compounds or ionizing radiation that enhance the effects of such agents are administered.

[0051] In one embodiment of the composition according to the disclosure, the CD79b antibody-drug conjugate is having the formula Ab-(L-D)p, wherein

(a) Ab is the CD79b antibody as defined herein;

(b) L is a linker;
(c) D is a drug moiety.

[0052] In one embodiment of the composition according to the disclosure, the CD79b antibody-drug conjugate is having the formula Ab-(L-D)p, wherein L is selected from 6-maleimidocaproyl (MC), maleimidopropanoyl (MP), valine-citrulline (val-cit), alanine-phenylalanine (ala-phe), p-aminobenzyloxycarbonyl (PAB), N-Succinimidyl 4-(2-pyridylthio) pentanoate (SPP), N-succinimidyl 4-(N-maleimidomethyl) cyclohexane-1 carboxylate (SMCC), and N-Succinimidyl (4-iodo-acetyl) aminobenzoate (SIAB).

[0053] In one embodiment of the composition according to the disclosure, the CD79b antibody-drug conjugate is having the formula Ab-(L-D)p, wherein D is selected from the group consisting of auristatin, dolostantin, DM1, DM3, DM4, MMAE and MMAF.

[0054] In one embodiment of the composition according to the disclosure, the CD79b antibody-drug conjugate is is anti-CD79b-MC-vc-PAB-MMAE for the treatment of cancer. In a specific embodiment, the anti-CD79b antibody in said conjugate is huMA79b.v28. 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 CD79b antibody-drug conjugate.

[0055] One embodiment of the disclosure 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 CD79b antibody-drug conjugate, to a patient in the need of such treatment.

[0056] In one embodiment according to the disclosure, the method is characterized in that said cancer is a CD20 expressing cancer.

[0057] In one embodiment according to the disclosure, the method is characterized in that said CD20 expressing cancer is a lymphoma or lymphocytic leukemia.

[0058] In one embodiment according to the disclosure, the method is characterized in that said anti-CD20 antibody is a humanized B-Ly1 antibody.

[0059] In one embodiment according to the disclosure, the method is characterized in that said anti-CD20 antibody is obinutuzumab.

[0060] In one embodiment according to the disclosure, the method is characterized in that one or more additional other cytotoxic, chemotherapeutic or anti-cancer agents, or compounds or ionizing radiation that enhance the effects of such agents are administered.

[0061] In one embodiment according to the disclosure, the method is characterized in that said CD79b antibody in the CD79b antibody-drug conjugate comprises at least one, two, three, four, five or six HVRs selected from the group consisting of:

(i) HVR-L1 comprising sequence A1-A15, wherein A1-A15 is KASQSVDYDGDSFLN (SEQ ID NO: 31)

(ii) HVR-L2 comprising sequence B1-B7, wherein B1-B7 is AASNLES (SEQ ID NO: 32)

(iii) HVR-L3 comprising sequence C1-C9, wherein C1-C9 is QQSNEDPLT (SEQ ID NO: 33)

(iv) HVR-H1 comprising sequence D1-D10, wherein D1-D10 is GYTFSSYWIE (SEQ ID NO: 34)

(v) HVR-H2 comprising sequence E1-E18, wherein E1-E18 is GEILPGGGDTNYNEIFKG (SEQ ID NO: 35) and

(vi) HVR-H3 comprising sequence F1-F10, wherein F1-F10 IS TRRVPVYFDY (SEQ ID NO: 36).

[0062] In one embodiment of the method according to the disclosure, the CD79b antibody in the CD79b antibody-drug conjugate comprises a variable light chain sequence selected from the group consisting of light chain human kappa I consensus sequence (labeled as "huKI"; SEQ ID NO: 25) with VL-FR1, VL-FR2, VL-FR3, VL-FR4 (SEQ ID NOs: 39-42, respectively), murine anti-CD79b antibody (labeled as "MA79b"; SEQ ID NO: 26), MA79b-grafted "humanized" antibody (labeled as "huMA79b graft"; SEQ ID NO: 27), MA79b-grated "humanized" antibody variant 17 (labeled as "huMA79b.v17"; SEQ ID NO: 53), MA79b-grafted "humanized" antibody variant 18 (labeled as "huMA79b.v18"; SEQ ID NO: 61), MA79b-grafted "humanized" antibody variant 28 (labeled as "huMA79b.v28"; SEQ ID NO: 69) and MA79b-grafted "humanized" antibody variant 32 (labeled as "huMA79b.v32"; SEQ ID NO: 77).

