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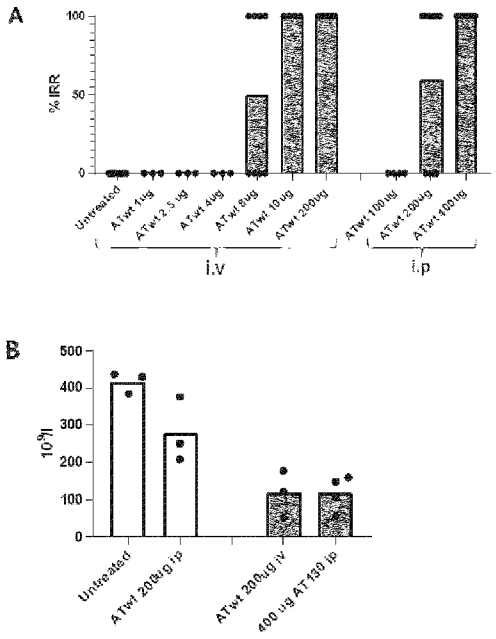
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(54) Title: IMPROVING ANTIBODY TOLERABILTY ASSOCIATED WITH INTRAVENOUS ADMINISTRATION

Figure 1



(57) Abstract: Also described herein is a model for predicting if a therapeutic antibody binding to a human target will be associated with a tolerability issue in connection with intravenous administration and/or for predicting if pre-treatment, altered administration route or modification of the antibody can prevent a tolerability issue associated with intravenous administration to a human of the therapeutic antibody. The model comprises administering the antibody intravenously or intraperitoneally to mice and observing the mice immediately after the administration for any transient display of the macroscopic symptoms isolation and decreased activity. The model may also comprise administration of a pre-treatment in combination with administration of the antibody, administration of the therapeutic antibody by a route of administration other than intravenous or intraperitoneal administration or administration of a modified format of the antibody to mice and observing the mice immediately after such administration for any transient display of the macroscopic symptoms isolation and decreased activity and comparing this with the transient display of the macroscopic symptoms isolation and decreased activity after the intravenous or intraperitoneal administration of the unmodified antibody without pre-treatment.

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IMPROVING ANTIBODY TOLERABILTY ASSOCIATED WITH INTRAVENOUS ADMINISTRATION

FIELD OF THE INVENTION

The invention generally relates to therapeutic systems, combinations for use in dosage regimens, uses, methods, and kits for improving tolerability of an antibody molecule that binds specifically to FcγRIIb in a subject. The present invention also relates to a method or model that can be used to predict if a therapeutic antibody molecule binding specifically to a human target will be associated with a tolerability issue in connection with intravenous administration to a human, and/or to predict if a prophylactic or therapeutic treatment, an altered administration route and/or a modification of the therapeutic antibody molecule can prevent or mitigate a tolerability issue associated with intravenous administration to a human of a therapeutic antibody molecule binding specifically to a human target.

BACKGROUND

Therapeutic antibodies constitute a well-proven class of drugs, which have been approved for therapy of diverse diseases including cancer, inflammatory diseases, autoimmune diseases, and infectious disease.

Monoclonal antibody therapies, in particular those used for cancer therapy, may be administered by intravenous infusion, allowing high immediate drug exposure that can be maintained through repeated dosing. In many cases however, the patient or subject may experience an adverse reaction to the infusion of the therapeutic antibody, which is termed an infusion-related reaction ("IRR").

IRRs can be experienced by subjects during the infusion of the therapeutic antibody (a "uniphasic" reaction) and/or within hours of the infusion (a "biphasic" or "delayed" reaction), and they include hypersensitivity reactions and cytokine release syndromes ("CRS"). According to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 published November 27, 2017 by the U.S. Department of Health and Human Services, the severity of adverse events, such as IRRs, is categorized in different grades, ranging from 1 (the least severe) to 5 (the most severe).

Common IRRs include but are not limited to respiratory conditions such as nasal congestion, cough, allergic rhinitis, throat irritation, and dyspnea, and non-respiratory conditions such as chills and nausea. Often the IRRs occur with the first dose administered to a subject, but they can also occur after the second or subsequent administration. In many cases the IRRs are mild, but more serious IRRs can sometimes occur which risk

being fatal if not managed appropriately. An IRR may affect any organ system in the body.

Severe CRS can represent a life-threatening adverse event that requires prompt and aggressive treatment. Reduction of tumor burden, limitations on the dose of administered therapy, and premedication with steroids have reduced the incidence of severe CRS, as have the use of anti-cytokine treatments.

Tolerability issues may vary between different therapeutic antibodies and between subjects with varying frequency duration, severity and being of different nature.

The conventional management of hypersensitivity reactions, such as IRRs, includes temporary interruption of infusion, lowering the infusion rate, and/or treatment with antihistamines, antipyretics, and/or corticosteroids or in severe case interruption / cessation of infusions. In such severe cases, cautious re-introduction of infusions, at a slower rate with increases as tolerated may be considered. Pre-treatment with antipyretics and/or antihistamines may prevent reactions subsequent infusions.

Corticosteroids are often used to prevent or dampen infusion related reactions (IRR's) and associated toxicities seen with therapeutic antibodies. The corticosteroid regimen, i.e. type of corticosteroid, dose, and timing of administration, depends both on the therapeutic antibody of use and on the indication. Rituxan (rituximab) is a CD20-directed cytolytic antibody commonly used both in CD20-positive B cell lymphomas (Non-Hodgkin's Lymphoma (NHL) and Chronic Lymphocytic Leukemia (CLL)) as well as chronic inflammatory disorders such as Rheumatoid Arthritis (RA). In the case of NHL and CLL, corticosteroids are often used to lower the risk of IRR's and then administrated 30 minutes prior to the first rituximab cycle, and only at subsequent cycles if severe infusion-related adverse events were experienced during the first cycle. In the case of NHL corticosteroids (i.e. prednisone) are also used as part of in combination therapy. i.e. rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). In the case of RA, corticosteroid is recommended 30 minutes prior to each infusion. When administering another CD20-directed antibody Gazyva (obinutuzumab), corticosteroid premedication is also recommended prior to the first treatment cycle and prior to following cycles only in patients where grade 3 IRR was experienced with the previous infusion or with a lymphocyte count > 25 x 109/L prior to next treatment. In the case of Gazyva corticosteroid premedication should be given at least 1 hour prior to the antibody infusion. A third example of a therapeutic antibody where corticosteroids are used to lower the risk of IRR's is Darzalex (daratumumab), a CD38-directed antibody indicated for the treatment

of patients with multiple myeloma. Corticosteroids are in this case recommended pre and post every infusion, 1-3 hour prior to infusion and then again on each of the 2 days following infusion.

WO 2020/047389 describes dosing strategies and administration regimens for therapeutic protein, such as antibodies (e.g., bispecific antibodies targeting T cells), that mitigate the prevalence and severity of cytokine release syndrome or an infusion-related reaction in patients undergoing immunotherapy. comprising: (i) administering fractions of a primary dose (D1) of the therapeutic protein in week 1 of the dosing regimen, wherein the primary dose comprises no more than 10 mg of the therapeutic protein, a first dose fraction (F1D1) comprises 40% to 60% of the total primary dose and is administered to the subject on day 1 of week 1, and a second dose fraction (F2D1) comprises the remaining 40% to 60% of the total primary dose and is administered to the subject from 12 to 96 hours following administration of the F1D1; (ii) administering fractions of a secondary dose (D2) of the therapeutic protein in week 2 of the dosing regimen, wherein the secondary dose is no more than one-half of a maximum weekly dose of the therapeutic protein, a first dose fraction (F1D2) comprises 40% to 60% of the total secondary dose, a second dose fraction (F2D2) comprises the remaining 40% to 60% of the total secondary dose, and the F2D2 is administered to the subject from 12 to 96 hours following administration of the F1D2 during week 2 of the dosing regimen; and (iii) administering the maximum weekly dose of the therapeutic protein to the subject as a single dose in a subsequent week of the dosing regimen. Fractionated dosing is not ideal, since dosing with suboptimally efficacious doses risk limiting therapeutic benefit, in the worst case resulting in no clinical benefit of the intended therapeutic treatment or induction of disease progression.

WO 2020/037024 mentions the use of an additional therapeutic agent, such as an antihistamine, acetaminophen or a corticosteroid, to prevent or reduce the severity of adverse events, such as an infusion-related reaction, in treatment of ovarian cancer, peritoneal cancer or fallopian tube cancer with an anti-tissue factor antibody or an antigen-binding fragment thereof conjugated to a monomethyl auristatin or a functional analog or derivative thereof or a functional derivative thereof.

Management of the toxicities associated with immunotherapy is a challenging clinical problem. Methods to reduce, suppress or overcome the tolerability issues associated with intravenous administration of different antibodies are greatly needed. However, the heterogeneity in nature and frequency of tolerability issues associated with antibodies to different targets, and the poor molecular and cellular understanding of the mechanisms underlying these, mean that numerous disparate approaches have been developed, and

the effectiveness of each can vary significantly depending on the type of therapeutic antibody with which they are used.

The above demonstrates that intravenous administration of antibodies to different targets often is associated with tolerability issues. Such tolerability issues may vary between different therapeutic antibodies and between patients with varying frequency duration, severity and being of different nature.

Accordingly, methods to reduce, suppress or overcome the different tolerability issues associated with iv administration of different antibodies directed to the same target (e.g. anti-CD20 antibodies rituximab compared with Obinutuzumab) or to different targets (e.g. anti-CD38 antibodies compared with anti-CD20 antibodies) differ greatly, and comprise administration of different agents e.g. corticosteroids or antihistamines immediately before, concomitantly, and/or following intravenous administration of the therapeutic antibody.

There is a great need and value of methods enabling prediction of whether or not tolerability issues are likely to occur in association with intravenous administration of antibodies to different targets, and equally importantly of methods enabling discovery of means that help prevent, suppress or overcome tolerability issues associated with iv administration of antibodies to given targets. Preclinical methods allowing for such prediction and screening at early stages of therapeutic antibody development at a relatively lower cost and higher throughput compared to the human clinical setting are of outstanding importance.

SUMMARY AND DETAILED DESCRIPTION

Against this background, the inventors have developed a surprisingly advantageous approach for administering an antibody molecule that specifically binds to FcγRIIb in a subject. As demonstrated in the accompanying Examples, the inventors' approach maintains the therapeutic effectiveness of such an antibody, whilst reducing and/or preventing IRRs associated with its administration. The inventors' approach involves administering several separate doses of the antibody, including an initial sub-maximal therapeutic dose of the antibody, and performing that antibody administration after a corticosteroid has been given to the subject. The inventors' approach therefore provides an improved regimen for administering such antibodies, as it does so in a way that reduces and/or prevents tolerability issues in the subject.

In addition, the inventors have developed a method or model that can be used to predict if a therapeutic antibody molecule binding specifically to a human target will be associated with a tolerability issue in connection with intravenous administration to a human, and/or to predict if a prophylactic or therapeutic treatment, an altered administration route and/or a modification of the therapeutic antibody molecule can prevent or mitigate a tolerability issue associated with intravenous administration to a human of a therapeutic antibody molecule binding specifically to a human target.

FIRST TO FIFTH ASPECTS OF THE INVENTION

In a first aspect, the invention provides a therapeutic system for use in improving tolerability of an antibody molecule that specifically binds to FcγRIIb in a subject, wherein the therapeutic system comprises:

(i) an antibody molecule that specifically binds to FcγRIIb, wherein the antibody molecule is administered to the subject as at least a first dose and a second dose; and

(ii) a corticosteroid,

wherein the first dose of the antibody molecule is lower than the maximum therapeutically effective dose of the antibody molecule; and wherein the corticosteroid is administered to the subject before the first dose of the antibody molecule.

In a second aspect, the invention provides a combination comprising an antibody molecule and a corticosteroid for use in a dosage regimen for improving tolerability of an antibody molecule that specifically binds to FcγRIIb in a subject, wherein the dosage regimen comprises the following steps:

(i) administration of a corticosteroid before administration of a first dose of the antibody molecule;
(ii) administration of the first dose of the antibody molecule that specifically binds to FcγRIIb that is lower than the maximum therapeutically effective dose; and
(iii) administration of a second dose (and, preferably, at least a second dose) of the antibody molecule that specifically binds to FcγRIIb, wherein the first dose of the antibody molecule is administered prior to the second dose.

In a third aspect, the invention provides use of:

(i) an antibody molecule that specifically binds to FcyRIIb; and
(ii) a corticosteroid,

in the manufacture of a medicament for improving tolerability of an antibody molecule that specifically binds to FcyRIIb in a subject, wherein the medicament comprises at least a first dose and a second dose of the antibody molecule; and wherein the first dose of the antibody molecule is lower than the maximum therapeutically effective dose of the antibody molecule; and wherein the corticosteroid is administered before the first dose of the antibody molecule.

In a fourth aspect, the invention provides a method for improving tolerability of an antibody molecule that specifically binds to FcyRIIb in a subject comprising:

(i) administration of a corticosteroid before administration of a first dose of the antibody molecule;
(ii) administration of the first dose of the antibody molecule that specifically binds to FcyRIIb that is lower than the maximum therapeutically effective dose; and
(iii) administration of a second dose (and, preferably, at least a second dose) of the antibody molecule that specifically binds to FcyRIIb, wherein the first dose of the antibody molecule is administered prior to the second dose.

The inventors have surprisingly found that a combination of a dose of a corticosteroid, followed by a first dose of the antibody molecule that specifically binds to FcyRIIb that is lower than the maximum therapeutically effective dose, followed by a second dose of the antibody molecule leads to surprising improvements in the tolerability of the antibody molecule that specifically binds FcyRIIb.

Antibody molecules are well known to those skilled in the art of immunology and molecular biology. Typically, an antibody comprises two heavy (H) chains and two light (L) chains. Herein, we sometimes refer to this complete antibody molecule as a full-size or full-length antibody. The antibody's heavy chain comprises one variable domain (VH) and three constant domains (CH1, CH2 and CH3), and the antibody's molecule light chain comprises one variable domain (VL) and one constant domain (CL). The variable domains (sometimes collectively referred to as the F_V region) bind to the antibody's target, or antigen. Each variable domain comprises three loops, referred to as complementary determining regions (CDRs), which are responsible for target binding. The constant

domains are not involved directly in binding an antibody to an antigen, but exhibit various effector functions. Depending on the amino acid sequence of the constant region of their heavy chains, antibodies or immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG and IgM, and in humans several of these are further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, and IgG4; IgA1 and IgA2.

Another part of an antibody is the Fc region (otherwise known as the fragment crystallisable domain), which comprises two of the constant domains of each of the antibody's heavy chains. As mentioned herein, the Fc region is responsible for interactions between the antibody and Fc receptor.

The term antibody molecule, as used herein, encompasses full-length or full-size antibodies as well as functional fragments of full length antibodies and derivatives of such antibody molecules.

Functional fragments of a full-size antibody have the same antigen binding characteristics as the corresponding full-size antibody and include either the same variable domains (i.e. the VH and VL sequences) and/or the same CDR sequences as the corresponding full-size antibody. That the functional fragment has the same antigen binding characteristics as the corresponding full-size antibody means that it binds to the same epitope on the target as the full-size antibody. Such a functional fragment may correspond to the Fv part of a full-size antibody. Alternatively, such a fragment may be a Fab, also denoted F(ab), which is a monovalent antigen-binding fragment that does not contain a Fc part, or a $F(ab')_2$, which is an divalent antigen-binding fragment that contains two antigen-binding Fab parts linked together by disulfide bonds, or a F(ab'), i.e. a monovalent-variant of a $F(ab')_2$. Such a fragment may also be single chain variable fragment (scFv).

A functional fragment does not always contain all six CDRs of a corresponding full-size antibody. It will be appreciated that molecules containing three or fewer CDR regions (in some cases, even just a single CDR or a part thereof) are capable of retaining the antigen-binding activity of the antibody from which the CDR(s) are derived. For example, in Gao *et al.,* 1994, J. Biol. Chem., 269: 32389-93 it is described that a whole VL chain (including all three CDRs) has a high affinity for its substrate.

