or a CAR T cell, that binds to the wild type version of CD117, but shows a substantially decreased or no binding to the altered version of CD117, i.e. the variant of CD117 is immunologically distinguishable from the wild type version of CD117. Most single amino acid substitution in any given target protein will only affect the binding of a moiety, if the amino acid substitution is part of, or is close to, the epitope of the binding moiety. As also will be appreciated, many single amino acid substitutions that do affect binding of a binding moiety to a target antigen will also impact the functionality of the target antigen. It is therefore a highly sophisticated and unpredictable task to identify those amino acid substitutions that fulfill both requirements that do affect binding a moiety to a target antigen and which at the same time do not, or not substantially, affect its function.

Several anti-CD117 moieties are known in the art, some of which are currently in development. Antibody SR-1 was originally isolated from a hybridoma (WO1992017505). Humanized versions of SR-1 were generated (WO2007127317; WO2020112687). Anti-CD117 drug conjugates are described in WO2016020791. Other anti-CD117 antibodies are described in WO2015050959 and WO2019084064. Certain anti-CD117 antibodies are also available commercially, e.g. antibody 104D2 Dianova (#117PE-100T). These and other anti-CD117 moieties may be used in the context of the present disclosure. WO2021041945 discloses genomic alterations of antigens, including CD117, generated by base editing. These antigen alterations were however not characterized, in particular the biological function of the variants was not tested.

SUMMARY

One of the objectives of the present disclosure is to develop a safer method for the treatment of malignancies, in particular cancer, hematological malignancies, myeloid diseases. The inventors thus sought variations of the surface protein CD117 which are immunologically distinguishable while retaining or substantially retaining normal function, and where amino acid changes originate from a single or multiple amino acid or nucleotide variations. In particular, the inventors identified rationally designed and naturally occurring

variants of CD117 and showed that these mutations change the antigenicity of CD117 to a specific antibody while retaining its normal expression and function, in particular binding to SCF, SCF-dependent proliferation and/or SCF-dependent phosphorylation.

In one example, the present disclosure relates to a mammalian cell or a population of cells expressing a first isoform of CD117 for use in a medical treatment in a patient in need thereof, said patient having cells expressing a second isoform of CD117, wherein said cell expressing said first isoform comprises genomic DNA with at least one polymorphism or genetically engineered allele, wherein said polymorphism or genetically engineered allele is not present in the genome of the patient having cells expressing said second isoform of CD117 and preferably wherein said first and second isoforms are functional. Alternatively said first isoform is generated via RNA editing.

In a particular example, the present disclosure relates to the mammalian cell or population of cells, preferably hematopoietic stem cells for use in a medical treatment in a patient in need thereof wherein said medical treatment comprises: administering a therapeutically efficient amount of said cell or population of cells expressing said first isoform of CD117 to said patient in need thereof, in combination with a therapeutically efficient amount of a depleting agent comprising at least a first antigen-binding region that binds specifically to said second isoform of CD117 to specifically deplete patient cells expressing said second isoform of CD117, preferably to restore normal hematopoiesis after immunotherapy in the treatment of hematopoietic disease, preferably malignant hematopoietic disease such as acute myeloid leukemia (AML), myeloblastic syndrome (MDS), blastic plasmacytoid dendritic cell neoplasm (BPDCN), chronic myeloid leukemia (CML), B-acute lymphoblastic leukemia (B-ALL) or mastocytosis.

In other examples the medical treatment relates to the restoration of the hematopoietic or the immune function in genetic diseases of the hematopoietic or immune system, such as severe combined immunodeficiency syndrome (SCID), sickle cell disease (SCD), beta-thalassemia, Fanconi anemia or Diamond-Blackfan anemia.

In other examples the medical treatment relates to the restoration of the normal function in genetic diseases that are not originating in the hematopoietic and immune system but that can be treated by use of modified hematopoietic cells.

In other examples the medical treatment relates to the restoration of the normal immune function in autoimmune diseases, such as systemic lupus erythematosus (SLE), systemic sclerosis (SSc) or multiple sclerosis (MS).

