

SRRM2 binders for treating and diagnosing blood cancer**TECHNICAL FIELD OF THE INVENTION**

[0001] The present invention provides a pharmaceutical composition comprising an antibody, which binds to human SRRM2 present on the cell surface of a target cell and optionally a pharmaceutically acceptable carrier, diluent or excipient. The present invention further provides said pharmaceutical composition for use in a method for the treatment of blood cancer in a patient in which the patient to be treated has a weight of between 16 and 150 kilograms. Furthermore, a method is provided for determining whether a patient may suffer from blood cancer, comprising determining in a sample obtained from said patient whether SRRM2 is present on the cell surface of cells comprised by said sample. Additionally, an antibody which binds to human SRRM2 present on the cell surface of a target cell is provided. The present invention further provides an antibody, which binds to human SRRM2 present on the cell surface of a target cell for use in a method of killing said target cell having SRRM2 present on the cell surface. Further, a method of killing a target cell having SRRM2 present on the cell surface of said target cell, comprising administering an antibody, which binds to human SRRM2 present on the cell surface of said target cell is provided.

BACKGROUND OF THE INVENTION

[0002] Blood cancers are those cancers that arise from hyperproliferation of blood cells, disrupting the physiological functions of blood, bone marrow, and lymph tissue, thereby typically resulting in immune dysfunction. Blood cancers are usually divided into three groups, leukemias, lymphomas, and myelomas, based on the cell type(s) primarily affected. Worldwide, blood cancers kill 720,000 people per year, accounting for ~7% of total cancer-related deaths (Bray et al., 2018). Whilst survival rates are improving thanks to innovations in treatment, certain types of blood cancer still show relatively low 5-year survival rates, with the 5-year survival rate in multiple myeloma (MM) standing at just 50-55% and decreasing greatly if diagnosis occurs at a late-stage of disease progression. For acute myeloid leukemia (AML), with the existing treatment modalities, only 35-45% and 10-15% of the patients with AML aged <60 years and those aged ≥60 years respectively, achieve long-term survival (Short et al. 2018). Several tumor antigens have been investigated as potential target antigens for immunotherapy of MM and AML, however, the overall therapeutic outcomes have mostly remained disappointing. Improved methods of both treatment and diagnosis are therefore

much needed. Blood cancers are predominantly a disease of old age, so as global longevity continues to increase, the need for improved treatments will only increase further.

[0003] The present invention provides technical advancements to both treatment and diagnosis in blood cancer. The underlying technical problem is thus to address these aspects.

SUMMARY OF THE INVENTION

[0004] The technical problem is solved by the subject-matter as defined in the claims, described in the claims, demonstrated in the examples, and illustrated in the figures. The inventors surprisingly found that serine/arginine repetitive matrix protein 2 (SRRM2; UniProt Q9UQ35), typically localized to the nucleus, is expressed on the surface of blood cancer cells, but not on healthy, non-cancer cells. Thus, surface SRRM2 on the cells obtained from a patient is a biomarker for blood cancer. Furthermore, this selective expression of SRRM2 on the surface of blood cancer cells allows the development of novel blood cancer-specific therapies. The utility of the present invention was demonstrated by its use in successfully treating blood cancer in two patients, as defined herein. Specifically, a significantly increased number of surface SRRM2-positive (abnormal) plasma cells could be detected in MM patients, when compared to the number of SRRM2-positive cells in a healthy subject. Further, treatment of MM and PCL patients with SRRM2 specific CAR-T cells led to reduction of cancer-associated plasma cells. Moreover, surface SRRM2 was also found to be significantly elevated on leukemia cells, specifically leukemic blast cells of AML and MM patients, when compared to the expression on normal blood cells and HSC. Notably, AML patients with FMS-like tyrosine kinase-3 (FLT3) mutation showed a significantly higher expression of surface SRRM2 than AML patients without any genetic mutation or other mutations. Further, SRRM2 was highly expressed on newly diagnosed and previously diagnosed MM patients. Moreover, SRRM2 specific CAR-T cells showed potent killing activity *in vitro* in myeloid leukemia cell lines. Further, leukemia blast elimination could be observed *in vivo* in an AML tumor-bearing mouse model. In addition, significant tumor suppression could be observed in a KMS-11-luc CDX MM mouse model. In sum, the data provided herein strongly point to SRRM2 as an optimal and promising target for immunotherapy in blood cancer patients, particularly AML, PCL or MM patients, as well as diagnosing blood cancer, particularly AML, PCL or MM, based on SRRM2 located at the cell surface.

[0005] Accordingly, the present invention provides an antibody that binds to human serine/arginine repetitive matrix protein 2 (SRRM2) present on the cell surface of a target cell, for use in a method for the treatment of blood cancer in a human patient, in which the patient to be treated has a weight of between 16 and 150 kilograms.

[0006] The antibody that binds to human SRRM2 shall be used in a method of treatment wherein the patient to be treated has a weight of between 16 and 150kg, preferably 18 to 140kg, more preferably 20 to 130kg, more preferably still 22 to 120kg.

[0007] The antibody that binds to human SRRM2 may be used in a method of treatment wherein the patient to be treated is at least 1 year old, preferably 2 years, more preferably between 2 and 80 years old.

[0008] The antibody that binds to human SRRM2 may be used in a method of treatment wherein the patient to be treated has a body height between 70 and 220cm, preferably between 80 and 200cm, more preferred between 90 and 190cm.

[0009] The antibody that binds to human SRRM2 may have cytotoxic activity, preferably antigen-dependent cellular cytotoxicity (ADCC) and/or complement-dependent cytotoxicity (CDC).

[0010] The antibody that binds to human SRRM2 may be part of a chimeric antigen receptor (CAR).

[0011] The antibody that binds to human SRRM2 may be part of a chimeric antigen receptor (CAR), wherein said CAR is expressed by a T cell (herein termed "CAR-T cell"), NK cell, NK-T cell or macrophage.

[0012] The antibody that binds to human SRRM2 may be expressed by an autologous cell population.

[0013] The antibody that binds to human SRRM2 may be expressed by an allogeneic cell population.

[0014] The antibody that binds to human SRRM2 may be used in a method of treatment wherein SRRM2 present on the cell surface of a target cell is externalized.

[0015] The antibody that binds to human SRRM2 wherein the antibody may not be an intracellular antibody.

[0016] The antibody that binds to human SRRM2 may be used in a method of treatment wherein said blood cancer to be treated is a blood cancer characterized by cells expressing human SRRM2 on their cell surface.

[0017] The antibody that binds to human SRRM2 may be used in a method of treatment wherein said blood cancer to be treated is multiple myeloma.

[0018] The antibody that binds to human SRRM2 may be used in a method of treatment wherein said blood cancer to be treated is leukemia, including acute erythroid leukemia, acute lymphoblastic leukemia (ALL), acute megakaryoblastic leukemia, acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), chronic myelomonocytic leukemia (CMML), childhood leukemia, hairy cell leukemia (HCL), large granular lymphocytic leukemia (LGLL), mast cell leukemia (MCL) or plasma cell leukemia (PCL).

[0019] The antibody that binds to human SRRM2 may be used in a method of treatment wherein said blood cancer to be treated is acute myeloid leukemia (AML).

[0020] The antibody that binds to human SRRM2 may be used in a method of treatment of AML, wherein said AML to be treated is characterized by cells expressing human SRRM2 on their cell surface and further having a genetic mutation, preferably an FMS-like tyrosine kinase-3 (FLT3) mutation.

[0021] The antibody that binds to human SRRM2 may be used in a method of treatment wherein said blood cancer to be treated is plasma cell leukemia (PCL). The PCL may be primary or secondary PCL.

[0022] The antibody that binds to human SRRM2 may be used in a method of treatment wherein said blood cancer to be treated is lymphoma, including Burkitt lymphoma, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma, MALT lymphoma, mantle cell lymphoma, small lymphocytic lymphoma (SLL), post-transplant lymphoproliferative disorder (PTLD), or Waldenström macroglobulinaemia (WM).

[0023] The antibody that binds to human SRRM2 may be used in a method of treatment wherein said blood cancer to be treated is a myelodysplastic syndrome, a myeloproliferative neoplasm (including polycythaemia vera, essential thrombocythaemia, or myelofibrosis), Erdheim-Chester disease, Langerhans cell histiocytosis, mastocytosis, or mast cell leukemia.

[0024] It is further envisaged in the context of the present invention that the blood cancer patient to be treated with the antibody binding to human SRRM2 is refractory to previous cancer therapy and/or in relapse after previous cancer therapy.

[0025] The antibody that binds to human SRRM2 may be used in a method of treatment wherein the route of antibody administration is parenteral, including, but not limited to, intravenous, intradermal, intramuscular, intrathecal, epidural, intracerebral, or intraperitoneal administration.

[0026] The antibody that binds to human SRRM2 present on the cell surface of a target cell may be conjugated with a cytotoxic substance.

[0027] The antibody that binds to human SRRM2 present on the cell surface of a target cell may bind to non-permeabilised cells.

[0028] The antibody that binds to human SRRM2 present on the cell surface of a target cell may bind to living cells.

[0029] Furthermore, the present invention relates to an antibody that binds to human SRRM2 wherein the antibody is used in a method for determining whether a patient may suffer from blood cancer, comprising determining in a sample obtained from said patient whether SRRM2 is present on the cell surface of cells comprised by said sample and/or whether SRRM2 is present on the surface of extracellular vesicles. In the method for determining whether a patient may suffer from blood cancer, an increased amount of SRRM2 on the cell surface of cells and/or present on the surface of extracellular vesicles comprised by a sample obtained from said patient compared to the amount of SRRM2 on the cell surface and/or extracellular vesicles in a sample obtained from a healthy subject indicates that the patient may suffer from blood cancer. No difference in the amount of SRRM2 on the cell surface of cells and/or present on the surface of extracellular vesicles comprised by a sample obtained from said patient when compared to the amount of SRRM2 on the cell surface and/or extracellular vesicles in a sample obtained from a healthy subject indicates that the patient may not suffer from blood cancer.

[0030] The antibody that binds to human SRRM2 may preferably be an antibody comprising (a) a heavy chain variable region having the amino acid sequence as set forth in SEQ ID NO: 1, and a light chain variable region having the amino acid sequence as set forth in SEQ ID NO: 2, (b) a heavy chain variable region having the amino acid sequence as set forth in SEQ ID NO: 3,

and a light chain variable region having the amino acid sequence as set forth in SEQ ID NO: 4,
(c) a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 5,
and a light chain variable region having the amino acid sequence as set forth in SEQ ID NO: 6,
or (d) a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 5,
and light chain variable region having the amino acid sequence as set forth in SEQ ID NO: 7.

[0031] The antibody that binds to human SRRM2 may preferably be an antibody comprising,
(a) a heavy chain variable region comprising heavy chain CDR1 having the amino acid
sequence as set forth in SEQ ID NO: 9, heavy chain CDR2 having the amino acid sequence
as set forth in SEQ ID NO: 10, and heavy chain CDR3 having the amino acid sequence as set
forth in SEQ ID NO: 11, and

a light chain variable region comprising light chain CDR1 having the amino acid sequence as
set forth in SEQ ID NO: 12, light chain CDR2 having the amino acid sequence as set forth in
SEQ ID NO: 13, and light chain CDR3 having the amino acid sequence as set forth in SEQ ID
NO: 14;

(b) a heavy chain variable region comprising heavy chain CDR1 having the amino acid
sequence as set forth in SEQ ID NO: 15, heavy chain CDR2 having the amino acid sequence
as set forth in SEQ ID NO: 16, and heavy chain CDR3 having the amino acid sequence as set
forth in SEQ ID NO: 17, and

a light chain variable region comprising light chain CDR1 having the amino acid sequence as
set forth in SEQ ID NO: 18, light chain CDR2 having the amino acid sequence as set forth in
SEQ ID NO: 19, and light chain CDR3 having the amino acid sequence as set forth in SEQ ID
NO: 20;

(c) a heavy chain variable region comprising heavy chain CDR1 having the amino acid
sequence as set forth in SEQ ID NO: 21, heavy chain CDR2 having the amino acid sequence
as set forth in SEQ ID NO: 22, and heavy chain CDR3 having the amino acid sequence as set
forth in SEQ ID NO: 23, and

a light chain variable region comprising light chain CDR1 having the amino acid sequence as
set forth in SEQ ID NO: 24, light chain CDR2 having the amino acid sequence as set forth in
SEQ ID NO: 25, and light chain CDR3 having the amino acid sequence as set forth in SEQ ID
NO: 26; or

(d) a heavy chain variable region comprising heavy chain CDR1 having the amino acid
sequence as set forth in SEQ ID NO: 21, heavy chain CDR2 having the amino acid sequence
as set forth in SEQ ID NO: 22, and heavy chain CDR3 having the amino acid sequence as set
forth in SEQ ID NO: 23, and

a light chain variable region comprising light chain CDR1 having the amino acid sequence as
set forth in SEQ ID NO: 27, light chain CDR2 having the amino acid sequence as set forth in

SEQ ID NO: 28, and light chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 29.

[0032] The antibody that binds to human SRRM2 may be used in method for determining whether a patient may suffer from blood cancer, wherein said blood cancer is multiple myeloma.

[0033] The antibody that binds to human SRRM2 may be used in method for determining whether a patient may suffer from blood cancer, wherein said blood cancer is leukemia, including acute erythroid leukemia, acute lymphoblastic leukemia (ALL), acute megakaryoblastic leukemia, acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), chronic myelomonocytic leukemia (CMML), childhood leukemia, hairy cell leukemia (HCL), large granular lymphocytic leukemia (LGLL), mast cell leukemia (MCL) or plasma cell leukemia (PCL).

[0034] The antibody that binds to human SRRM2 may be used in method for determining whether a patient may suffer from blood cancer, wherein said blood cancer is acute myeloid leukemia (AML).

[0035] The antibody that binds to human SRRM2 may be used in method for determining whether a patient may suffer from blood cancer, wherein said blood cancer is plasma cell leukemia (PCL). The PCL may be primary or secondary PCL.

[0036] The antibody that binds to human SRRM2 may be used in method for determining whether a patient may suffer from blood cancer, wherein said blood cancer is lymphoma, including Burkitt lymphoma, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma, MALT lymphoma, mantle cell lymphoma, small lymphocytic lymphoma (SLL), post-transplant lymphoproliferative disorder (PTLD), or Waldenström macroglobulinaemia (WM).

[0037] The antibody that binds to human SRRM2 may be used in method for determining whether a patient may suffer from blood cancer, wherein said blood cancer is a myelodysplastic syndrome, a myeloproliferative neoplasm (including polycythaemia vera, essential thrombocythaemia, or myelofibrosis), Erdheim-Chester disease, Langerhans cell histiocytosis, mastocytosis, or mast cell leukemia.

[0038] The antibody that binds to human SRRM2 may be used in a pharmaceutical composition wherein said antibody is contained in a composition comprising a buffer or a buffer and sodium chloride.

BRIEF DESCRIPTION OF THE DRAWINGS

[0039] The invention will be better understood with reference to the detailed description when considered in conjunction with the non-limiting examples and the drawings, in which:

[0040] **Figure 1A** shows that the majority of abnormal plasma cells are surface SRRM2 positive. An example of the immunophenotyping strategy of white blood cells (WBCs) or bone marrow cells from a patient with plasma cell leukemia is shown.

[0041] **Figure 1b:** shows that immunophenotyping of WBCs, as described above, revealed that 92.94% of Patient 1's abnormal plasma cells stained positive for SRRM2.

[0042] **Figure 2** shows the reduction in CD138⁺ cells following SRRM2 CAR-T cells treatment. CD138 immunohistochemistry was performed on bone marrow extracted from Patient 2.

[0043] **Figure 3** shows that abnormal plasma cells are eliminated by SRRM2 CAR-T cell treatment. Bone marrow smears of Patient 2 are shown before and at day 50 after SRRM2 CAR-T cell infusion.

[0044] **Figure 4** shows that *in vivo* expansion of the SRRM2 specific CAR T cell population, quantified as a proportion of total number of T cells present per sample, peaks at week 3 post-infusion. A single-dose of 5×10^7 SRRM2-specific CAR-T cells was infused into Patient 2 (=day 0) and blood samples were taken at regular intervals post-infusion to assess proliferation of CAR-T cells.

[0045] **Figure 5** shows that treatment with SRRM2-targeting CAR-T cells restores blood kappa / lambda light-chain ratio. Measurements of immunoglobulin (Ig) light chains in the serum of Patient 2 are shown, as measured with an automated immunoassay. Given are the total concentrations (upper graph) and the kappa / lambda ratio (lower graph).

[0046] **Figure 6** shows the reduction of cancer-associated plasma cells in Patient 2 upon infusion of SRRM2-specific CAR-T cells, as quantified by counting the number of abnormal plasma cells (gated), which are characterized by the combination of markers CD138⁺CD19⁻CD56⁻CD45^{dim}.

[0047] Figure 7 shows clinical data from Patient 1, indicating antitumor activity of the infused SRRM2 CAR-T cells.

[0048] Figure 8 shows the workflow (gating strategy) for the detection of SRRM2-positive abnormal plasma cells in the blood of myeloma patients. In this example 90.02% of myeloma plasma cells were surface SRRM2 positive, while normal cells were surface SRRM2 negative (not shown). EX-02 is the internal name for the SRRM2 antibodies described herein. A preferred EX-02 antibody is 23A7 or 13F11 described herein.

[0049] Figure 9 shows the decrease of plasma cells (CD38++CD138+CD19-CD56-CD45dim) in the peripheral blood of Patient 1 from 43% before infusion of SRRM2 CAR-T cells (pre) to 6.4% of the total number of white blood cells at day 16 after infusion. SRRM2 CAR-T cells were infused twice (arrows): 3.4×10^7 at day 0 (pre) and 1.18×10^8 at day 2.

[0050] Figure 10 shows that infusion of SRRM2 CAR-T cells resulted in a recovery of hematopoietic function in Patient 2 50 days post-infusion with no blood transfusion to assist hematopoietic recovery. Platelet level increased from just 36g/L on the day of infusion to 62g/L at day 50 post-infusion.

[0051] Figure 11 shows the correlational analysis between expression of SRRM2 on leukemia blasts and clinical data of patients with AML. (A) Survival analysis based on SRRM2 RNA levels. Data extracted from a public database (TCGA, <https://www.cancer.gov/ccg/>). (B) SRRM2 RNA levels in AML cells with cytogenetic abnormalities as well as in normal hematopoietic stem cells (HSC). Data extracted from a public database (TCGA, <https://www.cancer.gov/ccg/>). (C) Surface SRRM2 expression on leukemia blasts from bone marrow (BM) and peripheral blood (PB). (D-E) Surface SRRM2 expression levels in patients of different age and sex. (F) Surface SRRM2 expression in newly diagnosed (ND) and relapsed/refractory (RR) cases of AML. (G) Surface SRRM2 expression in AMLs with normal karyotypes and abnormalities in the karyotype. (H) Surface SRRM2 expression in patients with and without genetic mutations. (I-J) Surface SRRM2 expression on the tumor cell membrane of the patients with AML carrying different gene mutations. Surface SRRM2 expression as shown in Figures 11C-J was measured by flow cytometry using EX-02 as the primary antibody and an anti-rat IgG antibody labelled with Alexa647 as the secondary antibody.

[0052] Figure 12 shows the expression of surface SRRM2 on peripheral blood cells from AML patients and healthy donors. (A-B) SRRM2 expression on the surfaces of leukemia blasts, lymphocytes, monocytes, and neutrophils from two patients with AML was evaluated by flow cytometry using the SRRM2-specific EX-02 antibody. (C) Surface SRRM2 on peripheral

lymphocytes, monocytes, and neutrophils from healthy donors. (D) Surface SRRM2 on lymphocytes, monocytes, neutrophils, and hematopoietic stem cells in the bone marrow from healthy donors.

[0053] Figure 13 shows surface SRRM2 expression on different AML cell lines. Anti-SRRM2 as described herein and a suitable secondary antibody was used to identify SRRM2 expression.

[0054] Figure 14 shows the optimization of conditions for SRRM2-specific CAR-T cell preparation. (A) Schematic diagram of the SRRM2 CAR construct, consisting of a SRRM2-specific single chain variable fragment (SRRM2-scFv); a hinge region from CD8; a transmembrane domain (TMD) and 4-1BB and CD3 ζ intracellular costimulatory domains (B) Workflow of CAR-T preparation. (C-G) Transfection rates of CAR-T cells under different culture conditions. HSA = human serum albumin.

[0055] Figure 15 shows the potency of SRRM2 CAR-T cells *in vitro*. (A-D) *In vitro* cytotoxicity of SRRM2 CAR-T cells against four AML cell lines as measured with a LDH cytotoxicity assay. Non-transduced T cells (Mock-T) were used as control. The effector-target (E:T) ratios were 1.0:1, 2.5:1 and 5.0:1, and triplicates were used for each condition. (E) cytotoxicity of SRRM2 CAR-T cells against the four AML cell lines revealed the highest cytotoxicity against the FLT3^{mut+} cell line MOLM-13.