[0063] In one embodiment of the method according to the disclosure, the CD79b antibody in the CD79b antibody-drug conjugate comprises a variable heavy chain sequence selected from the group consisting of: heavy chain human subgroup III consensus sequence (labeled as "humIII"; SEQ ID NO: 28) with VH-FR1, VH-FR2, VH-FR3, and VH-FR4 (SEQ ID NOs: 43-46), murine anti-CD79b antibody (labeled as "MA79b"; SEQ ID NO: 29), MA79b-grafted "humanized" antibody (labeled as "huMA79b graft"; SEQ ID NO: 30) (containing 71A, 73T and 78A), MA79b-grated "humanized" antibody variant 17 (labeled as "huMA79b.v17"; SEQ ID NO: 54) (containing 71A, 73T and 78A), MA79b-grafted "humanized" antibody variant 18 (labeled as "huMA79b.v18"; SEQ ID NO: 62) (containing 71A, 73T and 78A), MA79b-grafted "humanized" antibody variant 28 (labeled as "huMA79b.v28"; SEQ ID NO: 70) (containing 71A, 73T and 78A) and MA79b-grafted "humanized" antibody variant 32 (labeled as "huMA79b.v32"; SEQ ID NO: 78) (containing 71A, 73T and 78A).

[0064] In one embodiment of the method according to the disclosure, the CD79b antibody-drug conjugate is having the formula Ab-(L-D)p, wherein

(a) Ab is the CD79b antibody as disclosed herein;

(b) L is a linker;

(c) D is a drug moiety.

[0065] In one embodiment of the method according to the disclosure, the CD79b antibody-drug conjugate is having the formula Ab-(L-D)p, wherein L is selected from 6-maleimidocaproyl (MC), maleimidopropanoyl (MP), valine-citrulline (val-cit), alanine-phenylalanine (ala-phe), p-aminobenzyloxycarbonyl (PAB), N-Succinimidyl 4-(2-pyridylthio) pentanoate (SPP), N-succinimidyl 4-(N-maleimidomethyl) cyclohexane-1 carboxylate (SMCC), and N-Succinimidyl (4-iodo-acetyl) aminobenzoate (SIAB).

[0066] In one embodiment of the method according to the disclosure, the CD79b antibody-drug conjugate is having the formula Ab-(L-D)p, wherein D is selected from the group consisting of auristatin, dolostantin, DM1, DM3, DM4, MMAE and MMAF.

[0067] In one embodiment of the method according to the disclosure, the CD79b antibody-drug conjugate is anti-CD79b-MC-vc-PAB-MMAE.

[0068] In one embodiment of the method according to the disclosure, the anti-CD79b antibody in said CD79b antibody-drug conjugate is huMA79b.v28.

[0069] One embodiment according to the disclosure 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 CD79b antibody-drug conjugate.

[0070] One embodiment of the use according to the disclosure is characterized in that said cancer is a CD20 expressing cancer.

[0071] One embodiment of the use according to the disclosure is characterized in that said CD20 expressing cancer is a lymphoma or lymphocytic leukemia.

[0072] One embodiment of the use according to the disclosure is characterized in that said anti-CD20 antibody is a humanized B-Ly1 antibody.

[0073] One embodiment of the use according to the disclosure is characterized in that said anti-CD20 antibody is obinutuzumab.

[0074] One embodiment of the use according to the disclosure is characterized in that one or more additional other cytotoxic, chemotherapeutic or anti-cancer agents, or compounds or ionizing radiation that enhance the effects of such agents are administered.

[0075] One embodiment of the use according to the disclosure is characterized characterized in that said CD79b antibody in the CD79b antibody-drug conjugate comprises at least one, two, three, four, five or six HVRs selected from the group consisting of:

(i) HVR-L1 comprising sequence A1-A15, wherein A1-A15 is KASQSVDYDGDSFLN (SEQ ID NO: 31)

(ii) HVR-L2 comprising sequence B1-B7, wherein B1-B7 is AASNLES (SEQ ID NO: 32)

(iii) HVR-L3 comprising sequence C1-C9, wherein C1-C9 is QQSNEDPLT (SEQ ID NO: 33)

(iv) HVR-H1 comprising sequence D1-D10, wherein D1-D10 is GYTFSSYWIE (SEQ ID NO: 34)

(v) HVR-H2 comprising sequence E1-E18, wherein E1-E18 is GEILPGGGDTNYNEIFKG (SEQ ID NO: 35) and

(vi) HVR-H3 comprising sequence F1-F10, wherein F1-F10 IS TRRVPVYFDY (SEQ ID NO: 36).

