Claims in response to second Written Opinion

1. A radioimmunoconjugate comprising,
   - a monoclonal antibody targeting CD37,
   - an optional linker,
   - a radionuclide,

for use in upregulating antigen expression of an antigen on the surface of B-cell cancer cells, wherein;
   - the upregulated antigen is CD20,
   - the upregulation is followed by anti-CD20 antibody therapy in a single administration or in a repeated administration pattern, and
   - the administration of anti-CD20 antibody is 0-15 days after administration of radioimmunoconjugate.

2. a) A radioimmunoconjugate comprising,
- a monoclonal antibody targeting CD37,
- an optional linker,
- a radionuclide, and

b) an anti-CD20 antibody,

for use in the treatment of a B-cell malignancy selected from the group consisting of non-Hodgkin lymphoma, acute Lymphoblastic Leukemia, and chronic lymphocytic leukemia, wherein;
- the radioimmunoconjugate upregulates antigen expression of an antigen expressed on the surface of B-cell cancer cells,
- the upregulated antigen is CD20,
- the upregulation is followed by anti-CD20 antibody therapy in a single administration or in a repeated administration pattern, and
- the administration of anti-CD20 antibody is 0-15 days after administration of radioimmunoconjugate.

3. The radioimmunoconjugate and anti-CD20 antibody according to claims 1-2, wherein the administration of anti-CD20 antibody is at least one day after radioimmunoconjugate administration.

4. The radioimmunoconjugate for the use according to claim 1, wherein the anti-CD20 antibody is rituximab or obinutuzumab.

5. The radioimmunoconjugate for the use according to anyone of claims 1-4, wherein the upregulation is done prior to immunotherapy or immunoconjugate therapy in a patient suffering from cancer.

6. The radioimmunoconjugate for the use according to anyone of claims 5, wherein the patient is suffering from a B-cell malignancy selected from the group consisting of non-Hodgkin lymphoma and chronic lymphocytic leukemia.

7. The radioimmunoconjugate for the use according to anyone of claims 1-6, wherein the radiolabeled monoclonal antibody is HH1.

8. The radioimmunoconjugate for the use according to anyone of claims 1-7, wherein the linker is a chelating linker selected from the group consisting of p-SCN-bn-DOTA, DOTA-NHS-ester, p-SCN-Bn-DTPA and CHX-A''-DTPA.

9. The radioimmunoconjugate for the use according to anyone of claims 1-8, wherein the radionuclide is selected from the group consisting of ^{47}Sc, ^{67}Cu, ^{90}Y, ^{105}Rh, ^{117m}Sn, ^{131}I, ^{149}Tb, ^{153}Sm, ^{161}Tb, ^{165}Dy, ^{177}Lu, ^{186}Re, ^{188}Re, ^{211}At, ^{212}Pb, ^{212}Bi, ^{213}Bi, ^{223}Ra, ^{224}Ra, ^{225}Ac, and ^{227}Th.

10. The radioimmunoconjugate for the use according to anyone of claims 1-9, wherein the radioimmunoconjugate is formulated as a pharmaceutical composition.

11. The radioimmunoconjugate for the use according to anyone of claims 1-10, wherein the pharmaceutical composition comprises one or more pharmaceutically acceptable carriers or adjuvants.

12. Use of a radioimmunoconjugate comprising, a monoclonal antibody targeting CD37, an optional linker, and a radionuclide, in the manufacture of a medicament for treating a B-cell malignancy selected from the group consisting of non-Hodgkin lymphoma, acute Lymphoblastic Leukemia, and chronic lymphocytic leukemia, the use comprising:

- a radioimmunoconjugate, to be administered, comprising,
- a monoclonal antibody targeting CD37,
- an optional linker,
- a radionuclide, and

- an anti-CD20 antibody to be administered, wherein

the radioimmunoconjugate upregulates antigen expression of an antigen expressed on the surface of B-cell cancer cells, the upregulated antigen is CD20, the upregulation is followed by anti-CD20 antibody therapy to be administered in a single administration or in a repeated administration pattern, and wherein anti-CD20 antibody is to be administered 0-15 days after administration of radioimmunoconjugate.

Thus, it is known in the field that external beam high doserate irradiation can cause increased antigen expression and that radioimmunotherapy and monoclonal antibody therapy can cause reduced antigen expression in cancer cells.

The present standard of administration radioimmunotherapy as a reduction treatment, e.g., rituximab (the antibody) is given as a conditioning treatment before Zevalin (the radioimmunoconjugate).

A problem with this approach is that experimental work and clinical data have indicated that antibody therapy can cause antigen drift that is a selection pressure towards cells with low antigen expression, which become treatment resistant (Musto and D'Auria, 2011). This has also been indicated in experimental RIT (Elgström et al, 2012).

Therefore would a targeted therapeutic option that could cause the opposite, i.e., an increase of antigens on treated cells be a very valuable therapeutic tool.

Summary

The present disclosure relates to radioimmunoconjugates that are capable of upregulating expression of one or more antigens. The upregulated antigens can be the antigens that are targeted by the radioimmunoconjugates, different antigens expressed on the same cells or a combination.
This expression allows targeting and specific inhibition of cancer cells and cells of the immune system.