In another particular example, the present disclosure relates to the mammalian cell or population of cells for use in a medical treatment in a patient in need thereof, wherein said medical treatment comprises: administering a therapeutically efficient amount of said cell or population of cells expressing said first isoform to said patient in need thereof in combination with a therapeutically efficient amount of a depleting agent comprising at least a second antigen-binding region that binds specifically to said first isoform to specifically deplete transferred cells expressing first isoform, preferably for use in adoptive cell transfer therapy, more preferably for the treatment of malignant hematopoietic disease such as acute myeloid leukemia (AML), myeloblastic syndrome (MDS), blastic plasmacytoid dendritic cell neoplasm (BPDCN), chronic myeloid leukemia (CML), B-acute lymphoblastic leukemia (B-ALL) or mastocytosis, again more preferably wherein said depleting agent is administered subsequently to said cell or population of cells expressing said first isoform of surface protein to avoid eventual severe side effects such as graft-versus-host disease due to the transplantation.

In another example, the present disclosure relates to a pharmaceutical composition comprising a mammalian cell, preferably a hematopoietic stem cell or an immune cell such as T-cell as described above and preferably a depleting agent and a pharmaceutically acceptable carrier.

In yet another example, the present disclosure also relates to a depleting agent for use in preventing or reducing the risk of severe side effects in a patient having received a cell expressing a first isoform of CD117, wherein said patient's native cells express a second isoform of CD117, and wherein said depleting agent comprises at least a second antigen-binding region which

binds specifically to said first isoform of CD117 and does not bind to said second isoform of CD117. In certain embodiments said depleting agent binds substantially weaker to said second isoform of CD117.

In another example, the present disclosure also relates to a depleting agent for use in preventing or reducing the risk of severe side effects in a patient having received a cell expressing a first isoform of CD117, wherein said patient's native cells express a second isoform of CD117, and wherein said depleting agent comprises at least a second antigen-binding region which binds specifically to said first isoform of CD117 and does not bind to said second isoform of CD117, and wherein said first and second isoforms are substantially functionally identical. In certain embodiments said depleting agent binds substantially weaker to said second isoform of CD117.

In yet another example, the present disclosure also relates to a depleting agent for use in preventing or reducing the risk of severe side effects in a patient having received a cell expressing a first isoform of CD117, wherein said patient's native cells express a second isoform of CD117, and wherein said depleting agent comprises at least a second antigen-binding region which binds specifically to said first isoform of CD117 and does not bind to said second isoform of CD117, and wherein said first and second isoforms bind to SCF, lead to SCF-dependent proliferation and/or lead to SCF-dependent phosphorylation. In certain embodiments said depleting agent binds substantially weaker to said second isoform of CD117.

In one example, the present disclosure also relates to a depleting agent for use in preventing or reducing the risk of severe side effects in a patient having received a cell expressing a first isoform of CD117, wherein said patient's native cells express a second isoform of CD117, and wherein said depleting agent comprises at least a second antigen-binding region which binds specifically to said first isoform of CD117 and does not bind to said second isoform of CD117, wherein said polymorphic or genetically engineered allele is characterized by at least one substitution of an amino acid in position E73, T74, V120, D121, R122, S123, Y125, K127, K193, I201, K203, S239, Y259, N260, S261, D266, Y269 or R271 of SEQ ID NO: 1, preferably by at least one, substitution of an amino acid in position E73, V120, D121, R122, S123, K127, K193, S239, Y259 or S261 of SEQ ID NO: 1, more preferably by at least one

substitution of an amino acid in position E73, D121, R122, S123, S239, Y259 or S261, and most preferably by at least one substitution of an amino acid in position E73, D121, or S123 of SEQ ID NO: 1. In certain embodiments said depleting agent binds substantially weaker to said second isoform of CD117.