[0076] In one embodiment of the use according to the disclosure, the CD79b antibody in the CD79b antibody-drug conjugate comprises a variable light chain sequence selected from the group consisting of light chain human kappa I consensus sequence (labeled as "huKI"; SEQ ID NO: 25) with VL-FR1, VL-FR2, VL-FR3, VL-FR4 (SEQ ID NOs: 39-42, respectively), murine anti-CD79b antibody (labeled as "MA79b"; SEQ ID NO: 26), MA79b-grafted "humanized" antibody (labeled as "huMA79b graft"; SEQ ID NO: 27), MA79b-grated "humanized" antibody variant

17 (labeled as "huMA79b.v17"; SEQ ID NO: 53), MA79b-grafted "humanized" antibody variant 18 (labeled as "huMA79b.v18"; SEQ ID NO: 61), MA79b-grafted "humanized" antibody variant 28 (labeled as "huMA79b.v28"; SEQ ID NO: 69) and MA79b-grafted "humanized" antibody variant 32 (labeled as "huMA79b.v32"; SEQ ID NO: 77).

[0077] In one embodiment of the use according to the disclosure, the CD79b antibody in the CD79b antibody-drug conjugate comprises a variable heavy chain sequence selected from the group consisting of: heavy chain human subgroup III consensus sequence (labeled as "humIII"; SEQ ID NO: 28) with VH-FR1, VH-FR2, VH-FR3, and VH-FR4 (SEQ ID NOs: 43-46), murine anti-CD79b antibody (labeled as "MA79b"; SEQ ID NO: 29), MA79b-grafted "humanized" antibody (labeled as "huMA79b graft"; SEQ ID NO: 30) (containing 71A, 73T and 78A), MA79b-grated "humanized" antibody variant 17 (labeled as "huMA79b.v17"; SEQ ID NO: 54) (containing 71A, 73T and 78A), MA79b-grafted "humanized" antibody variant 18 (labeled as "huMA79b.v18"; SEQ ID NO: 62) (containing 71A, 73T and 78A), MA79b-grafted "humanized" antibody variant 28 (labeled as "huMA79b.v28"; SEQ ID NO: 70) (containing 71A, 73T and 78A) and MA79b-grafted "humanized" antibody variant 32 (labeled as "huMA79b.v32"; SEQ ID NO: 78) (containing 71A, 73T and 78A).

[0078] One embodiment of the use according to the disclosure is characterized in that the CD79b antibody-drug conjugate is having the formula Ab-(L-D)p, wherein

(a) Ab is the CD79b antibody as disclosed herein;

(b) L is a linker;

(c) D is a drug moiety.

[0079] One embodiment of the use according to the disclosure is characterized in that the CD79b antibody-drug conjugate is having the formula Ab-(L-D)p, wherein L is selected from 6-maleimidocaproyl (MC), maleimidopropanoyl (MP), valine-citrulline (val-cit), alanine-phenylalanine (ala-phe), p-aminobenzyloxycarbonyl (PAB), N-Succinimidyl 4-(2-pyridylthio) pentanoate

(SPP), N-succinimidyl 4-(N-maleimidomethyl) cyclohexane-1 carboxylate (SMCC), and N-Succinimidyl (4-iodo-acetyl) aminobenzoate (SIAB).

[0080] One embodiment of the use according to the disclosure is characterized in that the CD79b antibody-drug conjugate is having the formula Ab-(L-D)p, wherein D is selected from the group consisting of auristatin, dolostantin, DM1, DM3, DM4, MMAE and MMAF.

[0081] One embodiment of the use according to the disclosure is characterized in that the CD79b antibody-drug conjugate is anti-CD79b-MC-vc-PAB-MMAE.

[0082] One embodiment of the use according to the disclosure is characterized in that the anti-CD79b antibody in said CD79b antibody-drug conjugate is huMA79b.v28.

[0083] One embodiment of the use according to the disclosure is characterized in that one or more additional other cytotoxic, chemotherapeutic or anti-cancer agents, or compounds or ionizing radiation that enhance the effects of such agents are administered.