Molecules containing two CDR regions are described, for example, by Vaughan & Sollazzo 2001, Combinatorial Chemistry & High Throughput Screening, 4: 417-430. On page 418 (right column – 3 Our Strategy for Design) a minibody including only the H1 and H2 CDR

hypervariable regions interspersed within framework regions is described. The minibody is described as being capable of binding to a target. Pessi *et al.*, 1993, Nature, 362: 367-9 and Bianchi *et al.,* 1994, J. Mol. Biol., 236: 649-59 are referenced by Vaughan & Sollazzo and describe the H1 and H2 minibody and its properties in more detail. In Qiu *et al.*, 2007, Nature Biotechnology, 25:921-9 it is demonstrated that a molecule consisting of two linked CDRs are capable of binding antigen. Quiocho 1993, Nature, 362: 293-4 provides a summary of "minibody" technology. Ladner 2007, Nature Biotechnology, 25:875-7 comments that molecules containing two CDRs are capable of retaining antigen-binding activity.

Antibody molecules containing a single CDR region are described, for example, in Laune *et al.*, 1997, JBC, 272: 30937-44, in which it is demonstrated that a range of hexapeptides derived from a CDR display antigen-binding activity and it is noted that synthetic peptides of a complete, single, CDR display strong binding activity. In Monnet *et al.,* 1999, JBC, 274: 3789-96 it is shown that a range of 12-mer peptides and associated framework regions have antigen-binding activity and it is commented on that a CDR3-like peptide alone is capable of binding antigen. In Heap *et al.,* 2005, J. Gen. Virol., 86: 1791-1800 it is reported that a "micro-antibody" (a molecule containing a single CDR) is capable of binding antigen and it is shown that a cyclic peptide from an anti-HIV antibody has antigen-binding activity and function. In Nicaise *et al.*, 2004, Protein Science, 13:1882-91 it is shown that a single CDR can confer antigen-binding activity and affinity for its lysozyme antigen.

Thus, antibody molecules having five, four, three or fewer CDRs are capable of retaining the antigen binding properties of the full-length antibodies from which they are derived.

The antibody molecule may also be a derivative of a full-length antibody or a fragment of such an antibody. When a derivative is used it should have the same antigen binding characteristics as the corresponding full-length antibody in the sense that it binds to the same epitope on the target as the full-length antibody.

Thus, by the term "antibody molecule", as used herein, we include all types of antibody molecules and functional fragments thereof and derivatives thereof, including: monoclonal antibodies, polyclonal antibodies, synthetic antibodies, recombinantly produced antibodies, multi-specific antibodies, bi-specific antibodies, human antibodies, antibodies of human origin, humanized antibodies, chimeric antibodies, single chain antibodies, single-chain Fvs (scFv), Fab fragments, $F(ab')_2$ fragments, F(ab') fragments, disulfide-linked Fvs (sdFv), antibody heavy chains, antibody light chains, homo-dimers of antibody

heavy chains, homo-dimers of antibody light chains, heterodimers of antibody heavy chains, heterodimers of antibody light chains, antigen binding functional fragments of such homo- and heterodimers.

Further, the term "antibody molecule", as used herein, includes all classes of antibody molecules and functional fragments, including: IgG, IgG1, IgG2, IgG3, IgG4, IgA, IgM, IgD, and IgE, unless otherwise specified.

As outlined above, different types and forms of antibody molecules are encompassed by the invention, and would be known to the person skilled in immunology. It is well known that antibodies used for therapeutic purposes are often modified with additional components which modify the properties of the antibody molecule.

Accordingly, we include that an antibody molecule of the invention or an antibody molecule used in accordance with the invention (for example, a monoclonal antibody molecule, and/or polyclonal antibody molecule, and/or bi-specific antibody molecule) comprises a detectable moiety and/or a cytotoxic moiety.

By "detectable moiety", we include one or more from the group comprising of: an enzyme; a radioactive atom; a fluorescent moiety; a chemiluminescent moiety; a bioluminescent moiety. The detectable moiety allows the antibody molecule to be visualised *in vitro,* and/or *in vivo*, and/or *ex vivo*.

By "cytotoxic moiety", we include a radioactive moiety, and/or enzyme, wherein the enzyme is a caspase, and/or toxin, wherein the toxin is a bacterial toxin or a venom; wherein the cytotoxic moiety is capable of inducing cell lysis.

We further include that the antibody molecule may be in an isolated form and/or purified form, and/or may be PEGylated. PEGylation is a method by which polyethylene glycol polymers are added to a molecule such as an antibody molecule or derivative to modify its behaviour, for example to extend its half-life by increasing its hydrodynamic size, preventing renal clearance.

As discussed above, the CDRs of an antibody bind to the antibody target. The assignment of amino acids to each CDR described herein is in accordance with the definitions according to Kabat EA et al. 1991, In "Sequences of Proteins of Immunological Interest" Fifth Edition, NIH Publication No. 91-3242, pp xv- xvii.

As the skilled person would be aware, other methods also exist for assigning amino acids to each CDR. For example, the International ImMunoGeneTics information system (IMGT(R)) (http://www.imgt.org/ and Lefranc and Lefranc "The Immunoglobulin FactsBook" published by Academic Press, 2001).

In some embodiments, the antibody molecule specifically binds to FcγRIIb. Fc receptors are well known in the art as membrane proteins which are found on the cell surface of immune effector cells, such as macrophages. The name is derived from their binding specificity for the Fc region of antibodies, which is the usual way an antibody binds to the receptor. However, certain antibodies can also bind the Fc receptors via the antibodies' complementarity determining regions ("CDR") sequences in the case of antibodies specifically binding to one or more Fc receptors.

A subgroup of the Fc receptors are Fcγ receptors (Fc-gamma receptors, FcgammaR), which are specific for IgG antibodies. There are two types of Fcγ receptors: activating Fcγ receptors (also denoted activatory Fcγ receptors) and inhibitory Fcγ receptors. The activating and the inhibitory receptors transmit their signals via immunoreceptor tyrosine-based activation motifs (ITAM) or immunoreceptor tyrosine-based inhibitory motifs (ITIM), respectively. In humans, FcγRIIb (CD32b) is an inhibitory Fcγ receptor, while FcγRI (CD64), FcγRIIa (CD32a), FcγRIIc (CD32c), FcγRIIIa (CD16a) and FcγRIV are activating Fcγ receptors. FcγRIIIb is a GPI-linked receptor expressed on neutrophils that lacks an ITAM motif but through its ability to cross-link lipid rafts and engage with other receptors is also considered activatory. In mice, the activating receptors are FcγRI, FcγRIII and FcγRIV.

It is well-known that antibodies modulate immune cell activity through interaction with Fcγ receptors. Specifically, how antibody immune complexes modulate immune cell activation is determined by their relative engagement of activating and inhibitory Fcγ receptors. Different antibody isotypes bind with different affinity to activating and inhibitory Fcγ receptors, resulting in different A:I ratios (activation:inhibition ratios) (Nimmerjahn *et al; Science.* 2005 Dec 2;310(5753):1510-2).

By binding to an inhibitory Fcγ receptor, an antibody can inhibit, block and/or downmodulate effector cell functions.

By binding to an activatory Fcγ receptor, an antibody can activate effector cell functions and thereby trigger mechanisms such as antibody-dependent cellular cytotoxicity (ADCC), antibody dependent cellular phagocytosis (ADCP), cytokine release, and/or antibody

dependent endocytosis, as well as NETosis (i.e. activation and release of NETs, Neutrophil extracellular traps) in the case of neutrophils. Antibody binding to an activating Fcγ receptor can also lead to an increase in certain activation markers, such as CD40, MHCII, CD38, CD80 and/or CD86.

The antibody molecule according to the invention that specifically binds FcγRIIb, binds to or interacts with this Fcγ receptor via the Fab region of the antibody, i.e. via the antigen-binding region on an antibody that binds to antigens which is composed of one constant and one variable domain of each of the heavy and the light chain. In particular, it binds to FcγRIIb present on an immune effector cell, and in particular to FcγRIIb present on the surface of an immune effector cell.

In some preferred embodiments, the antibody molecule according to the invention that specifically binds FcγRIIb can also bind to Fcγ receptors via its Fc region. In some embodiments, these are activatory or inhibitory Fcγ receptors. In some preferred embodiments, the antibody molecule may be an IgG1, IgG2, IgG3, or IgG4 type antibody molecule.

In some other embodiments, the antibody molecule that specifically binds FcγRIIb may be engineered for enhanced binding to Fcγ receptors via its Fc region, for example via afucosylation.

In some other embodiments, the antibody molecule according to the invention has reduced or impaired binding for Fcγ receptors via its Fc region. It is well known that aglycosylation of antibodies, specifically in the 297 position (such as one of the following mutations: N297A, N297Q or N297G), render both human and mouse IgG impaired for binding to FcγR. The antibody molecule may also have reduced or impaired binding if it lacks an Fc region. Furthermore, impaired or abrogated FcγR binding means that the modified format does not bind at all to FcγR or that it binds less strongly to FcγR than the unmodified antibody.

By "reduced binding to Fcγ receptors" (also referred to as "binding with reduced affinity") we include that the antibody molecule has reduced Fc mediated binding to Fcγ receptors, or in other words that the Fc region of the antibody molecule that specifically binds FcγRIIb binds to an activating Fcγ receptor with lower affinity than the Fc region of a normal human IgG1. The reduction in binding can be assessed using techniques such as surface plasmon resonance. In this context "normal IgG1" means a conventionally produced IgG1 with a non-mutated Fc region that has not been produced so as to alter its glycosylation. As a

reference for this "normal IgG1" it is possible to use rituximab produced in CHO cells without any modifications (Tipton et al, Blood 2015 125:1901-1909; rituximab is described in, for example, EP 0 605 442). Human IgG2 and human IgG4 are examples of antibody isotypes that bind with reduced affinity to Fcγ receptors compared with human IgG1. Therefore, antibodies based on human IgG2 and IgG4 have "reduced binding to Fcγ receptors" within the meaning of this term.

In some other embodiments, the antibody molecule according to the invention may not have an Fc region (and therefore cannot bind Fcγ receptors via an Fc region). Such fragments are discussed above and include Fv, Fab (also denoted F(ab)), $F(ab')_2$, F(ab'), or scFv. The antibody molecule according to the invention may also be a bi-specific antibody fragment, for example an scFv, Fab, or Fab´2, specific for FcgRIIB and an additional FcgR.

The therapeutic antibody molecule may then be an antibody molecule described in WO 2012/022985, WO 2015/173384 and/or WO 2019/138005. In some embodiments it is an antibody having the CDR sequences SEQ ID Nos: 83-88 as described in WO 2012/022985. In some embodiments, it is an antibody having a VH with Seq ID No: 12 and a VL with Seq ID No: 25 as described in WO 2012/022985.

In some embodiments, it is the antibody described in WO 2012/022985 as having a VH with Seq ID No: 12, a VL with Seq ID No: 25; a CH with Seq ID No: 1 and a CL with Seq ID No: 2 (corresponding to the antibody disclosed herein with a light chain having SEQ. ID. No: 1 and a heavy chain having SEQ. ID. No: 2). In some preferred embodiments, the antibody molecule of the invention has a light chain with SEQ ID No:1. In some additional embodiments, the antibody molecule of the invention has a heavy chain with SEQ ID No:2.

Light chain:

QSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYADDHRPSGVPDRFSG
SKSGTSASLAISGLRSEDEADYYCASWDDSQRAVIFGGGTKLTVLGQPKAAPSVTLFPPSSEELQAN
KATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQ
VTHEGSTVEKTVAPTECS (SEQ ID No:1)

Heavy chain:

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWMAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARELYDAFDIWGQGTLVTVSSASTKGPSVFPLAPSS
KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI

CNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV
SHEDPEVKFNWYVDGVEVHNAKTKPREEQY**N**STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI
EKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD
SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID No:2)

In some embodiments, the antibody molecule of the invention has a light chain with SEQ ID No:1 and a heavy chain with SEQ ID No:2 (this antibody is denoted as BI-1206).

As mentioned above, the antibody molecule of the invention, may in some embodiments, have reduced or impaired binding for Fcγ receptors via its Fc region. In this case, the therapeutic antibody molecule is an Fc receptor binding antibody and the modified format is an antibody having the same Fv variable sequence but having impaired or abrogated FcγR binding compared with the therapeutic antibody molecule.

In some embodiments, the therapeutic antibody is an Fc receptor binding anti-FcγRIIB antibody, and in some such cases, the modified format is anti-FcγRIIB antibody is the antibody having a light chain with SEQ ID No:1 and a heavy chain with SEQ ID No:195.

A modified format of BI-1206 is format wherein the glycosylation site at N297 (marked in bold above in SEQ ID NO:2) is mutated to a Q (marked in bold below), i.e. an N297Q mutation, resulting in the following heavy chain:

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWMAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARELYDAFDIWGQGTLVTVSSASTKGPSVFPLAPSS
KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI
CNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV
SHEDPEVKFNWYVDGVEVHNAKTKPREEQY**Q**STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI
EKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD
SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ. ID. No:195)

The CDR regions of the light chain of SEQ ID No:1, and the CDR regions of the heavy chain of SEQ ID No:2 or 195, are shown below:

Heavy chain CDRs:

CDRH1:	SYGMH	(SEQ ID No:196)
CDRH2:	VISYDGSNKYYADSVKG	(SEQ ID No:197)
CDRH3:	ELYDAFDI	(SEQ ID No:198)

Light chain CDRs:

CDRL1:	TGSSSNIGAGYDVH	(SEQ ID No:199)
CDRL2:	ADDHRPS	(SEQ ID No:200)
CDRL3:	ASWDDSQRAVI	(SEQ ID No:201)

Accordingly, in some embodiments, the antibody molecule of the invention comprises one or more of the CDR sequences of SEQ ID No:196-201. For example, the antibody molecule comprises two or more, or three or more, or four or more, or five or more, or all six of the CDR sequences of SEQ ID No:196-201. For example, the antibody molecule may comprise: one or more, or two or more, or three of the light chain CDR regions (i.e. SEQ ID No:199, 200, and 201); and/or one or more, or two or more, or three of the heavy chain CDR regions (i.e. SEQ ID No:196, 197, and 198).

Preferably, the antibody molecule of the invention comprises the following constant regions (CH and CL):

IgG1-CH [SEQ ID No:202]:
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS
VVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM
ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNG
QPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

λ-CL [SEQ ID No:203]:
QPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAA
SSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

Thus, in a preferred embodiment, the antibody molecule of the invention comprises:

- A light chain with SEQ ID No:1, and a heavy chain with SEQ ID No:2, and constant regions with SEQ ID No:202 and 203; or
- A light chain with SEQ ID No:1, and a heavy chain with SEQ ID No:195, and constant regions with SEQ ID No:202 and 203.

In alternative embodiments, the antibody molecule that specifically binds FcγRIIb is an antibody as described in published PCT patent applications WO 2012/022985, WO 2015/173384 and/or WO 2019/138005.

