Type II antibodies, as e.g. Tositumomab (B1), 11B8, AT80 or humanized B-Ly1 antibodies, effectively initiate target cell death via caspase-independent apoptosis with concomitant phosphatidylserine exposure.

The sharing common features of type I and type II anti-CD20 antibodies are summarized in Table 1.

Table 1: Properties of type I and type II anti-CD20 antibodies

type I anti-CD20 antibodies	type II anti-CD20 antibodies
type I CD20 epitope	type II CD20 epitope
Localize CD20 to lipid rafts	Do not localize CD20 to lipid rafts
Increased CDC (if IgG1 isotype)	Decreased CDC (if IgG1 isotype)
ADCC activity (if IgG1 isotype)	ADCC activity (if IgG1 isotype)
Full binding capacity	Reduced binding capacity
Homotypic aggregation	Stronger homotypic aggregation
Apoptosis induction upon cross-linking	Strong cell death induction without cross-linking

Summary

In an aspect, there is provided an antibody which binds to CSF-1R for use in inducing lymphocytosis of leukemic cells in lymphomas or leukemias.

The disclosure relates to the use of an antibody which binds to CSF-1R for inducing lymphocytosis of leukemic cells in lymphomas or leukemias.

The disclosure relates to a method of treatment , the method comprising the administration of an effective amount of an antibody which binds to CSF-1R for inducing lymphocytosis of leukemic cells in lymphomas or leukemias.

One embodiment is the use of an antibody which binds to CSF-1R for the manufacture of a medicament for inducing lymphocytosis of leukemic cells in lymphomas or leukemias.

In one embodiment the lymphocytosis increases the percentage of CD19 expressing and/or CD20 expressing circulating leukemic cells in the peripheral blood.

In one embodiment the lymphocytosis increases the percentage of CD19 expressing and/or CD20 expressing circulating leukemic cells in the peripheral blood and renders the lymphoma or leukemia susceptible to a treatment with an anti-CD19 antibody and /or an anti-CD20 antibody.

In one embodiment the lymphocytosis increases the circulating leukemic cells expressing CD20.

In one embodiment the lymphocytosis increases the percentage of CD20 expressing circulating leukemic cells and renders the lymphoma or leukemia susceptible to a treatment with an anti-CD20 antibody.

In another aspect, there is provided an antibody which binds to human CSF-1R wherein the antibody is for use in combination with an antibody which binds to human CD20 wherein the antibody is

i) for use in the treatment of a CD20 expressing cancer; or

ii) for use in stimulating an immune response or function, such as T cell activity; or

iii) for use in stimulating a cell mediated immune response, particularly stimulating cytotoxic T-lymphocytes, stimulating T cell activity, or stimulating macrophage activity; or

iv) for use in delaying progression of cancer; or

v) for use in prolonging the survival of a patient suffering from cancer.

wherein the antibody which binds to human CSF-1R used in the combination therapy is characterized in comprising

a) a heavy chain variable domain VH of SEQ ID NO:23 and a light chain variable domain VL of SEQ ID NO:24, or

b) a heavy chain variable domain VH of SEQ ID NO:31 and a light chain variable domain VL of SEQ ID NO:32, or

c) a heavy chain variable domain VH of SEQ ID NO:39 and a light chain variable domain VL of SEQ ID NO:40, or

d) a heavy chain variable domain VH of SEQ ID NO:47 and a light chain variable domain VL of SEQ ID NO:48, or

e) a heavy chain variable domain VH of SEQ ID NO:55 and a light chain variable domain VL of SEQ ID NO:56;

and wherein the antibody which binds to human CD20 used in the combination therapy is characterized in comprising

a) a heavy chain variable domain VH of SEQ ID NO:69 and a light chain variable domain VL of SEQ ID NO:76, or

b) a heavy chain variable domain VH of SEQ ID NO:70 and a light chain variable domain VL of SEQ ID NO:76, or

c) a heavy chain variable domain VH of SEQ ID NO:71 and a light chain variable domain VL of SEQ ID NO:76, or

d) a heavy chain variable domain VH of SEQ ID NO:72 and a light chain variable domain VL of SEQ ID NO:76, or

e) a heavy chain variable domain VH of SEQ ID NO:73 and a light chain variable domain VL of SEQ ID NO:76, or

f) a heavy chain variable domain VH of SEQ ID NO:74 and a light chain variable domain VL of SEQ ID NO:76, or

g) a heavy chain variable domain VH of SEQ ID NO:75 and a light chain variable domain VL of SEQ ID NO:76.

In another aspect, there is provided a method of targeting a CD20 expressing cancer with an anti-CD20 antibody in combination with a CSF-1R inhibitor for preventing escape from CD20 targeting therapies by targeting macrophages.