[0056] Figure 16 demonstrates the strong anti-tumor activity of SRRM2 CAR-T cells *in vivo*. (A) Schematic representation of the *in vivo* experiment using SRRM2 CAR-T cells in an AML model in NCG mice (NOD-Prkdc^{em26Cd52}Il2rg^{em26Cd22}/NjuCrI; Charles River). (B) Wright-Giemsa staining in the mouse model of AML, showing the successful elimination of leukemia blast cells upon treatment with SRRM2 CAR-T cells, in contrast to treatment with mock-T cells. The magnifications of the images shown in the panels are $\times 10$ and $\times 100$. (C) CAR copy numbers in cardiac blood samples as analysed by PCR using the CAR gene copy number detection kit (Hillgene, PX-CA001). (D) Continuous monitoring of mouse body weight revealed no differences between groups before the administration of CAR-T or MOCK-T cells. However, over time, after CAR-T injection, the differences in body weight between the two groups became statistically significant. (E) Kaplan-Meyer curves for the two groups.

[0057] Figure 17 shows that commercial antibodies fail to bind to cell-surface SRRM2 on living cells, whilst the SRRM2-specific antibody EX-02 of the present invention binds to cell-surface SRRM2 on living cells.

[0058] **Figure 18** shows the decrease of plasma cells (CD38++CD138+CD19-CD56-CD45dim) in the peripheral blood of Patient 3 from 29.0% before infusion of SRRM2 CAR-T cells (pre), e.g. EX-02 CAR-T cells, to 0.55% of the total number of peripheral blood plasma cells at day 28 after infusion. SRRM2 CAR-T cells were infused i.v. three times (EX-02 CAR T cells / kg: 0.54×10^7 at day 0 (pre), 2.34×10^7 at day 1 and 1.06×10^7 at day 18).

[0059] **Figure 19** summarizes flow cytometry data on lymphocytes/plasma cells in multiple myeloma (MM), Plasma Cell Leukemia (PCL), reactive plasmacytosis and other plasma cell disorders patients' bone marrow and peripheral blood samples. (A) Surface SRRM2 expression on plasma cells of newly diagnosed MM (N=35, all from bone marrow). (B) Surface SRRM2 expression on plasma cells of previously diagnosis of plasma cell disorders patients (N=67, including relapsed and refractory MM, PCL, reactive plasmacytosis, and other plasma cell disorders) under or after conventional treatment.

[0060] **Figure 20** demonstrates the strong anti-tumor activity of SRRM2 CAR-T cells *in vivo*. MM model. (A) Schematic representation of the *in vivo* experiment using SRRM2 CAR-T cells in a xenograft model with human MM KMS-11 cells in NSG mice, which is engineered to overexpress luciferase reporter in cells. Mice (n=5 per group) received 3.3×10^6 Kawasaki Medical School (KMS)-11-luc cells intravenously at day -5 and either 1.5×10^6 EX-02 CAR-T cells (CAR-T) or the same number of mock T-cells (Mock-T) five days later (=day 0). CAR-T cells for this experiment had been generated from T cells isolated from the peripheral blood of a healthy donor. (B) Longitudinal monitoring of the bioluminescent signals of Luc+ KMS-11 cells in NSG mice in both intravenously injected Mock-T and CAR-T cell treatment groups, imaging at days 7, 15, 24, 34 and 50. The y axis indicates the photon flux (p s⁻¹ cm⁻² sr⁻¹). (C) Blood was drawn on the same days and analyzed for human CD4+ and CD8+ cells by flow cytometry. The ratio CD8/CD4 was calculated. (D) Bioluminescence images of the animals from the experiment described in **Figure 20** demonstrate the therapeutic effect of EX-02 CAR-T cells as compared to Mock T cells.

[0061] **Figure 21** shows in (A) the number of human CAR-T cells per mL in the peripheral blood drawn at day 50 of mice from the experiment described in **Figure 20**. (B) shows the number of human CAR-T cells identified in the spleens of the animals. Spleens were isolated at day 50 of the experiment described in **Figure 20**. (C) Body weight of the animals used in the experiment described in **Figure 20**.

DETAILED DESCRIPTION OF THE INVENTION

[0062] The present inventors surprisingly found that SRRM2 is present on the cell surface of cancer cells, as it is widely described in prior art as being a protein localized to the nucleus, in particular in nuclear speckles. Serine/arginine repetitive matrix protein 2 (SRRM2; UniProt Q9UQ35) plays an important role in pre-mRNA splicing and is a major component of the spliceosome. As such, it is not present on the cell surface of healthy cells. However, within the context of cancer, SRRM2 can be seen to become “externalized”, i.e. it is no longer only present in the nucleus, but also present on the cell surface of a cancer cell. Antibodies binding SRRM2 have been described in the art. However, these commercially available antibodies are not able to bind SRRM2 exposed on the surface of living cells (**Figure 17**). Thus, contrary to the antibody used in the context of the present invention, these prior art antibodies have different binding properties and cannot be used in determining or treating blood cancer characterized by cells having a significantly increased amount of membrane-expressed, i.e. externalized, SRRM2. However, thanks to the present invention it is known that SRRM2 is present on the cell surface of blood cancer cells. Hence, it is also possible to provide further antibodies against SRRM2 present on the cell surface of blood cancer cells. Thus, up to now, SRRM2 was not considered an accessible target molecule for e.g. antibodies or CAR-T cells due to its assumed localization in the nucleus. However, as the present inventors surprisingly found that SRRM2 is present on the cell surface of blood cancer cells, those cells can now be targeted for the treatment of cancer. An exemplary sequence of SRRM2 is provided by UniProt database entry Q9UQ35, version 2 of 6 March 2007 and exemplified in SEQ ID NO: 8. The utility of the present invention was demonstrated by its use in successfully treating blood cancer in patients, as defined herein. Specifically, treatment of multiple myeloma and plasma cell leukemia patients with SRRM2 specific CAR-T cells led to reduction of cancer-associated plasma cells in said patients, and a significantly increased number of SRRM2-positive plasma cells could be detected in the blood and bone marrow of said patients, when compared to the number of SRRM2-positive cells of a healthy subject.

[0063] Further, surface SRRM2 was found to be significantly elevated on leukemia cells, specifically leukemia blast cells of AML patients, when compared to the expression on normal blood cells and HSC. This implies a low probability of on-target off-tumor toxicity associated with SRRM2, positioning it as a potential candidate for CAR-T therapy. Notably, SRRM2 was expressed on the cell membrane and was specifically elevated in AML blasts and cell lines, especially in cells harbouring an FMS-like tyrosine kinase-3 (FLT3) mutation (FLT3^{mut}). This observation could be attributed to FLT3 mutations, which led to constitutive activation of FLT3, independent of its ligand, thereby sustaining the survival and proliferation of tumor cells. This suggests that AML patients, especially those with FLT3 mutations, showcasing elevated

SRRM2 expression, could be considered promising candidates for SRRM2 CAR-T therapy. Moreover, the functionality of SRRM2 CAR-T was investigated, revealing its specific cytotoxicity against SRRM2-positive AML cell lines in vitro. Finally, SRRM2 CAR-T therapy demonstrated remarkable safety and efficacy in AML-cell-bearing mice.

[0064] Accordingly, the data provided herein impressively underline that membrane expressed SRRM2 is significantly elevated in blood cancer patients, such as MM, PCL and AML patients, and therefore an optimal target for immunotherapy, specifically CAR-T cell therapy.

[0065] The present invention thus comprises an antibody that binds to human serine/arginine repetitive matrix protein 2 (SRRM2) present on the cell surface of a target cell, for use in a method for the treatment of blood cancer in a human patient, in which the patient to be treated has preferably a weight of between 16 and 150 kilograms.

[0066] The SRRM2 protein within the context of the present invention may be a SRRM2 protein having SEQ ID NO: 8 or may be a modified protein having an amino acid sequence derived from the sequence described above by the modification of one or more amino acids. Examples of the modified protein having a sequence derived from the sequence described above by the modification of one or more amino acids can include polypeptides having 70 % or more, preferably 80 % or more, more preferably 90 % or more, even more preferably 95 % or more homology to the amino acid sequence. Alternatively, partial peptides of these SRRM2 proteins may be used.

[0067] The term "homology" as used herein in its usual meaning includes identical amino acids as well as amino acids, which are regarded to be conservative substitutions (for example, exchange of a glutamate residue by an aspartate residue) at equivalent positions in the linear amino acid sequence of two proteins that are compared with each other. By "identity" or "sequence identity" is meant a property of sequences that measures their similarity or relationship. The term "sequence identity" or "identity" as used in the present invention means the percentage of pair-wise identical residues - following (homology) alignment of a sequence of a polypeptide of the invention with a sequence in question - with respect to the number of residues in the longer of these two sequences. Identity is measured by dividing the number of identical residues by the total number of residues and multiplying the product by 100.

[0068] The percentage of sequence homology or sequence identity can, for example, be determined herein using the program BLASTP, version blastp 2.2.5 (November 16, 2002; cf. Altschul, S. F. et al. (1997) Nucl. Acids Res. 25, 3389-3402). In this embodiment, the

percentage of homology is based on the alignment of the entire polypeptide sequences (matrix: BLOSUM 62; gap costs: 11.1; cutoff value set to 10-3), optionally including the propeptide sequences, using the human IL-4 as reference in a pairwise comparison. It is calculated as the percentage of numbers of "positives" (homologous amino acids) indicated as result in the BLASTP program output divided by the total number of amino acids selected by the program for the alignment. It is noted in this connection that this total number of selected amino acids can differ from the length of the porcine NTCP.

[0069] The SRRM2 protein used in the present invention is not limited by its origin and is preferably a human SRRM2 protein.

[0070] The term "antibody" as used herein and in the context of the present invention may comprise chimeric antibodies, humanized antibodies, monovalent antibodies, polyvalent antibodies, low-molecular antibodies, a diabody or a scFv.

[0071] Chimeric antibodies refer to antibodies comprising variable and constant regions of different origins ligated with each other. For example, mouse-human heterogeneous chimeric antibodies are antibodies comprising the heavy and light chain variable regions of a mouse antibody and the heavy and light chain constant regions of a human antibody. Mouse antibody variable region-encoding DNAs are ligated with human antibody constant region-encoding DNAs, and the ligation products can be incorporated into expression vectors to prepare chimeric antibody-expressing recombinant vectors. Cells transformed with these vectors (recombinant cells) can be cultured for the expression of the DNA insert to obtain the chimeric antibodies produced during the culture.

[0072] In general, the chimeric antibodies comprise non-human animal-derived antibody variable regions and human antibody-derived constant regions. By contrast, the humanized antibodies comprise non-human animal-derived antibody complementarity-determining regions (CDRs), human antibody-derived framework regions (FRs), and human antibody-derived constant regions. The humanized antibodies are also called reshaped human antibodies. Specifically, for example, humanized antibodies comprising non-human animal (e.g., mouse) antibody CDRs grafted in human antibodies are known in the art. The humanized antibodies are useful as active ingredients for a therapeutic agent of the present invention, owing to their reduced antigenicity in the human body.

[0073] Each antibody variable region usually comprises 3 CDRs flanked by 4 FRs. The CDR regions substantially determine the binding specificity of the antibody. The CDRs have diverse amino acid sequences. On the other hand, amino acid sequences constituting the FRs often

exhibit high homology among antibodies having different binding specificities. Therefore, in general, the binding specificity of a certain antibody can allegedly be transplanted to other antibodies through CDR grafting.

[0074] The antibody, which binds to human SRRM2 present in a pharmaceutical composition of the present invention may encompass bivalent antibodies typified by IgG (IgG1, IgG2, IgG4, etc.) and also monovalent antibodies or polyvalent antibodies typified by IgM, as long as these antibodies bind to the SRRM2 protein. The polyvalent antibody that may be present in the pharmaceutical composition of the present invention may encompass polyvalent antibodies having antigen-binding sites, all of which are the same as each other or some or all of which are different from each other. Preferably, the antibody, which binds to human SRRM2 is an IgG antibody.

[0075] The antibody, which binds to human SRRM2 present in the pharmaceutical composition of the present invention may also be a low-molecular antibody that encompasses an antibody fragment deficient in a portion of the whole antibody (e.g. whole IgG). Such partial deficiency of the antibody molecule is accepted as long as the resultant antibody fragment is capable of binding to the SRRM2. It is preferred that the antibody fragment employed in the pharmaceutical composition according to the present invention should contain one or both of heavy chain variable (VH) and light chain variable (VL) regions. It is also preferred that the antibody fragment employed in the pharmaceutical composition according to the present invention should contain CDRs. The number of CDRs contained in the antibody fragment employed in the pharmaceutical composition of the present invention is not particularly limited and is preferably at least 6 CDRs: heavy chain CDR1, CDR2, and CDR3 and light chain CDR1, CDR2, and CDR3.

[0076] The amino acid sequence of VH or VL can contain one or more substitution, deletion, addition, and/or insertion. Furthermore, the antibody or antibody fragment that may be employed in the pharmaceutical composition of the present invention may be deficient in a portion of one or both of VH and VL, as long as the resultant antibody fragment is capable of binding to the human SRRM2. Moreover, its variable region may be chimerized or humanized. Specific examples of the antibody fragment can include Fab, Fab', F(ab')₂, and Fv. Moreover, specific examples of the low-molecular antibody can include Fab, Fab', F(ab')₂, Fv, scFv (single chain Fv), diabody, sc(Fv)₂ (single chain (Fv)₂), and scFv-Fc. In the present invention, the low molecular antibody is preferably a diabody or sc(Fv)₂. These antibody multimers (e.g., dimers, trimers, tetramers, and polymers) are also encompassed by the low-molecular antibody that may be employed in the pharmaceutical composition of the present invention.

[0077] The term “diabody” as used herein and in the context of the present invention may refer to a bivalent antibody fragment constructed by gene fusion. The diabody is a dimer comprising two polypeptide chains. Usually, each of the polypeptide chains constituting the dimer comprises heavy and light chain variable regions linked via a linker on the same chain. The linker in the diabody is generally too short to allow pairing between heavy and light chain variable regions on the same chain. Specifically, the number of amino acid residues constituting the linker is, for example, approximately 5 residues. Therefore, heavy and light chain variable regions encoded on the same polypeptide chain cannot together form a single chain variable region fragment. Instead, they form a dimer by pairing with another single chain variable region fragment. As a result, the diabody has two antigen-binding sites.

[0078] The scFv, as used in the context of the present invention, may be obtained by linking heavy and light chain variable regions of the antibody. In the scFv, the heavy and light chain variable regions are linked via a linker, preferably, a peptide linker. The heavy and light chain variable regions in the scFv can be derived from any of the antibodies described in the present specification. The peptide linker that links the variable regions is not particularly limited. For example, an arbitrary single chain peptide of approximately 3 to 25 residues can be used as the linker.

[0079] The antibody which binds to human SRRM2 as used in the pharmaceutical composition and the antibody, which binds to human SRRM2 according to the present invention, may also encompass binding entities, such as lipocalins, an aptamer or an anticalin.

[0080] The antibody which binds to human SRRM2 used in the present invention can have various formats. However, it needs to bind to the SRRM2 protein and is not particularly limited by its origin, type, shape, etc., but may have a cytotoxic activity. Specifically, an antibody can be used, such as a non-human animal-derived antibody (e.g., a mouse, rat, or camel antibody), a human-derived antibody, a chimeric antibody, or a humanized antibody as described above. The antibody, which binds to human SRRM2 used in the present invention may in one embodiment be a polyclonal or monoclonal antibody and is preferably a monoclonal antibody.

[0081] The antibody which binds to human SRRM2 used in the present invention can be obtained as a polyclonal or monoclonal antibody using means known in the art. The antibody used in the present invention is in particular preferably a mammal-derived monoclonal antibody. The mammal-derived monoclonal antibody encompasses, for example, those

produced by hybridomas and those produced by hosts transformed with expression vectors containing an antibody gene by a genetic engineering approach.

[0082] In some embodiments of the present invention, the antibody which binds to human SRRM2 may be modified to form a chimeric antigen receptor (CAR), expressed by an immune cell(s), preferably NK cells, NK-T cells, or macrophages, most preferably T cells (CAR T cells). CARs (also known as chimeric immunoreceptors, chimeric T cell receptors or artificial T cell receptors) are receptor proteins that have been engineered to give T cells the ability to target a specific protein. CARs link an extracellular antigen recognition domain with an internal signalling domain capable of mediating T cell activation upon antigen binding. In the present invention, the extracellular region may comprise the light and heavy chains of the antibody that recognizes human SRRM2, formed into a single-chain variable fragment (scFv). A CAR so described shall result in T cell activation upon SRRM2 binding. In addition, a hinge region and transmembrane domain shall also form parts of the CAR.

[0083] In some embodiments of the present invention, the antibody which binds to human SRRM2 may be modified to form a chimeric antigen receptor (CAR) expressed by an immune cell(s), including, but not limited, to T cells, NK cells, NK-T cells, or macrophages, wherein said immune cells may be derived from induced pluripotent stem cells (iPSCs)

[0084] In some embodiments of the present invention, the antibody which binds to human SRRM2 may be modified to form a chimeric antigen receptor (CAR), expressed by an immune cell(s), including but not limited to T cells, NK cells, NK-T cells, or macrophages, wherein said immune cells are immune cells in which β 2-immunoglobulin has been inactivated.

[0085] As set forth above, the present invention comprises the finding that SRRM2 is present on the cell surface of blood cancer cells obtained from blood cancer patients, e.g. MM and AML patients, and can be bound by the antibody used in the present invention. Accordingly, it is particularly envisaged in the context of the present invention that the antibody which binds to human SRRM2 on the surface of a target cell binds to non-permeabilised cells. "Permeabilization of cells" refers to the break up of the cell membrane by electrical, mechanical or chemical means, i.e. the cell membrane becomes permeable. However, contrary thereto, the cells bound by the antibody of the present invention have an intact cell membrane expressing SRRM2, i.e. these cells are non-permeabilised. It is equally envisaged that the antibody used in the context of the present invention which binds to human SRRM2 on the surface of a target cell binds to living cells. A "living cell" is a structural and functional unit comprising at least an intact cell membrane, a nucleus, and the cytoplasm, that controls the substances that go into and out of the cell and is able to function independently.

[0086] The antibody which binds to human SRRM2 may be modified with various molecules such as polyethylene glycol (PEG). Further, the antibody, which binds to human SRRM2 may also be modified with a cytotoxic substance such as a chemotherapeutic agent, a toxic peptide, a radioactive chemical, or the like having a cytotoxic activity.

[0087] Specific examples of the antibody used in the present invention, which recognizes SRRM2 present on the cell surface of a target cell such as a blood cancer cell and binds thereto, may include the antibodies given and described herein.

[0088] As described above, an antibody, which binds to human SRRM2 of the present invention or as used in the pharmaceutical composition of the present invention or as used in the methods of the present invention including the substitution, deletion, addition, and/or insertion of one or more amino acids is also incorporated in the scope of the present invention and may be prepared or occur naturally. Examples of a method for introducing a mutation in the polypeptide include site-directed mutagenesis (Hashimoto-Gotoh, T. et al., 1995) (Zoller, MJ, and Smith, M., 1983) (Kramer, W. et al., 1984) (Kramer W, and Fritz HJ, 1987) (Kunkel, TA, 1985) (Kunkel, 1988). This is one of the methods well known by those skilled in the art for preparing a polypeptide functionally equivalent to a certain polypeptide. Those skilled in the art can appropriately introduce a mutation in the antibody of the present invention or the antibody as used in the pharmaceutical composition of the present invention or as used in the methods of the present invention using such a method and thereby prepare an antibody functionally equivalent to such antibody. Moreover, amino acid mutations may occur in the natural world. Such an antibody that has an amino acid sequence derived from the amino acid sequence of the antibody of the present invention or the antibody as used in the pharmaceutical composition of the present invention or as used in the methods of the present invention comprising the mutation of one or more amino acids, is functionally equivalent or a variant to the antibody and is also encompassed by the antibody of the present invention or the antibody as used in the pharmaceutical composition of the present invention or as used in the methods of the present invention.

[0089] The number of amino acids mutated in such a variant is usually within 50 amino acids, preferably within 30 amino acids, more preferably within 10 amino acids (e.g. within 5 amino acids).

[0090] For amino acid residues to be mutated, it is preferred that this mutation should be performed conservatively between amino acids having the same side chain property. For example, the following classification based on the properties of amino acid side chains has been established: hydrophobic amino acids (A, I, L, M, F, P, W, Y, and V), hydrophilic amino

acids (R, D, N, C, E, Q, G, H, K, S, and T), amino acids having an aliphatic side chain (G, A, V, L, I, and P), amino acids having a hydroxyl group-containing side chain (S, T, and Y), amino acids having a sulphur atom-containing side chain (C and M), amino acids having a side chain containing carboxylic acid and amide (D, N, E, and Q), amino acids having a base-containing side chain (R, K, and H), and amino acids having an aromatic group-containing side chain (H, F, Y, and W) (all symbols within the parentheses represent single letter codes of amino acids).