The antibody that specifically binds FcγRIIb may comprise one or more sequences of the following clones:

Antibody clone: 1A01

1A01-VH [SEQ ID NO: 3]
EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYYMNWIRQTPGKGLEWVSLIGWDGGSTYYADSVK
GRFTISRDNSENTLYLQMNSLRAEDTAVYYCARAYSGYELDYWGQGTLVTVSS

1A01-VL [SEQ ID NO: 27]
QSVLTQPPSASGTPGQRVTISCSGSSSNIGNNAVNWYQQLPGTAPKLLIYDNNNRPSGVPDRFSGS
KSGTSASLAISGLRSEDEADYYCAAWDDSLNASIFGGGTKLTVLG

CDR regions

CDRH1: DYYMN [SEQ ID NO: 51]
CDRH2: LIGWDGGSTYYADSVKG [SEQ ID NO: 52]
CDRH3: AYSGYELDY [SEQ ID NO: 53]
CDRL1: SGSSSNIGNNAVN [SEQ ID NO: 54]
CDRL2: DNNNRPS [SEQ ID NO: 55]
CDRL3: AAWDDSLNASI [SEQ ID NO: 56]

Antibody clone: 1B07

1B07-VH [SEQ ID NO: 4]
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAFTRYDGSNKYYADSVR
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARENIDAFDVWGQGTLVTVSS

1B07-VL [SEQ ID NO: 28]
QSVLTQPPSASGTPGQRVTISCSGSSSNIGNNAVNWYQQLPGTAPKLLIYDNQQRPSGVPDRFSGS
KSGTSASLAISGLRSEDEADYYCEAWDDRLFGPVFGGGTKLTVLG

CDR regions

CDRH1: SYGMH [SEQ ID NO: 57]
CDRH2: FTRYDGSNKYYADSVRG [SEQ ID NO: 58]
CDRH3: ENIDAFDV [SEQ ID NO: 59]
CDRL1: SGSSSNIGNNAVN [SEQ ID NO: 60]

CDRL2: DNQQRPS [SEQ ID NO: 61]
CDRL3: WDDRLFGPV [SEQ ID NO: 62]

Antibody clone: 1C04

1C04-VH [SEQ ID NO: 5]
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSISDSGAGRYYADSVE
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARTHDSGELLDAFDIWGQGTLVTVSS

1C04-VL [SEQ ID NO: 29]
QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNHVLWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGS
KSGTSASLAISGLRSEDEADYYCAAWDDSLNGWVFGGGTKLTVLG

CDR regions

CDRH1: SYAMS [SEQ ID NO: 63]
CDRH2: SISDSGAGRYYADSVEG [SEQ ID NO: 64]
CDRH3: THDSGELLDAFDI [SEQ ID NO: 65]
CDRL1: SGSSSNIGSNHVL [SEQ ID NO: 66]
CDRL2: GNSNRPS [SEQ ID NO: 67]
CDRL3: AAWDDSLNGWV [SEQ ID NO: 68]

Antibody clone: 1E05

1E05-VH [SEQ ID NO: 6]
EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYAMNWVRQVPGKGLEWVAVISYDGSNKNYVDSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARNFDNSGYAIPDAFDIWGQGTLVTVSS

1E05-VL [SEQ ID NO: 30]
QSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYDNNSRPSGVPDRFSG
SKSGTSASLAISGLRSEDEADYYCAAWDDSLGGPVFGGGTKLTVLG

CDR regions

CDRH1: TYAMN [SEQ ID NO: 69]
CDRH2: VISYDGSNKNYVDSVKG [SEQ ID NO: 70]
CDRH3: NFDNSGYAIPDAFDI [SEQ ID NO: 71]
CDRL1: TGSSSNIGAGYDVH [SEQ ID NO: 72]

CDRL2: DNNSRPS [SEQ ID NO: 73]
CDRL3: AAWDDSLGGPV [SEQ ID NO: 74]

Antibody clone: 2A09

2A09-VH [SEQ ID NO: 7]
EVQLLESGGGLVQPGGSLRLSCAASGFTFSNAWMSWVRQAPGKGLEWVAYISRDADITHYPASVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCTTGFDYAGDDAFDIWGQGTLVTVSS

2A09-VL [SEQ ID NO: 31]
QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNAVNWYQQLPGTAPKLLIYGNSDRPSGVPDRFSGS
KSGTSASLAISGLRSEDEADYYCAAWDDSLNGRWVFGGGTKLTVLG

CDR regions

CDRH1: NAWMS [SEQ ID NO: 75]
CDRH2: YISRDADITHYPASVKG [SEQ ID NO: 76]
CDRH3: GFDYAGDDAFDI [SEQ ID NO: 77]
CDRL1: SGSSSNIGSNAVN [SEQ ID NO: 78]
CDRL2: GNSDRPS [SEQ ID NO: 79]
CDRL3: AAWDDSLNGRWV [SEQ ID NO: 80]

Antibody clone: 2B08

2B08-VH [SEQ ID NO: 8]
EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYYMSWVRQAPGKGLEWVALIGHDGNNKYYLDSLE
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARATDSGYDLLYWGQGTLVTVSS

2B08-VL [SEQ ID NO: 32]
QSVLTQPPSASGTPGQRVTISCSGSSSNIGNNAVNWYQQLPGTAPKLLIYYDDLLPSGVPDRFSGS
KSGTSASLAISGLRSEDEADYYCTTWDDSLSGVVFGGGTKLTVLG

CDR regions

CDRH1: DYYMS [SEQ ID NO: 81]
CDRH2: LIGHDGNNKYYLDSLEG [SEQ ID NO: 82]
CDRH3: ATDSGYDLLY [SEQ ID NO: 83]
CDRL1: SGSSSNIGNNAVN [SEQ ID NO: 84]

CDRL2: YDDLLPS [SEQ ID NO: 85]
CDRL3: TTWDDSLSGVV [SEQ ID NO: 86]

Antibody clone: 2E08

2E08-VH [SEQ ID NO: 9]
EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYYMSWIRQAPGKGLEWVSAIGFSDDNTYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAGGDGSGWSFWGQGTLVTVSS

2E08-VL [SEQ ID NO: 33]
QSVLTQPPSASGTPGQRVTISCSGSSSNIGNNAVNWYQQLPGTAPKLLIYDNNKRPSGVPDRFSGS
KSGTSASLAISGLRSEDEADYYCATWDDSLRGWVFGGGTKLTVLG

CDR regions

CDRH1: DYYMS [SEQ ID NO: 87]
CDRH2: AIGFSDDNTYYADSVKG [SEQ ID NO: 88]
CDRH3: GDGSGWSF [SEQ ID NO: 89]
CDRL1: SGSSSNIGNNAVN [SEQ ID NO: 90]
CDRL2: DNNKRPS [SEQ ID NO: 91]
CDRL3: ATWDDSLRGWV [SEQ ID NO: 92]

Antibody clone: 5C04

5C04-VH [SEQ ID NO: 10]
EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREWRDAFDIWGQGTLVTVSS

5C04-VL [SEQ ID NO: 34]
QSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYSDNQRPSGVPDRFSG
SKSGTSASLAISGLRSEDEADYYCAAWDDSLSGSWVFGGGTKLTVLG

CDR regions

CDRH1: NYGMH [SEQ ID NO: 93]
CDRH2: VISYDGSNKYYADSVKG [SEQ ID NO: 94]
CDRH3: WRDAFDI [SEQ ID NO: 95]
CDRL1: TGSSSNIGAGYDVH [SEQ ID NO: 96]

CDRL2: SDNQRPS [SEQ ID NO: 97]
CDRL3: AAWDDSLSGSWV [SEQ ID NO: 98]

Antibody clone: 5C05

5C05-VH [SEQ ID NO: 11]
EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARENFDAFDVWGQGTLVTVSS

5C05-VL [SEQ ID NO: 35]
QSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYSNSQRPSGVPDRFSG
SKSGTSASLAISGLRSEDEADYYCAAWDDSLNGQVVFGGGTKLTVLG

CDR regions

CDRH1: TYGMH [SEQ ID NO: 99]
CDRH2: VISYDGSNKYYADSVKG [SEQ ID NO: 100]
CDRH3: ENFDAFDV [SEQ ID NO: 101]
CDRL1: TGSSSNIGAGYDVH [SEQ ID NO: 102]
CDRL2: SNSQRPS [SEQ ID NO: 103]
CDRL3: AAWDDSLNGQVV [SEQ ID NO: 104]

Antibody clone: 5D07

5D07-VH [SEQ ID NO: 12]
EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYGMHWVRQAPGKGLEWVAVIAYDGSKKDYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREYRDAFDIWGQGTLVTVSS

5D07-VL [SEQ ID NO: 36]
QSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYGNSNRPSGVPDRFSG
SKSGTTASLAISGLRSEDEADYYCAAWDDSVSGWMFGGGTKLTVLG

CDR regions

CDRH1: TYGMH [SEQ ID NO: 105]
CDRH2: VIAYDGSKKDYADSVKG [SEQ ID NO: 106]
CDRH3: EYRDAFDI [SEQ ID NO: 107]
CDRL1: TGSSSNIGAGYDVH [SEQ ID NO: 108]

CDRL2: GNSNRPS [SEQ ID NO: 109]
CDRL3: AAWDDSVSGWM [SEQ ID NO: 110]

Antibody clone: 5E12

5E12-VH [SEQ ID NO: 13]
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGINKDYADSMK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARERKDAFDIWGQGTLVTVSS

5E12-VL [SEQ ID NO: 37]
QSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYSNNQRPSGVPDRFSG
SKSGTSASLAISGLRSEDEADYYCATWDDSLNGLVFGGGTKLTVLG

CDR regions

CDRH1: SYGMH [SEQ ID NO: 111]
CDRH2: VISYDGINKDYADSMKG [SEQ ID NO: 112]
CDRH3: ERKDAFDI [SEQ ID NO: 113]
CDRL1: TGSSSNIGAGYDVH [SEQ ID NO: 114]
CDRL2: SNNQRPS [SEQ ID NO: 115]
CDRL3: ATWDDSLNGLV [SEQ ID NO: 116]

Antibody clone: 5G08

5G08-VH [SEQ ID NO: 14]
EVQLLESGGGLVQPGGSLRLSCAASGFTFNNYGMHWVRQAPGKGLEWVAVISYDGSNRYYADSVK
GRFTMSRDNSKNTLYLQMNSLRAEDTAVYYCARDRWNGMDVWGQGTLVTVSS

5G08-VL [SEQ ID NO: 38]
QSVLTQPPSASGTPGQRVTISCSGSSSNIGAGYDVHWYQQLPGTAPKLLIYANNQRPSGVPDRFSG
SKSGTSASLAISGLRSEDEADYYCAAWDDSLNGPWVFGGGTKLTVLG

CDR regions

CDRH1: NYGMH [SEQ ID NO: 117]
CDRH2: VISYDGSNRYYADSVKG [SEQ ID NO: 118]
CDRH3: DRWNGMDV [SEQ ID NO: 119]
CDRL1: SGSSSNIGAGYDVH [SEQ ID NO: 120]

CDRL2: ANNQRPS [SEQ ID NO: 121]
CDRL3: AAWDDSLNGPWV [SEQ ID NO: 122]

Antibody clone: 5H06

5H06-VH [SEQ ID NO: 15]
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSDTAYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDHSVIGAFDIWGQGTLVTVSS

5H06-VL [SEQ ID NO: 39]
QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIYDNNKRPSGVPDRFSGS
KSGTSASLAISGLRSEDEADYYCSSYAGSNNVVFGGGTKLTVLG

CDR regions

CDRH1: SYGMH [SEQ ID NO: 123]
CDRH2: VISYDGSDTAYADSVKG [SEQ ID NO: 124]
CDRH3: DHSVIGAFDI [SEQ ID NO: 125]
CDRL1: SGSSSNIGSNTVN [SEQ ID NO: 126]
CDRL2: DNNKRPS [SEQ ID NO: 127]
CDRL3: SSYAGSNNVV [SEQ ID NO: 128]

Antibody clone: 6A09

6A09-VH [SEQ ID NO: 16]
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVTSYDGNTKYYANSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREDCGGDCFDYWGQGTLVTVSS

6A09-VL [SEQ ID NO: 40]
QSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYGNSNRPSGVPDRFSG
SKSGTSASLAISGLRSEDEADYYCAAWDDSLNEGVFGGGTKLTVLG

CDR regions

CDRH1: SYGMH [SEQ ID NO: 129]
CDRH2: VTSYDGNTKYYANSVKG [SEQ ID NO: 130]
CDRH3: EDCGGDCFDY [SEQ ID NO: 131]

CDRL1: TGSSSNIGAGYDVH [SEQ ID NO: 132]
CDRL2: GNSNRPS [SEQ ID NO: 133]
CDRL3: AAWDDSLNEGV [SEQ ID NO: 134]

Antibody clone: 6B01

6B01-VH [SEQ ID NO: 17]
EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDQLGEAFDIWGQGTLVTVSS

6B01-VL [SEQ ID NO: 41]
QSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYDNNKRPSGVPDRFSG
SKSGTSASLAISGLRSEDEADYYCATWDDSLSGPVFGGGTKLTVLG

CDR regions

CDRH1: NYGMH [SEQ ID NO: 135]
CDRH2: VISYDGSNKYYADSVKG [SEQ ID NO: 136]
CDRH3: DQLGEAFDI [SEQ ID NO: 137]
CDRL1: TGSSSNIGAGYDVH [SEQ ID NO: 138]
CDRL2: DNNKRPS [SEQ ID NO: 139]
CDRL3: ATWDDSLSGPV [SEQ ID NO: 140]

Antibody clone: 6C11

6C11-VH [SEQ ID NO: 18]
EVQLLESGGGLVQPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWVSAISGSGSSTYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAGGDIDYFDYWGQGTLVTVSS

6C11-VL [SEQ ID NO: 42]
QSVLTQPPSASGTPGQRVTISCTGSSSNFGAGYDVHWYQQLPGTAPKLLIYENNKRPSGVPDRFSG
SKSGTSASLAISGLRSEDEADYYCAAWDDSLNGPVFGGGTKLTVLG

CDR regions

CDRH1: DYGMS [SEQ ID NO: 141]
CDRH2: AISGSGSSTYYADSVKG [SEQ ID NO: 142]
CDRH3: GDIDYFDY [SEQ ID NO: 143]

CDRL1: TGSSSNFGAGYDVH [SEQ ID NO: 144]
CDRL2: ENNKRPS [SEQ ID NO: 145]
CDRL3: AAWDDSLNGPV [SEQ ID NO: 146]

Antibody clone: 6C12

6C12-VH [SEQ ID NO: 19]
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARERRDAFDIWGQGTLVTVSS

6C12-VL [SEQ ID NO: 43]
QSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYSDNQRPSGVPDRFSG
SKSGTSASLAISGLRSEDEADYYCATWDSDTPVFGGGTKLTVLG

CDR regions

CDRH1: SYGMH [SEQ ID NO: 147]
CDRH2: VISYDGSNKYYADSVKG [SEQ ID NO: 148]
CDRH3: ERRDAFDI [SEQ ID NO: 149]
CDRL1: TGSSSNIGAGYDVH [SEQ ID NO: 150]
CDRL2: SDNQRPS [SEQ ID NO: 151]
CDRL3: ATWDSDTPV [SEQ ID NO: 152]

Antibody clone: 6D01

6D01-VH [SEQ ID NO: 20]
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAMYYCARDHSAAGYFDYWGQGTLVTVSS

6D01-VL [SEQ ID NO: 44]
QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIYGNSIRPSGGPDRFSGS
KSGTSASLAISGLRSEDEADYYCASWDDSLSSPVFGGGTKLTVLG

CDR regions

CDRH1: SYGMH [SEQ ID NO: 153]
CDRH2: VISYDGSNKYYADSVKG [SEQ ID NO: 154]
CDRH3: DHSAAGYFDY [SEQ ID NO: 155]

CDRL1: SGSSSNIGSNTVN [SEQ ID NO: 156]
CDRL2: GNSIRPS [SEQ ID NO: 157]
CDRL3: ASWDDSLSSPV [SEQ ID NO: 158]

Antibody clone: 6G03

6G03-VH [SEQ ID NO: 21]
EVQLLESGGGLVQPGGSLRLSCAASGFTFGSYGMHWVRQAPGKGLEWVSGISWDSAIIDYAGSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDEAAAGAFDIWGQGTLVTVSS

6G03-VL [SEQ ID NO: 45]
QSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYGNTDRPSGVPDRFSG
SKSGTSASLAISGLRSEDEADYYCAAWDDSLSGPVVFGGGTKLTVLG

CDR regions

CDRH1: SYGMH [SEQ ID NO: 159]
CDRH2: GISWDSAIIDYAGSVKG [SEQ ID NO: 160]
CDRH3: DEAAAGAFDI [SEQ ID NO: 161]
CDRL1: TGSSSNIGAGYDVH [SEQ ID NO: 162]
CDRL2: GNTDRPS [SEQ ID NO: 163]
CDRL3: AAWDDSLSGPVV [SEQ ID NO: 164]

Antibody clone: 6G08

6G08-VH [SEQ ID NO: 22]
EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYGISWVRQAPGKGLEWVSGISGSGGNTYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCASSVGAYANDAFDIWGQGTLVTVSS

6G08-VL [SEQ ID NO: 46]
QSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYGDTNRPSGVPDRFSG
SKSGTSASLAISGLRSEDEADYYCAAWDDSLNGPVFGGGTKLTVLG