In another example, the present disclosure also relates to a depleting agent for use in preventing or reducing the risk of severe side effects in a patient having received a cell expressing a first isoform of CD117, wherein said patient's native cells express a second isoform of CD117, and wherein said depleting agent comprises at least a second antigen-binding region which binds specifically to said first isoform of CD117 and does not bind to said second isoform of CD117, wherein amino acid residue E73 is substituted with an amino acid selected from the group consisting of K, L, Q, G, A, Y, R, F, I, M, P and W or where residue E73 is deleted, preferably selected from the group consisting K, L, Q, G, A, Y and R, more preferably selected from the group consisting of K, Y, and R, and/or residue D121 is substituted with S, V, Y, H, K, R or T, more preferably Y, H, K, R or T, and most preferably H or K, and/or residue S123 is substituted with V, I, L, P, F, Y, M, D, E, K or R, more preferably with P, F or K, and most preferably K, and/or residue S239 is substituted with an amino acid selected from the group consisting of H and K, and/or residue Y259 is substituted with an amino acid selected from the group consisting of E, A, G, P, C and H, preferably P, A or G, most preferably A, and/or residue K193 is substituted with an amino acid selected from the group consisting G, T, M, D and E. In certain embodiments said depleting agent binds substantially weaker to said second isoform of CD117.

In yet another example, the present disclosure also relates to a method for improving engraftment of hematopoietic stem cell transplants. Conditioning (depletion of HSCs) prior to hematopoietic stem cell transplantation (HSCT) is used to promote engraftment. Indeed, conditioning efficacy is associated with improved engraftment. One disadvantage of myeloablative (toxic) conditioning is that it can lead to increasing levels of chimerism. Avoiding toxic conditioning is an important goal that can be achieved with the present disclosure. Current methods for conditioning involve the use of intravenous busulfan.

Busulfan is a DNA alkylating drug originally designed to treat hematologic diseases, such as acute myeloid leukemia (AML). However, busulfan carries the risk of significant side effects, including sterility, primary or secondary malignancy, and additional acute and chronic toxicities.

In another example, the present disclosure also relates to an anti-CD117 agent which competes with an antigen binding region for binding to CD117 or a variant of CD117, wherein said anti-CD117 agent comprises:

a) an antibody heavy chain variable domain (VH) comprising the three CDRs VHCDR1, VHCDR2 and VHCDR3 wherein VHCDR1 is SEQ ID NO: 17, VHCDR2 is SEQ ID NO: 18 and VHCDR3 is SEQ ID NO: 19; and
b) an antibody light chain variable domain (VL) comprising the three CDRs VLCDR1, VLCDR2 and VLCDR3 wherein VLCDR1 is SEQ ID NO: 20, VLCDR2 is SEQ ID NO: 21 and VLCDR3 is SEQ ID NO: 22. In certain embodiments said antigen binding region comprises the following mutations:

a) the asparagine in the VLCDR1 region (SEQ ID NO: 20) is replaced by glutamic acid, and
b) the aspartic acid in the VLCDR3 region (SEQ ID NO: 22) is replaced by glutamic acid, and optionally,
c) the second asparagine in the VLCDR3 region (SEQ ID NO: 22) is replaced by lysine. Preferably said -anti-CD117 agent does not bind to a E73K variant of CD117. Also preferably said -anti-CD117 agent does not bind to a D121K variant of CD117. Also preferably said -anti-CD117 agent does not bind to a S123K variant of CD117.

In yet another example, the present disclosure also relates to an anti-CD117 agent which competes with an antigen binding region for binding to CD117 or a variant of CD117, wherein said anti-CD117 agent comprises:

a) an antibody heavy chain variable domain (VH) comprising the three CDRs VHCDR1, VHCDR2 and VHCDR3 wherein VHCDR1 is SEQ ID NO: 25, VHCDR2 is SEQ ID NO: 26 and VHCDR3 is SEQ ID NO: 27; and

b) an antibody light chain variable domain (VL) comprising the three CDRs VLCDR1, VLCDR2 and VLCDR3 wherein VLCDR1 is SEQ ID NO: 28, VLCDR2 is SEQ ID NO: 29 and VLCDR3 is SEQ ID NO: 30.