[0091] A polypeptide having an amino acid sequence modified from a certain amino acid sequence by the deletion and/or addition of one or more amino acid residue(s) and/or the substitution thereof by other amino acids is already known to maintain the biological activity of the original polypeptide (Mark, D. F. et al., 1984) (Wang, A. et al., 1982). Specifically, when amino acids in an amino acid sequence constituting a certain polypeptide are substituted by amino acids classified in the same group thereas, it is generally said that the polypeptide is likely to maintain its activity. In the present invention, the substitution between amino acids within the same amino acid group described above is referred to as conservative substitution.

[0092] The term “surface” or specifically “cell surface” as used herein means the cell membrane. The cell membrane, which may also be known as plasma membrane, is the thin membrane that surrounds every living cell, delimiting the cell from the environment around it. Enclosed by this cell membrane are the cell’s constituents, often large, water-soluble, highly charged molecules such as proteins, nucleic acids, carbohydrates, and substances involved in cellular metabolism. The cell membrane, therefore, has at least two functions: first, to be a barrier keeping the constituents of the cell in and unwanted substances out and, second, to be a gate allowing transport into the cell of essential nutrients and removal of waste products from the cell. ER-derived vesicles may also participate in the building or formation of the cell membrane.

[0093] The antibody, which binds to human SRRM2 is preferably capable of binding to a SRRM2 polypeptide extracellularly. In other words, an antibody as described herein may be capable of binding to SRRM2 when it is outside the cell, which also comprises SRRM2 to be specifically on the surface of the cell. Accordingly, the antibody, which binds to human SRRM2 is preferably not an intracellular antibody, which is also called an intrabody. An “intrabody” (from intracellular and antibody) is an antibody that works within the cell to bind to an intracellular protein. This requires the expression of the antibody within the target cell, which can be accomplished, e.g. in transgenic animals or by gene therapy. As a result, intrabodies are antibodies that have been modified for intracellular localization and include antibodies, which are produced in prokaryotes or other non-target cells. The term “intrabody” can apply to

several types of protein targeting: the antibody may remain in the cytoplasm, or it may have a nuclear localization signal, or it may undergo co-translational translocation across the membrane into the lumen of the endoplasmic reticulum, provided that it is retained in that compartment through a KDEL sequence.

[0094] The “target cell” is preferably a blood cancer cell. The term “blood cancer”, as used herein, can comprise any one or more of the following: multiple myeloma; leukemia including acute erythroid leukemia, acute lymphoblastic leukemia (ALL), acute megakaryoblastic leukemia, acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), chronic myelomonocytic leukemia (CMML), childhood leukemia, hairy cell leukemia (HCL), large granular lymphocytic leukemia (LGLL), mast cell leukemia (MCL) or plasma cell leukemia (PCL); lymphoma including Burkitt lymphoma, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, hodgkin lymphoma, non-Hodgkin lymphoma, MALT lymphoma, mantle cell lymphoma, small lymphocytic lymphoma (SLL), or post-transplant lymphoproliferative disorder (PTLD); or Waldenström macroglobulinaemia (WM); myelodysplastic syndrome, a myeloproliferative neoplasm (including polycythaemia vera, essential thrombocythaemia, or myelofibrosis), Erdheim-Chester disease, Langerhans cell histiocytosis, mastocytosis, or mast cell leukemia.

[0095] The term “pharmaceutically acceptable carrier, diluent or excipient” as used in the context of the present invention, may comprise any pharmaceutically acceptable carrier, diluent or excipient for a pharmaceutical composition known by the person skilled in the art. It will be understood that such antibodies or pharmaceutical composition as described herein may be mixed with carriers or diluents, which will not interfere with the intended purpose of the present invention. For example, such a carrier as used within the present invention may be a carrier protein, such as bovine serum albumin (BSA) or keyhole limpet haemocyanin (KLH).

[0096] In one embodiment of the pharmaceutical composition of the present invention, said antibody, which binds to human SRRM2, has cytotoxic activity. In the context of the present invention, the phrase “cytotoxic activity” may refer to having a SRRM2 binding activity and may also include having an activity equivalent to that of the antibody, which binds to human SRRM2 of the present invention. In the present invention, the equivalent activity is not necessarily required to be an identical activity and may be, for example, 50% or more, preferably 70% or more, more preferably 90% or more activity compared with the activity of any of the antibodies (a) to (e) as described herein. Examples of the upper limit of the activity can include, but is not particularly limited to, 1000% or less, 500% or less, 300% or less, 150% or less, and 100% or less.

[0097] In one further embodiment of the pharmaceutical composition of the present invention, said antibody, which binds to human SRRM2 has antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC). Thus, examples of the cytotoxic activity according to the present invention can include ADCC and/or CDC activities. In the context of the present invention, the ADCC activity means the activity of damaging target cells through the binding of Fc γ receptor-bearing cells (immunocytes, etc.) via the Fc γ receptors to the Fc domains of antibodies specifically attached to the cell surface antigens of the target cells. On the other hand, the CDC activity means a cytotoxic activity mediated by the complement system. Whether or not the antibody has an ADCC activity or has a CDC activity can be determined by a method known in the art.

[0098] Thus, the antibody, which binds to human SRRM2 employed in the pharmaceutical composition of the present invention may have activities such as an ADCC activity and as such, may be useful as a pharmaceutical drug, preferably, an anti-cancer agent, wherein the cancer is a blood cancer e.g. acute erythroid leukemia, acute lymphoblastic leukemia (ALL), acute megakaryoblastic leukemia, acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), chronic myelomonocytic leukemia (CMML), childhood leukemia, hairy cell leukemia (HCL), large granular lymphocytic leukemia (LGLL), mast cell leukemia (MCL) or plasma cell leukemia (PCL), Burkitt lymphoma, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, hodgkin lymphoma, non-Hodgkin lymphoma, MALT lymphoma, mantle cell lymphoma, small lymphocytic lymphoma (SLL), post-transplant lymphoproliferative disorder (PTLD), or Waldenström macroglobulinaemia (WM), myelodysplastic syndrome, a myeloproliferative neoplasm (including polycythaemia vera, essential thrombocythaemia, or myelofibrosis), Erdheim-Chester disease, Langerhans cell histiocytosis, mastocytosis, or mast cell leukemia.

[0099] In one embodiment of the present invention, said antibody, which binds to human SRRM2, is conjugated with a cytotoxic substance.

[0100] In one preferred embodiment, the antibody, which binds to human SRRM2 may be conjugated with a cytotoxic substance, such as a chemotherapeutic agent, a toxic peptide, or a radioactive chemical. Such a modified antibody (hereinafter, referred to as an antibody conjugate) can be obtained by chemically modifying the obtained antibody. A method for the antibody modification has already been established in the art.

[0101] Examples of the chemotherapeutic agent whose cytotoxic activity functions through the conjugation to the antibody that binds SRRM2 can include the following chemotherapeutic

agents: azaribine, anastrozole, azacytidine, bleomycin, bortezomib, bryostatin-1, busulfan, camptothecin, 10-hydroxycamptothecin, carmustine, celebrex, chlorambucil, cisplatin, irinotecan, carboplatin, cladribine, cyclophosphamide, cytarabine, dacarbazine, docetaxel, dactinomycin, daunomycin glucuronide, daunorubicin, dexamethasone, diethylstilbestrol, doxorubicin, doxorubicin glucuronide, epirubicin, ethinyl estradiol, estramustine, etoposide, etoposide glucuronide, floxuridine, fludarabine, flutamide, fluorouracil, fluoxymesterone, gemcitabine, hydroxyprogesterone caproate, hydroxyurea, idarubicin, ifosfamide, leucovorin, lomustine, mechlorethamine, medroxyprogesterone acetate, megestrol acetate, melphalan, mercaptopurine, methotrexate, mitoxantrone, mithramycin, mitomycin, mitotane, phenylbutyrate, prednisone, procarbazine, paclitaxel, pentostatin, semustine, streptozocin, tamoxifen, taxanes, taxol, testosterone propionate, thalidomide, thioguanine, thiotepa, teniposide, topotecan, uracil mustard, vinblastine, vinorelbine, vincristine.

[0102] The chemotherapeutic agent is preferably a low-molecular chemotherapeutic agent. The low-molecular chemotherapeutic agent is unlikely to interfere with the antibody even after its conjugation to the antibody. The low-molecular chemotherapeutic agent usually has a molecular weight of 100 to 2000, preferably 200 to 1000. All of the chemotherapeutic agents exemplified above are low-molecular chemotherapeutic agents. These chemotherapeutic agents encompass prodrugs that are converted *in vivo* to active chemotherapeutic agents. The prodrug activation may be an enzymatic conversion or a non-enzymatic conversion.

[0103] Examples of toxic peptides are snake venom peptides comprising Three-Finger Toxins (3FTxs), a disintegrin, a Kunitz-type inhibitor, a natriuretic peptide, or a Sarafotoxin as reviewed in Munawar et al., 2018. Further examples are a trypsin inhibitor, an islanditoxin, a pallotoxin, or an amatoxin as mentioned in Khan et al., 2018.

[0104] Examples of a radioactive chemical are chemicals having a cytotoxic radionuclide, such radionuclide could be for example iodine-131, indium-111, yttrium-90, lutetium-177, actinium-225, gallium-68, or bismuth-213 as reviewed in Hofland et al., 2022 and Martiniova et al., 2022. The antibody coupled to the cytotoxic substance could be used for delivering the cytotoxic substance specifically to the target cell which may reduce unwanted side effects.

[0105] In one embodiment of the pharmaceutical composition of the present invention, said antibody, which binds to human SRRM2, is less than 20 % cross-reactive with SRRM2-related proteins. This means preferably that said antibody, which binds to human SRRM2, is less than 20 % cross-reactive with other serine/arginine repetitive matrix proteins such as SRRM1, SRRM3, SRRM4 or SRRM5. More preferably, said antibody, which binds to human SRRM2 is

less than 15 % cross-reactive with SRRM2-related proteins, e.g. SRRM1, SRRM3, SRRM4 or SRRM5. Even more preferably, said antibody, which binds to human SRRM2, is less than 10 % cross-reactive with SRRM2-related proteins, e.g. SRRM1, SRRM3, SRRM4 or SRRM5. Even more preferably, said antibody, which binds to human SRRM2, is less than 5 % cross-reactive with SRRM2-related proteins, e.g. SRRM1, SRRM3, SRRM4 or SRRM5. Even more preferably, said antibody, which binds to human SRRM2, is less than 3 % cross-reactive with SRRM2-related proteins, e.g. SRRM1, SRRM3, SRRM4 or SRRM5. Even more preferably, said antibody, which binds to human SRRM2, is less than 2 % cross-reactive with SRRM2-related proteins, e.g. SRRM1, SRRM3, SRRM4 or SRRM5. Even more preferably, said antibody, which binds to human SRRM2, is less than 1 % cross-reactive with SRRM2-related proteins, e.g. SRRM1, SRRM3, SRRM4 or SRRM5.

[0106] In one embodiment, said antibody, which binds to human SRRM2, is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 85% identity to the amino acid sequence shown in SEQ ID NO: 1 and a light chain variable region having an amino acid sequence with at least 85% identity to the amino acid sequence shown in SEQ ID NO: 2 or an antibody, which binds to the same epitope.

[0107] In one embodiment, said antibody, which binds to human SRRM2, is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 90% identity to the amino acid sequence shown in SEQ ID NO: 1 and a light chain variable region having an amino acid sequence with at least 90% identity to the amino acid sequence shown in SEQ ID NO: 2 or an antibody, which binds to the same epitope.

[0108] In one embodiment, said antibody, which binds to human SRRM2, is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 95% identity to the amino acid sequence shown in SEQ ID NO: 1 and a light chain variable region having an amino acid sequence with at least 95% identity to the amino acid sequence shown in SEQ ID NO: 2 or an antibody, which binds to the same epitope.

[0109] In one embodiment, said antibody, which binds to human SRRM2, is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 99% identity to the amino acid sequence shown in SEQ ID NO: 1 and a light chain variable region having an amino acid sequence with at least 99% identity to the amino acid sequence shown in SEQ ID NO: 2 or an antibody, which binds to the same epitope.

[0110] In one embodiment, said antibody, which binds to human SRRM2, is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 85% identity to the amino acid sequence shown in SEQ ID NO: 3 and a light chain variable region having an amino acid sequence with at least 85% identity to the amino acid sequence shown in SEQ ID NO: 4 or an antibody, which binds to the same epitope.

[0111] In one embodiment, said antibody, which binds to human SRRM2, is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 90% identity to the amino acid sequence shown in SEQ ID NO: 3 and a light chain variable region having an amino acid sequence with at least 90% identity to the amino acid sequence shown in SEQ ID NO: 4 or an antibody, which binds to the same epitope.

[0112] In one embodiment, said antibody, which binds to human SRRM2, is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 95% identity to the amino acid sequence shown in SEQ ID NO: 3 and a light chain variable region having an amino acid sequence with at least 95% identity to the amino acid sequence shown in SEQ ID NO: 4 or an antibody, which binds to the same epitope.

[0113] In one embodiment, said antibody, which binds to human SRRM2 is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 99% identity to the amino acid sequence shown in SEQ ID NO: 3 and a light chain variable region having an amino acid sequence with at least 99% identity to the amino acid sequence shown in SEQ ID NO: 4 or an antibody, which binds to the same epitope.

[0114] In one embodiment, said antibody, which binds to human SRRM2, is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 85% identity to the amino acid sequence shown in SEQ ID NO: 5 and a light chain variable region having an amino acid sequence with at least 85% identity to the amino acid sequence shown in SEQ ID NO: 6 or an antibody, which binds to the same epitope.

[0115] In one embodiment, said antibody, which binds to human SRRM2, is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 90% identity to the amino acid sequence shown in SEQ ID NO: 5 and a light chain variable region having an amino acid sequence with at least 90% identity to the amino acid sequence shown in SEQ ID NO: 6 or an antibody, which binds to the same epitope.

[0116] In one embodiment, said antibody, which binds to human SRRM2, is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 95% identity to the amino acid sequence shown in SEQ ID NO: 5 and a light chain variable region having an amino acid sequence with at least 95% identity to the amino acid sequence shown in SEQ ID NO: 6 or an antibody, which binds to the same epitope.

[0117] In one embodiment, said antibody, which binds to human SRRM2, is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 99% identity to the amino acid sequence shown in SEQ ID NO: 5 and a light chain variable region having an amino acid sequence with at least 99% identity to the amino acid sequence shown in SEQ ID NO: 6 or an antibody, which binds to the same epitope.

[0118] In one embodiment, said antibody, which binds to human SRRM2, is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 85% identity to the amino acid sequence shown in SEQ ID NO: 5 and a light chain variable region having an amino acid sequence with at least 85% identity to the amino acid sequence shown in SEQ ID NO: 7 or an antibody, which binds to the same epitope.

[0119] In one embodiment, said antibody, which binds to human SRRM2, is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 90% identity to the amino acid sequence shown in SEQ ID NO: 5 and a light chain variable region having an amino acid sequence with at least 90% identity to the amino acid sequence shown in SEQ ID NO: 7 or an antibody, which binds to the same epitope.

[0120] In one embodiment, said antibody, which binds to human SRRM2, is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 95% identity to the amino acid sequence shown in SEQ ID NO: 5 and a light chain variable region having an amino acid sequence with at least 95% identity to the amino acid sequence shown in SEQ ID NO: 7 or an antibody, which binds to the same epitope.

[0121] In one embodiment, said antibody, which binds to human SRRM2, is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 99% identity to the amino acid sequence shown in SEQ ID NO: 5 and a light chain variable region having an amino acid sequence with at least 99% identity to the amino acid sequence shown in SEQ ID NO: 7 or an antibody, which binds to the same epitope.

[0122] In one embodiment, said antibody, which binds to human SRRM2, is an antibody comprising a heavy chain variable region comprising heavy chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 9, heavy chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 10, and heavy chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 11, and a light chain variable region comprising light chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 12, light chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 13, and light chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 14, or an antibody, which binds to the same epitope.

[0123] In one embodiment, said antibody, which binds to human SRRM2 is an antibody comprising a heavy chain variable region comprising heavy chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 15, heavy chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 16, and heavy chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 17, and a light chain variable region comprising light chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 18, light chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 19, and light chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 20, or an antibody, which binds to the same epitope.

[0124] In one embodiment, said antibody, which binds to human SRRM2, is an antibody comprising a heavy chain variable region comprising heavy chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 21, heavy chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 22, and heavy chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 23, and a light chain variable region comprising light chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 24, light chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 25, and light chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 26, or an antibody, which binds to the same epitope.

[0125] In one embodiment of the pharmaceutical composition of the present invention, said antibody, which binds to human SRRM2, is an antibody comprising a heavy chain variable region comprising heavy chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 21, heavy chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 22, and heavy chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 23, and a light chain variable region comprising light chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 27, light chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 28, and light chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 29, or an antibody, which binds to the same epitope.

[0126] The antibodies described herein may contain constant regions. The constant regions used are not particularly limited, and any constant region may be used. Preferable examples of the constant regions used in the present invention can include human-derived constant regions. For example, a human IgG1-derived, human IgG2-derived, human IgG3-derived, or human IgG4-derived constant region can be used as a heavy chain constant region. Also, for example, human κ chain-derived or human λ chain-derived constant region can be used as a light chain constant region. The constant regions used in the present invention may be constant regions having a native sequence or may be modified constant regions having a sequence derived from the native sequence by the modification of one or more amino acids.

[0127] The antibodies described herein may also contain framework regions (FRs). The FRs used are not particularly limited, and any FR may be used as long as the resulting antibody maintains its binding activity to human SRRM2 present on the cell surface of a target cell. Preferable examples of the FRs used in the present invention can include human antibody derived FRs. Since the technique of FR replacement with the antigen binding activity of an antibody maintained is known in the art, those skilled in the art can appropriately select FRs. The FRs used in the present invention may be FRs having a native sequence or may be FRs having a sequence derived from the native sequence by the modification of one or more amino acids.

[0128] Whether or not an antibody shares an epitope with a certain antibody can be confirmed based on their competition for the same epitope. The competition between the antibodies is detected by cross-blocking assay or the like. The cross-blocking assay is preferably, for example, competitive ELISA assay. Specifically, in the cross-blocking assay, SRRM2 proteins coated on the wells of a microtiter plate may be pre-incubated in the presence or absence of a candidate competing antibody and the antibody, which binds to human SRRM2 of the present invention is then added to the wells. The amount of the antibody of the present invention bound to the SRRM2 protein in the well indirectly correlates with the binding ability of the candidate competing antibody (antibody to be tested) that competes therewith for the binding to the same epitope. Specifically, the larger affinity the antibody to be tested has for the same epitope, the smaller amount of the antibody of the present invention is bound to the SRRM2 protein-coated well, while the larger amount of the antibody to be tested is bound to the SRRM2 protein-coated well.

[0129] The amount of the antibody bound to the well can be measured easily by labelling the antibody in advance. For example, a biotin-labelled antibody can be measured by use of an avidin-peroxidase conjugate and an appropriate substrate. The cross-blocking assay using

enzyme (e.g., peroxidase) labelling is particularly referred to as competitive ELISA assay. The antibody can be labelled with other detectable or measurable labelling substances. Specifically, radio-labelling or fluorescent labelling or the like is known in the art.

[0130] Provided that a candidate antibody can bind to human SRRM2 present on the cell surface of a target cell by at least 80%, preferably at least 85%, more preferably at least 90%, even more preferably at least 95%, even more preferably at least 99%, compared to the binding activity obtained in a control test performed in the absence of the candidate antibody, this candidate antibody is determined as an antibody that binds to substantially the same epitope as that to which the antibody of the present invention binds or to which the antibody, which binds to human SRRM2 used in the pharmaceutical composition binds.

[0131] In a further aspect the antibody as referred to herein is comprised by a pharmaceutical composition which is for use in a method for the treatment of blood cancer in a patient. It is preferred for said embodiment that said blood cancer is characterized by cells, wherein human SRRM2 is present on their cell surface, i.e. the SRRM2 bound by the antibody of the present invention is membrane-expressed SRRM2. It is also preferred for said embodiment that said blood cancer is multiple myeloma (MM). It is equally preferred for said embodiment that said blood cancer is plasma cell leukemia (PCL). It is equally preferred for said embodiment that said blood cancer is acute myeloid leukemia (AML).

[0132] The present invention also covers the use of the pharmaceutical composition according to the present invention for the manufacture of a medicament for the treatment of blood cancer, preferably MM, PCL and AML.

[0133] In one embodiment, the present invention also covers the use of an antibody, which binds to human SRRM2 as described herein, for the manufacture of a medicament for the treatment of blood cancer, preferably MM, PCL and AML.

[0134] In some embodiments of the present invention, it is further envisaged that the AML treated with the antibody of the present invention is characterized by cells having a genetic mutation. Preferably, said genetic mutation is a FMS-like tyrosine kinase-3 (FLT-3) mutation. Thus, said AML to be treated is characterized by cells expressing human SRRM2 on the cancer cell membrane and harbouring a genetic mutation, preferably a FLT3 mutation. Mutations in FLT3 are the most common genetic alteration in AML and occur in approximately 30% of all AML cases, with the internal tandem duplication (ITD) representing the most

common type of FLT3 mutation. FLT3-ITD is a driver mutation that presents with a high leukemic burden and confers a poor prognosis in patients with AML (Daver et al., 2019).