CDR regions

CDRH1: SYGIS [SEQ ID NO: 165]
CDRH2: GISGSGGNTYYADSVKG [SEQ ID NO: 166]
CDRH3: SVGAYANDAFDI [SEQ ID NO: 167]

CDRL1: TGSSSNIGAGYDVH [SEQ ID NO: 168]
CDRL2: GDTNRPS [SEQ ID NO: 169]
CDRL3: AAWDDSLNGPV [SEQ ID NO: 170]

Antibody clone: 6G11

6G11-VH [SEQ ID NO: 23]
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWMAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARELYDAFDIWGQGTLVTVSS

6G11-VL [SEQ ID NO: 47]
QSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYADDHRPSGVPDRFSG
SKSGTSASLAISGLRSEDEADYYCASWDDSQRAVIFGGGTKLTVLG

CDR regions

CDRH1: SYGMH [SEQ ID NO: 171]
CDRH2: VISYDGSNKYYADSVKG [SEQ ID NO: 172]
CDRH3: ELYDAFDI [SEQ ID NO: 173]
CDRL1: TGSSSNIGAGYDVH [SEQ ID NO: 174]
CDRL2: ADDHRPS [SEQ ID NO: 175]
CDRL3: ASWDDSQRAVI [SEQ ID NO: 176]

Antibody clone: 6H08

6H08-VH [SEQ ID NO: 24]
EVQLLESGGGLVQPGGSLRLSCAASGFTFNNYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISKDNSKNTLYLQMNSLRAEDTAVYYCAREYKDAFDIWGQGTLVTVSS

6H08-VL [SEQ ID NO: 48]
QSVLTQPPSASGTPGQRVTISCTGSSSNIGSNTVNWYQQLPGTAPKLLIYDNNKRPSGVPDRFSGS
KSGTSASLAISGLRSEDEADYYCQAWGTGIRVFGGGTKLTVLG

CDR regions

CDRH1: NYGMH [SEQ ID NO: 177]
CDRH2: VISYDGSNKYYAD SVKG [SEQ ID NO: 178]
CDRH3: EYKDAFDI [SEQ ID NO: 179]

CDRL1: TGSSSNIGSNTVN [SEQ ID NO: 180]
CDRL2: DNNKRPS [SEQ ID NO: 181]
CDRL3: QAWGTGIRV [SEQ ID NO: 182]

Antibody clone: 7C07

7C07-VH [SEQ ID NO: 25]
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYYADSVK
GRFTISRDNSQNTLYLQMNSLRAEDTAVYYCAREFGYIILDYWGQGTLVTVSS

7C07-VL [SEQ ID NO: 49]
QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIYRDYERPSGVPDRFSGS
KSGTSASLAISGLRSEDEADYYCMAWDDSLSGVVFGGGTKLTVLG

CDR regions

CDRH1: SYGMH [SEQ ID NO: 183]
CDRH2: VISYDGSNKYYADSVKG [SEQ ID NO: 184]
CDRH3: EFGYIILDY [SEQ ID NO: 185]
CDRL1: SGSSSNIGSNTVN [SEQ ID NO: 186]
CDRL2: RDYERPS [SEQ ID NO: 187]
CDRL3: MAWDDSLSGVV [SEQ ID NO: 188]

Antibody clone: 4B02

4B02-VH [SEQ ID NO: 26]
EVQLLESGGGLVQPGGSLRLSCAASGFTFSNHGMHWVRQAPGKGLEWVAVISYDGTNKYYADSVR
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARETWDAFDVWGQGTLVTVSS

4B02-VL [SEQ ID NO: 50]
QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNNANWYQQLPGTAPKLLIYDNNKRPSGVPDRFSGS
KSGTSASLAISGLRSEDEADYYCQAWDSSTVVFGGGTKLTVLG

CDR regions

CDRH1: NHGMH [SEQ ID NO: 189]
CDRH2: VISYDGTNKYYADSVRG [SEQ ID NO: 190]
CDRH3: ETWDAFDV [SEQ ID NO: 191]

CDRL1: SGSSSNIGSNNAN [SEQ ID NO: 192]
CDRL2: DNNKRPS [SEQ ID NO: 193]
CDRL3: QAWDSSTVV [SEQ ID NO: 194]

In some embodiments the antibody molecule that specifically binds FcγRIIb is a human antibody.

In some embodiments, the antibody molecule that specifically binds FcγRIIb is an antibody of human origin, i.e. an originally human antibody that has been modified as described herein.

In some embodiments, the antibody molecule that specifically binds FcγRIIb is a humanized antibody, i.e. an originally non-human antibody that has been modified to increase its similarity to a human antibody. The humanized antibodies may, for example, be murine antibodies or llama antibodies.

As discussed above, the first antibody may be a monoclonal antibody or an antibody molecule of monoclonal origin.

It is well known that an antibody specifically binds to or interacts with a defined target molecule or antigen. That is to say, the antibody preferentially and selectively binds its target and not a molecule which is not a target.

Methods of assessing protein binding are known to the person skilled in biochemistry and immunology. It would be appreciated by the skilled person that those methods could be used to assess binding of an antibody to a target and/or binding of the Fc region of an antibody to an Fc receptor; as well as the relative strength, or the specificity, or the inhibition, or prevention, or reduction in those interactions. Examples of methods that may be used to assess protein binding are, for example, immunoassays, BIAcore, western blots, radioimmunoassay (RIA) and enzyme-linked immunosorbent assays (ELISAs) (See Fundamental Immunology Second Edition, Raven Press, New York at pages 332-336 (1989) for a discussion regarding antibody specificity).

Accordingly, by "antibody molecule that specifically binds" we include that the antibody molecule specifically binds a target but does not bind to non-target, or binds to a non-target more weakly (such as with a lower affinity) than the target.

We also include the meaning that the antibody specifically binds to the target at least two-fold more strongly, or at least five-fold more strongly, or at least 10-fold more strongly, or at least 20-fold more strongly, or at least 50-fold more strongly, or at least 100-fold more strongly, or at least 200-fold more strongly, or at least 500-fold more strongly, or at least than about 1000-fold more strongly than to a non-target.

Additionally, we include the meaning that the antibody specifically binds to the target if it binds to the target with a K_d of at least about 10^{-1} K_d, or at least about 10^{-2} K_d, or at least about 10^{-3} K_d, or at least about 10^{-4} K_d, or at least about 10^{-5} K_d, or at least about 10^{-6} K_d, or at least about 10^{-7} K_d, or at least about 10^{-8} K_d, or at least about 10^{-9} K_d, or at least about 10^{-10} K_d, or at least about 10^{-11} K_d, or at least about 10^{-12} K_d, or at least about 10^{-13} K_d, or at least about 10^{-14} K_d, or at least about 10^{-15} K_d.

As discussed above, the system, combination, method or use of the present invention is for improving tolerability of an antibody molecule that specifically binds to FcγRIIb in a subject. It is well known that the administration of therapeutic antibodies may be associated with tolerability issues. In some embodiments, these issues may be associated with intravenous administration of said antibody.

The term "tolerability" as used herein refers to the degree to which adverse effects of a therapeutic agent can be tolerated by a subject. By "adverse effect" we include any effect caused by the therapeutic agent, either directly or indirectly, that is not the desired therapeutic effect, or any other beneficial effect attributable to the therapeutic agent, either directly or indirectly.

By "improving tolerability" we include preventing or mitigating tolerability issues associated with administration of the antibody molecule. In another definition, we include reducing or preventing adverse effects associated with administration of the antibody molecule.

The term "tolerability issue" as used herein encompasses different types of adverse effects that may occur in connection with administration, and in particular intravenous administration, of the antibody molecule to a human. These may be, for example, infusion related reactions (IRRs), cytokine release syndrome, thrombocytopenia, hepatic toxicities such as elevated liver enzymes, fever, hypotension and/or dermatological toxicities, including rashes such as urticaria. Herein these different tolerability issues are defined in the way they are defined in the Common Terminology Criteria for Adverse Events (CTCAE)

version 5.0 (published by the US Department of Health and Human Services, 27 November 2017), as further described below.

Tolerability issues may be of different grades, i.e. of different severity for the subjects experiencing them. In some cases, they lead to discomfort for the subject, while in others they may cause severe problems that may prevent continued treatment with the therapeutic antibody molecule. In worse cases, the tolerability issues may even lead to death of the subject.

The tolerability issues that may be predicted, prevented and/or mitigated as described herein are adverse events that occur in connection with intravenous administration of the therapeutic antibody molecule to a subject, i.e. immediately when the therapeutic antibody molecule is administered, such as within a few minutes up to a few hours or within 24 hours from administration of the therapeutic antibody molecule to the subject. In many cases, the first tolerability issues are observed within less 30 minutes.

In some preferred embodiments, it is of particular interest to improve the tolerability of the antibody that specifically binds to FcγRIIb specifically in relation to IRRs. In some embodiments, these antibodies may be more likely to cause or lead to IRRs of varying severities in a human subject. It is therefore advantageous to prevent or mitigate such IRRs, as they improve the experience of the subject and also allow the therapeutic antibody to be administered for longer and at higher doses before needing to stop treatment due to tolerability issues (if this is needed at all).

In some cases, it may be of interest to prevent in particular thrombocytopenia and/or hepatic toxicities.

The IRR that may be prevented or mitigated as described herein and/or that may be predicted with the method described herein may be any IRR. The adverse event denoted "Infusion related reaction" in the CTCAE version 5.0 is used for disorders characterized by adverse reaction to the infusion of pharmacological or biological substances; belonging to the group of "Injury, poisoning and procedural complications". The five grades identified in the CTCAE are the following:

1) Mild transient reaction; infusion interruption not indicated; intervention not indicated

2) Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours
3) Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae
4) Life-threatening consequences; urgent intervention indicated
5) Death.

Based on the above classifiers, the person skilled in the art would be able to identify an infusion related reaction in a subject following administration of the antibody molecule defined herein, for example by observing a subject for the symptoms of an IRR. These may include, in some embodiments, pruritus, urticaria, fever, rigors/chills, diaphoresis, bronchospasms, nausea, muscle pain, and cardiovascular collapse

In some preferred embodiments, IRRs associated with the antibody molecule described herein are reduced or completely prevented by the dosage regimen described herein.

The adverse event denoted "Cytokine release syndrome" in the CTCAE version 5.0 is used for disorders characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines, belonging to the group of "Immune system disorders". The five grades identified in the CTCAE are the following:

1) Fever with or without constitutional symptoms
2) Hypotension responding to fluids; hypoxia responding to <40% O_2
3) Hypotension managed with one pressor; hypoxia requiring ≥ 40% O_2
4) Life-threatening consequences; urgent intervention indicated
5) Death

The adverse event denoted "Platelet count decreased" (i.e. thrombocytopenia) in the CTCAE version 5.0 is used for findings based on laboratory test results that indicate a decrease in number of platelets in a blood specimen, belonging to the group of "Investigations". The five grades identified in the CTCAE are the following:

1) <LLN – 75,000/mm3; <LLN – 75.0 x 10e9 /L
2) <75,000 – 50,000/mm3; <75.0 – 50.0 x 10e9 /L
3) <50,000 – 25,000/mm3; <50.0 – 25.0 x 10e9 /L
4) <25,000/mm3; <25.0 x 10e9 /L

5) –

The associated toxicity may also be a hepatic adverse event or hepatic toxicities. Examples of such toxicities are an elevation of one or both of the two enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Like thrombocytopenia, the adverse events denoted "Aspartate aminotransferase increased" and "Alanine aminotransferase increased" in the CTCAE version 5.0 belong to the group of "Investigations". Increased AST or ALT, respectively, is a finding based on laboratory test results that indicate an increase in the level of AST (or SGOT) and ALT (or SGPT), respectively, in a blood specimen. The five grades identified in the CTCAE both for increased AST and increased ALT are the following:

1) >ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal
2) >3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal
3) >5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal
4) >20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
5) -.

The adverse event denoted "Fever" in the CTCAE version 5.0 is used for disorders characterized by elevation of the body's temperature above the upper limit of normal, belonging to the group of "General disorders and administration site conditions". The five grades identified in the CTCAE are the following:

1) 38.0 - 39.0 °C
2) >39.0 - 40.0 °C
3) >40.0 °C for ≤24 hours
4) >40.0 °C for >24 hours
5) Death.

The adverse event denoted "Hypotension" in the CTCAE version 5.0 is used for disorders characterized by a blood pressure that is below the normal expected for an individual in a given environment, belonging to the group of "Vascular disorders". The five grades identified in the CTCAE are the following:

1) Asymptomatic, intervention not indicated

2) Non-urgent medical intervention indicated
3) Medical intervention indicated; hospitalization indicated
4) Life-threatening consequences and urgent intervention indicated
5) Death.

The adverse event denoted "Urticaria" in the CTCAE version 5.0 is used for disorders characterized by an itchy skin eruption characterized by wheals with pale interiors and well-defined red margins, belonging to the group of "Skin and subcutaneous tissue disorders". The five grades identified in the CTCAE are the following:

1) Urticarial lesions covering <10% BSA; topical intervention indicated
2) Urticarial lesions covering 10 - 30% BSA; oral intervention indicated
3) Urticarial lesions covering >30% BSA; IV intervention indicated
4) -
5) -.

In some other embodiments, the improvement in tolerability is associated with the reduction or prevention of adverse effects observed upon administration of the antibody. These may be effects attributed either directly or indirectly to administration of the antibody, in some embodiments.

In some embodiments, the above mentioned tolerability issues and/or adverse effects cause changes in several subject observations outside of normal levels. In some embodiments, these observations include one or more of the following: body temperature; platelet count; blood levels of liver enzymes (e.g. alanine aminotransferase (ALAT) and/or aspartate aminotransferase (ASAT)); blood levels of cytokines (e.g. IL-6, TNF-α, IL-8, IFN-γ, MIP-1β, IL-10, IL-4, IL-1b, IL-2, IL-12).

The normal levels of each of the above measurements are typically defined as follows:

- Body temperature: from 36.1°C to 37.9°C;
- Platelet count: from 145 x 10^9 to 400 x 10^9 per litre;
- Blood level of ALAT: from 0 to 1.09 µkat/L, 16-63 U/L;
- Blood level of ASAT: from 0 to 0.759 µkat/L, 15-37 U/L;
- Blood level IL-6: from 0.16 to 27.2 pg/ml, with a median value of 0.47 pg/ml.

In some embodiments, the system, combination, method or use of the present invention reduces changes in each of the above parameters. By "reduces changes", we mean that

the degree of change in each of the above measurements is less when the therapeutic system or dosage regime of the invention is used, compared to when a single dose, equivalent to the sum of the first and second doses (in mg) of the invention as defined herein, of the antibody molecule is administered. Preferably these changes are reduced to within acceptable levels.

By "acceptable levels" we mean that the above measurements, after treatment with the second dose of the antibody molecule, remain within the normal ranges as defined above. In some embodiments, the values of the above measurements remain within the normal ranges defined above after administration of the second dose of the antibody molecule. In some other embodiments, by "acceptable levels" we include that the clinical grading of the IRR (as defined in the art and herein using the CTCAE scale) is reduced to at least grade 2. In some preferred embodiments, the grading of the IRR is reduced to grade 1. As discussed herein, the skilled person will be aware of how to grade an IRR according to the CTCAE scale.

In some preferred embodiments, these values remain within normal levels, or are changed within acceptable levels, for at least 24 hours after administration of the second dose of the antibody molecule.

As discussed above, the invention provides a system, combination, method, or use, in which a corticosteroid is administered to the subject before the first dose of the antibody molecule. Corticosteroids are a well-known class of steroid hormones that have been used for a wide variety of clinical applications.

As shown in Example 1, corticosteroids have surprisingly been found to provide a protective effect against infusion related reactions associated with administration of the therapeutic antibody of the invention. As also shown in Example 2, other compounds that have been previously used to treat IRRs in the clinic did not provide a protective effect (or simply provided an additive effect). These other compounds that have been commonly used to treat IRRs include but are not limited to the following: anti-histamines (e.g. H1 and H2 blockers), anti-PAF, anti-IL-6R, and a leukotriene receptor antagonist (e.g. montelukast). This renders the protective effect of corticosterioids alone surprising in the context of the present invention, as none of these other commonly used therapies provided a similar protective effect.