In a further example, the present disclosure also relates to an anti-CD117 agent which competes with an antigen binding region for binding to CD117 or a variant of CD117, wherein said anti-CD117 agent comprises:

a) an antibody heavy chain variable domain (VH) comprising the three CDRs VHCDR1, VHCDR2 and VHCDR3 wherein VHCDR1 is SEQ ID NO: 33, VHCDR2 is SEQ ID NO: 34 and VHCDR3 is SEQ ID NO: 35; and
b) an antibody light chain variable domain (VL) comprising the three CDRs VLCDR1, VLCDR2 and VLCDR3 wherein VLCDR1 is SEQ ID NO: 36, VLCDR2 is SEQ ID NO: 37 and VLCDR3 is SEQ ID NO: 38.

In one aspect, the present disclosure refers to use of a mammalian cell or a population of cells expressing a first isoform of CD117 in the manufacture of a medicament for medical treatment in a patient in need thereof, said patient having cells expressing a second isoform of CD117, wherein said cell expressing said first isoform comprises genomic DNA with at least one polymorphism or genetically engineered allele, wherein said polymorphism or genetically engineered allele is not present in the genome of the patient having cells expressing said second isoform of CD117, wherein said polymorphic or genetically engineered allele is characterized by at least one substitution of an amino acid in position E73, D121, R122, S123, S239, Y259 and/or S261 of SEQ ID NO: 1.

In another aspect, the present disclosure refers to a pharmaceutical composition comprising a mammalian cell or population of cells as described herein, optionally a depleting agent as described herein and a pharmaceutically acceptable carrier.

In yet another aspect, the present disclosure refers to use of a depleting agent in the manufacture of a medicament for preventing or reducing the risk of severe side effects in a patient having received a cell expressing a first isoform of CD117, wherein said patient's native cells express a second isoform of CD117, and wherein said depleting agent

comprises at least a second antigen-binding region which binds specifically to said first isoform of CD117 and does not bind or binds substantially weaker to said second isoform of CD117, wherein said patient's native cells express a second isoform of CD117 and wherein said depleting agent comprises at least a antigen-binding region which binds specifically to said second isoform of CD117, and wherein said first antigen-binding region of said depleting binds specifically to an epitope including the amino acids E73, D121, R122, S123, S239, Y259 and/or S261 of SEQ ID NO: 1, more preferably to an epitope including the amino acids E73, S123, K127 and/or Y259 of SEQ ID NO: 1.

In a further aspect, the present disclosure refers to a combination of a) a mammalian cell or a population of cells expressing an isoform of CD117, wherein said isoform of CD117 is characterized by a substitution of the aspartic acid at position 121 of wild type CD117 to a lysine, and b) a depleting agent comprising i. an antibody heavy chain variable domain (VH) comprising the three CDRs VHCDR1, VHCDR2 and VHCDR3 wherein VHCDR1 is SEQ ID NO: 17, VHCDR2 is SEQ ID NO: 18 and VHCDR3 is SEQ ID NO: 19, and an antibody light chain variable domain (VL) comprising the three CDRs VLCDR1, VLCDR2 and VLCDR3 wherein VLCDR1 is SEQ ID NO: 20, VLCDR2 is SEQ ID NO: 21 and VLCDR3 is SEQ ID NO: 22, ii. an antibody heavy chain variable domain (VH) comprising the three CDRs VHCDR1, VHCDR2 and VHCDR3 wherein VHCDR1 is SEQ ID NO: 17, VHCDR2 is SEQ ID NO: 18 and VHCDR3 is SEQ ID NO: 19, and an antibody light chain variable domain (VL) comprising the three CDRs VLCDR1, VLCDR2 and VLCDR3 wherein VLCDR1 is SEQ ID NO: 59, VLCDR2 is SEQ ID NO: 21 and VLCDR3 is SEQ ID NO: 60, or iii. an antibody heavy chain variable domain (VH) comprising the three CDRs VHCDR1, VHCDR2 and VHCDR3 wherein VHCDR1 is SEQ ID NO: 17, VHCDR2 is SEQ ID NO: 18 and VHCDR3 is SEQ ID NO: 19, and an antibody light chain variable domain (VL) comprising the three CDRs VLCDR1, VLCDR2 and VLCDR3 wherein VLCDR1 is SEQ ID NO: 59, VLCDR2 is SEQ ID NO: 21 and VLCDR3 is SEQ ID NO: 61, preferably for use in a medical treatment in a patient in need thereof.