[0135] In some embodiments of the present invention, it is further envisaged that the PCL treated with the antibody of the present invention is a primary or a secondary PCL. "Primary PCL" means in this respect that the PCL is occurring *de novo*, i.e. without that the patient was previously diagnosed with MM (see Patient 1 described in the Examples). "Secondary PCL" means in this respect that the patient was previously diagnosed with MM. In this case the MM undergoes leukemic transformation, i.e. it progressed to PCL (see Patient 3 described in the Examples).

[0136] It is further envisaged in the context of the present invention that the blood cancer patient to be treated with the antibody binding to human SRRM2 as described herein is refractory to previous cancer therapy and/or in relapse after previous cancer therapy, i.e. said patient has already received a first (or even several) cancer treatment(s), but is now in the condition or need to receive a further cancer treatment. Said previous blood cancer therapy or treatment may comprise e.g. one or several cycles of chemotherapy, targeted cancer therapy and/or allogeneic stem cell therapy known to those skilled in the art. "Relapsed" means in this respect that the blood cancer returns after it has been in remission after the previous cancer treatment. "Refractory" means in this respect that the blood cancer has stopped responding to previous cancer treatment

[0137] The present invention also comprises a method of treating blood cancer, wherein the method comprises administering a therapeutically effective amount of the pharmaceutical composition according to the present invention to a patient. The pharmaceutical composition according to the present invention is preferred to be administered via parenteral routes, including, but not limited to, intravenous, intradermal, intramuscular, intrathecal, or intraperitoneal administration. Alternate routes include, but are not limited to: oral, rectal, ophthalmic (including intravitreal or intracameral), nasal, topical (including buccal and sublingual), intrauterine, vaginal or subcutaneous, intracranial, intratracheal, epidural, transdermal, intracerebroventricular, intracerebral, intravaginal, intrauterine, or intraspinal routes.

[0138] Further, the present invention comprises a method of treating blood cancer, wherein the method comprises administering a therapeutically effective amount of the antibody, which binds to human SRRM2 described herein to a patient. It is preferred for said embodiment that said blood cancer is characterized by cells, wherein human SRRM2 is present on their cell surface. In this respect it is also envisaged that the method for the treatment of blood cancer

in a subject comprises, prior to the treatment of the blood cancer in said subject, determining whether a target cell of said subject has SRRM2 present on the cell surface as described elsewhere herein.

[0139] The term “therapeutically effective amount” refers to an amount of the antibody or pharmaceutical composition according to the present invention or drug effective to “treat” cancer in the patient. Specifically, in the case of cancer, the therapeutically effective amount of the antibody/pharmaceutical composition/drug can reduce the number of cancer cells; reduce the tumour size; inhibit or stop cancer cell infiltration into peripheral organs; inhibit and stop tumour metastasis; inhibit and stop tumour growth; relieve to some extent one or more of the symptoms associated with the cancer, or a combination of such effects on cancer cells. To the extent the antibody/pharmaceutical composition/drug prevents the growth and/or kills existing cancer cells, it can be referred to as cytostatic and/or cytotoxic.

[0140] Terms such as “treating” or “treatment” or “to treat” refer to both 1) therapeutic measures that cure, slow down, lessen symptoms of, and/or halt progression of a diagnosed pathologic condition or disorder and 2) prophylactic or preventative measures that prevent or slow the development of a targeted pathologic condition or disorder. Thus, those in need of treatment include those already with the disorder; those prone to have the disorder; and those in whom the disorder is to be prevented. A subject is successfully “treated” according to the methods of the present invention or with the pharmaceutical composition or antibody, which binds to human SRRM2 according to the present invention if the patient shows one or more of the following: a reduction in the number of or complete absence of cancer cells; a reduction in the tumour size; inhibition of or an absence of cancer cell infiltration into peripheral organs including the spread of cancer into soft tissue and bone; inhibition of or an absence of tumour metastasis; inhibition or an absence of tumour growth; relief of one or more symptoms associated with the specific cancer; reduced morbidity and mortality; and improvement in quality of life.

[0141] The antibody to be administered to humans can also be converted to a genetically recombinant antibody that has been engineered artificially, for example, for the purpose of reducing heteroantigenicity in humans. The genetically recombinant antibody encompasses, for example, chimeric antibodies and humanized antibodies as defined herein. These engineered antibodies can be produced using a method known in the art.

[0142] In a further aspect, the present invention provides a method for determining whether a patient may suffer from blood cancer, comprising determining in a sample obtained from said

patient whether SRRM2 is present on the cell surface of (blood cancer) cells comprised by said sample and/or whether SRRM2 is present on the surface of extracellular vesicles.

[0143] “Extracellular vesicles” (EV) as used herein may relate to lipid bilayer-delimited particles that are naturally released from almost all types of cell and, unlike a cell, cannot replicate. EVs typically range in diameter from near the size of the smallest physically possible unilamellar liposome (around 20-30 nanometers) to as large as 10 µm or more, although the vast majority of EVs are smaller than 200 nm.

[0144] EVs can be divided according to size and synthesis route into exosomes, microvesicles and apoptotic bodies. Accordingly, the EV is preferably selected from the group consisting of exosomes, microvesicles and apoptotic bodies. Usually, they carry a cargo of proteins, nucleic acids, lipids, metabolites, and even organelles from the parent cell. Diverse EV subtypes have been proposed. Accordingly, the EV may also be one or more of the following: ectosomes, microvesicles, microparticles, exosomes, oncosomes, apoptotic bodies, exomeres and the like. Preferably, the EV is an oncosome. In the context of EVs, the sample preferably is ascites fluid.

[0145] EVs may be isolated and/or enriched from the sample by using an antibody or antibody fragment that specifically binds to a biomarker present on the surface of an EV prior to determining in a sample obtained from said patient whether SRRM2 is present on the surface of extracellular vesicles. Such biomarkers for EV include, e.g., for exosomes Alix, Tsg101, tetraspanins such as CD81, CD63 and CD9 or flotillin, for microvesicles integrins, selectins or CD40 and for apoptotic bodies Annexin V or phosphatidylserine. Antibodies against these markers are commercially available, e.g., from Abcam. Methods for isolating and/or enriching EVs are further described in Campos-Silva et al. (2019), Scientific Reports, 9:2042(2019) or Pugholm et al. (2015), Biomed Res Int., 2015:524817, both of which are hereby incorporated by reference in its entirety.

[0146] The antibody referred to herein can also be contained in a diagnostic composition, preferably in case it is used in the context of a method for determining whether a patient may suffer from blood cancer. Accordingly, the present invention also relates to a diagnostic composition, comprising an antibody, preferably a monoclonal antibody, which binds to human Serine/arginine repetitive matrix protein 2 (SRRM2) present on the cell surface of a target cell, preferably a blood cancer cell, and optionally a pharmaceutically acceptable carrier, diluent or excipient.

[0147] Said method for determining whether a patient may suffer from blood cancer may comprise the following steps:

- providing a sample obtained from said patient,
- determining in said sample obtained from said patient whether SRRM2 is present on the cell surface of (blood cancer) cells comprised by said sample,
- correlating the presence of SRRM2 on the cell surface of (blood cancer) cells comprised by said sample with determining whether the patient may suffer from blood cancer.

[0148] In this respect the amount of SRRM2 present on the cell surface of (blood cancer) cells, or present on the surface of extracellular vesicles, comprised by the sample from said patient may be compared to reference data, e.g. to reference data from a healthy subject known to not suffer from blood cancer. An increased amount of SRRM2 on the surface of cells and/or on the surface of extracellular vesicles comprised by said sample when compared to the amount of SRRM2 on the cell surface and/or the surface of extracellular vesicles in a sample obtained from a healthy subject indicates that the patient may suffer from blood cancer. No difference in the amount of SRRM2 on the cell surface and/or present on the surface of extracellular vesicles comprised by a sample obtained from said patient when compared to the amount of SRRM2 on the cell surface and/or the surface of extracellular vesicles in a sample obtained from a healthy subject indicates that the patient may not suffer from blood cancer.

[0149] For determining or diagnosing whether a patient may suffer from blood cancer, the antibody which binds to human SRRM2 on the cell surface of a target cell may be modified with a substance used for said diagnostic purpose, e.g. a radioactive chemical, a magnetic chemical, or a fluorescence moiety known to those skilled in the art.

[0150] A “subject” or “patient” in the context of the present invention is a human being. For example, the patient may be a patient being suspected of having a disease or clinical condition associated with blood cancer or being diagnosed with such a disease or clinical condition.

[0151] Said “sample” obtained from said patient is preferably, but not limited to, a sample of blood, lymph fluid, lymphatic tissue or bone marrow.

[0152] The step of “determining in said sample obtained from said patient whether SRRM2 is present on the cell surface of target cells comprised by said sample” may comprise to determine the presence of SRRM2 or the fragments thereof by contacting the sample with at

least one SRRM2 binder. The at least one binder may, for example, be the antibody according to the present invention or as described herein. It is preferred that at least one binder is less than 20% cross-reactive with other proteins, particularly other peroxiredoxins such as SRRM1, SRRM3, SRRM4 or SRRM5, more preferably less than 15 %, more preferably less than 10%, more preferably less than 5%, even more preferably less than 3%, even more preferably less than 2% and even more preferably less than 1% cross reactive.

[0153] In some embodiments, the antibody, which binds to human SRRM2, of the present invention or described herein may contain human Fc regions that are modified to enhance effector function, for example, antigen-dependent cell-mediated cytotoxicity (ADCC) and/or complement dependent cytotoxicity (CDC). This can be achieved by introducing one or more amino acid substitutions in a Fc region of the antibody. For example, cysteine residue(s) can be introduced in the Fc region to allow interchain disulfide bond formation in this region to improve complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). Homodimeric antibodies with enhanced anti-tumour activity can also be prepared using heterobifunctional cross-linkers as known to the person skilled in the art. Alternatively, an antibody may be engineered, which has dual Fc regions.

[0154] Furthermore, the antibodies as described herein may have substitution, deletion, addition and/or insertion of one or more amino acids in their CDR sequences as long as the resulting antibodies are functionally equivalent to the antibodies (a) to (d). The term "functionally equivalent" refers to being comparable in avidity for SRRM2 and cytotoxicity. The term "equivalent" refers to having at least 50%, preferably having at least 60%, more preferably having at least 70%, more preferably having at least 80%, even more preferably at least 90%, even more preferably at least 95% and even more preferably at least 99% activity, compared with the antibodies (a) to (d). The upper limit of the activity is not particularly limited and may be higher than that of the antibodies (a) to (d). The avidity or cytotoxicity can be assayed by a method generally known by those skilled in the art.

[0155] The present invention further relates to an antibody, which binds to human serine/arginine repetitive matrix protein 2 (SRRM2) present on the cell surface of a target cell for use in a method of killing said target cell, wherein said target cell is a blood cancer cell having SRRM2 present on the cell surface. Specifically, the present invention provides for an antibody, which binds to human serine/arginine repetitive matrix protein 2 (SRRM2) present on the cell surface of a target cell for use in a method of treating blood cancer as defined elsewhere herein.

[0156] "Target cell", as used herein, refers to a blood cancer cell that expresses human serine/arginine repetitive matrix protein 2 (SRRM2) on its surface, unless otherwise stated.

[0157] In one embodiment of the antibody for use in a method of killing said target cell having SRRM2 present on the cell surface, said antibody is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 85% identity to the amino acid sequence shown in SEQ ID NO: 1 and a light chain variable region having an amino acid sequence with at least 85% identity to the amino acid sequence shown in SEQ ID NO: 2 or an antibody, which binds to the same epitope.

[0158] In one embodiment of the antibody for use in a method of killing said target cell having SRRM2 present on the cell surface, said antibody is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 90% identity to the amino acid sequence shown in SEQ ID NO: 1 and a light chain variable region having an amino acid sequence with at least 90% identity to the amino acid sequence shown in SEQ ID NO: 2 or an antibody, which binds to the same epitope.

[0159] In one embodiment of the antibody for use in a method of killing said target cell having SRRM2 present on the cell surface, said antibody is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 95% identity to the amino acid sequence shown in SEQ ID NO: 1 and a light chain variable region having an amino acid sequence with at least 95% identity to the amino acid sequence shown in SEQ ID NO: 2 or an antibody, which binds to the same epitope.

[0160] In one embodiment of the antibody for use in a method of killing said target cell having SRRM2 present on the cell surface, said antibody is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 99% identity to the amino acid sequence shown in SEQ ID NO: 1 and a light chain variable region having an amino acid sequence with at least 99% identity to the amino acid sequence shown in SEQ ID NO: 2 or an antibody, which binds to the same epitope.

[0161] In one embodiment of the antibody for use in a method of killing said target cell having SRRM2 present on the cell surface, said antibody is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 85% identity to the amino acid sequence shown in SEQ ID NO: 3 and a light chain variable region having an amino acid sequence with at least 85% identity to the amino acid sequence shown in SEQ ID NO: 4 or an antibody, which binds to the same epitope.

[0162] In one embodiment of the antibody for use in a method of killing said target cell having SRRM2 present on the cell surface, said antibody is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 90% identity to the amino acid sequence shown in SEQ ID NO: 3 and a light chain variable region having an amino acid sequence with at least 90% identity to the amino acid sequence shown in SEQ ID NO: 4 or an antibody, which binds to the same epitope.

[0163] In one embodiment of the antibody for use in a method of killing said target cell having SRRM2 present on the cell surface, said antibody is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 95% identity to the amino acid sequence shown in SEQ ID NO: 3 and a light chain variable region having an amino acid sequence with at least 95% identity to the amino acid sequence shown in SEQ ID NO: 4 or an antibody, which binds to the same epitope.

[0164] In one embodiment of the antibody for use in a method of killing said target cell having SRRM2 present on the cell surface, said antibody is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 99% identity to the amino acid sequence shown in SEQ ID NO: 3 and a light chain variable region having an amino acid sequence with at least 99% identity to the amino acid sequence shown in SEQ ID NO: 4 or an antibody, which binds to the same epitope.

[0165] In one embodiment of the antibody for use in a method of killing said target cell having SRRM2 present on the cell surface, said antibody is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 85% identity to the amino acid sequence shown in SEQ ID NO: 5 and a light chain variable region having an amino acid sequence with at least 85% identity to the amino acid sequence shown in SEQ ID NO: 6 or an antibody, which binds to the same epitope.

[0166] In one embodiment of the antibody for use in a method of killing said target cell having SRRM2 present on the cell surface, said antibody is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 90% identity to the amino acid sequence shown in SEQ ID NO: 5 and a light chain variable region having an amino acid sequence with at least 90% identity to the amino acid sequence shown in SEQ ID NO: 6 or an antibody, which binds to the same epitope.

[0167] In one embodiment of the antibody for use in a method of killing said target cell having SRRM2 present on the cell surface, said antibody is an antibody comprising a heavy chain

variable region having an amino acid sequence with at least 95% identity to the amino acid sequence shown in SEQ ID NO: 5 and a light chain variable region having an amino acid sequence with at least 95% identity to the amino acid sequence shown in SEQ ID NO: 6 or an antibody, which binds to the same epitope.

[0168] In one embodiment of the antibody for use in a method of killing said target cell having SRRM2 present on the cell surface, said antibody is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 99% identity to the amino acid sequence shown in SEQ ID NO: 5 and a light chain variable region having an amino acid sequence with at least 99% identity to the amino acid sequence shown in SEQ ID NO: 6 or an antibody, which binds to the same epitope.

[0169] In one embodiment of the antibody for use in a method of killing said target cell having SRRM2 present on the cell surface, said antibody is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 85% identity to the amino acid sequence shown in SEQ ID NO: 5 and a light chain variable region having an amino acid sequence with at least 85% identity to the amino acid sequence shown in SEQ ID NO: 7 or an antibody, which binds to the same epitope.

[0170] In one embodiment of the antibody for use in a method of killing said target cell having SRRM2 present on the cell surface, said antibody is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 90% identity to the amino acid sequence shown in SEQ ID NO: 5 and a light chain variable region having an amino acid sequence with at least 90% identity to the amino acid sequence shown in SEQ ID NO: 7 or an antibody, which binds to the same epitope.

[0171] In one embodiment of the antibody for use in a method of killing said target cell having SRRM2 present on the cell surface, said antibody is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 95% identity to the amino acid sequence shown in SEQ ID NO: 5 and a light chain variable region having an amino acid sequence with at least 95% identity to the amino acid sequence shown in SEQ ID NO: 7 or an antibody, which binds to the same epitope.

[0172] In one embodiment of the antibody for use in a method of killing said target cell having SRRM2 present on the cell surface, said antibody is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 99% identity to the amino acid sequence shown in SEQ ID NO: 5 and a light chain variable region having an amino acid

sequence with at least 99% identity to the amino acid sequence shown in SEQ ID NO: 7 or an antibody, which binds to the same epitope.

[0173] In one embodiment of the antibody for use in a method of killing said target cell having SRRM2 present on the cell surface, said antibody is an antibody comprising a heavy chain variable region comprising heavy chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 9, heavy chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 10, and heavy chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 11, and a light chain variable region comprising light chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 12, light chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 13, and light chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 14, or an antibody, which binds to the same epitope.

[0174] In one embodiment of the antibody for use in a method of killing said target cell having SRRM2 present on the cell surface, said antibody is an antibody comprising a heavy chain variable region comprising heavy chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 15, heavy chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 16, and heavy chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 17, and a light chain variable region comprising light chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 18, light chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 19, and light chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 20, or an antibody, which binds to the same epitope.

[0175] In one embodiment of the antibody for use in a method of killing said target cell having SRRM2 present on the cell surface, said antibody is an antibody comprising a heavy chain variable region comprising heavy chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 21, heavy chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 22, and heavy chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 23, and a light chain variable region comprising light chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 24, light chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 25, and light chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 26, or an antibody, which binds to the same epitope.

[0176] In one embodiment of the antibody for use in a method of killing said target cell having SRRM2 present on the cell surface, said antibody is an antibody comprising a heavy chain variable region comprising heavy chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 21, heavy chain CDR2 having the amino acid sequence as set forth in SEQ ID

NO: 22, and heavy chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 23, and a light chain variable region comprising light chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 27, light chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 28, and light chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 29, or an antibody, which binds to the same epitope.

[0177] All embodiments, which have been described herein for the pharmaceutical composition of the present invention and the antibody, which binds to human SRRM2 present on the cell surface of a target cell of the present invention and the methods of the present invention as described herein as well as the respective definitions as described above, also apply for the antibody for use in a method of killing said target cell having SRRM2 present on the cell surface of the present invention as described herein.

[0178] The present invention also relates to a method of killing a target cell having serine/arginine repetitive matrix protein 2 (SRRM2) present on the cell surface of said target cell, comprising administering an antibody, which binds to human SRRM2 present on the cell surface of said target cell.

[0179] In one embodiment of the method of killing a target cell having serine/arginine repetitive matrix protein 2 (SRRM2) present on the cell surface of said target cell, said antibody is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 85% identity to the amino acid sequence shown in SEQ ID NO: 1 and a light chain variable region having an amino acid sequence with at least 85% identity to the amino acid sequence shown in SEQ ID NO: 2 or an antibody, which binds to the same epitope.

[0180] In one embodiment of the method of killing a target cell having serine/arginine repetitive matrix protein 2 (SRRM2) present on the cell surface of said target cell, said antibody is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 90% identity to the amino acid sequence shown in SEQ ID NO: 1 and a light chain variable region having an amino acid sequence with at least 90% identity to the amino acid sequence shown in SEQ ID NO: 2 or an antibody, which binds to the same epitope.

[0181] In one embodiment of the method of killing a target cell having serine/arginine repetitive matrix protein 2 (SRRM2) present on the cell surface of said target cell, said antibody is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 95% identity to the amino acid sequence shown in SEQ ID NO: 1 and a light chain variable region having an amino acid sequence with at least 95% identity to the amino acid sequence shown in SEQ ID NO: 2 or an antibody, which binds to the same epitope.

[0182] In one embodiment of the method of killing a target cell having serine/arginine repetitive matrix protein 2 (SRRM2) present on the cell surface of said target cell, said antibody is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 99% identity to the amino acid sequence shown in SEQ ID NO: 1 and a light chain variable region having an amino acid sequence with at least 99% identity to the amino acid sequence shown in SEQ ID NO: 2 or an antibody, which binds to the same epitope.

[0183] In one embodiment of the method of killing a target cell having serine/arginine repetitive matrix protein 2 (SRRM2) present on the cell surface of said target cell, said antibody is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 85% identity to the amino acid sequence shown in SEQ ID NO: 3 and a light chain variable region having an amino acid sequence with at least 85% identity to the amino acid sequence shown in SEQ ID NO: 4 or an antibody, which binds to the same epitope.