In preferred embodiments of the system, combination, method or use of the present invention, the corticosteroid is administered to the subject at a time point from 10 minutes

to 48 hours before the first dose of the antibody molecule that specifically binds to FcyRIIb. More preferably, the corticosteroid is administered to the subject at a time point from 10 minutes to 24 hours before the first dose of the antibody molecule that specifically binds to FcyRIIb.

Thus, in embodiments of the invention, the corticosteroid is administered at a time point of about 10 minutes, or about 20 minutes, or about 30 minutes, or about 40 minutes, or about 50 minutes, or about 1 hour, or about 2 hours, or about 3 hours, or about 4 hours, or about 5 hours, or about 6 hours, or about 7 hours, or about 8 hours, or about 9 hours, or about 10 hours, or about 11 hours, or about 12 hours, or about 13 hours, or about 14 hours, or about 15 hours, or about 16 hours, or about 17 hours, or about 18 hours, or about 19 hours, or about 20 hours, or about 21 hours, or about 22 hours, or about 23 hours, or about 24 hours, or about 25 hours, or about 26 hours, or about 27 hours, or about 28 hours, or about 29 hours, or about 30 hours, or about 31 hours, or about 32 hours, or about 33 hours, or about 34 hours, or about 35 hours, or about 36 hours, or about 37 hours, or about 38 hours, or about 39 hours, or about 40 hours, or about 41 hours, or about 42 hours, or about 43 hours, or about 44 hours, or about 45 hours, or about 46 hours, or about 47 hours, or about 48 hours, before the first dose of the antibody molecule that specifically binds to FcyRIIb.

In embodiments of the invention, the corticosteroid may be administered in more than one dose before the first dose of the antibody molecule that binds specifically to FcyRIIb. For instance, the corticosteroid may be administered in two doses, three doses, four doses, five doses, six doses, seven doses, eight doses, nine doses, ten doses, eleven doses, twelve doses, or more than twelve doses, before the first dose of the antibody molecule that binds specifically to FcyRIIb.

In some additional or alternative embodiments, when more than one dose of the corticosteroid is administered, the corticosterioid may be administered both before and after the first dose of the antibody molecule that binds specifically to FcyRIIb (but before the second dose of the antibody that binds specifically to FcyRIIb). At least one dose of the corticosterioid will be administered before the first dose of the antibody molecule, but the other, subsequent, corticosteroid doses described will be administered after the first dose of the antibody molecule, and may be distributed between the antibody doses in any order.

In these embodiments, the corticosteroid administration before the second dose of the antibody that binds specifically to FcyRIIb may be at a time point about 10 minutes, or

about 20 minutes, or about 30 minutes, or about 40 minutes, or about 50 minutes, or about 1 hour, or about 2 hours, or about 3 hours, or about 4 hours, or about 5 hours, or about 6 hours, or about 7 hours, or about 8 hours, or about 9 hours, or about 10 hours, or about 11 hours, or about 12 hours, or about 13 hours, or about 14 hours, or about 15 hours, or about 16 hours, or about 17 hours, or about 18 hours, or about 19 hours, or about 20 hours, or about 21 hours, or about 22 hours, or about 23 hours, or about 24 hours, or about 25 hours, or about 26 hours, or about 27 hours, or about 28 hours, or about 29 hours, or about 30 hours, or about 31 hours, or about 32 hours, or about 33 hours, or about 34 hours, or about 35 hours, or about 36 hours, or about 37 hours, or about 38 hours, or about 39 hours, or about 40 hours, or about 41 hours, or about 42 hours, or about 43 hours, or about 44 hours, or about 45 hours, or about 46 hours, or about 47 hours, or about 48 hours, before the second dose of the antibody molecule that specifically binds to FcyRIIb.

Preferably, the corticosteroid is administered as a first dose and a second dose, before the first dose of the antibody that binds specifically to FcyRIIb. Preferably, when the corticosteroid is administered as a first dose and a second dose, the first dose of the corticosteroid is administered at a time point from 16 hours to 48 hours before the first dose of the antibody molecule that specifically binds to FcyRIIb, and the second dose of the corticosteroid is administered at a time point from 10 minutes to 2 hours before the first dose of the antibody molecule that binds specifically to FcyRIIb.

It will be appreciated that, in such embodiments of the invention, the first dose of the corticosteroid may be administered at any time point between 16 hours to 48 hours before the first dose of the antibody molecule – for example, at a time point of about 16 hours, or about 17 hours, or about 18 hours, or about 19 hours, or about 20 hours, or about 21 hours, or about 22 hours, or about 23 hours, or about 24 hours, or about 25 hours, or about 26 hours, or about 27 hours, or about 28 hours, or about 29 hours, or about 30 hours, or about 31 hours, or about 32 hours, or about 33 hours, or about 34 hours, or about 35 hours, or about 36 hours, or about 37 hours, or about 38 hours, or about 39 hours, or about 40 hours, or about 41 hours, or about 42 hours, or about 43 hours, or about 44 hours, or about 45 hours, or about 46 hours, or about 47 hours, or about 48 hours, before the first dose of the antibody molecule that specifically binds to FcyRIIb. It will also be appreciated that, in such embodiments of the invention, the second dose of the corticosteroid may be administered at any time point between 10 minutes to 2 hours before the first dose of the antibody molecule – for example, at a time point of about 10 minutes, or about 20 minutes, or about 30 minutes, or about 40 minutes, or about 50

minutes, or about 1 hour, or about 2 hours, before the first dose of the antibody molecule that specifically binds to FcγRIIb.

In further preferred embodiments of the invention, a further dose of corticosteroid is administered before the second dose of antibody molecule that specifically binds to FcγRIIb. Thus, in such embodiments, the further dose of corticosteroid is administered after the first dose of the antibody molecule but before the second dose of the antibody molecule. Preferably, one or more further dose of corticosteroid is administered – such as one further dose; or two further doses; or three further doses; or four further doses; or five further doses; or six further doses; or seven further doses; or eight further doses; or nine further doses; or ten further doses; or eleven further doses; or twelve further doses, or more.

Preferably, the further dose of corticosteroid is administered at a time point from 16 hours to 48 hours before the second dose of the antibody molecule that specifically binds to FcγRIIb. Accordingly, in such embodiments of the invention, the further dose of the corticosteroid may be administered at any time point between 16 hours to 48 hours before the second dose of the antibody molecule – for example, at a time point of about 16 hours, or about 17 hours, or about 18 hours, or about 19 hours, or about 20 hours, or about 21 hours, or about 22 hours, or about 23 hours, or about 24 hours, or about 25 hours, or about 26 hours, or about 27 hours, or about 28 hours, or about 29 hours, or about 30 hours, or about 31 hours, or about 32 hours, or about 33 hours, or about 34 hours, or about 35 hours, or about 36 hours, or about 37 hours, or about 38 hours, or about 39 hours, or about 40 hours, or about 41 hours, or about 42 hours, or about 43 hours, or about 44 hours, or about 45 hours, or about 46 hours, or about 47 hours, or about 48 hours, before the second dose of the antibody molecule that specifically binds to FcγRIIb.

In some embodiments, the dosage regimens described herein can be repeated as many times as necessary in a particular patient. For instance, this dosage regimen can be employed each and every time the antibody molecule that specifically binds to FcγRIIb is administered to the patient. In some embodiments, the exact format of the dosage regimen (in terms of timing and amounts of doses) may be varied between repeat administrations to the patient. The advantage of using the dosage regimens described herein repeatedly is that it ensures that the improved tolerability (for example a reduction in infusion related reactions) is achieved with each administration of the antibody that specifically binds FcγRIIb.

Corticosterioids of the invention can be administered at a dose of from 0.5 to 20 mg. In preferred embodiments of the invention, the corticosteroid is administered at a dose of from about 4 mg to about 20 mg, such as at a dose of from about 12 mg to about 20 mg, or at a dose of from about 4 mg to about 12 mg. For example, the corticosteroid is administered at a dose of about 4mg or greater, such as at about 5mg or greater, or about 6mg or greater, or about 7mg or greater, or about 8mg or greater, or about 9mg or greater, or about 10mg or greater, or about 11mg or greater, or about 12mg or greater, or about 13mg or greater, or about 14mg or greater, or about 15mg or greater, or about 16mg or greater, or about 17mg or greater, or about 18mg or greater, or about 19mg or greater, or about 20mg or greater.

In some preferred embodiments, the corticosteroid is dexamethasone. In some additional or alternative embodiments, the corticosteroid is betamethasone. In some embodiments, a combination of dexamethasone and betamethasone is used. A skilled person will appreciate that other corticosteroids are contemplated by the present invention, for example, one or more of the following: cortisone; hydrocortisone; prednisone; prednisolone; triamcinolone; and methylprednisolone; or combinations thereof.

In some embodiments, when the corticosteroid is dexamethasone, the dose of dexamethasone is from 0.5 mg to 20 mg. In some embodiments, when dexamethasone is used, the dose of dexamethasone is about 4mg or greater, such as about 4-20mg in a preferred embodiment. In some embodiments, the dose of dexamethasone is about 12mg or greater, such as about 12-20mg. In some embodiments, the dose of dexamethasone is about 4-12mg. In particularly preferred embodiments, the dose of dexamethasone is about about 12mg or is about about 20mg.

In particularly preferred embodiments of the invention, a first dose and a second dose of the corticosteroid dexamethasone is administered. More preferably in these embodiments of the invention when dexamethasone is used: the first dose is about 4-20mg and/or the second dose is about 4-25mg; or the first dose is about 4-20mg and second dose is about 4-25mg; or the first dose is about 10-12mg and/or the second dose is about 20mg; or the first dose is about 10-12mg and the second dose is about 20mg.

In some embodiments, when the corticosteroid is betamethasone, the dose of betamethasone is from 0.5 mg to 20 mg. In some embodiments, when betamethasone is used, the dose of betamethasone is about 3.2mg or greater, such as about 4mg or greater, such as about 3.2-16mg, or about 4-20mg. In some embodiments, the dose of betamethasone is about 12 mg or greater, such as about 12-20mg. In some

embodiments, the dose of betamethasone is about 4-12mg. In particularly preferred embodiments, the dose of betamethasone is about about 12mg or is about about 20mg.

In particularly preferred embodiments of the invention, a first dose and a second dose of the corticosteroid betamethasone is administered. More preferably in these embodiments of the invention when betamethasone is used: the first dose is about 3.2-16mg and/or the second dose is about 3.2-20mg; or the first dose is about 3.2-16mg and second dose is about 3.2-20mg; or the first dose is about 8-9.6mg and/or the second dose is about 16mg; or the first dose is about 8-9.6mg and the second dose is about 16mg.

A skilled person will appreciate that other corticosteroids are known in the art, in addition to those described herein; as corticosteroids function in a similar manner, it will be appreciated that any corticosteroid could be used in the present invention.

As discussed above, the invention provides a system, combination, method, or use, in which an antibody molecule that specifically binds to FcyRIIb is administered to the subject as at least a first dose and a second dose.

In preferred embodiments of the invention, the first dose of the antibody molecule that specifically binds to FcyRIIb is administered at a time point from about one to about 24 hours before the second dose of the antibody molecule that specifically binds to FcyRIIb. Accordingly, in such embodiments of the invention, the first dose of the antibody molecule is administered at any time point between about one to about 24 hours before the second dose of the antibody molecule – for example, at a time point of about 1 hour, or about 2 hours, or about 3 hours, or about 4 hours, or about 5 hours, or about 6 hours, or about 7 hours, or about 8 hours, or about 9 hours, or about 10 hours, or about 11 hours, or about 12 hours, or about 13 hours, or about 14 hours, or about 15 hours, or about 16 hours, or about 17 hours, or about 18 hours, or about 19 hours, or about 20 hours, or about 21 hours, or about 22 hours, or about 23 hours, or about 24 hours, before the second dose of the antibody molecule that specifically binds to FcyRIIb.

Most preferably in that embodiment of the invention, the first dose of the antibody molecule that specifically binds to FcyRIIb is administered about one hour before the second dose of the antibody molecule that specifically binds to FcyRIIb, or is administered about 24 hours before the second dose of the antibody molecule that specifically binds to FcyRIIb.

In another embodiment, the first dose of the antibody molecule that specifically binds to FcyRIIb is administered at a time point from about 24 hours to about 48 hours before the second dose of the antibody molecule that specifically binds to FcyRIIb. Accordingly, in such embodiments of the invention, the first dose of the antibody molecule is administered at any time point between about 24 hours to about 48 hours before the second dose of the antibody molecule – for example, at a time point of about 24 hours, or about 25 hours, or about 26 hours, or about 27 hours, or about 28 hours, or about 29 hours, or about 30 hours, or about 31 hours, or about 32 hours, or about 33 hours, or about 34 hours, or about 35 hours, or about 36 hours, or about 37 hours, or about 38 hours, or about 39 hours, or about 40 hours, or about 41 hours, or about 42 hours, or about 43 hours, or about 44 hours, or about 45 hours, or about 46 hours, or about 47 hours, or about 48 hours, before the second dose of the antibody molecule that specifically binds to FcyRIIb.

As discussed above, the invention provides a system, combination, method, or use, in which the first dose of the antibody molecule is lower than the maximum therapeutically effective dose of the antibody molecule.

Those skilled is the art will be aware that for approved antibody therapies, certain doses (typically expressed in mg/kg) are recommended for use in certain patient groups or for subjects with a particular type of cancer. Often, recommended doses are described in the labelling or prescription information of an approved antibody therapeutic. The recommended dose may be calculated for a particular subject, i.e. based on the type of cancer, the stage of the cancer, their weight, Body Mass Index (BMI) and other factors.

The skilled person will appreciate that the recommended dose will differ depending on the identity of the antibody molecule. Where the antibody molecule is not described in labelling or prescription information, it would be apparent to the skilled person how to determine the recommended dose using techniques well known in the art.

The "recommended dose" is typically referred to as the "approved dose", "maximal tolerated dose (MTD)" or the "therapeutically effective dose" of an antibody molecule. The MTD is a well-recognised term in drug development and refers to the highest dose of the drug that can be used with an acceptable level of tolerability.

By "therapeutically effective dose" we mean any dose that would be considered to be therapeutically active (i.e. which produces the desired therapeutic effect in a subject defined herein).

By the "maximum therapeutically effective dose", we mean the (lowest) dose that achieves maximal therapeutic activity, without consideration of tolerability (which may be sub-optimal or not tolerated in absence of appropriate measures of administration to mitigate adverse effects). This is the ideal dosage that will be attempted to be used by those skilled in the art when administering the antibody molecule to a subject in need thereof.

By "therapeutically active" we include where the dose produces the desired therapeutic effect in a subject. By "therapeutic effect" we include all effects that are attributable directly or indirectly to use of the therapy in question. This may be a measurable therapeutic effect, such as reduced tumour volume or reduced tumour size (which may be determined by a CT scan, for example), or effectiveness of a therapeutic antibody or treatment. In other cases, this may be a more subjective effect, such as a reduction in severity of symptoms reported by the subject. The measurement of therapeutic effects in subjects in response to the administration of therapeutic antibodies is well known in the art. Furthermore, the level of survival of a subject or group of subjects over a defined time period is an alternative read-out of therapeutic effect.

The present invention is based on the inventors' surprising discovery that tolerability of an antibody molecule that specifically binds to FcγRIIb in a subject is improved when the subject is administered a corticosteroid, and is subsequently administered the antibody molecule in at least a first dose and a second dose, in which the first dose is lower than the "maximum therapeutically effective dose" of that antibody. Put another way, the first dose of the antibody molecule is a sub-maximal therapeutic dose – that is, it is a lower dose than the maximum therapeutically effective dose of the antibody.

In preferred embodiments of the invention, the first dose of the antibody molecule that specifically binds to FcγRIIb is lower than the maximum tolerated therapeutic dose. As discussed above, the maximum tolerated therapeutic dose is the highest dose of the drug that can be used that is considered to be tolerated (i.e. does not produce unacceptable levels of toxicity or side effects in the patient, and this may be lower than the maximum therapeutically effective dose. This differs from the maximum therapeutically effective dose in that the dose must be tolerated in the patient. The level of side-effects/toxicity that can be tolerated by a particular patient depend on factors such as the stage or severity of disease.