In yet another aspect, the present disclosure refers to a combination of a) a mammalian cell or a population of cells expressing an isoform of CD117, wherein said isoform of CD117 is characterized by a substitution of the serine at position 123 of wild type CD117 to a lysine,

and b) a depleting agent comprising i. an antibody heavy chain variable domain (VH) comprising the three CDRs VHCDR1, VHCDR2 and VHCDR3 wherein VHCDR1 is SEQ ID NO: 17, VHCDR2 is SEQ ID NO: 18 and VHCDR3 is SEQ ID NO: 19, and an antibody light chain variable domain (VL) comprising the three CDRs VLCDR1, VLCDR2 and VLCDR3 wherein VLCDR1 is SEQ ID NO: 20, VLCDR2 is SEQ ID NO: 21 and VLCDR3 is SEQ ID NO: 22, ii. an antibody heavy chain variable domain (VH) comprising the three CDRs VHCDR1, VHCDR2 and VHCDR3 wherein VHCDR1 is SEQ ID NO: 17, VHCDR2 is SEQ ID NO: 18 and VHCDR3 is SEQ ID NO: 19, and an antibody light chain variable domain (VL) comprising the three CDRs VLCDR1, VLCDR2 and VLCDR3 wherein VLCDR1 is SEQ ID NO: 59, VLCDR2 is SEQ ID NO: 21 and VLCDR3 is SEQ ID NO: 60, or iii. an antibody heavy chain variable domain (VH) comprising the three CDRs VHCDR1, VHCDR2 and VHCDR3 wherein VHCDR1 is SEQ ID NO: 17, VHCDR2 is SEQ ID NO: 18 and VHCDR3 is SEQ ID NO: 19, and an antibody light chain variable domain (VL) comprising the three CDRs VLCDR1, VLCDR2 and VLCDR3 wherein VLCDR1 is SEQ ID NO: 59, VLCDR2 is SEQ ID NO: 21 and VLCDR3 is SEQ ID NO: 61, preferably for use in a medical treatment in a patient in need thereof.

FIGURE LEGENDS

Figure 1 shows the binding of anti-CD117 antibodies to HEK-293T cells transfected with human wild-type CD117 or with an empty vector. Serial dilutions of each antibody were tested for immunoreactivity via flow cytometry. All six antibodies in Mab format bind to human CD117 in a concentration dependent manner. CD117-negative HEK-293T cells (transfected with an empty vector) did not show any antibody binding.

Figure 2 shows the binding of anti-CD117 Fab fragments to HEK-293T cells transfected with human wild-type CD117 or with an empty vector. Like the full length antibodies, also the Fab fragments bind to human CD117 in a concentration dependent manner. CD117-negative HEK-293T cells (transfected with an empty vector) did not show any antibody binding.

CLAIMS

1. Use of a mammalian cell or a population of cells expressing a first isoform of CD117 in the manufacture of a medicament for medical treatment in a patient in need thereof, said patient having cells expressing a second isoform of CD117,
wherein said cell expressing said first isoform comprises genomic DNA with at least one polymorphism or genetically engineered allele,
wherein said polymorphism or genetically engineered allele is not present in the genome of the patient having cells expressing said second isoform of CD117,
wherein said polymorphic or genetically engineered allele is characterized by at least one substitution of an amino acid in position E73, D121, R122, S123, S239, Y259 and/or S261 of SEQ ID NO: 1.