[0184] In one embodiment of the method of killing a target cell having serine/arginine repetitive matrix protein 2 (SRRM2) present on the cell surface of said target cell, said antibody is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 90% identity to the amino acid sequence shown in SEQ ID NO: 3 and a light chain variable region having an amino acid sequence with at least 90% identity to the amino acid sequence shown in SEQ ID NO: 4 or an antibody, which binds to the same epitope.

[0185] In one embodiment of the method of killing a target cell having serine/arginine repetitive matrix protein 2 (SRRM2) present on the cell surface of said target cell, said antibody is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 95% identity to the amino acid sequence shown in SEQ ID NO: 3 and a light chain variable region having an amino acid sequence with at least 95% identity to the amino acid sequence shown in SEQ ID NO: 4 or an antibody, which binds to the same epitope.

[0186] In one embodiment of the method of killing a target cell having serine/arginine repetitive matrix protein 2 (SRRM2) present on the cell surface of said target cell, said antibody is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 99% identity to the amino acid sequence shown in SEQ ID NO: 3 and a light chain variable region having an amino acid sequence with at least 99% identity to the amino acid sequence shown in SEQ ID NO: 4 or an antibody, which binds to the same epitope.

[0187] In one embodiment of the method of killing a target cell having serine/arginine repetitive matrix protein 2 (SRRM2) present on the cell surface of said target cell, said antibody is an

antibody comprising a heavy chain variable region having an amino acid sequence with at least 85% identity to the amino acid sequence shown in SEQ ID NO: 5 and a light chain variable region having an amino acid sequence with at least 85% identity to the amino acid sequence shown in SEQ ID NO: 6 or an antibody, which binds to the same epitope.

[0188] In one embodiment of the method of killing a target cell having serine/arginine repetitive matrix protein 2 (SRRM2) present on the cell surface of said target cell, said antibody is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 90% identity to the amino acid sequence shown in SEQ ID NO: 5 and a light chain variable region having an amino acid sequence with at least 90% identity to the amino acid sequence shown in SEQ ID NO: 6 or an antibody, which binds to the same epitope.

[0189] In one embodiment of the method of killing a target cell having serine/arginine repetitive matrix protein 2 (SRRM2) present on the cell surface of said target cell, said antibody is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 95% identity to the amino acid sequence shown in SEQ ID NO: 5 and a light chain variable region having an amino acid sequence with at least 95% identity to the amino acid sequence shown in SEQ ID NO: 6 or an antibody, which binds to the same epitope.

[0190] In one embodiment of the method of killing a target cell having serine/arginine repetitive matrix protein 2 (SRRM2) present on the cell surface of said target cell, said antibody is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 99% identity to the amino acid sequence shown in SEQ ID NO: 5 and a light chain variable region having an amino acid sequence with at least 99% identity to the amino acid sequence shown in SEQ ID NO: 6 or an antibody, which binds to the same epitope.

[0191] In one embodiment of the method of killing a target cell having serine/arginine repetitive matrix protein 2 (SRRM2) present on the cell surface of said target cell, said antibody is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 85% identity to the amino acid sequence shown in SEQ ID NO: 5 and a light chain variable region having an amino acid sequence with at least 85% identity to the amino acid sequence shown in SEQ ID NO: 7 or an antibody, which binds to the same epitope.

[0192] In one embodiment of the method of killing a target cell having serine/arginine repetitive matrix protein 2 (SRRM2) present on the cell surface of said target cell, said antibody is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 90% identity to the amino acid sequence shown in SEQ ID NO: 5 and a light chain

variable region having an amino acid sequence with at least 90% identity to the amino acid sequence shown in SEQ ID NO: 7 or an antibody, which binds to the same epitope.

[0193] In one embodiment of the method of killing a target cell having serine/arginine repetitive matrix protein 2 (SRRM2) present on the cell surface of said target cell, said antibody is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 95% identity to the amino acid sequence shown in SEQ ID NO: 5 and a light chain variable region having an amino acid sequence with at least 95% identity to the amino acid sequence shown in SEQ ID NO: 7 or an antibody, which binds to the same epitope.

[0194] In one embodiment of the method of killing a target cell having serine/arginine repetitive matrix protein 2 (SRRM2) present on the cell surface of said target cell, said antibody is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 99% identity to the amino acid sequence shown in SEQ ID NO: 5 and a light chain variable region having an amino acid sequence with at least 99% identity to the amino acid sequence shown in SEQ ID NO: 7 or an antibody, which binds to the same epitope.

[0195] In one embodiment of the method of killing a target cell having serine/arginine repetitive matrix protein 2 (SRRM2) present on the cell surface of said target cell, said antibody is an antibody comprising a heavy chain variable region comprising heavy chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 9, heavy chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 10, and heavy chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 11, and a light chain variable region comprising light chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 12, light chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 13, and light chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 14, or an antibody, which binds to the same epitope.

[0196] In one embodiment of the method of killing a target cell having serine/arginine repetitive matrix protein 2 (SRRM2) present on the cell surface of said target cell, said antibody is an antibody comprising a heavy chain variable region comprising heavy chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 15, heavy chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 16, and heavy chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 17, and a light chain variable region comprising light chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 18, light chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 19, and light chain CDR3 having

the amino acid sequence as set forth in SEQ ID NO: 20, or an antibody, which binds to the same epitope.

[0197] In one embodiment of the method of killing a target cell having serine/arginine repetitive matrix protein 2 (SRRM2) present on the cell surface of said target cell, said antibody is an antibody comprising a heavy chain variable region comprising heavy chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 21, heavy chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 22, and heavy chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 23, and a light chain variable region comprising light chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 24, light chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 25, and light chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 26, or an antibody, which binds to the same epitope.

[0198] In one embodiment of the method of killing a target cell having serine/arginine repetitive matrix protein 2 (SRRM2) present on the cell surface of said target cell, said antibody is an antibody comprising a heavy chain variable region comprising heavy chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 21, heavy chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 22, and heavy chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 23, and a light chain variable region comprising light chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 27, light chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 28, and light chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 29, or an antibody, which binds to the same epitope.

[0199] In one embodiment of the antibody for use in a method for the treatment of blood cancer in a subject, optionally comprising, prior to the treatment of said blood cancer in said subject, determining whether a target cell of said subject has SRRM2 present on the cell surface as described herein, said antibody used in a method for the treatment of blood cancer or used in a method of determining whether a patient may suffer from blood cancer is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 85% identity to the amino acid sequence shown in SEQ ID NO: 1 and a light chain variable region having an amino acid sequence with at least 85% identity to the amino acid sequence shown in SEQ ID NO: 2 or an antibody, which binds to the same epitope.

[0200] In one embodiment the antibody for use in a method for the treatment of blood cancer or used in a method of determining whether a patient may suffer from blood cancer is an

antibody comprising a heavy chain variable region having an amino acid sequence with at least 90% identity to the amino acid sequence shown in SEQ ID NO: 1 and a light chain variable region having an amino acid sequence with at least 90% identity to the amino acid sequence shown in SEQ ID NO: 2 or an antibody, which binds to the same epitope.

[0201] In one embodiment the antibody for use in a method for the treatment of blood cancer or used in a method of determining whether a patient may suffer from blood cancer is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 95% identity to the amino acid sequence shown in SEQ ID NO: 1 and a light chain variable region having an amino acid sequence with at least 95% identity to the amino acid sequence shown in SEQ ID NO: 2 or an antibody, which binds to the same epitope.

[0202] In one embodiment the antibody for use in a method for the treatment of blood cancer or used in a method of determining whether a patient may suffer from blood cancer is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 99% identity to the amino acid sequence shown in SEQ ID NO: 1 and a light chain variable region having an amino acid sequence with at least 99% identity to the amino acid sequence shown in SEQ ID NO: 2 or an antibody, which binds to the same epitope.

[0203] In one embodiment the antibody for use in a method for the treatment of blood cancer or used in a method of determining whether a patient may suffer from blood cancer is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 85% identity to the amino acid sequence shown in SEQ ID NO: 3 and a light chain variable region having an amino acid sequence with at least 85% identity to the amino acid sequence shown in SEQ ID NO: 4 or an antibody, which binds to the same epitope.

[0204] In one embodiment the antibody for use in a method for the treatment of blood cancer or used in a method of determining whether a patient may suffer from blood cancer is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 90% identity to the amino acid sequence shown in SEQ ID NO: 3 and a light chain variable region having an amino acid sequence with at least 90% identity to the amino acid sequence shown in SEQ ID NO: 4 or an antibody, which binds to the same epitope.

[0205] In one embodiment the antibody for use in a method for the treatment of blood cancer or used in a method of determining whether a patient may suffer from blood cancer is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 95% identity to the amino acid sequence shown in SEQ ID NO: 3 and a light chain variable

region having an amino acid sequence with at least 95% identity to the amino acid sequence shown in SEQ ID NO: 4 or an antibody, which binds to the same epitope.

[0206] In one embodiment the antibody for use in a method for the treatment of blood cancer or used in a method of determining whether a patient may suffer from blood cancer is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 99% identity to the amino acid sequence shown in SEQ ID NO: 3 and a light chain variable region having an amino acid sequence with at least 99% identity to the amino acid sequence shown in SEQ ID NO: 4 or an antibody, which binds to the same epitope.

[0207] In one embodiment the antibody for use in a method for the treatment of blood cancer or used in a method of determining whether a patient may suffer from blood cancer is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 85% identity to the amino acid sequence shown in SEQ ID NO: 5 and a light chain variable region having an amino acid sequence with at least 85% identity to the amino acid sequence shown in SEQ ID NO: 6 or an antibody, which binds to the same epitope.

[0208] In one embodiment the antibody for use in a method for the treatment of blood cancer or used in a method of determining whether a patient may suffer from blood cancer is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 90% identity to the amino acid sequence shown in SEQ ID NO: 5 and a light chain variable region having an amino acid sequence with at least 90% identity to the amino acid sequence shown in SEQ ID NO: 6 or an antibody, which binds to the same epitope.

[0209] In one embodiment the antibody for use in a method for the treatment of blood cancer or used in a method of determining whether a patient may suffer from blood cancer is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 95% identity to the amino acid sequence shown in SEQ ID NO: 5 and a light chain variable region having an amino acid sequence with at least 95% identity to the amino acid sequence shown in SEQ ID NO: 6 or an antibody, which binds to the same epitope.

[0210] In one embodiment the antibody for use in a method for the treatment of blood cancer or used in a method of determining whether a patient may suffer from blood cancer is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 99% identity to the amino acid sequence shown in SEQ ID NO: 5 and a light chain variable region having an amino acid sequence with at least 99% identity to the amino acid sequence shown in SEQ ID NO: 6 or an antibody, which binds to the same epitope.

[0211] In one embodiment the antibody for use in a method for the treatment of blood cancer or used in a method of determining whether a patient may suffer from blood cancer is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 85% identity to the amino acid sequence shown in SEQ ID NO: 5 and a light chain variable region having an amino acid sequence with at least 85% identity to the amino acid sequence shown in SEQ ID NO: 7 or an antibody, which binds to the same epitope.

[0212] In one embodiment the antibody for use in a method for the treatment of blood cancer or used in a method of determining whether a patient may suffer from blood cancer is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 90% identity to the amino acid sequence shown in SEQ ID NO: 5 and a light chain variable region having an amino acid sequence with at least 90% identity to the amino acid sequence shown in SEQ ID NO: 7 or an antibody, which binds to the same epitope.

[0213] In one embodiment the antibody for use in a method for the treatment of blood cancer or used in a method of determining whether a patient may suffer from blood cancer is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 95% identity to the amino acid sequence shown in SEQ ID NO: 5 and a light chain variable region having an amino acid sequence with at least 95% identity to the amino acid sequence shown in SEQ ID NO: 7 or an antibody, which binds to the same epitope.

[0214] In one embodiment the antibody for use in a method for the treatment of blood cancer or used in a method of determining whether a patient may suffer from blood cancer is an antibody comprising a heavy chain variable region having an amino acid sequence with at least 99% identity to the amino acid sequence shown in SEQ ID NO: 5 and a light chain variable region having an amino acid sequence with at least 99% identity to the amino acid sequence shown in SEQ ID NO: 7 or an antibody, which binds to the same epitope.

[0215] In one embodiment the antibody for use in a method for the treatment of blood cancer or used in a method of determining whether a patient may suffer from blood cancer is an antibody comprising a heavy chain variable region comprising heavy chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 9, heavy chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 10, and heavy chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 11, and a light chain variable region comprising light chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 12, light chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 13, and light chain CDR3 having

the amino acid sequence as set forth in SEQ ID NO: 14, or an antibody, which binds to the same epitope.

[0216] In one embodiment the antibody for use in a method for the treatment of blood cancer or used in a method of determining whether a patient may suffer from blood cancer is an antibody comprising a heavy chain variable region comprising heavy chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 15, heavy chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 16, and heavy chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 17, and a light chain variable region comprising light chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 18, light chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 19, and light chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 20, or an antibody, which binds to the same epitope.

[0217] In one embodiment the antibody for use in a method for the treatment of blood cancer or used in a method of determining whether a patient may suffer from blood cancer is an antibody comprising a heavy chain variable region comprising heavy chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 21, heavy chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 22, and heavy chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 23, and a light chain variable region comprising light chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 24, light chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 25, and light chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 26, or an antibody, which binds to the same epitope.

[0218] In one embodiment the antibody for use in a method for the treatment of blood cancer or used in a method of determining whether a patient may suffer from blood cancer is an antibody comprising a heavy chain variable region comprising heavy chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 21, heavy chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 22, and heavy chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 23, and a light chain variable region comprising light chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 27, light chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 28, and light chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 29, or an antibody, which binds to the same epitope.

[0219] All embodiments, which are described herein for the pharmaceutical composition of the present invention, the antibody, which binds to human SRRM2 present on the cell surface of a target cell of the present invention, the method of determining whether a patient may suffer from cancer of the present invention as described herein as well as the respective definitions as described above, also apply for the antibody for use in a method for the treatment of blood cancer in a subject, comprising, prior to the treatment of blood cancer in said subject, determining whether a target cell of said subject has SRRM2 present on the cell surface as described herein.

[0220] The description of the sequences, shown in the sequence listing and as used in the context of the present invention, is as follows:

SEQ ID NO: 1 shows the amino acid sequence of the VH-region of antibody 13F11.

SEQ ID NO: 2 shows the amino acid sequence of the VL-region of antibody 13F11.

SEQ ID NO: 3 shows the amino acid sequence of the VH-region of antibody 23A7.

SEQ ID NO: 4 shows the amino acid sequence of the VL-region of antibody 23A7.

SEQ ID NO: 5 shows the amino acid sequence of the VH-region of antibody 18A4 and of antibody 18A4-2.

SEQ ID NO: 6 shows the amino acid sequence of the VL-region of antibody 18A4.

SEQ ID NO: 7 shows the amino acid sequence of the VL-region of antibody 18A4-2.

SEQ ID NO: 8 shows the amino acid sequence of SRRM2 as shown in UniProt database entry Q9UQ35, version 2 of 6 March 2007.

SEQ ID NO: 9 shows the amino acid sequence of the VH-CDR1 of antibody 13F11.

SEQ ID NO: 10 shows the amino acid sequence of the VH-CDR2 of antibody 13F11.

SEQ ID NO: 11 shows the amino acid sequence of the VH-CDR3 of antibody 13F11.

SEQ ID NO: 12 shows the amino acid sequence of the VL-CDR1 of antibody 13F11.

SEQ ID NO: 13 shows the amino acid sequence of the VL-CDR2 of antibody 13F11.

SEQ ID NO: 14 shows the amino acid sequence of the VL-CDR3 of antibody 13F11.

SEQ ID NO: 15 shows the amino acid sequence of the VH-CDR1 of antibody 23A7.

SEQ ID NO: 16 shows the amino acid sequence of the VH-CDR2 of antibody 23A7.

SEQ ID NO: 17 shows the amino acid sequence of the VH-CDR3 of antibody 23A7.

SEQ ID NO: 18 shows the amino acid sequence of the VL-CDR1 of antibody 23A7.

SEQ ID NO: 19 shows the amino acid sequence of the VL-CDR2 of antibody 23A7.

SEQ ID NO: 20 shows the amino acid sequence of the VH-CDR3 of antibody 23A7.

SEQ ID NO: 21 shows the amino acid sequence of the VH-CDR1 of antibody 18A4 and of antibody 18A4-2.

SEQ ID NO: 22 shows the amino acid sequence of the VH-CDR2 of antibody 18A4 and of antibody 18A4-2.

SEQ ID NO: 23 shows the amino acid sequence of the VH-CDR3 of antibody 18A4 and of antibody 18A4-2.

SEQ ID NO: 24 shows the amino acid sequence of the VL-CDR1 of antibody 18A4.

SEQ ID NO: 25 shows the amino acid sequence of the VL-CDR2 of antibody 18A4.

SEQ ID NO: 26 shows the amino acid sequence of the VL-CDR3 of antibody 18A4.

SEQ ID NO: 27 shows the amino acid sequence of the VL-region of antibody 18A4-2.

SEQ ID NO: 28 shows the amino acid sequence of the VL-CDR1 of antibody 18A4-2.

SEQ ID NO: 29 shows the amino acid sequence of the VL-CDR2 of antibody 18A4-2.

[0221] An overview of the SEQ ID NOs and detailed sequences, as used in the context of the present invention, is given in the following Table 1 (in case of conflict between the sequences shown in Table 1 and the sequences of the sequence listing, which has to be filed for formal reasons, the sequences of Table 1 supercede the sequences of the sequence listing):

Table 1:

SEQ ID NO:	Designation	Sequence (CDRs are underlined in the order CDR 1, 2, 3 starting from left upper line)
1	13F11 VH	EVQLVESGGGLVQPGRSLKLSCAASRFTFSNYDMAWVRQAP TKGLEWVASISPSNVNTYYRDSVKGRFTVSRD ¹ NAKSSLYLQM DSLRS ² EDTATYYCARLVHSFWYDFWGP ³ GMTVTVSS
2	13F11 VL	DIVMTQTPSSQAVSAGEKVTMRCKSSQSLLYSKNKKNYLAWY QQKPGQSPKLLIYWASTRESGVPDRFLGSGSGTDFTLT ¹ ISSV QAEDLAVYYCQQYYKFPPTFGGGTKLELKRA

3	23A7 VH	EVQLVESGGDLVQPGRSLKLSCAASGFTFSNYDMAWVRQAP TQGLEWVASISGSGGTYYRDSVKGRFTVSRDNAKSTLYLQM DGLRSEDATATYFCARHPPSFYFDWFPGPSMVTVSS
4	23A7 VL	DIVMTQTPSSQAVSAGEKVTMSCKSGQSLLFNKNKKDYLA WYQRKPGQSPKLLIYWASTRESGVPDRFIGGSGTDFTLTIS SVQAEDLAVYYCQQYYRFPPTFGHGKLELKRA
5	18A4 VH and 18A4-2 VH	EVQLVESGGGLVQPGRSLKLSCAASGFTFSNYDMAWVRQAP TKGLEWVASISPSGGSIIYRDSVKGRFTVSRNNAKSSLYLQM DSLRS EDTATYYCARLTTFYFDWFPGPTMTVSS
6	18A4 VL	DIQMTQSPSFLSASVGDRVITNCKASQNSNKYLNWYQQKLGE APKLLIYNTNQLQTGIPSRFSGSGSGTDYTLTISSLQPEDVATY FCLQHSSRMDTFGAGTKLELKRA
7	18A4-2 VL	DIVMTQTPSSQAVSAGEKVTMSCKSSQSLLYSENKKNYLA WYQQKPGQSPKLLIYWASTRESGVPDRFIGSGSGTDFTLTIS SVQAEDLAVYYCQQYYKFPPTFGSGTKLEIK
8	SRRM2	MYNGIGLPTPRSGTNGYVQRNLSLVRGRRGERPDYKGEEE LRRLEAALVKRPNPDILDHERKRRVELRCLEEMMEEQGYE EQQIQEKVATFRLMLLEKDVNPGGKEETPGQRPVAVTETHQLA ELNEKKNERLRAAFGISDSYVDGSSFDPPRRAREAKQPAPEP PKPYSLVRESSSSRSPTPKQKKKKKKKDRGRRSESSSPRRE RKKSSKKKKHRSESESKKRKHSPTPKSKRKSCKDKRKRSR STTPAPKSRRAHRSTSADSASSSDTSRSRSRSAAAKTHTTAL AGRSPSPASGRRGEGDAPFSEP GTTSTQRPSSPETATKQPS SPYEDKDKDKKEKSATRPSPSPERSSTGPEPPAPTPLAERH GGSPQPLATTPLSQEPVNPPSEASPTRDRSPPKSPEKLPQSS SSESSPPSPQPTKVS RHASSSPESPKPAPAPGSHREISSSPT SKNRSHGRAKRDKSHSHTPSRRMGRSRSPATAKGRSRSR TPTKRGHRSRSPQWRRSRSAQRWGRSRSPQRRGRSRSP QRPGWRSRNTQRRGRSRSAARRGRSHSRSPATRGRSRSR PARRGRSRSRTPARRRSRRTPTRRRSRRTPARRRGRSRSR TPARRRSRTRSPVRRRSRSPARRSGRSRRTPARRRGRSR SRTPARRGRSRSRTPARRSGRSRRTPARRRGRSRSRTPRR GRSRSRSLVRRGRSHSRTPQRRGRSGSSSERKNKSRTSQR RSRSNSSPEMKKSRISSRRSRSLSSPRSKAKSRLSLRRSLSG SSPCPKQKSQTTPRRSRSGSSQPKAKSRTPPRRSRSSSP PKQKSKTPSRQSHSSSSPHPKVKSGTTPRQGSITSPQANEQS VTPQRRSCFESSPDPELKSRTPSRHSCSGSSPPRVKSSTPPR QSPSRSSSPQPKVKAISPRQRSHSGSSSPSRVTSRTTPR RSRSVSPCSNVESRLLPRYSHSGSSSPDTKVKPETPPRQSHS GSISPYPKVKAQTPPGPSLSGSKSPCPQEKS KDSLVSQCPGS