In one ~~aspect~~example, ~~the present invention refers to~~ disclosed herein is a radioimmunoconjugate comprising a monoclonal antibody targeting CD37, an optional linker, a radionuclide, in upregulating antigen expression of an antigen on the surface of B-cell cancer cells, wherein; the upregulated antigen is CD20, the upregulation is followed by anti-CD20 antibody therapy in a single administration or in a repeated administration pattern, and the administration of anti-CD20 antibody is 0-15 days after administration of radioimmunoconjugate. In another aspect, the present invention refers to a) a radioimmunoconjugate comprising, a monoclonal antibody targeting CD37, an optional linker, a radionuclide, and b) an anti-CD20 antibody, for use in the treatment of a B-cell malignancy selected from the group consisting of non-Hodgkin lymphoma, acute Lymphoblastic Leukemia, and chronic lymphocytic leukemia, wherein the radioimmunoconjugate upregulates antigen expression of an antigen expressed on the surface of B-cell cancer cells, the upregulated antigen is CD20, the upregulation is followed by anti-CD20 antibody therapy in a single administration or in a repeated administration pattern, and the administration of anti-CD20 antibody is 0-15 days

after administration of radioimmunoconjugate. In yet another aspect, the present invention refers to use of a radioimmunoconjugate comprising, a monoclonal antibody targeting CD37, an optional linker, and a radionuclide, in the manufacture of a medicament for treating a B-cell malignancy selected from the group consisting of non-Hodgkin lymphoma, acute Lymphoblastic Leukemia, and chronic lymphocytic leukemia, the use comprising a radioimmunoconjugate, to be administered, comprising, a monoclonal antibody targeting CD37, an optional linker, a radionuclide, and an anti-CD20 antibody to be administered, wherein the radioimmunoconjugate upregulates antigen expression of an antigen expressed on the surface of B-cell cancer cells, the upregulated antigen is CD20, the upregulation is followed by anti-CD20 antibody therapy to be administered in a single administration or in a repeated administration pattern, and wherein anti-CD20 antibody is to be administered 0-15 days after administration of radioimmunoconjugate.

Thus, one example of the present disclosure describes a radioimmunoconjugate comprising a monoclonal antibody, an optional linker, and a radionuclide, for use in upregulating antigen expression of one or more antigens.

In one example of the present disclosure are the one or more upregulated antigens expressed on the surface of B-cell cancer cells.

In one aspect, the present invention refers to use of a radioimmunoconjugate comprising, a monoclonal antibody targeting CD37, an optional linker, and a radionuclide, in the manufacture of a medicament for treating a B-cell malignancy selected from the group consisting of non-Hodgkin lymphoma, acute Lymphoblastic Leukemia, and chronic lymphocytic leukemia, the use comprising a radioimmunoconjugate, to be administered, comprising, a monoclonal antibody targeting CD37, an optional linker, a radionuclide, and an anti-CD20 antibody to be administered, wherein the radioimmunoconjugate upregulates antigen expression of an antigen expressed on the surface of B-cell cancer cells, the upregulated antigen is CD20, the upregulation is followed by anti-CD20 antibody therapy to be administered in a single administration or in a repeated administration pattern, and wherein anti-CD20 antibody is to be administered 0-15 days after administration of radioimmunoconjugate.

Claims

1. Use of a radioimmunoconjugate comprising, a monoclonal antibody targeting CD37, an optional linker, and a radionuclide, in the manufacture of a medicament for treating a B-cell malignancy selected from the group consisting of non-Hodgkin lymphoma, acute Lymphoblastic Leukemia, and chronic lymphocytic leukemia, the use comprising:

- a radioimmunoconjugate, to be administered, comprising,

- a monoclonal antibody targeting CD37,

- an optional linker,

- a radionuclide, and

- an anti-CD20 antibody to be administered, wherein

the radioimmunoconjugate upregulates antigen expression of an antigen expressed on the surface of B-cell cancer cells, the upregulated antigen is CD20, the upregulation is followed by anti-CD20 antibody therapy to be administered in a single administration or in a repeated administration pattern, and wherein anti-CD20 antibody is to be administered 0-15 days after administration of radioimmunoconjugate.

2. The use of the radioimmunoconjugate according to claim 1, wherein the administration of anti-CD20 antibody is at least one day after radioimmunoconjugate administration.

3. The use of the radioimmunoconjugate according to claims 1-2, wherein the anti-CD20 antibody is rituximab or obinutuzumab.

4. The use of the radioimmunoconjugate according to any one of claims 1-3, wherein the upregulation is done prior to immunotherapy or immunoconjugate therapy in a patient suffering from cancer.

5. The use of the radioimmunoconjugate according to any one of claims 1-4, wherein the patient is suffering from a B-cell malignancy selected from the group consisting of non-Hodgkin lymphoma and chronic lymphocytic leukemia.

6. The use of the radioimmunoconjugate according to any one of claims 1-5, wherein the radiolabeled monoclonal antibody is selected from the group consisting of HH1, chimeric HH1, humanized HH1, chHH1.1, or chHH1.3.

7. The use of the radioimmunoconjugate according to any one of claims 1-6, wherein the linker is a chelating linker selected from the group consisting of p-SCN-bn-DOTA, DOTA-NHS-ester, p-SCN-Bn-DTPA and CHX-A''-DTPA.

8. The use of the radioimmunoconjugate according to any one of claims 1-7, wherein the radionuclide is selected from the group consisting of ^{47}Sc, ^{67}Cu, ^{90}Y, ^{105}Rh, ^{117}mSn, ^{131}I, ^{149}Tb, ^{153}Sm, ^{161}Tb, ^{165}Dy, ^{177}Lu, ^{186}Re, ^{188}Re, ^{211}At, ^{212}Pb, ^{212}Bi, ^{213}Bi, ^{223}Ra, ^{224}Ra, ^{225}Ac, and ^{227}Th.

9. The use of the radioimmunoconjugate according to any one of claims 1-8, wherein the radioimmunoconjugate is formulated as a pharmaceutical composition.

10. The use of the radioimmunoconjugate according to any one of claims 1-9, wherein the pharmaceutical composition comprises one or more pharmaceutically acceptable carriers or adjuvants.