2. The use according to claim 1, wherein a therapeutically efficient amount of said cell or population of cells expressing said first isoform of CD117 is to be administered to said patient in need thereof, in combination with a therapeutically efficient amount of a depleting agent comprising an antigen-binding region that binds specifically to said second isoform of CD117 to specifically deplete patient cells expressing said second isoform of CD117, for said medical treatment.

3. The use according to claim 1 or 2, wherein said first and second isoforms are substantially functionally identical, preferably wherein said first and second isoforms bind to SCF, lead to SCF-dependent proliferation and/or lead to SCF-dependent phosphorylation, or
wherein said first and said second isoform of CD117 bind to SCF at a substantially similar degree, more preferably wherein the KD of said first isoform of CD117 to SCF is less than four-fold, preferably less than three-fold, more preferably less than two-fold and most preferably less than 1.5-fold higher, than the KD of the second isoform of CD117 to SCF.

4. The use according to any one of the preceding claims, wherein residue E73 is substituted with an amino acid selected from the group consisting of K, L, Y, and R, and/or residue D121 is substituted with an amino acid selected from the group consisting of Y, H, K, R or T, and most preferably H or K, and/or said residue S123 is substituted with an amino acid selected from the group consisting of P, F or K, preferably K, and/or said residue S239 is substituted with H or K and/or said residue Y259 is substituted with an amino acid selected from the group consisting of E, A, G, P, C and H, preferably P, A or G, and most preferably A, and/or said residue K193 is substituted with an amino acid selected from the group consisting G, T, M, D and E.

5. The use according to any one of the preceding claims, wherein said first isoform of CD117 is obtained by modifying the nucleic acid sequence encoding said first isoform of CD117 by gene editing, preferably by introducing into a cell a gene editing enzyme capable of inducing site-specific mutations(s) within a target sequence encoding a CD117 surface protein region involved in the binding of agent comprising at least a first antigen-binding region.

6. The use according to any one of the preceding claims, wherein said medical treatment restores normal haematopoiesis after immunotherapy in the treatment of hematopoietic disease, and preferably in the treatment of malignant hematopoietic disease such as acute myeloid leukemia (AML), myelodysblastic syndrome (MDS), systemic mastocytosis, chronic myeloid leukemia (CML), blastic plasmacytoid dendritic cell neoplasm (BPDCN), or B-acute lymphoblastic leukemia (B-ALL).

7. The use according to any one of the claims 2-6, wherein said depleting agent is an antibody, antibody-drug conjugate or an immune cell, preferably a T-cell bearing a chimeric antigen receptor (CAR) comprising a first antigen-binding region which binds specifically to said second isoform and does not bind or binds substantially weaker to said first isoform.

8. The use according to anyone of the claims 2-7, wherein said first antigen-binding region comprises:

a) an antibody heavy chain variable domain (VH) comprising the three CDRs VHCDR1, VHCDR2 and VHCDR3 wherein VHCDR1 is SEQ ID NO: 17, VHCDR2 is SEQ ID NO: 18 and VHCDR3 is SEQ ID NO: 19; and

an antibody light chain variable domain (VL) comprising the three CDRs VLCDR1, VLCDR2 and VLCDR3 wherein VLCDR1 is SEQ ID NO: 20, VLCDR2 is SEQ ID NO: 21, VLCDR3 is SEQ ID NO: 22, or

b) an antibody heavy chain variable domain (VH) comprising the three CDRs VHCDR1, VHCDR2 and VHCDR3 wherein VHCDR1 is SEQ ID NO: 17, VHCDR2 is SEQ ID NO: 18 and VHCDR3 is SEQ ID NO: 19, and

an antibody light chain variable domain (VL) comprising the three CDRs VLCDR1, VLCDR2 and VLCDR3 wherein VLCDR1 is SEQ ID NO: 59, VLCDR2 is SEQ ID NO: 21 and VLCDR3 is SEQ ID NO: 60, or

c) an antibody heavy chain variable domain (VH) comprising the three CDRs VHCDR1, VHCDR2 and VHCDR3 wherein VHCDR1 is SEQ ID NO: 17, VHCDR2 is SEQ ID NO: 18 and VHCDR3 is SEQ ID NO: 19; and

an antibody light chain variable domain (VL) comprising the three CDRs VLCDR1, VLCDR2 and VLCDR3 wherein VLCDR1 is SEQ ID NO: 59, VLCDR2 is SEQ ID NO: 21 and VLCDR3 is SEQ ID NO: 61.