In one embodiment, the macrophages are targeted with an anti-CSF1R antibody.

In one embodiment, within such method the antibody which binds to human CSF-1R used in the combination therapy is characterized in comprising

a) a heavy chain variable domain VH of SEQ ID NO:23 and a light chain variable domain VL of SEQ ID NO:24, or

b) a heavy chain variable domain VH of SEQ ID NO:31 and a light chain variable domain VL of SEQ ID NO:32, or

c) a heavy chain variable domain VH of SEQ ID NO:39 and a light chain variable domain VL of SEQ ID NO:40, or

d) a heavy chain variable domain VH of SEQ ID NO:47 and a light chain variable domain VL of SEQ ID NO:48, or

e) a heavy chain variable domain VH of SEQ ID NO:55 and a light chain variable domain VL of SEQ ID NO:56;

and wherein the antibody which binds to human CD20 used in the combination therapy is characterized in comprising

a) a heavy chain variable domain VH of SEQ ID NO:69 and a light chain variable domain VL of SEQ ID NO:76, or

b) a heavy chain variable domain VH of SEQ ID NO:70 and a light chain variable domain VL of SEQ ID NO:76, or

c) a heavy chain variable domain VH of SEQ ID NO:71 and a light chain variable domain VL of SEQ ID NO:76, or

d) a heavy chain variable domain VH of SEQ ID NO:72 and a light chain variable domain VL of SEQ ID NO:76, or

e) a heavy chain variable domain VH of SEQ ID NO:73 and a light chain variable domain VL of SEQ ID NO:76, or

f) a heavy chain variable domain VH of SEQ ID NO:74 and a light chain variable domain VL of SEQ ID NO:76, or

g) a heavy chain variable domain VH of SEQ ID NO:75 and a light chain variable domain VL of SEQ ID NO:76.

In one embodiment the antibody is for use in the treatment of cancer.

In another aspect, there is provided the antibody, use or method as defined above for use in the treatment of lymphomas and lymphocytic leukemias.

In one preferred embodiment the antibody is for use in the treatment of a CD20 expressing cancer as lymphomas (preferably B-Cell Non-Hodgkin's lymphomas (NHL)) and lymphocytic leukemias.

In another aspect, there is provided the antibody, use or method as defined above for use in the treatment of B-Cell Non-Hodgkin's lymphomas (NHL).

In one preferred embodiment the antibody is for use in the treatment of multiple myeloma.

In one preferred embodiment the antibody is for use in the treatment of follicular lymphoma.

In one preferred embodiment the antibody is for use in the treatment of Hodgkin's disease.

In another aspect, there is provided the antibody, use or method as defined above for use in the treatment of multiple myeloma, of follicular lymphoma, or of Hodgkin's disease.

In one embodiment the antibody is for use in the prevention or treatment of metastasis.

In another aspect, there is provided the antibody, use or method as defined above for use in the prevention or treatment of metastasis.

In one embodiment the antibody is for use in the treatment of inflammatory diseases.

In another aspect, there is provided the antibody, use or method as defined above for use in the treatment of inflammatory diseases.

In one embodiment the antibody is for use in treating or delaying progression of an immune related disease such as tumor immunity.

In another aspect, there is provided the antibody, use or method as defined above for use in treating or delaying progression of an immune related disease such as tumor immunity.

In one embodiment the antibody is for use in stimulating an immune response or function, such as T cell activity.

In another aspect, there is provided the antibody, use or method as defined above for use in stimulating an immune response or function, such as T cell activity.

The inventors have found that a set of molecular interactions supporting the in vivo dependence of leukemic cells on monocytes/macrophages. The present disclosure relates to finding that CSF1R inhibition reduces leukemic cell load especially in the bone marrow and increases circulating CD20+ leukemic cells, thus suggesting the therapeutic combination of two different antibodies, one targeting TAMs and the other targeting CD20 molecule on leukemic cells.

Such combination therapies of the specific antibodies described herein show benefits for patients in need of an CSF-1R and CD20 targeting therapy. The inventors found that the administration of an anti-CSF1R antibody induced significant lymphocytosis, which renders lymphomas and leukemias more susceptiple to anti-CD20 and or anti-CD19 antibody treatment. Furthermore, they show that macrophage depletion-associated increase of circulating CD20+ leukemic cells represents a therapeutic opportunity for combination with anti-CD20 antibodies. Based on the increased percentage of CD19+CD20+ circulating leukemic cells, an effective combination therapy with specific anti-CSF-1R and anti-CD20 antibody can be administered to patients afflicted with lymphomas and leukemias, especially CD20 expressing lymphomas and leukemias. More strikingly, the leukemic cell depletion increased significantly when the anti-human CSF1R moAb was associated to GA101. This observation suggested a novel