Improving drug tolerability and the therapeutic window is not only important for treatment of severely ill patients e.g. those with cancer, but can be critical for use in patients with

non-life-threatening disease e.g. autoimmune or infectious diseases where moderate or even mild side-effects may not be acceptable.

In some other cases, the dose that is lower than the maximum therapeutically effective dose or the maximum tolerated therapeutic dose is lower than the lowest dose thought to be therapeutically effective (i.e. the minimum effective dose). In other words, the first dose of the antibody molecule may be a dose that would not be therapeutically effective when administered alone as a single dose.

In some other cases, the first dose of the antibody is lower than the maximum feasible dose. In some cases practicalities, such as formulation considerations, may limit the maximum dose that can be administered. The maximum such dose taking into account such factors is termed the maximum feasible dose.

In some other cases, the dose that is lower than the tolerated therapeutic dose is lower than the recommended tolerated therapeutic dose. In some embodiments, this may include the recommended dose for the indication included in the drug label.

It will be apparent to the skilled person in the art how the particular tolerated therapeutic dose is defined for any particular antibody, generally using dose escalation studies during clinical trials. Tolerated therapeutic doses for antibodies that have not yet been approved may be based on the tolerated therapeutic doses of similar antibodies that have been approved or have undergone extensive clinical testing.

In preferred embodiments of the present invention, the first dose of the antibody molecule that specifically binds to FcyRIIb is at least 50% lower than the maximum therapeutically effective dose. For example, the first dose of the antibody molecule is at least 60% lower, or at least 70% lower, or at least 80% lower, or at least 90% lower than the maximum therapeutically effective dose.

In one embodiment of the invention, the antibody molecule that specifically binds to FcyRIIb is administered in a first dose that results in high receptor saturation of the FcyRIIb receptor, such as: at least 50% receptor saturation; or at least 60% receptor saturation; or at least 70% receptor saturation; or at least 80% receptor saturation; or at least 90% receptor saturation; or at least 95% receptor saturation; or at least 96% receptor saturation; or at least 97% receptor saturation; or at least 98% receptor saturation; or at least 99% receptor saturation; or close to 100% receptor saturation; or 100% receptor saturation as measured at a time-point between end of infusion and up to immediately

before the second antibody infusion. Methods for measuring receptor saturation are well known to those skilled in the art.

Preferably, the high receptor saturation is at least transient, but may be maintained for longer periods. By transient receptor saturation we mean indicated saturation is maintained for at least 15 min, and preferably 1 to 6 hours, and most preferably lasting until the second antibody administration. As discussed herein, the time period between the first and second antibody molecule doses may vary from between about 1 hour to about 48 hours.

As discussed herein, the dose of an antibody molecule can be expressed based on the weight of subject to whom it is to be administered – typically in mg of the antibody molecule per kg weight of the subject.

In preferred embodiments of the present invention, the first dose of the antibody molecule that specifically binds to FcyRIIb is administered at a dose of from about 0.2mg/kg to about 0.6mg/kg; for example, at a dose of from about 0.3mg/kg to about 0.5mg/kg. It will therefore be appreciated that the first dose of the antibody molecule may be administered at a dose of: about 0.2mg/kg, or at about 0.3mg/kg, or at about 0.4mg/kg, or at about 0.5mg/kg, or at about 0.6mg/kg.

It will be appreciated, that depending on the weight of the subject to whom the antibody molecule is to be administered, the first dose of the antibody molecule that specifically binds to FcyRIIb may be administered at a dose of from about 10mg to about 20mg. In other embodiments, the first dose of the antibody may be administered at a dose of from about 20mg to about 40mg, or more; for example, at a dose of from about 20mg to 30mg, or from about 30mg to 40mg, or from about 40mg to 50mg, or from about 50mg to 60mg, or from about 60mg to 70mg, or more. It will therefore be appreciated that the first dose of the antibody molecule may be administered at a dose of: about 10 mg, about 20mg, or about 25mg, or about 30mg, or about 35mg, or about 40mg, or about 45mg, or about 50mg, or about 55mg, or about 60mg, or about 65mg, or about 70mg, or more.

In one embodiment of the invention, the antibody molecule that specifically binds to FcyRIIb is administered in a dose that results in high receptor saturation, at least transiently, of the FcyRIIb receptor, such as: at least 50% receptor saturation; or at least 60% receptor saturation; or at least 70% receptor saturation; or at least 80% receptor saturation; or at least 90% receptor saturation; or at least 95% receptor saturation; or at least 96% receptor saturation; or at least 97% receptor saturation; or at least 98%

receptor saturation; or at least 99% receptor saturation; or close to 100% receptor saturation; or 100% receptor saturation. Methods for measuring receptor saturation are well known to those skilled in the art.

By transient receptor saturation we mean indicated saturation is maintained for at least 15 min, and preferably 1 to 6 hours, and most preferably lasting until the second antibody administration.

As discussed above, the invention provides a system, combination, method, or use, in which a second dose of the antibody molecule that specifically binds to FcyRIIb is administered to the subject.

Preferably, the second dose of the antibody molecule that specifically binds to FcyRIIb is a therapeutically effective dose. In some embodiments, the second dose of the antibody molecule may be the maximum therapeutically effective dose as defined herein.

More preferably, the second dose of the antibody molecule that specifically binds to FcyRIIb is the maximum tolerated therapeutic dose or the maximum feasible therapeutic dose.

More preferably, the second dose of the antibody molecule that specifically binds to FcyRIIb is lower than a therapeutically effective dose.

In some embodiments, the second dose of the antibody molecule is higher than the first dose of the antibody molecule. In alternative embodiments, the second dose of the antibody molecule is lower than the first dose of the antibody molecule.

In some embodiments, the total amount of antibody that specifically binds to FcyRIIb administered between the first dose and the second dose is from around 30 mg to around 3000 mg. In some embodiments, the total dose of antibody that specifically binds to FcyRIIb administered between the first dose and the second dose is from around 0.3 mg/kg to around 20 mg/kg. In some other embodiments, the total dose between the first and second antibody doses is a dose that results in high receptor saturation, at least transiently, of the FcyRIIb receptor, for example at least 90% receptor saturation. In some preferred embodiments, this high receptor saturation persists for a total duration ranging from about 1 hour to about 4 weeks.

The skilled person will appreciate that the second dose of the antibody molecule that binds specifically to FcyRIIb may be adjusted based on the amount of the first dose of the antibody molecule that is administered.

In some preferred embodiments, the second dose of the antibody molecule that specifically binds to the FcyRIIb receptor is administered at a dose of from about 0.1 mg/kg to about 19.8 mg/kg.

It will be appreciated that, depending on the weight of the subject to whom the antibody molecule is to be administered, the second dose of the antibody molecule that specifically binds to FcyRIIb may be administered at a dose of from about 20 mg to about 2900 mg.

In preferred embodiments of the invention, further additional doses of the antibody molecule that specifically binds to FcyRIIb are administered to the subject following the second dose of the antibody molecule that specifically binds to FcyRIIb.

In preferred embodiments, the further additional doses of the antibody molecule that specifically binds to FcyRIIb are also administered according to the dosage regimens disclosed herein. For instance, this dosage regimen can be employed each and every time the antibody molecule that specifically binds to FcyRIIb is administered to the patient. In some embodiments, the exact format of the dosage regimen (in terms of timing and amounts of doses) may be varied between repeat administrations to the patient. The advantage of using the dosage regimens described herein repeatedly is that it ensures that the improved tolerability (for example a reduction in infusion related reactions) is achieved with each administration of the antibody that specifically binds FcyRIIb. In some other embodiments, the further additional doses of the antibody molecule are administered at the maximum therapeutically effective dose as defined herein. Typically, repeat doses will be similar in magnitude to the previously administered dose - for example:

- if the previous administered antibody dose was 1.3 mg/kg (e.g. 0.3 mg/kg (first dose) + 1mg/kg (second dose)), the subsequent additional dose would also be 1.3 mg/kg;

- if the previous administered antibody dose was 2.5 mg/kg (e.g. 0.5 mg/kg (first dose) + 2mg/kg (second dose)), the subsequent additional dose would also be 2.5 mg/kg;

- if the previous administered antibody dose was 3.3 mg/kg (0.3 mg/kg (first dose) + 3mg/kg (second dose)), the subsequent additional dose would also be 3.3 mg/kg;

- if the previous administered antibody dose was 5.4 mg/kg (e.g. 0.4 mg/kg (first dose) + 5mg/kg (second dose)), the subsequent additional dose would also be 5.4 mg/kg;

- if the previous administered antibody dose" was 10.5 mg/kg (e.g. 0.5 mg/kg (first dose) + 10mg/kg (second dose)), the subsequent additional dose would also be 10.5 mg/kg.

However, as a person skilled in the art will appreciate, repeat dosing could also utilise higher or lower total doses as guided by patient tolerability. Analogous flat dosing-based, or receptor-occupancy guided, dosing regimens regimens could be used.
It will be appreciated that an antibody molecule that specifically binds to FcγRIIb has particular utility when administered with certain therapeutic antibodies, and particularly therapeutic antibodies used in the treatment of cancer or an inflammatory disease.

It is well known that many therapeutic antibodies exert their therapeutic effects by stimulating the removal of cancer and other unwanted cells by recruiting natural effector systems such as cytotoxic cells (e.g. macrophages) and enzymes (e.g. complement) which then target the cell to which the therapeutic antibody is bound. For example, Type I anti-CD20 monoclonal antibodies (such as the current market leader rituximab) work by binding to CD20 molecules on the surface of B cells, and deleting these target B cells. They do this through recruiting and activating effector cells which interact with the Fc domains of the therapeutic antibody through Fcγ (i.e. Fc-gamma) receptors expressed on the surface of these effector cells.

It is known that a factor determining the effectiveness of such therapeutic antibodies (such as those to antigens such as CD20) is interaction with the inhibitory FcγRIIb (also known as and including, CD32, CD32B, CD32B1, CD32B2, FcRII, FcγRII or FcRIIB). FcgRIIB may reduce therapeutic effectiveness and promote resistance to cancer by several mechanisms acting in cis i.e. on a cell targeted by a therapeutic antibody, or trans i.e. on a neihbouring effector cell which engages through its Fc gamma receptors in binding to the constant domain of antibodies coated on the surface of the antibody targeted cell. For example, this interaction may lead to internalisation of the therapeutic antibody by the target cell, thus removing its ability to interact with effector cell Fc receptors. It is known that agents

which bind to FcyRIIb on the target cell (such as an antibody molecule that specifically binds to FcyRIIb) block this internalisation, and improve the activity of the therapeutic antibody.

Accordingly, in particularly preferred embodiments, the invention provides a system, combination, use, or method which further comprises administration of one or more therapeutic antibodies for the treatment of cancer or an inflammatory disease in a subject.

Preferably, the one or more therapeutic antibody is selected from the group consisting of:

- one or more anti-PD1 antibody (such as pembrolizumab, nivolumab, cemiplimab, camrelizumab, dostarlimab, and/or biosimilars thereof);
- one or more anti-CD20 antibody (such as rituximab, obinutuzumab, ofatumumab, and/or biosimilars thereof; for example as discussed in Roghanian et al., Cancer Cell, 2015, 27:473-488);
- one or more anti-CD19 antibody (such as Loncastuximab tesirine);
- one or more anti-CD40 antibody (such as CP-870,893);
- one or more anti-CD38 antibody (for example, as described in Vaughan et al., Blood, 2014, 123:669-677 or daratumumab or a daratumumab biosimilar);
- one or more anti-Her2 antibody (such as trastuzumab or a trastuzumab biosimilar);
- one or more anti-EGFR antibody (such as cetuximab or a cetuximab biosimilar).

Preferably, the therapeutic antibody is one or more selected from the group comprising: rituximab; pembrolizumab; nivolumab; cemiplimab; camrelizumab; dostarlimab; obinutuzumab; ofatumumab, and biosimilars or equivalents thereof.

It will be appreciated that the doses and dosage regimens of each of the therapeutic antibodies discussed and contemplated herein would be dependent on the approved doses/regimens for these therapeutic antibodies, and would also vary depending on the inidication (for example type of cancer/stage) and subject (for example BMI or age).

For example, in some embodiments wherein the therapeutic antibody is rituximab, the dose and dosage regimen may be as defined in the FDA label (see https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103705s5311lbl.pdf). As described therein, the doses may be as follows:

- Non-Hodgkin's lymphoma (NHL): 375mg/m2 once weekly for 4-8 doses;
- Chronic Lymphocytic Leukemia (CLL): 375mg/m2 the day prior to initiation of FC chemotherapy, then 500mg/m2 of day 1 of cycles 2-6 (every 28 days);

- Rheumatoid Arthritis (RA): administer as two 1000mg insfusions separated by two weeks.

In another example, wherein the therapeutic antibody is pembrolizumab, the dose and dosage regimen may be as defined in the FDA label (see https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125514s040lbl.pdf). As described therein, the doses may be as follows:

- Melanoma: 200 mg every 3 weeks;
- Non-small cell lung cancer (NSCLC): 200 mg every 3 weeks;
- Head and neck squamos cell carcinoma (HNSCC): 200 mg every 3 weeks;
- Classical Hodgkin lymphoma (cHL) or Primary mediastinal large B-cell lymphoma (PMBCL): 200 mg every 3 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics;
- Urothelial Carcinoma: 200 mg every 3 weeks;
- Microsatellite instability-high (MSI-H) Cancer: 200 mg every 3 weeks for adults and 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics;
- Gastric Cancer: 200 mg every 3 weeks;
- Cervical Cancer: 200 mg every 3 weeks;
- Hepatocellular carcinoma (HCC): 200 mg every 3 weeks;
- Merkel cell carcinoma (MCC): 200 mg every 3 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics.

The term "subject" (which herein is used interchangeably with "patient") includes any animal, including a human, that is in need of treatment with an antibody molecule that specifically binds to FcγRIIb. The subject or patient may be mammalian or non-mammalian. Preferably, the subject is mammalian, such as a horse, or a cow, or a sheep, or a pig, or a camel, or a dog, or a cat. Most preferably, the mammalian patient is a human.

Preferably, the subject is one that has been diagnosed as having cancer or an inflammatory disease, or that has been identified as likely to have cancer or an inflammatory disease and/or that exhibits symptoms of cancer or an inflammatory disease.

In other preferred embodiments, the subject is one that has been diagnosed as having an infectious disease, or that has been identified as likely to have an infectious disease and/or that exhibits symptoms of an infectious disease. By infectious disease we include any disease caused by bacteria, fungi, parasites or viruses that can be transmitted between persons (either directly or indirectly).

In some other embodiments, the subject has cancer and/or an inflammatory disease and/or an infectious disease and the dosage regimens described herein are used in conjunction with administration of a vaccine aimed at boosting humoral or cellular responses in order to treat and/or prevent said cancer or disease.

By "exhibits", we include that the subject displays a cancer symptom and/or a cancer diagnostic marker, and/or the cancer symptom and/or a cancer diagnostic marker can be measured, and/or assessed, and/or quantified. It would be readily apparent to the person skilled in medicine what the cancer symptoms and cancer diagnostic markers would be and how to measure and/or assess and/or quantify whether there is a reduction or increase in the severity of the cancer symptoms, or a reduction or increase in the cancer diagnostic markers; as well as how those cancer symptoms and/or cancer diagnostic markers could be used to form a prognosis for the cancer.

In some embodiments, the cancer is a FcγRIIb-positive cancer. In other embodiments, the cancer is an FcγRIIb-negative cancer.

By "FcγRIIb-positive cancer", we include any cancer that expresses FcγRIIb, albeit at different levels. FcγRIIb expression is most pronounced in chronic lymphocytic leukaemia and mantle cell lymphomas, moderately so in diffuse large B cell lymphoma and least pronounced in follicular lymphomas. However, in some cases subjects with cancers that generally express low levels of FcγRIIB (*e.g.* follicular lymphomas) may have very high levels of FcγRIIb expression.

By "FcγRIIb negative cancer" we include any cancer that does not present any FcγRIIb receptors. This can be tested using anti-FcγRIIB specific antibodies in a variety of methods including immunohistochemistry and flow cytometry such as indicated in Tutt *et al*, *J Immunol*, 2015, 195 (11) 5503-5516.