9. The use according to claim 1, wherein:

a therapeutically efficient amount of said cell or population of cells expressing said first isoform of CD117 to said patient in need thereof is to be administered in combination with a therapeutically efficient amount of a depleting agent comprising an antigen-binding region that binds specifically to said first isoform of CD117 to specifically deplete transferred cells expressing first isoform of CD117, for said medical treatment, and

wherein said medical treatment is adoptive cell transfer therapy, preferably for the treatment of malignant hematopoietic disease such as acute myeloid leukemia (AML),

blastic plasmacytoid dendritic cell neoplasm (BPDCN), or B-acute lymphoblastic leukemia (B-ALL).

10. The use according to claim 9 , wherein said depleting agent is to be administered subsequently to said cell or population of cells expressing said first isoform of CD117 to avoid eventual severe side effects such as graft-versus-host disease due to the transplantation.

11. A pharmaceutical composition comprising a mammalian cell or population of cells as defined in any one of the preceding claims, optionally a depleting agent according to any one of claims 2 to 10 and a pharmaceutically acceptable carrier.

12. Use of a depleting agent in the manufacture of a medicament for preventing or reducing the risk of severe side effects in a patient having received a cell expressing a first isoform of CD117, wherein said patient's native cells express a second isoform of CD117, and wherein said depleting agent comprises at least a second antigen-binding region which binds specifically to said first isoform of CD117 and does not bind or binds substantially weaker to said second isoform of CD117, wherein said patient's native cells express a second isoform of CD117 and wherein said depleting agent comprises at least a antigen-binding region which binds specifically to said second isoform of CD117, and wherein said first antigen-binding region of said depleting binds specifically to an epitope including the amino acids E73, D121, R122, S123, S239, Y259 and/or S261 of SEQ ID NO: 1, more preferably to an epitope including the amino acids E73, S123, K127 and/or Y259 of SEQ ID NO: 1.

13. The use according to claim 12, wherein said antigen-binding region comprises:

a) an antibody heavy chain variable domain (VH) comprising the three CDRs VHCDR1, VHCDR2 and VHCDR3 wherein VHCD1 is SEQ ID NO: 17, VHCD2 is SEQ ID NO: 18 and VHCDR3 is SEQ ID NO: 19; and

an antibody light chain variable domain (VL) comprising the three CDRs VLCDR1, VLCDR2 and VLCDR3 wherein VLCDR1 is SEQ ID NO: 20, VLCDR2 is SEQ ID NO: 21, VLCDR3 is SEQ ID NO: 22, or

b) an antibody heavy chain variable domain (VH) comprising the three CDRs VHCDR1, VHCDR2 and VHCDR3 wherein VHCDR1 is SEQ ID NO: 17, VHCDR2 is SEQ ID NO: 18 and VHCDR3 is SEQ ID NO: 19, and

an antibody light chain variable domain (VL) comprising the three CDRs VLCDR1, VLCDR2 and VLCDR3 wherein VLCDR1 is SEQ ID NO: 59, VLCDR2 is SEQ ID NO: 21 and VLCDR3 is SEQ ID NO: 60, or

c) an antibody heavy chain variable domain (VH) comprising the three CDRs VHCDR1, VHCDR2 and VHCDR3 wherein VHCDR1 is SEQ ID NO: 17, VHCDR2 is SEQ ID NO: 18 and VHCDR3 is SEQ ID NO: 19; and

an antibody light chain variable domain (VL) comprising the three CDRs VLCDR1, VLCDR2 and VLCDR3 wherein VLCDR1 is SEQ ID NO: 59, VLCDR2 is SEQ ID NO: 21 and VLCDR3 is SEQ ID NO: 61.