		LSLCAGVKSSTPPGESYFGVSSLQLKGQSQTSPDHRSDTSSP EVRQSHSESPSLQSKSQTSPKGGRSRSSSPVTELASRSPIRQ DRGEFSASPMKSGMSPEQSRFQSDSSSYPTVDSNSLLGQS RLETAESKEKMALPPQEDATASPPRQKDKFSPFPVQDRPESS LVFKDTRLTPPRERSGAGSSPETKEQNSALPTSSQDEELMEV VEKSEEPAGQILSHLSSELKEMSTSNFESSPEVEERPAVSLTL DQSQSQASLEAVEVPSMASSWGGPHFSPEHKELSN SPLREN SFGSPLEFRNSGPLGTEMNTGFSSEVKEDLNGPFLNQLETDP SLDMKEQSTRSSGHSSSELSPDAVEKAGMSSNQSISSPVLDA VPRTPSRERSSSASSPEMKDGLPRTPSRRRSRSGSSPGLRDG SGTPSRHSLSGSSPGMKDIPRTPSRGRSECDSSPEPKALPQT PRPRSRSPSSPELNNKCLTPQRERSGSESSVDQKT VARTPLG QRSRSGSSQELDVKPSASPQERSESDSSPDSKAKTRTPLRQ RSRSGSSPEVDSKSRLSPRRSRSGSSPEVKDKPRAAPRAQS GSDSSPEPKAPAPRALPRRSRSGSSSKGRGPSPEGSSSTES SPEHPPKSRTARRGSRSSPEPKTSRTPPRRRSSRSPELTR KARLSRRRSRSASSSPETRSTPPRHRRSPSVSSPEPAEKSR SRRRRSASSPRTKTTSRGRSPSPKPRGLQRSRSR SRREKT RTTRRRDRSGSSQSTSRRRQRSRSRSRVTRRRRRGGSGYHS RSPARQESSRTSSRRRRGRSRT PPTS RKR SRSTSPAPWKR SRSRASPATHRRSRSTPLISRRRSRSTSPVSRRRSRST VTRRRSRSRASPVSRRRSRSTPPVTRRRSRSTPTTRRRS RSRTPPVTRRRSRSTPPVTRRRSRSTSPITRRRSRSTSP VTRRRSRSTSPVTRRRSRSTSPVTRRRSRSTPPAIRRRS RSRTPLLPRKRSRSRSLAIRRRSRSTPRTARGKRSLTRSP PAIRRRSASGSSSDRSRSATPPATRNHSGSRTPPVALNSSRM SCFSRPSMSPTPLDRCRSPGMLEPLGSSRTPM SVLQQAGGS MMDGPGPRIPDHQRTSVPENHAQSRIALALTAISLGARPPPS MSAAGLAARMSQVPAPVPLMSLRTAPAAANLASRIPAASAAAM NLASARTPAIPTAVNLADSRTPAAAAAMNLASRTAVAPSAVN LADPRTPTAPAVNLAGARTPAALAALSLTGSGTPPTAANY PSS SRTPQAPASANLVGPRSAHATAPVNIAGSRTAAALAPASLTSA RMAPALSGANLTSPRVPLSAYERVSGRTSPPLDRARSRTPP SAPSQSRMTSERAPSPSSRMGQAPSQSLLPPAQDQPRSPVP SAFSDQSRCLIAQTTPVAGSQSLSSGAVATTTSSAGDHNGML SVPAPGVPHSDVGEPPASTGAQQPSALAALQPAKERRSSSS SS RVPSPTPAPKEAVREGRPPEPTPAKRKRSSSSSSSSSSSSSS SS PASPKKPPPGERRSRSPRKPIDSLRDSRSLSYSPVERRRPSP
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		QPSPRDQQSSSSERGSRRGQRGDSRSPSHKRRRETSPRP MRHRSSSRSP
9	13F11 VH-CDR1	NYDMA
10	13F11 VH-CDR2	SISPSNVNTYYRDSVKG
11	13F11 VH-CDR3	LVHSFWYFDF
12	13F11 VL-CDR1	KSSQSLLYSKNKKNYLA
13	13F11 VL-CDR2	WASTRES
14	13F11 VL-CDR3	QQYYKFPPT
15	23A7 VH-CDR1	NYDMA
16	23A7 VH-CDR2	SISGSGGTTYRDSVKG
17	23A7 VH-CDR3	HPPSFYWYFDF
18	23A7 VL-CDR1	KSGQSLLFNKNKKDYLA
19	23A7 VL-CDR2	WASTRES
20	23A7 VL-CDR3	QQYYRFPPT
21	18A4 VH-CDR1 and 18A4-2 VH-CDR1	NYDMA
22	18A4 VH-CDR2 and 18A4-2 VH-CDR2	SISPSGGSIYYRDSVKG
23	18A4 VH-CDR3 and 18A4-2 VH-CDR1	LTTYFWYFDF
24	18A4 VL-CDR1	KASQNSNKYLN
25	18A4 VL-CDR2	NTNNLQT
26	18A4 VL-CDR3	LQHSSRMDT
27	18A4-2 VL-CDR1	KSSQSLLYSENKKNYLA
28	18A4-2 VL-CDR2	WASTRES
29	18A4-2 VL-CDR3	QQYYKFPPT

[0222] The following abbreviations were used in the context of the present invention: VH = variable heavy chain; VH = variable heavy chain; VL = variable light chain; CDR = complementarity determining region; VH-CDR = CDR of a variable heavy region; VL-CDR = CDR of a variable light region; CDRs can be determined by using the Kabat algorithm, e.g., <http://abysis.org/abysis/>.

[0223] It is noted that as used herein, the singular forms “a”, “an”, and “the”, include plural references unless the context clearly indicates otherwise. Thus, for example, reference to “a reagent” includes one or more of such different reagents and reference to “the method” includes reference to equivalent steps and methods known to those of ordinary skill in the art that could be modified or substituted for the methods described herein.

[0224] Unless otherwise indicated, the term "at least" preceding a series of elements is to be understood to refer to every element in the series. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the present invention.

[0225] The term "and/or", wherever used herein, includes the meaning of "and", "or" and "all or any other combination of the elements connected by said term".

[0226] The term "less than" or in turn "more than" does not include the concrete number.

[0227] For example, "less than 20" means less than the number indicated. Similarly, "more than" or "greater than" means more than or greater than the indicated number, e.g. "more than 80 %" means more than or greater than the indicated number of 80 %.

[0228] Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps, but not the exclusion of any other integer or step or group of integer or step. When used herein the term "comprising" can be substituted with the term "containing" or "including" or sometimes, when used herein, with the term "having". When used herein, "consisting of" excludes any element, step, or ingredient not specified.

[0229] The term "including" means "including but not limited to". "Including" and "including but not limited to" are used interchangeably.

[0230] It should be understood that this invention is not limited to the particular methodology, protocols, material, reagents, and substances, etc., described herein and as such can vary. The terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention, which is defined solely by the claims.

[0231] All publications cited throughout the text of this specification (including all patents, patent application, scientific publications, instructions, etc.), whether supra or infra, are hereby incorporated by reference in their entirety. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention. To the

extent the material incorporated by reference contradicts or is inconsistent with this specification, the specification will supersede any such material.

[0232] The content of all documents and patent documents cited herein is incorporated by reference in their entirety.

[0233] A better understanding of the present invention and of its advantages will be had from the following examples, offered for illustrative purposes only. The examples are not intended to limit the scope of the present invention in any way. The term “example(s)” and “figure(s)” are used interchangeably in this document.

[0234] The invention is further characterized by the following items:

1. An antibody that binds to human serine/arginine repetitive matrix protein 2 (SRRM2) present on the cell surface of a target cell, for use in a method for the treatment of blood cancer in a human patient.
2. The antibody for the use of item 1, wherein the patient to be treated has a weight of between 16 and 150kg, preferably 18 to 140kg, more preferably 20 to 130kg, more preferably still 22 to 120kg.
3. The antibody for the use of any of the preceding items in which the patient to be treated is at least 1 year old, preferably 2 years, more preferably between 2 and 80 years old.
4. The antibody for the use of any of the preceding items, wherein the patient to be treated has a body height between 70 and 220cm, preferably between 80 and 200cm, more preferably between 90 and 200cm.
5. The antibody for the use of any of the preceding items, wherein said antibody has cytotoxic activity, preferably antigen-dependent cellular cytotoxicity (ADCC) and/or complement-dependent cytotoxicity (CDC).
6. The antibody for the use of any of the preceding items, wherein said antibody is part of a chimeric antigen receptor (CAR).
7. The antibody of item 6, wherein said CAR is expressed by a T cell, NK cell, NK-T cell or macrophage.

8. The antibody for the use of any of the preceding items, wherein said antibody is expressed by an autologous cell population.
9. The antibody for the use of any of the preceding items, wherein said antibody is expressed by an allogeneic cell population
10. The antibody for the use of any of the preceding items, wherein SRRM2 present on the cell surface of a target cell is externalized.
11. The antibody for the use of any of the preceding items, wherein the antibody is not an intracellular antibody.
12. The antibody for the use of any of the preceding items, wherein said blood cancer to be treated is a blood cancer characterized by cells expressing human SRRM2 on their cell surface.
13. The antibody for the use of any of items 1 to 12, wherein said blood cancer to be treated is multiple myeloma.
14. The antibody for the use of any of items 1 to 12, wherein said blood cancer to be treated is leukemia, including acute erythroid leukemia, acute lymphoblastic leukemia (ALL), acute megakaryoblastic leukemia, acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), chronic myelomonocytic leukemia (CMML), childhood leukemia, hairy cell leukemia (HCL), large granular lymphocytic leukemia (LGLL), mast cell leukemia (MCL), or plasma cell leukemia (PCL).
15. The antibody for the use of any of items 1 to 12, wherein said blood cancer to be treated is acute myeloid leukemia (AML).
16. The antibody for the use of item 15, wherein said AML is further characterized by cells having a genetic mutation, preferably a FMS-like tyrosine kinase-3 (FLT3) mutation.
17. The antibody for the use of any of items 1 to 12, wherein said blood cancer to be treated is plasma cell leukemia (PCL).
18. The antibody for the use of item 17, wherein said PCL is primary or secondary PCL.

19. The antibody for the use of any of items 1 to 12, wherein said blood cancer to be treated is lymphoma, including Burkitt lymphoma, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, hodgkin lymphoma, non-Hodgkin lymphoma, MALT lymphoma, mantle cell lymphoma, small lymphocytic lymphoma (SLL), post-transplant lymphoproliferative disorder (PTLD), or Waldenström macroglobulinaemia (WM).
20. The antibody for the use of any of items 1 to 12, wherein said blood cancer to be treated is a myelodysplastic syndrome, a myeloproliferative neoplasm (including polycythaemia vera, essential thrombocythaemia, or myelofibrosis), Erdheim-Chester disease, Langerhans cell histiocytosis, mastocytosis, or mast cell leukemia.
21. The antibody for the use of any of the preceding items, wherein the patient to be treated is refractory to previous cancer therapy and/or in relapse after previous cancer therapy.
22. The antibody for the use of any of the preceding items, wherein the route of antibody administration is parenteral, including, but not limited to, intravenous, intradermal, intramuscular, intrathecal, or intraperitoneal administration.
23. The antibody for the use of any of the preceding items, wherein said antibody is conjugated with a cytotoxic substance.
24. The antibody for the use of any of the preceding items, wherein said antibody binds to non-permeabilised cells.
25. The antibody for the use of any of the preceding items, wherein said antibody binds to living cells.
26. The antibody for the use of any of the preceding items, wherein said antibody is an antibody comprising
 - (a) a heavy chain variable region comprising heavy chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 9, heavy chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 10, and heavy chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 11, and
 - a light chain variable region comprising light chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 12, light chain CDR2 having the amino acid

- sequence as set forth in SEQ ID NO: 13, and light chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 14;
- (b) a heavy chain variable region comprising heavy chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 15, heavy chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 16, and heavy chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 17, and
- a light chain variable region comprising light chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 18, light chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 19, and light chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 20;
- (c) a heavy chain variable region comprising heavy chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 21, heavy chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 22, and heavy chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 23, and
- a light chain variable region comprising light chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 24, light chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 25, and light chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 26; or
- (d) a heavy chain variable region comprising heavy chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 21, heavy chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 22, and heavy chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 23, and
- a light chain variable region comprising light chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 27, light chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 28, and light chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 29.
27. The antibody for the use of any of the preceding items, wherein said antibody is an antibody comprising
- (a) a heavy chain variable region having the amino acid sequence as set forth in SEQ ID NO: 1 and a light chain variable region having the amino acid sequence as set forth in SEQ ID NO: 2,
- (b) a heavy chain variable region having the amino acid sequence as set forth in SEQ ID NO: 3, and a light chain variable region having the amino acid sequence as set forth in SEQ ID NO: 4,

- (c) a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 5, and light chain variable region having the amino acid sequence as set forth in SEQ ID NO: 6, or
- (d) a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 5, and light chain variable region having the amino acid sequence as set forth in SEQ ID NO: 7.
28. The antibody for the use of any of the preceding items, wherein said antibody is contained in composition comprising a buffer.
29. The antibody for the use of item 28, wherein said antibody is contained in a composition comprising a buffer and sodium chloride.
30. A method for determining whether a patient may suffer from blood cancer, comprising determining in a sample obtained from said patient whether SRRM2 is present on the cell surface of cells comprised by said sample and/or whether SRRM2 is present on the surface of extracellular vesicles.
31. The method of item 30, wherein an increased amount of SRRM2 on the cell surface of cells comprised by said sample and/or present on the surface of extracellular vesicles when compared to the amount of SRRM2 on the cell surface of cells comprised by said sample and/or present on the surface of extracellular vesicles in a sample obtained from a healthy subject indicates that the patient may suffer from blood cancer.
32. The method of item 30, wherein no difference in the amount of SRRM2 on the cell surface of cells and/or present on the surface of extracellular vesicles comprised by a sample obtained from said patient when compared to the amount of SRRM2 on the cell surface and/or extracellular vesicles in a sample obtained from a healthy subject indicates that the patient may not suffer from blood cancer.
33. The method of any of items 30 to 32, wherein said antibody is an antibody comprising (a) a heavy chain variable region comprising heavy chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 9, heavy chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 10, and heavy chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 11, and a light chain variable region comprising light chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 12, light chain CDR2 having the amino acid

- sequence as set forth in SEQ ID NO: 13, and light chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 14;
- (b) a heavy chain variable region comprising heavy chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 15, heavy chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 16, and heavy chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 17, and
- a light chain variable region comprising light chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 18, light chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 19, and light chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 20;
- (c) a heavy chain variable region comprising heavy chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 21, heavy chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 22, and heavy chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 23, and
- a light chain variable region comprising light chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 24, light chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 25, and light chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 26; or
- (d) a heavy chain variable region comprising heavy chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 21, heavy chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 22, and heavy chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 23, and
- a light chain variable region comprising light chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 27, light chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 28, and light chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 29.
34. The method of any of items 30 to 33, wherein said antibody is an antibody comprising
- (a) a heavy chain variable region having the amino acid sequence as set forth in SEQ ID NO: 1 and a light chain variable region having the amino acid sequence as set forth in SEQ ID NO: 2,
- (b) a heavy chain variable region having the amino acid sequence as set forth in SEQ ID NO: 3, and a light chain variable region having the amino acid sequence as set forth in SEQ ID NO: 4,
- (c) a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 5, and light chain variable region having the amino acid sequence as set forth in SEQ ID NO: 6, or

(d) a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 5, and light chain variable region having the amino acid sequence as set forth in SEQ ID NO: 7.

35. The method of any of items 30 to 34, wherein said cells are non-permeabilised cells.
36. The method of any of items 30 to 35, wherein said cells are living cells.
37. The method of any of items 30 to 36, wherein said blood cancer is multiple myeloma.
38. The method of any of items 30 to 36, wherein said blood cancer is leukemia, including acute erythroid leukemia, acute lymphoblastic leukemia (ALL), acute megakaryoblastic leukemia, acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), chronic myelomonocytic leukemia (CMML), childhood leukemia, hairy cell leukemia (HCL), large granular lymphocytic leukemia (LGLL), mast cell leukemia (MCL), or plasma cell leukemia (PCL).
39. The method of any of items 30 to 36, wherein said blood cancer is acute myeloid leukemia (AML).
40. The method of any of items 30 to 36, wherein said blood cancer is plasma cell leukemia (PCL).
41. The antibody for the use of item 40, wherein said PCL is primary or secondary PCL.
42. The method of any of items 30 to 36, wherein said blood cancer is lymphoma, including Burkitt lymphoma, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, hodgkin lymphoma, non-Hodgkin lymphoma, MALT lymphoma, mantle cell lymphoma, small lymphocytic lymphoma (SLL), post-transplant lymphoproliferative disorder (PTLD), or Waldenström macroglobulinaemia (WM).
43. The method of any of items 30 to 36, wherein said blood cancer is a myelodysplastic syndrome, a myeloproliferative neoplasm (including polycythaemia vera, essential thrombocythaemia, or myelofibrosis), Erdheim-Chester disease, Langerhans cell histiocytosis, mastocytosis, or mast cell leukemia.

EXAMPLES

Materials and Methods

Two patients received infusions of autologous CAR-T cells comprising a scFv derived from the antibody of the present invention. All data, unless otherwise stated, is derived from samples taken from these patients, termed Patient 1 and Patient 2.

Patient 1

[0235] Patient 1 was a 53-year old female patient diagnosed with primary plasma cell leukemia 4 years previously.

[0236] The patient received multiple courses of primary androgen deprivation therapy (PADT) treatment and chemotherapy containing daratumumab 12 times. The patient received autologous stem cell transplantation, autologous BCMA CAR-T cells and other treatments. Received BCMA CAR-T cells 1 year previously. The best curative effect was VGPR, and following a later relapse (in 6 months), there was no recommended effective treatment for clinical evaluation.

[0237] Flow cytometry revealed that peripheral plasma cells were > 90% positive for SRRM2:

- PLC: IgG-κ type, refractory/relapsed, 1q21 amplified peripheral plasma cells: CD38++CD138+CD19-CD56-CD45dim~ (increased to 43% before CAR-T treatment).
- Metastasis of extramedullary plasmacytoma: bilateral lungs, left orbit, left arm, left hip, abdominal cavity and pelvic cavity, comorbid pleural effusion, ascites and pelvic effusion, pulmonary infection, gastrointestinal bleeding, incomplete intestinal obstruction.
- The patient was bedridden, unable to eat or talk before CAR-T infusion. ECOG PS 4.

[0238] After the patient received bridging therapy with pomalidomide, dexamethasone and bortezomib, the condition deteriorated sharply, and she was injected with autologous SRRM2 CAR-T cells / kg (Day0 dose 0.69×10^6 , Day 2 dose 2.57×10^6). No CRS, no ICANS, no off-tumor targeted side effects observed in heart, liver, kidney, lung, or CNS.

[0239] After treatment :

- The patient's extramedullary tumour became soft and shrunk, and the symptoms of incomplete intestinal obstruction improved;

- 3 weeks after injection (Day 16 post-infusion), the proportion of peripheral blood plasma cells decreased from 43% to 6.4% (**Figure 9**), and the blood picture improved;
- Patient could get up and walk post-treatment - ECOG PS2;
- Heart, liver, kidney, lung, central nervous system did not observe any targeted side effects;
- From Day 0 to Day 14, the increase in platelets and reticulocytes indicates improving hematopoietic function.

Patient 2

[0240] Patient 2 was a 60-year old male patient diagnosed with relapsed and refractory multiple myeloma 11 years previously.

[0241] Multiple myeloma was diagnosed 11 years previously and the patient had received chemotherapy, autologous hematopoietic stem cell transplantation, and thalidomide maintenance therapy. The patient experienced fatigue accompanied by bone pain for 1-month, conventional anti-myeloma drug treatment was ineffective and disease progression continued with not response to MM therapies, ECOG 2.

