

2793-2799. Monoclonal antibody SJ25-C1 is commercially available (Product No. 4737, Sigma-Aldrich Co. USA, SEQ ID NO: 21 to 24). Antibodies with increased affinity to the FcγRIIIA are mentioned in WO 2008/022152.

5 Antibody against CD19 can have inhibitory or stimulating effects on B-cell activation. Binding of CD19 antibodies to mitogen-stimulated B-cells inhibits the subsequent rise in Ca²⁺ and the resulting activation and proliferation of these cells and B-cell proliferation and differentiation can either be inhibited or enhanced by CD19 antibody depending on the mitogenic stimulus used and the degree of crosslinking by the antibody.

10 In WO 2004/106381 pharmaceutical compositions comprising bispecific anti-CD3, anti-CD19 antibody constructs for the treatment of B-cell related disorders are reported. Anti-CD19 antibodies are reported in WO 2005/012493. In WO 2006/089133 anti-CD19 antibodies and uses in oncology are reported. Anti-CD19 antibodies and their uses are reported in WO 2007/002223. In WO 2006/133450
15 anti-CD19 antibody therapy for the transplantation is reported.

In WO 2011/147834 antibodies against CD19 and uses thereof are reported.

SUMMARY

Herein are provided antibodies against (human) CD19 which are useful as a therapeutic agent for treatment of an autoimmune disease, rheumatoid arthritis,
20 lupus, psoriasis, or a bone disease or for tumor treatment.

The disclosure is based, in part, on the finding that for removing multiple deamidation hotspots in a humanized anti-human CD19 antibody a single mutation is sufficient.

The antibodies as reported herein have properties causing a benefit for a patient
25 suffering from a disease associated with pathologic increase of B-cells.

One aspect as reported herein is an antibody that specifically binds to human CD19, wherein the antibody comprises

- (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 03,
- (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 11,
- 30 (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 05,
- (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 20 or 28,

- (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 07, and
- (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 08.

In one embodiment the antibody is a monoclonal antibody.

In one embodiment the antibody is a human, humanized or chimeric antibody.

- 5 In one embodiment the antibody is an antibody fragment that specifically binds to human CD19.

In one embodiment the antibody comprises

- (a) a VH sequence having at least 95 % sequence identity to the amino acid sequence of SEQ ID NO: 09 and a VL sequence having at least 95 % sequence identity to the amino acid sequence of SEQ ID NO: 19, or
- 10 (b) a VH sequence having at least 95 % sequence identity to the amino acid sequence of SEQ ID NO: 09 and a VL sequence having at least 95 % sequence identity to the amino acid sequence of SEQ ID NO: 27, or
- (c) a VH sequence and a VL sequence as in (a) or (b).

- 15 In one embodiment the antibody is a bispecific antibody that specifically binds to human CD19 and a second different antigen.

One aspect as reported herein is a pharmaceutical formulation comprising the antibody as reported herein and a pharmaceutically acceptable carrier.

- 20 As reported herein is the antibody as reported herein for the treatment of B-cell malignancies. In one embodiment the B-cell malignancy is selected from the group consisting of CLL, NHL and DLBCL.

One aspect as reported herein is the antibody as reported herein for use as a medicament.

- 25 In one embodiment the medicament is for the treatment of a B-cell cancer, an inflammatory disease, an autoimmune disease, rheumatoid arthritis, lupus, psoriasis, or a bone disease. In one embodiment the medicament is for the depletion of B-cells.

- 30 As reported herein is the antibody as reported herein for use in treating a B-cell cancer, an inflammatory disease, an autoimmune disease, rheumatoid arthritis, lupus, psoriasis, or a bone disease. One aspect as reported herein is the antibody as reported herein for use in the treatment of B-cell cancer.

One aspect as reported herein is the antibody as reported herein for use in depleting B-cells.

5 One aspect as reported herein is the use of the antibody as reported herein in the manufacture of a medicament. In one embodiment the medicament is for the treatment of a B-cell cancer, an inflammatory disease, an autoimmune disease, rheumatoid arthritis, lupus, psoriasis, or a bone disease. In one embodiment the medicament is for the depletion of B-cells.

10 As reported herein is a method of treating an individual having a B-cell cancer comprising administering to the individual an effective amount of the antibody as reported herein.

As reported herein is a method of depleting B-cells in an individual comprising administering to the individual an effective amount of the antibody as reported herein.

15 As reported herein is a method for the manufacture of a medicament for the treatment of a disease comprising an antibody as reported herein. In one embodiment the disease is a B-cell cancer, an inflammatory disease, an autoimmune disease, rheumatoid arthritis, lupus, psoriasis, or a bone disease.

As reported herein is an isolated nucleic acid encoding the antibody as reported herein.

20 As reported herein is a host cell comprising the nucleic acid as reported herein.

As reported herein is a method of producing an antibody comprising culturing the host cell comprising the nucleic acid encoding the antibody so that the antibody is produced, recovering the antibody from the cell or the cultivation medium and purifying the antibody.

25 As reported herein is an immunoconjugate comprising the antibody as reported herein and a cytotoxic agent.

Patent Claims

1. An antibody that specifically binds to human CD19, wherein the antibody comprises
 - (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 03,
 - (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 11,
 - 5 (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 05,
 - (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 20 or 28,
 - (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 07, and
 - (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 08.
- 10 2. The antibody according to claim 1, wherein the antibody is a monoclonal antibody.
3. The antibody according to any one of claims 1 to 2, wherein the antibody is a human, humanized or chimeric antibody.
4. The antibody according to any one of claim 1 to 3, wherein the antibody is

15 an antibody fragment that specifically binds to human CD19.
5. The antibody according to any one of claims 1 to 4, wherein the antibody comprises
 - (a) a VH sequence having at least 95 % sequence identity to the amino acid sequence of SEQ ID NO: 09 and a VL sequence having at least 95 %

20 sequence identity to the amino acid sequence of SEQ ID NO: 19, or
 - (b) a VH sequence having at least 95 % sequence identity to the amino acid sequence of SEQ ID NO: 09 and a VL sequence having at least 95 % sequence identity to the amino acid sequence of SEQ ID NO: 27, or
 - (c) a VH sequence and a VL sequence as in (a) or (b).
- 25 6. A pharmaceutical formulation comprising the antibody according to any one of claims 1 to 5 and a pharmaceutically acceptable carrier.
7. The antibody according to any one of claims 1 to 5 for use as a medicament.
8. The antibody according to any one of claims 1 to 5 for use in the treatment

30 of B-cell cancer.

9. The antibody according to any one of claims 1 to 5 for use in the depletion of B-cells.
10. Use of the antibody according to any one of claims 1 to 5 in the manufacture of a medicament.
- 5 11. The use according to claim 10, wherein the medicament is for the treatment of a B-cell cancer.
12. The use according to claim 10, wherein the medicament is for the depletion of B-cells.