[0083a] One aspect of the disclosure relates to obinutuzumab, for use in the treatment of cancer in combination with a CD79b antibody-drug conjugate anti-CD79b-MC-vc-PAB-MMAE, wherein the anti-CD79B antibody in said CD79b antibody-drug conjugate is huMA79b.v28 comprising the light chain variable domain SEQ ID NO: 69 and the heavy chain variable domain SEQ ID NO: 70.

[0083b] Another aspect of the disclosure relates to a composition for use in the treatment of cancer comprising obinutuzumab and a CD79b antibody-drug conjugate anti-CD79b-MC-vc-PAB-MMAE, wherein the anti-CD79B antibody in said CD79b antibody-drug conjugate is huMA79b.v28 comprising the light chain variable domain SEQ ID NO: 69 and the heavy chain variable domain SEQ ID NO: 70.

[0083c] Another aspect of the disclosure relates to use of obinutuzumab in the manufacture of a medicament for the treatment of a CD20 expressing cancer in combination with a CD79b antibody-drug conjugate anti-CD79b-MC-vc-PAB-MMAE, wherein the anti-CD79B antibody in said CD79b antibody-drug conjugate is huMA79b.v28 comprising the light chain variable domain SEQ ID NO: 69 and the heavy chain variable domain SEQ ID NO: 70.

Description of the Figures

[0084] **Figure 1:** Effect of obinutuzumab (GA101), rituximab, anti- CD79b-ADC and the combinations of CD79b with GA101 or rituximab on a disseminated Z138 mantle cell lymphoma (MCL) model in SCID beige mice

[0085] **Figure 2:** Statistical analysis of the data in Figure 1 by Pairwise Wilcoxon and Pairwise Log-Rank test

[0086] **Figures 3A (light chain) and 3B (heavy chain)** show amino acid sequences of an antibody of the invention (huMA79b.v17). Figures 3A (light chain) and 3B (heavy chain) show amino acid sequences of the framework (FR), hypervariable region (HVR), first constant domain (CL or CH1) and Fc region (Fc) of one embodiment of an antibody of the invention (huMA79b.v17) (SEQ ID NOs: 131-134, 47-49, and 135 (Figure 3A) and SEQ ID NOs: 136-139, 50-52, and 140-

Patent Claims

1. Obinutuzumab, for use in the treatment of cancer in combination with a CD79b antibody-drug conjugate anti-CD79b-MC-vc-PAB-MMAE, wherein the anti-CD79B antibody in said CD79b antibody-drug conjugate is huMA79b.v28 comprising the light chain variable domain SEQ ID NO: 69 and the heavy chain variable domain SEQ ID NO: 70.

2. Obinutuzumab according to claim 1, characterized in that said cancer is a CD20 expressing cancer.

3. Obinutuzumab according to any one of claims 1 to 2, characterized in that said CD20 expressing cancer is a lymphoma or lymphocytic leukemia.

4. Obinutuzumab according to any one of claims 1 to 3, characterized in that one or more additional other cytotoxic, chemotherapeutic or anti-cancer agents, or compounds or ionizing radiation that enhance the effects of such agents are administered.

5. A composition for use in the treatment of cancer comprising obinutuzumab and a CD79b antibody-drug conjugate anti-CD79b-MC-vc-PAB-MMAE, wherein the anti-CD79B antibody in said CD79b antibody-drug conjugate is huMA79b.v28 comprising the light chain variable domain SEQ ID NO: 69 and the heavy chain variable domain SEQ ID NO: 70.

6. The composition according to claim 5, characterized in that one or more additional other cytotoxic, chemotherapeutic or anti-cancer agents, or compounds or ionizing radiation that enhance the effects of such agents are administered.

7. Use of obinutuzumab in the manufacture of a medicament for the treatment of a CD20 expressing cancer in combination with a CD79b antibody-drug conjugate anti-CD79b-MC-vc-PAB-MMAE, wherein the anti-CD79B antibody in said CD79b antibody-drug conjugate is huMA79b.v28 comprising the light chain variable domain SEQ ID NO: 69 and the heavy chain variable domain SEQ ID NO: 70.

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

9. The use according to claim 7 or 8, characterized in that one or more additional other cytotoxic, chemotherapeutic or anti-cancer agents, or compounds or ionizing radiation that enhance the effects of such agents are administered.