In some preferred embodiments, the cancer is selected from the group consisting of carcinomas, sarcomas, and lymphomas. In some embodiments, the cancer is a carcinoma selected from the group consisting of adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, anaplastic or undifferentiated carcinoma, large cell carcinoma and small cell carcinoma. In some embodiments, the cancer is a sarcoma selected from the group consisting of osteosarcoma, chondrosarcoma, liposarcoma, and leiomyosarcoma.

In some preferred embodiments, the cancer is selected from the group of cancers indicated in the label of an approved therapeutic antibody to be co-administered with the anti-FcgRIIB antibody. By co-administered we mean an antibody used as part of the anti-FcgRIIB antibody comprising therapy, where the co-administered antibody may be administered before, concomitantly, or subsequent in time to the anti-FcgRIIB antibody.

In some preferred embodiments, the disease is selected from the group of diseases indicated in the label of an approved therapeutic antibody co-administered with the anti-FcgRIIB antibody. By co-administered we mean an antibody used as part of the anti-FcgRIIB antibody comprising therapy, where the co-administered antibody may be administered before, concomitantly, or subsequent in time to the anti-FcgRIIB antibody.

The cancer may be selected from the group comprising: melanoma, breast cancer, ovarian cancer, cervical cancer, prostate cancer, metastatic hormone-refractory prostate cancer, colorectal cancer, lung cancer, small cell lung carcinoma, small cell lung cancer (SCLC), non-small cell lung cancer, urothelial carcinoma, bladder cancer, kidney cancer, mesothelioma, Merkel cell carcinoma, head and neck cancer, and pancreatic cancer.

Preferably, the cancer is a B-cell cancer, such as a cancer selected from the group comprising: chronic lymphocytic leukaemia, mantle cell lymphoma, follicular lymphoma, diffuse large B cell lymphoma.

Each one of the above described cancers is well-known, and the symptoms and cancer diagnostic markers are well described, as are the therapeutic agents used to treat those cancers. Accordingly, the symptoms, cancer diagnostic markers, and therapeutic agents used to treat the above mentioned cancer types would be known to those skilled in medicine.

Clinical definitions of the diagnosis, prognosis and progression of a large number of cancers rely on certain classifications known as staging. Those staging systems act to collate a number of different cancer diagnostic markers and cancer symptoms to provide a summary of the diagnosis, and/or prognosis, and/or progression of the cancer. It would be known to the person skilled in oncology how to assess the diagnosis, and/or prognosis, and/or progression of the cancer using a staging system, and which cancer diagnostic markers and cancer symptoms should be used to do so.

By "cancer staging", we include the Rai staging, which includes stage 0, stage I, stage II, stage III and stage IV, and/or the Binet staging, which includes stage A, stage B and stage C, and/or the Ann Arbour staging, which includes stage I, stage II, stage III and stage IV.

It is known that cancer can cause abnormalities in the morphology of cells. These abnormalities often reproducibly occur in certain cancers, which means that examining these changes in morphology (otherwise known as histological examination) can be used in the diagnosis or prognosis of cancer. Techniques for visualizing samples to examine the morphology of cells, and preparing samples for visualization, are well known in the art; for example, light microscopy or confocal microscopy.

By "histological examination", we include the presence of small, mature lymphocyte, and/or the presence of small, mature lymphocytes with a narrow border of cytoplasm, the presence of small, mature lymphocytes with a dense nucleus lacking discernible nucleoli, and/or the presence of small, mature lymphocytes with a narrow border of cytoplasm, and with a dense nucleus lacking discernible nucleoli, and/or the presence of atypical cells, and/or cleaved cells, and/or prolymphocytes.

It is well known that cancer is a result of mutations in the DNA of the cell, which can lead to the cell avoiding cell death or uncontrollably proliferating. Therefore, examining these mutations (also known as cytogenetic examination) can be a useful tool for assessing the diagnosis and/or prognosis of a cancer. An example of this is the deletion of the chromosomal location 13q14.1 which is characteristic of chronic lymphocytic leukaemia. Techniques for examining mutations in cells are well known in the art; for example, fluorescence in situ hybridization (FISH).

By "cytogenetic examination", we include the examination of the DNA in a cell, and, in particular the chromosomes. Cytogenetic examination can be used to identify changes in DNA which may be associated with the presence of a refractory cancer and/or relapsed cancer. Such may include: deletions in the long arm of chromosome 13, and/or the deletion of chromosomal location 13q14.1, and/or trisomy of chromosome 12, and/or deletions in the long arm of chromosome 12, and/or deletions in the long arm of chromosome 11, and/or the deletion of 11q, and/or deletions in the long arm of chromosome 6, and/or the deletion of 6q, and/or deletions in the short arm of chromosome 17, and/or the deletion of 17p, and/or the t(11:14) translocation, and/or the (q13:q32) translocation, and/or antigen gene receptor rearrangements, and/or BCL2 rearrangements, and/or BCL6 rearrangements, and/or t(14:18) translocations, and/or t(11:14) translocations, and/or (q13:q32) translocations, and/or (3:v) translocations,

and/or (8:14) translocations, and/or (8:v) translocations, and/or t(11:14) and (q13:q32) translocations.

It is known that patients with cancer exhibit certain physical symptoms, which are often as a result of the burden of the cancer on the body. Those symptoms often reoccur in the same cancer, and so can be characteristic of the diagnosis, and/or prognosis, and/or progression of the disease. A person skilled in medicine would understand which physical symptoms are associated with which cancers, and how assessing those physical systems can correlate to the diagnosis, and/or prognosis, and/or progression of the disease. By "physical symptoms", we include hepatomegaly, and/or splenomegaly.

In some embodiments, the cancer is one that is resistant to treatment with a therapeutic anti-cancer antibody. Such resistant cancer may be a relapsed and/or refractory cancer.

A relapsed cancer is a cancer that has previously been treated and, as a result of that treatment, the subject made a complete or partial recovery (*i.e.* the subject is said to be in remission), but that after the cessation of the treatment the cancer returned or worsened. Put another way, a relapsed cancer is one that has become resistant to a treatment, after a period in which it was effective and the subject made a complete or partial recovery.

A refractory cancer is a cancer that has been treated but which has not responded to that treatment, and/or has been treated but which has progressed during treatment. Put another way, a refractory cancer is one that is resistant to a treatment. It will be appreciated that a cancer may be a refractory cancer due to an intrinsic resistance. By "intrinsic resistance", we include the meaning that the cancer and/or the subject and/or the target cell is resistant to a particular treatment from the first time at which it is administered, or before it is administered at all.

A relapsed cancer and/or refractory cancer would be readily diagnosed by one skilled in the art of medicine.

In embodiments of the invention, the antibody molecule that specifically binds to FcγRIIb is formulated and/or adapted for delivery by a route selected from the group comprising: intravenous; intramuscular; subcutaneous. In some embodiments, the antibody molecule that specifically binds to FcγRIIb is formulated and/or adapted for intravenous (i.e. i.v. or iv) delivery. In other embodiments, the antibody molecule that specifically binds to FcγRIIb is formulated and/or adapted for subcutaneous (i.e. s.c. or sc) delivery.

In embodiments of the invention, the antibody molecule that specifically binds to FcγRIIb is delivered to the subject by a route selected from the group comprising: intravenous; intramuscular; subcutaneous. Preferably, the antibody molecule that specifically binds to FcγRIIb is delivered intravenously.

Thus, in preferred embodiments, the first and/or second and/or further doses of the antibody molecule that specifically binds to FcγRIIb are formulated for intravenous delivery to the subject and/or are delivered by intravenous delivery to the subject.

Methods and formulations for intravenous administration of antibody molecules are well known in the art. In the present invention, any type of intravenous administration may be used, such as injection or infusion.

In embodiments of the invention, the corticosteroid is formulated and/or adapted for delivery by a route selected from the group comprising: intravenous; oral.

In embodiments of the invention, the corticosteroid is delivered to the subject by a route selected from the group comprising: intravenous; oral.

Thus, in preferred embodiments, the first and/or second and/or further doses of the corticosteroid are formulated for intravenous or oral delivery to the subject and/or are delivered by intravenous or oral delivery to the subject.

Methods and formulations for intravenous or oral administration of corticosteroids are well known in the art.

The antibody molecule that specifically binds FcγRIIb and/or the corticosteroid as defined herein may be combined with an excipient and/or a pharmaceutically acceptable carrier and/or a pharmaceutically acceptable diluent and/or an adjuvant.

For example, the antibody that specifically binds FcγRIIb and/or the corticosteroid may be formulated as an aqueous and/or non-aqueous sterile solution which may contain anti-oxidants, and/or buffers, and/or bacteriostats, and/or solutes which render the formulation isotonic with the blood of the intended recipient; and/or aqueous and/or non-aqueous sterile suspensions which may include suspending agents and/or thickening agents. Such formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (*i.e.* lyophilised) condition

requiring only the addition of the sterile liquid carrier, for example water, immediately prior to use.

Extemporaneous injection solutions and suspensions may be prepared from sterile powders, and/or granules, and/or tablets of the kind known in the art.

The antibody that specifically binds FcyRIIb and/or the corticosteroid may be formulated with pharmaceutically acceptable acid or base addition salts. The acids which are used to prepare the pharmaceutically acceptable acid addition salts are those which form non-toxic acid addition salts, *i.e.* salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulphate, bisulphate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulphonate, ethanesulphonate, benzenesulphonate, p- toluenesulphonate and pamoate [*i.e.* 1 ,1'-methylene-bis-(2-hydroxy-3 naphthoate)] salts, among others. Pharmaceutically acceptable base addition salts may also be used to produce pharmaceutically acceptable salt forms. The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts are those that form non-toxic base salts. Such non-toxic base salts include, but are not limited to those derived from such pharmacologically acceptable cations such as alkali metal cations (*e.g.* potassium and sodium) and alkaline earth metal cations (*e.g.* calcium and magnesium), ammonium or water-soluble amine addition salts such as N-methylglucamine-(meglumine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines, among others.

The antibody molecule that specifically binds FcyRIIb and/or corticosteroid may be lyophilised for storage and reconstituted in a suitable carrier prior to use. Any suitable lyophilisation method (*e.g.* spray drying, cake drying) and/or reconstitution techniques can be employed. It will be appreciated by those skilled in the art that lyophilisation and reconstitution can lead to varying degrees of antibody activity loss (*e.g.* with conventional immunoglobulins, IgM antibodies tend to have greater activity loss than IgG antibodies) and that use levels may have to be adjusted upward to compensate. In one embodiment, the lyophilised (freeze dried) antibody molecule loses no more than about 20%, or no more than about 25%, or no more than about 30%, or no more than about 35%, or no more than about 40%, or no more than about 45%, or no more than about 50% of its activity (prior to lyophilisation) when re-hydrated.

As discussed above and as demonstrated in the accompanying Examples, the system, combination, method or use of the present invention improves tolerability of an antibody

molecule that specifically binds to FcγRIIb in a subject. Put another way, the system, combination, method or use of the present invention reduces or prevents adverse effects associated with administration of the antibody molecule (and, particularly, with the intravenous administration of the antibody molecule).

In a preferred embodiment of the system, combination, method or use of the present invention, the infusion related reactions associated with the administration of the antibody molecule that specifically binds to FcγRIIb are reduced or eliminated. Such infusion related reactions are described herein, and it is contemplated that the system, combination, method or use of the present invention reduces or eliminates any one or more of those infusion related reactions.

In a preferred embodiment, changes to the body temperature and/or platelet count and/or blood levels of liver enzymes (e.g. ALAT or ASAT) and/or blood levels of cytokines (e.g. IL-6) of the subject are reduced. Preferably IRRs are reduced to acceptable levels, i.e. below grade 3 as defined by Common Terminology for Adrerse Events (CTCAE) as defined herein for at least 24 hours following administration of the second dose of the antibody molecule that specifically binds to FcγRIIb. Most preferably IRRs are completely prevented with normalized body temperature and/or platelet count and/or blood levels of liver enzymes (e.g. ALAT or ASAT) and/or blood levels of cytokines (e.g. IL-6) of the subject.

As defined above, the normal levels of some of these parameters are as follows:

- Body temperature: from 36.1°C to 37.9°C;
- Platelet count: from 145 x 10^9 to 400 x 10^9 per litre;
- Blood level of ALAT: from 0 to 1.09 µkat/L, 16-63 U/L;
- Blood level of ASAT: from 0 to 0.759 µkat/L, 15-37 U/L;
- Blood level IL-6: from 0.16 to 27.2 pg/ml, with a median value of 0.47 pg/ml.

By "acceptable levels" we include that the clinical grading of the IRR (as defined in the art and herein using the CTCAE scale) is reduced to at least grade 2. In some preferred embodiments, the grading of the IRR is reduced to grade 1. As discussed herein, the skilled person will be aware of how to grade an IRR according to the CTCAE scale.

A fifth aspect of the invention provides a kit comprising:

(i) an antibody molecule that specifically binds to FcγRIIb, preferably an antibody molecule as defined herein;

(ii) a corticosteroid, preferably a corticosteroid as defined herein; and

(iii) optionally, instructions for use,

wherein the antibody molecule is provided as at least a first dose and a second dose, wherein the first dose of the antibody molecule is lower than the maximum therapeutically effective dose of the antibody molecule, further optionally wherein the first dose is as defined herein, further optionally wherein the second dose is as defined herein. The antibody molecule and doses of that aspect of the invention are as defined herein.

Preferably, the kit of the invention is for improving the tolerability of the antibody molecule in a subject, as is described herein.

Preferably, in the kit of the invention, the corticosteroid is provided in a dose as defined herein.

In a preferred embodiment, the kit of the invention further comprises one or more therapeutic antibodies, as defined herein. For example, the therapeutic antibody is one or more selected from the group comprising: rituximab; pembrolizumab; nivolumab; cemiplimab; camrelizumab; dostarlimab; obinutuzumab; ofatumumab, and biosimilars or equivalents thereof.

It will be appreciated that, where one or more therapeutic antibody is present in the kit, the kit of the invention is for use in treating cancer in a subject, as is described herein.

FURTHER ASPECTS OF THE INVENTION

In a sixth aspect, disclosed herein is a method (or model) for predicting if a therapeutic antibody molecule binding specifically to a human target will be associated with a tolerability issue in connection with intravenous administration to a human, comprising the following step:

(i) intravenous or intraperitoneal administration of the therapeutic antibody molecule, if cross-reactive with murine target, or a surrogate antibody, to a mouse and observation of the mouse during a period following immediately after the administration of the therapeutic or surrogate antibody, wherein a display of the macroscopic symptoms isolation and decreased activity during the period followed by restoration of the state of the mouse to the normal state is an indication that

the intravenous administration of the therapeutic antibody molecule to a human will be associated with a tolerability issue,
and/or for predicting if a prophylactic or therapeutic treatment, an altered administration route and/or a modification of the therapeutic antibody molecule can prevent or mitigate a tolerability issue associated with intravenous administration to a human of a therapeutic antibody molecule binding specifically to a human target,
comprising the following step(s) in addition to (i) as set out above:

(ii) administration of a prophylactic or therapeutic agent to a mouse in conjunction with intravenous or intraperitoneal administration of the therapeutic or surrogate antibody to a mouse, and observation of the mouse during a period following immediately after the administration of the therapeutic or surrogate antibody, wherein a decreased display of the macroscopic symptoms compared to the macroscopic symptoms displayed by the mouse in (i) or no display of the macroscopic symptoms during the period is an indication that pre-treatment with the prophylactic or therapeutic agent in combination with administration of the therapeutic antibody molecule to a human can prevent or mitigate the tolerability issue that otherwise would be associated with intravenous administration of the therapeutic antibody molecule to a human;

(iii) administration of the therapeutic or surrogate antibody to a mouse by a route of administration other than intravenous or intraperitoneal administration, and observation of the mouse during a period following immediately after the administration of the therapeutic or surrogate antibody, wherein a decreased display of the macroscopic symptoms compared to the macroscopic symptoms displayed by the mouse in (i) or no display of the macroscopic symptoms during the period is an indication that the other route of administration can be used for administration of the therapeutic antibody molecule to a human to prevent or mitigate the tolerability issue that would be associated with intravenous administration of the therapeutic antibody molecule to a human; and/or

(iv) intravenous or intraperitoneal administration of a modified format of the therapeutic or surrogate antibody to a mouse by a route of administration other than intravenous or intraperitoneal administration, and observation of the mouse during a period following immediately after the administration of the modified therapeutic or surrogate antibody, wherein a decreased display of the macroscopic symptoms compared to the macroscopic symptoms displayed by the mouse in (i)

or no display of the macroscopic symptoms during the period is an indication that administration of the therapeutic antibody molecule in the modified format to a human can be used to prevent or mitigate the tolerability issue that would be associated with intravenous administration of the therapeutic antibody molecule to a human.