14. A combination of

a) a mammalian cell or a population of cells expressing an isoform of CD117, wherein said isoform of CD117 is characterized by a substitution of the aspartic acid at position 121 of wild type CD117 to a lysine, and

b) a depleting agent comprising

i. an antibody heavy chain variable domain (VH) comprising the three CDRs VHCDR1, VHCDR2 and VHCDR3 wherein VHCDR1 is SEQ ID NO: 17, VHCDR2 is SEQ ID NO: 18 and VHCDR3 is SEQ ID NO: 19, and

an antibody light chain variable domain (VL) comprising the three CDRs VLCDR1, VLCDR2 and VLCDR3 wherein VLCDR1 is SEQ ID NO: 20, VLCDR2 is SEQ ID NO: 21 and VLCDR3 is SEQ ID NO: 22,

ii. an antibody heavy chain variable domain (VH) comprising the three CDRs VHCDR1, VHCDR2 and VHCDR3 wherein VHCDR1 is SEQ ID NO: 17, VHCDR2 is SEQ ID NO: 18 and VHCDR3 is SEQ ID NO: 19, and

an antibody light chain variable domain (VL) comprising the three CDRs VLCDR1, VLCDR2 and VLCDR3 wherein VLCDR1 is SEQ ID NO: 59, VLCDR2 is SEQ ID NO: 21 and VLCDR3 is SEQ ID NO: 60, or

iii. an antibody heavy chain variable domain (VH) comprising the three CDRs VHCDR1, VHCDR2 and VHCDR3 wherein VHCDR1 is SEQ ID NO: 17, VHCDR2 is SEQ ID NO: 18 and VHCDR3 is SEQ ID NO: 19, and

an antibody light chain variable domain (VL) comprising the three CDRs VLCDR1, VLCDR2 and VLCDR3 wherein VLCDR1 is SEQ ID NO: 59, VLCDR2 is SEQ ID NO: 21 and VLCDR3 is SEQ ID NO: 61, preferably

for use in a medical treatment in a patient in need thereof.

15. A combination of

a) a mammalian cell or a population of cells expressing an isoform of CD117, wherein said isoform of CD117 is characterized by a substitution of the serine at position 123 of wild type CD117 to a lysine, and

b) a depleting agent comprising

i. an antibody heavy chain variable domain (VH) comprising the three CDRs VHCDR1, VHCDR2 and VHCDR3 wherein VHCDR1 is SEQ ID NO: 17, VHCDR2 is SEQ ID NO: 18 and VHCDR3 is SEQ ID NO: 19, and

an antibody light chain variable domain (VL) comprising the three CDRs VLCDR1, VLCDR2 and VLCDR3 wherein VLCDR1 is SEQ ID NO: 20, VLCDR2 is SEQ ID NO: 21 and VLCDR3 is SEQ ID NO: 22,

ii. an antibody heavy chain variable domain (VH) comprising the three CDRs VHCDR1, VHCDR2 and VHCDR3 wherein VHCDR1 is SEQ ID NO: 17, VHCDR2 is SEQ ID NO: 18 and VHCDR3 is SEQ ID NO: 19, and

an antibody light chain variable domain (VL) comprising the three CDRs VLCDR1, VLCDR2 and VLCDR3 wherein VLCDR1 is SEQ ID NO: 59, VLCDR2 is SEQ ID NO: 21 and VLCDR3 is SEQ ID NO: 60, or

iii. an antibody heavy chain variable domain (VH) comprising the three CDRs VHCDR1, VHCDR2 and VHCDR3 wherein VHCDR1 is SEQ ID NO: 17, VHCDR2 is SEQ ID NO: 18 and VHCDR3 is SEQ ID NO: 19, and

an antibody light chain variable domain (VL) comprising the three CDRs VLCDR1, VLCDR2 and VLCDR3 wherein VLCDR1 is SEQ ID NO: 59, VLCDR2 is SEQ ID NO: 21 and VLCDR3 is SEQ ID NO: 61, preferably

for use in a medical treatment in a patient in need thereof.

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