[0242] Diagnosis of primary plasma cell leukemia (IgGκ type, 1q21 amplification) following a bone marrow biopsy: a large number of diffuse hyperplasia of plasma cells could be seen between the bone trabeculae, accounting for about 90% of bone marrow nucleated cells (**Figure 2**); IgD-λ type, a rare subtype that is difficult to cure and is usually recurrent. Over 73% of bone marrow plasma cells were determined to be SRRM2 positive by flow cytometry.

[0243] Patient 2 received an infusion of SRRM2 CAR-T cells / kg (0.7×10^7 , 1.1×10^7 , 2.3×10^7) in day 1st, 114th and 287th. The CAR-T cell population expanded to 11.1% of overall T cell count in 3 weeks and remained at 7.4% 7 weeks after infusion.

[0244] 64 days after infusion of a single dose of SRRM2-specific CAR-T cells, the patient's bone pain symptoms disappeared, hemoglobin and platelets rebounded so that there was no need for a blood transfusion.

[0245] Serum Immunoglobulin Light Chain κ/λ Ratio recovery indicates positive therapy response. PR, stable disease for 11 months.

[0246] CRS grade 2, no ICANS, no on-target off-tumor toxicity (OTOT) was observed in the heart, liver, kidney, lung, and central nervous systems.

[0247] Standard flow cytometry was employed as known to individuals skilled in the art. For flow cytometric analysis of SRRM2 expression, cells were stained either with our SRRM2-specific antibody EX-02 in FACS-Buffer (PBS + 2 % FSC) or with an isotype control antibody for 20 min followed by staining with an anti-rat-Alexa Fluor® 647 secondary antibody (Jackson Immuno Research). All stainings were performed on ice. For cell identity analyses, a variety of antibodies were used, including anti-CD45 conjugated with PC7, anti-138 conjugated with PE-eFluor™ 610, anti-CD38 conjugated with allophycocyanin (APC)

Immunohistochemistry

[0248] Paraffin sections were mounted onto superfrost plus slides. After fixation in acetone, slides were incubated with the primary antibody followed by incubation with a suitable biotinylated secondary antibody. Slides were developed with 0.01 % 3-amino-9-ethylcarbazole (AEC) as chromogen. After counterstaining with hematoxylin, slides were cover-slipped with Kaiser's glycerol gelatine.

[0249] The presence of morphologically abnormal plasma cells, indicative of cancer-related plasma cells, was quantified in bone marrow smears via Wright-Giemsa staining.

Patient 3

[0250] Patient 3 was a 55-year old female patient diagnosed with plasma cell leukemia (PCL). The patient was suffering from multiple myeloma for 5 years. Achieved CR after 10 chemotherapy cycles. Progressed to PCL 3 years previously. Achieved CR after 7 chemotherapy cycles. In 2024: PCL relapsed, with worsening anaemia, kidney damage, disease progression with no response to treatments, ECOG 2.

[0251] Flow cytometry revealed that > 42% of peripheral blood plasma cells are SRRM2 positive.

[0252] Patient 3 received i.v. infusions of SRRM2 CAR-T (0.54×10^7 , 2.34×10^7 , 1.06×10^7 cells / kg at days 0, 1st and 18, respectively. 28 days post-infusion: Plasma cells in the peripheral blood decreased from 29.0% before CAR-T infusion (day=0) to 0.55% at day =28, indicating a very good partial response (VGPR) to CAR-T treatment (**Figure 18**). CRS grade 3, resolved with tocilizumab. No ICANS, no off-tumor targeted side effects observed in heart, liver, kidney, lung, or CNS.

Studies on AML

[0253] 65 patients with AML who were admitted at the Second Affiliated Hospital of Anhui Medical University between January 2022 and June 2023 were included in the present study. Peripheral blood (PB) and bone marrow (BM) samples were concurrently collected and analyzed from an additional subgroup comprising 20 patients. PB samples of 65 patients with AML were collected and analyzed.

Online database search

[0254] The GEPIA database (<http://gepia.cancer-pku.cn/>) was used to assess the gene expression profile of SRRM2 across all tumor samples and paired normal tissues. BloodSpot database (<https://servers.binf.ku.dk/bloodspot/>) was used to assess SRRM2 expression across patients with AML. Data for survival analysis were obtained from the Cancer Genome Atlas database (TCGA, <https://www.cancer.gov/ccg/>).

Flow cytometry analysis of SRRM2 expression

[0255] PB samples from the patients of AML were collected by Ficoll (Cytiva, 17544602) separation and divided into two tubes. Cells were counted and 100,000 cells each were stained with either the SRRM2 mAb EX-02 or isotype control antibody. The cells were then washed twice with phosphate-buffered saline (PBS) and stained with CD34-PE or CD117-PE, CD33-APC, CD45-PC7 (Beckman Coulter, USA), and FITC-labelled goat anti-rat IgG (Abcam, 150165, UK) in the dark at room temperature for 15 minutes. The samples were analyzed on a flow cytometer (Cytotflex, Beckman Coulter, USA). The CytExpert for Dx FLEX flow cytometry software was used to define gates for the target cell population progressively to facilitate the quantification of SRRM2 expression.

[0256] Bone marrow and PB samples from newly diagnosed and previously diagnosed MM patients were collected by Ficoll (Cytiva, 17544602) separation and divided into two tubes. Cells were counted and 100,000 cells each were stained with either the SRRM2 mAb EX-02 and isotype control antibody. The cells were then washed twice with phosphate-buffered saline (PBS) and stained with CD34-PE or CD117-PE, CD33-APC, CD45-PC7 (Beckman Coulter, USA), and FITC-labelled goat anti-rat IgG (Abcam, 150165, UK) in the dark at room temperature for 15 minutes. The samples were analyzed on a flow cytometer (Cytotflex, Beckman Coulter, USA). The CytExpert for Dx FLEX flow cytometry software was used to define gates for the target cell population progressively to facilitate the quantification of SRRM2 expression.

Cell culture

[0257] Myeloid leukemia cell lines, HL-60 and MOLM-13, were purchased from Nanjing Saihongrui Biotechnology Co. Ltd. The myeloid leukemia cell line, KG-1a, was procured from Guangzhou Cellcook Biotech Co. Ltd. The myeloid leukemia cell lines, MV4-11, SKM-1, and K562, were obtained from Hematology Laboratory of the Second Affiliated Hospital of Anhui Medical University. All experiments were performed using mycoplasma-free cells. Except for the HL-60 and MV4-11 lines, grown in the Iscove's modified Dulbecco's medium (IMDM, Cytiva, USA), the other cells were cultured in Roswell Park Memorial Institute (RPMI, Cytiva, USA) supplemented with 10% fetal bovine serum (FBS, ExCell, Uruguay). All cell lines were maintained at 37°C in a humidified atmosphere with 5% CO₂.

Construction of CAR and production of viral vectors

[0258] The Single-chain Variable Fragment (scFv) of the rat-derived antibody targeting SRRM2 was cloned in frame with a transmembrane domain (TMD) and a costimulatory domain of 4-1BB in addition to the CD3ζ signalling domain through a short hinge for CAR expression on T cells. The third-generation lentivirus packaging system was employed for transient functional lentiviral vector (LV) particle preparation. Specifically, four LV-producing plasmids, including the CAR encoding transfer plasmid and three helper plasmids provided by GenScript ProBio (LentiHelper™ VSV-G, Rev, and GagPol) were transfected into HEK293T packaging cells for LV production and purification following standard technologies. Eluted LV particles were stored at -80 °C.

Generation of CAR-T cells

[0259] Peripheral blood mononuclear cells (PBMCs) were isolated from the PB of healthy volunteers by Ficoll separation. The cells were seeded at a density of 2×10^6 cells/ml and stimulated using CD3/CD28 monoclonal antibody (mAb) (100 IU/ml or 300 IU/ml, Miltenyi, Germany) for 24 hour. T cells were transduced with LVs at a multiplicity of infection (MOI) of 5. Simultaneously, human serum albumin (HSA, 10ng/ml, Baxalta, USA) was added to optimize transfection efficiency. The cells were washed to remove the LV particles 24 hour after transduction. In contrast, mock-T cells in the uninfected group were grown following a procedure similar to that of CAR-T cells but devoid of any viral infection. T cells were expanded in PRIME-XV T cell chemical defined medium (CDM, Santa Ana, USA) for 4-7 days in the presence of IL-2 (300 IU/ml or 600 IU/ml, Quangan, China) or IL-7 and IL-15 (10ng/ml, SinoBio, China). Cell products were washed twice with PBS (Cytiva, USA) for subsequent experiments.

Quality control of SRRM2-specific CAR-T cells

[0260] CAR-T cells grown for 4-7 days were harvested, centrifuged to remove the culture medium, and resuspended in 100 µl PBS. The cells were stained with the Alexa647-labeled AffiniPure F(ab')₂ Fragment Donkey Anti-Rat IgG (H+L) (Jackson ImmunoResearch, USA) to and CD3 (FITC, Beckman Coulter, USA) to measure the number of CAR-positive CD3+ T cells and thus the transduction rate. Mycoplasma and endotoxin contamination were evaluated utilizing specific assay kits following the prescribed protocols. Detection of CAR gene expression in mice was conducted using a PCR-based CAR gene detection kit (Hillgene, PX-CA001, according to manufacturer's instructions).

In vitro functional assays

[0261] After co-culture with target cells at the indicated E:T ratios (1:1; 2.5:1;5:1) for 24 h, the cytotoxicity of SRRM2 CAR-T was determined using CytoTox 96® Non-Radioactive Cytotoxicity Assay (Dojindo Molecular Technologies, Inc, Japan) by measuring the release of lactate dehydrogenase (LDH). Assays were performed following the manufacturer's instructions. Control groups were set up to measure the (i) medium background (no cells added), (ii) spontaneous release (target cells only), and (iii) maximum release (target cells treated with 10 ml lysis buffer). The killing efficacy was calculated as follows: % Cytotoxicity= [Target plus Effector (OD 490nm) -Effector Spontaneous (OD 490nm)] / [(Target maximum (OD 490nm) - Target Spontaneous (OD 490nm))] × 100.

Constructing an AML tumor-bearing mouse model

[0262] Immunodeficient NSG mice were purchased from Jiangsu Jicui Pharmachem Biotechnology Co. The human AML tumor-bearing mouse model was established by injecting 4×10^6 SKM-1 cells into the tail vein of 4-6 week old mice. After 14 days, tumor-bearing mice were randomized into two groups (n=5) and intravenously administered either MOCK-T (non-transduced T cells) or CAR-T cells (1×10^7). BM or tumor tissues were isolated when the mice were sacrificed.

Wright-Giemsa staining

[0263] BM smears were air-dried and immediately fixed using the Wright-Giemsa Stain Reagent Kit (BASO, BA4107). Approximately 0.5-0.8 ml of Solution A was added to the smear, followed by incubation for 1 minute for staining. Subsequently, Solution B was added to Solution A (2-3 times the volume of Solution A). A gentle breeze was directed over the liquid surface to create ripples using an ear bulb, thereby ensuring thorough mixing of Solutions A and B. Incubation for staining lasted 4-10 minutes. Tap water was used for washing, and the slides were air-dried. Microscopic examination was conducted using an oil immersion lens.

[0264] A mouse model was established to analyze the in vivo efficacy of SRRM2-specific EX-02 CAR-T cells. For this, 3.3×10^6 Kawasaki Medical School (KMS)-11 multiple myeloma cells carrying a luciferase transgene to allow for bioluminescence imaging (KMS-11-luc) were injected intravenously (i.v.) into immunopromised NSG mice at day = 5. Five days later (day = 0) mice (n=5 per group) received either 1.3×10^6 EX-02 CAR-T cells or the same number of Mock T cells generated previously from T cells isolated from the peripheral blood of a healthy volunteer. Tumor development was monitored by bioluminescence imaging at different time points (days 7, 15, 24, 24 and 50). In parallel, the number of human CD4+ and CD8+ CAR-T cells in the peripheral blood was analyzed by flow cytometry. At the end of the experiment (day = 50) the number of CAR-T cells in the spleens were also analyzed.

Statistical analyses

[0265] Statistical analysis was performed using IBM SPSS Statistics 25 and GraphPad Prism 8.0. Continuous data are presented as mean±standard deviation. For comparison between the two groups, if the data followed a normal distribution, differences were assessed using the t-test, else the data were expressed as median and interquartile ranges and analyzed using a non-parametric rank-sum test. Survival time was defined as the time from the first diagnosis until death (all-cause mortality). A p-value less than 0.05 was considered statistically significant.

RESULTS

[0266] **Figure 1A** shows that the majority of abnormal plasma cells are surface SRRM2 positive. An example of the immunophenotyping strategy of white blood cells (WBCs) or bone marrow cells from a patient with plasma cell leukemia is shown (**Fig. 1A(A)**). 75.2% of all cells are CD38+CD138+ and identified as abnormal plasma cells (located in the upper right quadrant; Q1-UR). **Fig. 1A(B)** and **(C)** show that the majority of these plasma cells stain positive with the SRRM2 antibody (within the gate = 59.6% of all WBCs, and 90.02% of all CD38+CD138+ plasma cells). Normal lymphocytes, monocytes and granulocytes are SRRM2 negative (below in gate in (**Fig. 1A(B)**)). **Fig. 1A(D)** and **(E)** shows isotype control staining.

[0267] **Figure 1B:** shows that immunophenotyping of WBCs, as described above, revealed that 92.94% of Patient 1's abnormal plasma cells stained positive for SRRM2.

[0268] **Figure 2** shows the reduction in CD138+ cells following SRRM2 CAR-T cells treatment. CD138 immunohistochemistry was performed on bone marrow extracted from Patient 2. **Fig. 2A** shows that before CAR-T cell treatment, more than 90% of nucleated cells stained CD138-

positive (dark grey color). **Fig. 2B** shows that at day 50 after CAR-T cell infusion, less than 10% of nucleated cells stained CD138-positive (black arrows). Magnification 10x20.

[0269] **Figure 3** shows that abnormal plasma cells are eliminated by SRRM2 CAR-T cell treatment. Bone marrow smears of Patient 2 are shown before and at day 50 after SRRM2 CAR-T cell infusion. **Fig. 3A** shows plasma cells before treatment: primitive and immature plasma cells (black arrows) accounted for 5% of all nucleated cells. **Fig. 3B** shows plasma cells at day 50 after SRRM2 CAR-T cell infusion. It can be seen that no abnormal plasma cells are detectable. Cells are stained with Wright-Giemsa stain.

[0270] **Figure 4A** shows that *in vivo* expansion of the SRRM2 specific CAR T cell population, quantified as a proportion of total T cells present per sample, peaks at week 3 post-infusion. SRRM2-targeted CAR T cells were infused into Patient 2 in a single-dose of 5×10^7 cells and blood samples taken at regular intervals to assess proliferation of CAR T cells. Percentage of SRRM2 CAR T cells are shown at days 1, 3, 6, 16, 23, and 50. This data is quantified in **Fig. 4B**.

[0271] **Figure 5** shows that treatment with SRRM2-targeting CAR-T cells restores blood kappa/lambda light-chain ratio. Measurements of serum-free immunoglobulin (Ig) light chains in the blood of Patient 2 are shown, as measured with an automated immunoassay. Given are the total concentrations (upper graph) and the kappa / lambda ratio (lower graph). The patient's tumor cells are producing an antibody with an Ig lambda light chain. A decrease of the lambda concentration and a concomitant increase of the kappa concentration (and thus the ratio) is therefore indicative of a clinical efficacy of SRRM2 CAR-T cells.

[0272] **Figure 6** shows the reduction in cancer-associated plasma cells, as quantified by counting the number of abnormal plasma cells (gated), which are characterized by the combination of markers $CD138^+CD19^-CD56^-CD45^{dim}$. Bone marrow FACS of Patient 1 before (left) and at day 50 after SRRM2 CAR-T cell infusion (right) are shown.

[0273] **Figure 7** shows clinical data from Patient 1, evaluating antitumor activity of the infused SRRM2 CAR-T cells:

- Decrease of the ECOG from 4 to 2 (see e.g. <https://ecog-acrin.org/resources/ecog-performance-status/> for ECOG performance status scale)
- Reduction of minimal residual disease (MRD) in the blood
- Slight increase in hemoglobin (HB)
- Significant increase in the number of platelets (PIT)

- Significant decrease in the concentration of creatinine (Cr) indicative for improved renal function.

[0274] Figure 8 shows the workflow for the detection of SRRM2-positive abnormal plasma cells in the blood of myeloma patients. In this example 90.02% of myeloma plasma cells were membrane SRRM2 positive, while normal cells were SRRM2 membrane negative (not shown). **Fig. 8B** shows the percentage of SRRM2 positive plasma cells in the bone marrow of a total of 67 patients tested along the workflow shown in **Fig. 8A**.

[0275] Figure 9 shows the decrease of plasma cells (CD38++CD138+CD19-CD56-CD45dim) in the peripheral blood of Patient 1 from 43% before infusion of SRRM2 CAR-T cells (pre) to 6.4% of the total number of white blood cells at day 16 after infusion. SRRM2 CAR-T cells were infused twice (arrows): 3.4×10^7 at day 0 (pre) and 1.18×10^8 at day 2.

[0276] Figure 10 shows that infusion with SRRM2 CAR T cells results in a recovery of hematopoietic function 50 days post-infusion. Patient 2 received infusion of SRRM2 CAR T cells alone, with no blood transfusion to assist hematopoietic recovery. Platelet level increases from just 36g/L on the day of infusion to 62g/L by post-infusion day 50. Thrombocytopenia is a common (29%) symptom in multiple myeloma and may result in altered coagulation phenotypes.

[0277] Figure 11 shows the correlational analysis between SRRM2 expression and clinical data of patients with AML. (A) Survival analysis based on the database (Center for CancerGenomics-NCI) showed that patients with high SRRM2 expression had a shorter median survival time than those with low SRRM2 expression. (B) SRRM2 expression in AML cells with cytogenetic abnormalities and in normal HSC. (C) Surface SRRM2 expression on leukemia blasts from bone marrow (BM) and peripheral blood (PB). (D-E) SRRM2 expression among different age and sex groups. (F) Surface SRRM2 expression in newly diagnosed (ND) and relapsed/refractory (RR) cases of AML. (G) Surface SRRM2 expression in the patients with chromosomal karyotype abnormalities and those with normal chromosomal karyotypes. (H) Surface SRRM2 expression in the patients with and without gene mutations. (I-J) Surface SRRM2 expression on the tumor cell membrane of the patients with AML carrying different gene mutations. SRRM2 levels are highest in patients carrying the FLT3 mutation. ISO: Isotype control. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$, ns: no significant difference.

Survival analysis revealed that the patients with AML exhibiting a high expression of SRRM2 showed a significantly shorter median survival compared to those with low expression of SRRM2 (**Fig. 11A**). SRRM2 was significantly elevated in various types of AML blasts with different cytogenetic abnormalities compared to normal hematopoietic stem cells (HSC) (**Fig.**

11B). Flow cytometry was performed to evaluate the cell surface SRRM2 expression in 65 patients with AML and various myeloid leukemia cell lines. There were no statistically significant differences in the expression of SRRM2 among groups classified by specimen types, ages, and sex (**Fig. 11C-11E**). However, a significant correlation was observed between the disease status and chromosomal abnormalities of the patients with AML and the expression of SRRM2 (**Fig. 11F and 11G**). The expression of SRRM2 was elevated in the patients with AML harboring gene mutations compared to those without genetic mutations (**Fig. 11H**). Notably, the patients with AML carrying the FLT3 mutation (FLT3^{mut}) exhibited a significantly higher SRRM2 expression compared to the patients with FLT3 wild-type (FLT3^{WT}) and other genetic mutations (**Fig. 11I and 11J**).

[0278] Figure 12 shows the expression of SRRM2 in AML patients and healthy donors. (**A-B**) SRRM2 expression on the membrane surfaces of leukemia blasts, lymphocytes, monocytes, and neutrophils in two patients with AML was evaluated by flow cytometry. (**C**) Expression of SRRM2 on lymphocytes, monocytes, and neutrophils in PB of healthy donors. (**D**) Expression of SRRM2 on lymphocytes, monocytes, neutrophils, and hematopoietic stem cells in the BM from healthy donors.

In some cases, SRRM2 was significantly specifically expressed in leukemia blasts but not normal blood cells (**Fig. 12A and 12B**). In healthy donors, SRRM2 almost showed no or negligible expression on lymphocytes, monocytes, neutrophils, and HSCs (**Fig. 12C**: PB samples, **Fig. 2D**: BM samples). The expression of SRRM2 demonstrated a significant elevation in AML cell membrane surface, suggesting that it is a promising target for CAR-T therapy in AML.

[0279] Figure 13 shows the expression and localization of SRRM2 on different AML cell lines. Expression of surface SRRM2 on six AML cell lines as measured by flow cytometry using our SRRM2 antibody. ISO: Isotype control. ***p<0.001, ****p<0.0001. Anti-SRRM2 and goat anti-rabbit IgG (H+L)/AF647 antibodies (Bioss, catalog: bs-0295G-AF647) were used to identify SRRM2 expression.

Six AML cell lines were selected for subsequent experiments to validate the association between surface SRRM2 expression and FLT3^{mut} AML; among them, MOLM-13 and MV4-11 represented FLT3^{mut} cell lines. An elevated SRRM2 expression was observed in various AML cell lines. The FLT3^{mut} MOLM-13 cell line demonstrated higher surface SRRM2 levels than the other FLT3^{wild} cell lines

[0280] Figure 14 shows the optimization of conditions for SRRM2-CAR-T preparation. (**A**) Schematic diagram of an LV construct expressing SRRM2 CAR. scFv, single chain variable

fragment (SRRM2); Hinge (CD8); TMD, transmembrane domain; Intracellular domain: 4-1BB.CD3 ζ . (B) Workflow of the CAR-T preparation. (C-G) Transfection rates of CAR-T cells under different culture conditions. For all relevant groups, the data are expressed as mean standard deviation, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$, ns: no significant difference.

CAR-T cells specifically targeting SRRM2 were designed and constructed to achieve targeted therapy for SRRM2 in AML (Fig. 14A and 14B). The effect of CD3 and CD28 stimulation on the survival and expansion of SRRM2 CAR-T cells during transduction was assessed using 100 ng/ml or 300 ng/ml (Fig. 14C). The effect of IL-2 concentration on transduction efficiency was investigated by culturing SRRM2 CAR-T cells with different concentrations, 300 IU/ml or 600 IU/ml. Varying the IL-2 concentration had minimal effect on the transduction rate of SRRM2 CAR-T cells (Fig. 14C), suggesting that the IL-2 concentration did not significantly affect transduction efficiency under our experimental conditions. The effects of different proliferation factors (IL-2 only or the combination of IL-7 and IL-15) were compared on SRRM2 CAR-T cells transduction. The combination of IL-7 and IL-15 significantly enhanced the transduction rate compared to only IL-2 (Fig. 14C). HSA inclusion during viral transduction significantly improved the transduction success rate, with a significant increase in SRRM2 CAR expression compared to groups without HSA (Fig. 14C). Based on these findings, repeated experiments were conducted to establish optimal transduction conditions, which were CD3 and CD28 at 100 ng/ml, using both IL-7 and IL-15 as proliferation factors, and inclusion of HSA at 10 ng/ml (Fig. 14D). Under these optimized conditions, stable and high rates of SRRM2 CAR-T cell production were successfully achieved for the subsequent experiments.

[0281] Figure 15 shows the potency of SRRM2 CAR-T cells in vitro. (A-D) In vitro cytotoxicity of SRRM2 CAR against four AML cell lines as measured with a LDH-based cytotoxicity assay. Non-transduced T cells (Mock-T) were used as control. Three effector to target (E:T) ratios (1:1, 2.5:1, 5:1) were set for each group in triplicates. (E) At an E:T ratio of 1:1, the killing efficacy of CAR-T cells against MOLM-13 was much higher than that against the other three cell lines.

LDH release experiments were conducted to evaluate their cytolytic activity against different tumor cell types at varying E:T ratios to check the cytotoxicity of our prepared CAR-T cells against SRRM2-positive AML cells. The results demonstrated a significantly enhanced cytolytic capacity of SRRM2 CAR-T cells with increasing E:T ratios, clearly surpassing that of MOCK-T cells without viral transduction (Fig. 15A-15D). More than 50% dead target cells were observed at an E:T ratio of 1:1, and with an increase in the E:T ratio, the killing efficiency of SRRM2 CAR-T cells also increased. A comparative analysis of cytotoxicity was performed across four distinct AML cell lines with or without FLT3^{mut} for a balanced E:T ratio of 1:1. The

findings revealed a significantly superior cytolytic effect of SRRM2 CAR-T cells against FLT3^{mut} cells compared to FLT3^{WT} cells (Fig. 15E).

[0282] Figure 16 demonstrates potent anti-tumor capabilities of SRRM2 CAR-T cells in vivo. (A) Schematic representation of the in vivo experiment using SRRM2 CAR-T cells in NCG mice model of AML. Six-week-old immunodeficient NCG mice were used to construct the AML model by injection with SKM-1 cells. (B) Wright-Giemsa staining in the mouse model of AML. The magnifications of the images shown in the panels are $\times 10$ and $\times 100$. (C) Cardiac blood samples were collected for PCR analysis to assess CAR gene expression using the CAR gene copy number detection kit. (D) Continuous monitoring of mouse body weight revealed no differences before the administration of CAR-T or MOCK-T cells. However, over time, after CAR-T injection, the divergence in weight between the two groups increased and became statistically significant. (E) Mice in the CAR-T group exhibited statistically significant extended survival compared to mice of the MOCK-T group ($p=0.0044$). In all relevant groups, the data are expressed as mean standard deviation, $*p<0.05$, $**p<0.01$, $***p<0.001$, $****p<0.0001$, ns: no significant difference.

The efficacy and safety of SRRM2 CAR-T against AML tumor-bearing mice was assessed in vivo. Using SKM-1 cells that express surface SRRM2 (not shown), a xenograft mouse model in NSG mice was established (Fig. 16A). The success of modeling was confirmed 14 days after injection of AML cells by Wright-Giemsa staining (Fig. 16A). Subsequent administration involved a single injection of 1×10^7 MOCK-T or CAR-T cells on day 15 after AML cell injection. CAR-T cell amplification was detected in PB (Fig. 16C). The body weight of the mice was continuously monitored. No significant disparity in body weight was observed between the two groups before the administration of MOCK-T or CAR-T. However, over time, after CAR-T cell injection, the discrepancy in body weight between MOCK-T and CAR-T groups increased (Fig. 16D). Remarkably, tumor-bearing mice in the CAR-T group demonstrated significantly prolonged survival compared to those in the MOCK-T group (Fig. 16D). Treatment of mice with SRRM2 CAR-T cells revealed no cytokine release syndrome (CRS) and other commonly associated adverse reactions, leading to a significant improvement in leukemia blast elimination and survival rate (Fig. 16B and 16E). These findings demonstrated the remarkable efficacy and safety profiles of SRRM2 CAR-T therapy for AML in vivo.

[0283] Figure 17 shows the surface staining of living cells with different SRRM2 antibodies. Commercial antibodies fail to bind to cell-surface SRRM2 on living cells, whilst the SRRM2-specific antibody of the present invention (EX-02) does bind to cell-surface SRRM2 on living cells. Human A549 cells were analysed by flow cytometry for the binding of the antibodies indicated above each corresponding histogram. Antibody application (black lines) was

compared with a suitable isotype control antibody (gray lines), followed by incubation with a suitable Alexa-647 labelled secondary antibody. Only antibody EX-02 achieved binding to cell-surface localized SRRM2 on living human cells.

[0284] Figure 18 shows the decrease of plasma cells (CD38++CD138+CD19-CD56-CD45dim) in the peripheral blood of Patient 3 from 29.0% before infusion of SRRM2 CAR-T cells (day=0) to 0.55% of the total number of peripheral blood plasma cells at day 28 after infusion. SRRM2 CAR-T cells were i.v. infused three times: 0.54×10^7 , 2.34×10^7 , 1.06×10^7 cells / kg body weight at days 0, 1 and 18, respectively

[0285] Figure 19 shows that surface SRRM2 is both expressed on plasma cells of newly diagnosed MM patients (A) and on plasma cells of previously diagnosis of plasma cell disorders patients, including relapsed and refractory MM, PCL, reactive plasmacytosis, and other plasma cell disorders under or after conventional treatment (B).

[0286] Figure 20 shows significant tumor suppression of SRRM2 CAR-T cells in *in vivo*. MM model The efficacy and safety of SRRM2 CAR-T against MM tumor-bearing mice was assessed *in vivo*. Using KMS-11 cells that express surface SRRM2 (not shown), a xenograft mouse model in NSG mice was established (A). (B) After one dose of CAR-T cells administration (1.3×10^6), longitudinal monitoring of the bioluminescent signals of Luc+ KMS-11 cells in NSG mice in both intravenously injected Mock-T and CAR-T cell treatment groups showed CAR-T treatment significantly decrease the tumor burden in mice models. After 40 days of KMS-11-luc transplantation, tumor relapse was found in the ID CAR-6 mouse (symbol ▼) (C) CAR-T treatment led to obvious CD8+ T cells expansion and brought higher CD8/CD4 ratio in 4 mice blood samples, indicating a positive response to treatment. Whereas the ratio recession was spotted in mouse CAR-6 (symbol ○). (D) Bioluminescence imaging in NSG mice engrafted with luciferase-expressing KMS-11 tumors showed SRRM2 CAR-T cells suppressed tumor growth. Clear tumor burden difference was distinguished from day 24 after CAR-T infusion. 4 out of 5 CAR-T group mice were free of tumor on day 50 except for its relapse in CAR-6 mouse, while experiment of control group was stopped on day 34 due to high tumor burden.

[0287] Figure 21 shows CAR-T cell *in vivo* proliferation and no observed toxicity in the KMS-11 xenograft model. Examination of CAR-T cell count/ml blood (A) and CAR-T cell count/spleen (B) using day 50 samples showed CAR-T cells proliferated in CAR-T treatment group. Median value for Mock-T group vs. CAR-T group was 100 vs. 3140 counts/ml in blood and 404 vs. 9476 counts in spleen. (C) Monitoring of the changes in the body weight of tumor-bearing mice in both CAR-T and Mock-T groups did not find significant disparity between the

two groups after the administration of Mock- and CAR-T cells. No treatment associated toxicities were observed in the animals.

REFERENCES

- Altschul, S. F. et al. (1997) *Nucleic Acids Res.*, 25(17):3389-402.
- Bray, F. et al. (2018) *CA: A Cancer Journal for Clinicians*, 0:1-31
- Campos-Silva et al., (2019) *Sci Rep.*, 14,9(1):2042
- Dalbadie-McFarland, G. et al., *Proc. Natl. Acad. Sci. USA* (1982) 79, 6409-641.
- Daver et al. (2019), *Leukemia* volume 33, pages 299–312.
- Hashimoto-Gotoh, T. et al. (1995) *Gene*, 152, 271-275.
- Kramer, W. et al. (1984) *Nucleic Acids Res.*, 12, 9441-9456.
- Kramer W, and Fritz HJ. (1987) *Methods Enzymol.*, 154, 350-367
- Kunkel, TA (1985) *Proc Natl Acad Sci USA*. 82, 488-492.
- Kunkel (1988) *Methods Enzymol.* 85, 2763-2766.
- Mark, D. F. et al., *Proc. Natl. Acad. Sci. USA* (1984) 81, 5662-5666,
- Short, NJ et al. (2018) *Lancet* (London, England). 2018;392(10147):593-606.
- Wang, A. et al., *Science* 224, 1431-1433,
- Weidle, U. H., Maisel, D., Klostermann, S., Schiller, C., and Weiss, E. H. (2011)
- Zoller, M. J. and Smith, M., *Nucleic Acids Research* (1982) 10, 6487-6500.
- Zoller, M. J., and Smith, M. (1983) *Methods Enzymol.* 100, 468-500.64

Claims

1. An antibody that binds to human serine/arginine repetitive matrix protein 2 (SRRM2) present on the cell surface of a target cell, for use in a method for the treatment of blood cancer in a human patient.
2. The antibody for the use of claim 1, wherein the patient to be treated has a weight of between 16 and 150kg, preferably 18 to 140kg, more preferably 20 to 130kg, more preferably still 22 to 120kg.
3. The antibody for the use of any of the preceding claims in which the patient to be treated is at least 1 year old, preferably 2 years, more preferably between 2 and 80 years old.
4. The antibody for the use of any of the preceding claims, wherein the patient to be treated has a body height between 70 and 220cm, preferably between 80 and 200cm, more preferably between 90 and 200cm.
5. The antibody for the use of any of the preceding claims, wherein said antibody has cytotoxic activity, preferably antigen-dependent cellular cytotoxicity (ADCC) and/or complement-dependent cytotoxicity (CDC).
6. The antibody for the use of any of the preceding claims, wherein said antibody is part of a chimeric antigen receptor (CAR).
7. The antibody of claim 6, wherein said CAR is expressed by a T cell, NK cell, NK-T cell or macrophage.
8. The antibody for the use of any of the preceding claims, wherein said antibody is expressed by an autologous cell population.
9. The antibody for the use of any of the preceding claims, wherein said antibody is expressed by an allogeneic cell population
10. The antibody for the use of any of the preceding claims, wherein SRRM2 present on the cell surface of a target cell is externalized.

11. The antibody for the use of any of the preceding claims, wherein the antibody is not an intracellular antibody.
12. The antibody for the use of any of the preceding claims, wherein said blood cancer to be treated is a blood cancer characterized by cells expressing human SRRM2 on their cell surface.
13. The antibody for the use of any of claims 1 to 12, wherein said blood cancer to be treated is multiple myeloma.
14. The antibody for the use of any of claims 1 to 12, wherein said blood cancer to be treated is leukemia, including acute erythroid leukemia, acute lymphoblastic leukemia (ALL), acute megakaryoblastic leukemia, acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), chronic myelomonocytic leukemia (CMML), childhood leukemia, hairy cell leukemia (HCL), large granular lymphocytic leukemia (LGLL), mast cell leukemia (MCL), or plasma cell leukemia (PCL).
15. The antibody for the use of any of claims 1 to 12, wherein said blood cancer to be treated is acute myeloid leukemia (AML).
16. The antibody for the use of claim 15, wherein said AML is further characterized by cells having a genetic mutation, preferably a FMS-like tyrosine kinase-3 (FLT3) mutation.
17. The antibody for the use of any of claims 1 to 12, wherein said blood cancer to be treated is plasma cell leukemia (PCL).
18. The antibody for the use of claim 17, wherein said PCL is primary or secondary PCL.
19. The antibody for the use of any of claims 1 to 12, wherein said blood cancer to be treated is lymphoma, including Burkitt lymphoma, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, hodgkin lymphoma, non-Hodgkin lymphoma, MALT lymphoma, mantle cell lymphoma, small lymphocytic lymphoma (SLL), post-transplant lymphoproliferative disorder (PTLD), or Waldenström macroglobulinaemia (WM).
20. The antibody for the use of any of claims 1 to 12, wherein said blood cancer to be treated is a myelodysplastic syndrome, a myeloproliferative neoplasm (including polycythemia

vera, essential thrombocythaemia, or myelofibrosis), Erdheim-Chester disease, Langerhans cell histiocytosis, mastocytosis, or mast cell leukemia.

21. The antibody for the use of any of the preceding claims, wherein the patient to be treated is refractory to previous cancer therapy and/or in relapse after previous cancer therapy.
22. The antibody for the use of any of the preceding claims, wherein the route of antibody administration is parenteral, including, but not limited to, intravenous, intradermal, intramuscular, intrathecal, or intraperitoneal administration.
23. The antibody for the use of any of the preceding claims, wherein said antibody is conjugated with a cytotoxic substance.
24. The antibody for the use of any of the preceding claims, wherein said antibody binds to non-permeabilised cells.
25. The antibody for the use of any of the preceding claims, wherein said antibody binds to living cells.
26. The antibody for the use of any of the preceding claims, wherein said antibody is an antibody comprising
 - (a) a heavy chain variable region comprising heavy chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 9, heavy chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 10, and heavy chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 11, and
a light chain variable region comprising light chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 12, light chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 13, and light chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 14;
 - (b) a heavy chain variable region comprising heavy chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 15, heavy chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 16, and heavy chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 17, and
a light chain variable region comprising light chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 18, light chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 19, and light chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 20;

- (c) a heavy chain variable region comprising heavy chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 21, heavy chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 22, and heavy chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 23, and
a light chain variable region comprising light chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 24, light chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 25, and light chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 26; or
 - (d) a heavy chain variable region comprising heavy chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 21, heavy chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 22, and heavy chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 23, and
a light chain variable region comprising light chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 27, light chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 28, and light chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 29.
27. The antibody for the use of any of the preceding claims, wherein said antibody is an antibody comprising
- (a) a heavy chain variable region having the amino acid sequence as set forth in SEQ ID NO: 1 and a light chain variable region having the amino acid sequence as set forth in SEQ ID NO: 2,
 - (b) a heavy chain variable region having the amino acid sequence as set forth in SEQ ID NO: 3, and a light chain variable region having the amino acid sequence as set forth in SEQ ID NO: 4,
 - (c) a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 5, and light chain variable region having the amino acid sequence as set forth in SEQ ID NO: 6, or
 - (d) a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 5, and light chain variable region having the amino acid sequence as set forth in SEQ ID NO: 7.
28. The antibody for the use of any of the preceding claims, wherein said antibody is contained in composition comprising a buffer.
29. The antibody for the use of claim 28, wherein said antibody is contained in a composition comprising a buffer and sodium chloride.

30. A method for determining whether a patient may suffer from blood cancer, comprising determining in a sample obtained from said patient whether SRRM2 is present on the cell surface of cells comprised by said sample and/or whether SRRM2 is present on the surface of extracellular vesicles.
31. The method of claim 30, wherein an increased amount of SRRM2 on the cell surface of cells comprised by said sample and/or present on the surface of extracellular vesicles when compared to the amount of SRRM2 on the cell surface of cells comprised by said sample and/or present on the surface of extracellular vesicles in a sample obtained from a healthy subject indicates that the patient may suffer from blood cancer.
32. The method of claim 30, wherein no difference in the amount of SRRM2 on the cell surface of cells and/or present on the surface of extracellular vesicles comprised by a sample obtained from said patient when compared to the amount of SRRM2 on the cell surface and/or extracellular vesicles in a sample obtained from a healthy subject indicates that the patient may not suffer from blood cancer.
33. The method of any of claims 30 to 32, wherein said antibody is an antibody comprising
- (a) a heavy chain variable region comprising heavy chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 9, heavy chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 10, and heavy chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 11, and
a light chain variable region comprising light chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 12, light chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 13, and light chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 14;
 - (b) a heavy chain variable region comprising heavy chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 15, heavy chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 16, and heavy chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 17, and
a light chain variable region comprising light chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 18, light chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 19, and light chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 20;
 - (c) a heavy chain variable region comprising heavy chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 21, heavy chain CDR2 having the amino acid

- sequence as set forth in SEQ ID NO: 22, and heavy chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 23, and
a light chain variable region comprising light chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 24, light chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 25, and light chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 26; or
(d) a heavy chain variable region comprising heavy chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 21, heavy chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 22, and heavy chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 23, and
a light chain variable region comprising light chain CDR1 having the amino acid sequence as set forth in SEQ ID NO: 27, light chain CDR2 having the amino acid sequence as set forth in SEQ ID NO: 28, and light chain CDR3 having the amino acid sequence as set forth in SEQ ID NO: 29.
34. The method of any of claims 30 to 33, wherein said antibody is an antibody comprising
(a) a heavy chain variable region having the amino acid sequence as set forth in SEQ ID NO: 1 and a light chain variable region having the amino acid sequence as set forth in SEQ ID NO: 2,
(b) a heavy chain variable region having the amino acid sequence as set forth in SEQ ID NO: 3, and a light chain variable region having the amino acid sequence as set forth in SEQ ID NO: 4,
(c) a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 5, and light chain variable region having the amino acid sequence as set forth in SEQ ID NO: 6, or
(d) a heavy chain variable region having the amino acid sequence set forth in SEQ ID NO: 5, and light chain variable region having the amino acid sequence as set forth in SEQ ID NO: 7.
35. The method of any of claims 30 to 34, wherein said cells are non-permeabilised cells.
36. The method of any of claims 30 to 35, wherein said cells are living cells.
37. The method of any of claims 30 to 36, wherein said blood cancer is multiple myeloma.
38. The method of any of items claims 30 to 36, wherein said blood cancer is leukemia, including acute erythroid leukemia, acute lymphoblastic leukemia (ALL), acute

megakaryoblastic leukemia, acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), chronic myelomonocytic leukemia (CMML), childhood leukemia, hairy cell leukemia (HCL), large granular lymphocytic leukemia (LGLL), mast cell leukemia (MCL), or plasma cell leukemia (PCL).

39. The method of any of claims 30 to 36, wherein said blood cancer is acute myeloid leukemia (AML).
40. The method of any of claims 30 to 36, wherein said blood cancer is plasma cell leukemia (PCL).
41. The antibody for the use of claim 40, wherein said PCL is primary or secondary PCL.
42. The method of any of claims 30 to 36, wherein said blood cancer is lymphoma, including Burkitt lymphoma, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, hodgkin lymphoma, non-Hodgkin lymphoma, MALT lymphoma, mantle cell lymphoma, small lymphocytic lymphoma (SLL), post-transplant lymphoproliferative disorder (PTLD), or Waldenström macroglobulinaemia (WM).
43. The method of any of claims 30 to 36, wherein said blood cancer is a myelodysplastic syndrome, a myeloproliferative neoplasm (including polycythaemia vera, essential thrombocythaemia, or myelofibrosis), Erdheim-Chester disease, Langerhans cell histiocytosis, mastocytosis, or mast cell leukemia.