In a seventh aspect, disclosed herein is also a corticosteroid for use in a dosing regimen to prevent or mitigate a tolerability issue in connection with intravenous administration of a therapeutic antibody molecule to a subject,
wherein the therapeutic antibody molecule has been predicted to be associated with a tolerability issue in connection with intravenous administration to a human using the method described above, and/or wherein pre-treatment with the corticosteroid combination with administration of the therapeutic antibody molecule to a human has been predicted to prevent or mitigate the tolerability issue that otherwise would be associated with intravenous administration of the therapeutic antibody molecule to a human using the method described above,
and wherein the dosing regimen comprises administration of the corticosteroid to the subject in at least two doses prior to intravenous administration of the therapeutic antibody molecule, wherein one dose of the corticosteroid is administered 10-48 hours prior to start of the administration of therapeutic antibody molecule ("the first dose") and one dose of the corticosteroid is administered 5 minutes - 5 hours prior to the start of administration of the therapeutic antibody molecule ("the second dose").

A variant of this aspect relates to a corticosteroid for use in a dosing regimen to prevent or mitigate a tolerability issue in connection with intravenous administration of a therapeutic antibody molecule to a subject,
wherein the therapeutic antibody molecule is an anti-FcγRIIB antibody,
and wherein the dosing regimen comprises administration of the corticosteroid to the subject in at least two doses prior to intravenous administration of the therapeutic antibody molecule, wherein one dose of the corticosteroid is administered 10-48 hours prior to start of the administration of therapeutic antibody molecule ("the first dose") and one dose of the corticosteroid is administered 5 minutes - 5 hours prior to the start of administration of the therapeutic antibody molecule ("the second dose").

In an eighth aspect, disclosed herein is also a therapeutic antibody molecule for use in the treatment of cancer, wherein the therapeutic antibody molecule has been predicted to be associated with a tolerability issue in connection with intravenous administration to a human using the method described above and/or wherein the subcutaneous route of

administration of therapeutic antibody molecule to a human has been predicted to prevent or mitigate the tolerability issue that otherwise would be associated with intravenous administration of the therapeutic antibody molecule to a human using the method described above, and wherein the antibody is formulated for subcutaneous administration.

In a ninth aspect, disclosed herein is also a modified format of a therapeutic antibody molecule for use in the treatment of cancer, wherein the therapeutic antibody molecule has been predicted to be associated with a tolerability issue in connection with intravenous administration to a human using the method described above and/or wherein administration of the therapeutic antibody molecule in the modified format to a human has been predicted to prevent or mitigate the tolerability issue that otherwise would be associated with intravenous administration of the therapeutic antibody molecule to a human using the method described above, and wherein the therapeutic antibody molecule is an Fc receptor binding antibody and the modified format is an antibody having the same Fv variable sequence but having reduced, impaired or abrogated FcγR binding compared with the therapeutic antibody molecule.

In a tenth aspect, disclosed herein is also a method for preventing or mitigating a tolerability issue in connection with intravenous administration of a therapeutic antibody molecule to a subject comprising a corticosteroid dosing regimen, wherein the therapeutic antibody molecule has been predicted to be associated with a tolerability issue in connection with intravenous administration to a human using the predictive method described above, and/or wherein pre-treatment with the corticosteroid combination with administration of the therapeutic antibody molecule to a human has been predicted to prevent or mitigate the tolerability issue that otherwise would be associated with intravenous administration of the therapeutic antibody molecule to a human using the predictive method described above, and wherein the dosing regimen comprises administration of the corticosteroid to the subject in at least two doses prior to intravenous administration of the therapeutic antibody molecule, wherein one dose of the corticosteroid is administered 10-48 hours prior to start of the administration of therapeutic antibody molecule ("the first dose") and one dose of the corticosteroid is administered 5 minutes - 5 hours prior to the start of administration of the therapeutic antibody molecule ("the second dose").

In an eleventh aspect, disclosed is also a method for treatment of cancer comprising subcutaneous administration of a therapeutically active amount of a therapeutic antibody molecule which has been predicted to be associated with a tolerability issue in connection with intravenous administration to a human using the predictive method described above

and/or wherein the subcutaneous route of administration of therapeutic antibody molecule to a human has been predicted to prevent or mitigate the tolerability issue that otherwise would be associated with intravenous administration of the therapeutic antibody molecule to a human using the predictive method described above.

In a twelfth aspect, disclosed is also a method for treatment of cancer comprising administration of a therapeutically active amount of a modified format of a therapeutic antibody, wherein the therapeutic antibody molecule has been predicted to be associated with a tolerability issue in connection with intravenous administration to a human using the predictive method described above and/or wherein administration of the therapeutic antibody molecule in the modified format to a human has been predicted to prevent or mitigate the tolerability issue that otherwise would be associated with intravenous administration of the therapeutic antibody molecule to a human using the predictive method described above, and wherein the therapeutic antibody molecule is an Fc receptor binding antibody and the modified format is an antibody having the same Fv variable sequence but having impaired or abrogated FcγR binding compared with the therapeutic antibody molecule.

DETAILED DESCRIPTION OF THE FURTHER ASPECTS OF THE INVENTION

In brief, in these further aspects of the invention, we describe a model for predicting if a therapeutic antibody binding to a human target will be associated with a tolerability issue in connection with intravenous administration and/or for predicting if pre-treatment, altered administration route or modification of the antibody can prevent a tolerability issue associated with intravenous administration to a human of the therapeutic antibody. The model comprises administering the antibody intravenously or intraperitoneally to mice and observing the mice immediately after the administration for any transient display of the macroscopic symptoms isolation and decreased activity. The model may also comprise administration of a pre-treatment in combination with administration of the antibody, administration of the therapeutic antibody by a route of administration other than intravenous or intraperitoneal administration or administration of a modified format of the antibody to mice and observing the mice immediately after such administration for any transient display of the macroscopic symptoms isolation and decreased activity and comparing this with the transient display of the macroscopic symptoms isolation and decreased activity after the intravenous or intraperitoneal administration of the unmodified antibody without pre-treatment. Analyses of associated microscopic symptoms, changes in biochemical, or cellular parameters may help gathering information of the nature of the

IRR, and guide candidate preventative pre-medication or IRR reducing interventions to test in the model, as described below.

The predictive method described herein in the further aspects of the invention makes it possible to predict if a therapeutic antibody molecule to a given target will be associated with – or is likely to be associated with - a tolerability issue in connection with its intravenous administration to a human subject. Additionally or alternatively, it makes it possible to predict if a prophylactic or therapeutic treatment, an altered administration route and/or a modification of the therapeutic antibody molecule can be used to prevent or mitigate a tolerability issue associated with intravenous administration to a human of a therapeutic antibody molecule binding specifically to a human target.

In these further aspects of the invention, the therapeutic antibody molecule binds specifically to a human target. That the antibody binds specifically to the target means that it specifically binds to or interacts with a defined target molecule or antigen, and that this means that the antibody preferentially and selectively binds its target and not a molecule which is not a target.

The target to which the therapeutic antibody molecule binds may be a receptor or antigen found on any human cell. Examples of such cells are leukocytes, myeloid cells and B cells.

In some embodiments the target is FcγRII (CD32).
In some embodiments the target is FcγRIIB (CD32b).
In some embodiments the target is FcγRIIA (CD32a).
In some embodiments the target is CD40.

In these further aspects of the invention, the therapeutic antibody molecule may be any therapeutic antibody molecule that has received regulatory approval for use in humans or a therapeutic antibody molecule in clinical development or may be any antibody binding to a human target antigen intended or hypothesized to be of use for therapy of human disease. The term therapeutic antibody molecule as used herein also encompasses antibodies that are envisaged to be considered for, or are being developed for, therapeutic use, including antibodies in preclinical development. The therapeutic antibody molecule is thus an antibody that has therapeutic effects on humans. In the predictive method described herein, the therapeutic antibody molecule (if cross-reactive), or a surrogate antibody to the analogous mouse target, may be administered to a mouse. The mouse used is an immune competent laboratory mouse. Mice of different genetic background,

inbred or outbred, may be used. Further, mice transgenic for the human target of the therapeutic antibody molecule may be used.

Often, such a therapeutic antibody molecule is a monoclonal antibody. In many cases it is a human or humanized antibody.

In these further aspects of the invention, the therapeutic antibody molecule may be any type of antibody, such as immunoglobulin G (IgG), immunoglobulin A (IgA) or immunoglobulin M (IgM). In some embodiments, it is IgG. It may also be of any subclass, such as IgG1, IgG2, IgG3 or IgG4. It may also be an antibody molecule engineered for enhanced, reduced, or diminished FcγR-dependent engagement and function. Further, the therapeutic antibody molecule may be a mono-, bi- or tri-specific for the same or different targets and comprising or being fused to an antibody Fc domain. Moreover, the therapeutic antibody molecule may be a mono-, bi- or tri-specific for the same or different targets and not comprising an antibody Fc domain. Further, the therapeutic antibody molecule may be a functional fragment of an antibody, such as an Fv, consisting of the variable domain of an antibody, a Fab, also denoted F(ab), which is a monovalent antigen-binding fragment that does not contain a Fc part, or a $F(ab')_2$, which is an divalent antigen-binding fragment that contains two antigen-binding Fab parts linked together by disulfide bonds, or a F(ab'), i.e. a monovalent-variant of a $F(ab')_2$. Such a fragment may also be single chain variable fragment (scFv).

In some embodiments, the therapeutic antibody molecule is an antibody used in or intended for cancer therapy. Monoclonal antibodies have been and are being developed for a number of cancers, and more will likely follow. Some examples are brain cancer, breast cancer, chronic lymphocytic leukemia, colorectal cancer, head and neck cancers, Hodgkin's lymphoma, lung cancer, melanoma, non-Hodgkin's lymphoma, prostate cancer and stomach cancer. Some antibodies are approved for use in different indications. For example the anti-CD20 antibody rituximab is approved for use in both cancer (NHL and CLL) and autoimmune disease (rheumatoid arthritis). The method described herein is however not limited to antibodies used in cancer therapy or therapy of autoimmune/inflammatory disease.

As mentioned above, in some embodiments the target is FcγRIIB. In some preferred embodiments, the therapeutic antibody molecule has a light chain with SEQ ID No:1 and a heavy chain with SEQ ID No:2.

In these further aspects of the invention, the intravenous (iv) administration method used to administer the therapeutic antibody molecule to a human may be any type of intravenous administration, such as by injection or by infusion.

The predictive method described herein in these further aspects of the invention utilizes mice as a model to predict what will happen in humans. When the therapeutic antibody molecule to be tested is cross reactive with a known murine homologue of the human target, the therapeutic antibody molecule may be used in the predictive method. When the therapeutic antibody molecule to be tested is not cross reactive with a known murine homologue of the human target, it is necessary to use a surrogate antibody. The surrogate antibody is an antibody that is specific for a murine homologue of the human target to which the therapeutic antibody molecule binds. For example, in this context the murine homologue of the human target FcγRIIB is murine FcγRII, the murine homologue of the human target FcγRIIA is murine FcγRIII, and the murine homologue of the human target CD40 is murine CD40. The surrogate antibody may be a murine antibody or an antibody from another species, such as rat, rabbit, monkey or chicken. Sometimes, it may be preferable to use a surrogate antibody even if the therapeutic antibody molecule to be tested is cross reactive with a known murine homologue of the human target. This may be the case if the surrogate antibody's binding and interaction with mouse target antigen and mouse immune proteins regulating antibody activity e.g. FcγRs better reflect the interactions of the human candidate antibodies interaction with human target and human immune proteins regulating antibody activity e.g. FcγRs compared with the therapeutic antibody molecule itself. Preferably, and when available, both cross-reactive therapeutic antibody molecule and murine surrogate antibodies, may be used in parallel to test for tolerability issues as described herein.

In these further aspects of the invention, the therapeutic antibody molecule may be an antibody that binds or does not bind Fc receptors. A modified format can then be used, i.e. antibody variants with lower Fc-FcgR-engagement owing to isotype switching or Fc-engineering. If a surrogate antibody is used to predict or model tolerability issues of a therapeutic antibody molecule to the same or homologous target, then the Fc of the surrogate antibody should be chosen to match the therapeutic antibody molecule's Fc with respect to binding/non-binding (or engagement/non- engagement) of FcγR-binding and function. It is, for example, well known that both human IgG1, IgG3 and IgG4 productively bind and engage human FcγRs albeit with different absolute and relative affinities. Similarly, in the mouse, mIgG2a binds strongly and broadly to different mouse FcγRs, while mIgG1 binds only to mouse FcγRII and FcγRIII. It is further well known aglycosylation of antibodies, specifically in the 297 position (such as one of the following

mutations: N297A, N297Q or N297G), render both human and mouse IgG impaired and/or reduced, or severely reduced, for binding to FcγR. In this context, Fc binding means that the Fc part of the therapeutic antibody molecule binds to an FcγR which leads to engagement of Fc:FcγR dependent activities or functions. Furthermore, impaired or abrogated FcγR binding means that the modified format does not bind at all to FcγR or that it binds less strongly to FcγR than the therapeutic, unmodified antibody.

In these further aspects of the invention, the therapeutic antibody molecule or the surrogate antibody is administered intravenously or intraperitoneally to a mouse. In some cases, the dose of the therapeutic antibody molecule or the surrogate antibody administered to the mouse is the dose that results in high receptor saturation. In some cases, the dose of the therapeutic antibody molecule or the surrogate antibody administered to the mouse is the dose that results in at least 90% receptor saturation. In some cases, the dose of the therapeutic antibody molecule or the surrogate antibody administered to the mouse is the dose that results in close to 100% or 100% receptor saturation.

Once the antibody has been administered to the mouse the animal is observed for visual physical reactions, in particular behavior changes or macroscopic symptoms, are observed. If the therapeutic antibody molecule is an antibody that will be associated with a tolerability issue in connection with intravenous administration to a human, the mouse will starting to show the macroscopic symptoms isolation and decreased activity very shortly, i.e. within a few minutes, such as 5-10 minutes, after administration of the therapeutic or surrogate antibody. In some cases, the mouse will also display signs of impaired balance, piloerection, and/or hunching followed by un-natural body posture. These three additional macroscopic symptoms will be observed within the same time frame as the isolation and decreased activity, i.e. within a few minutes, such as 5-10 minutes, after administration of the therapeutic or surrogate antibody. The display of one, two or three of these additional macroscopic symptoms is a stronger predictive marker that the therapeutic antibody molecule binding specifically to a human target is likely to be associated with a tolerability issue in connection with intravenous administration to a human compared to if the mouse would only show signs of isolation and decreased activity.

A person experienced in working with laboratory mice will immediately notice if the above changes occurs in the mouse's behavior, since the signs are easy to observe and is a notable change of the mouse behavior prior to administration of the therapeutic or surrogate antibody. The symptoms are clearly manifested, and it is obvious that the mouse is not feeling well. After a period ending in about one hour, such as 45 minutes to 1.5

hours, after injection of the antibody (therapeutic or surrogate), the mouse no longer shows any macroscopic symptoms. Instead, its behavior is restored to the normal state, i.e. to the behavior prior to administration of the antibody (therapeutic or surrogate).

In addition to the above macroscopic symptoms, the mouse may demonstrate other symptoms. One such symptom is decreased blood pressure. Another such symptom is decreased platelet count. Another such symptom is elevated levels of the two liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Contrary to the macroscopic symptoms, these cannot be determined by simply observing the mouse. Instead they may be determined through blood analysis. To check these "non-macroscopic" symptoms, blood is drawn from the mouse approximately five minutes after injection of the antibody (therapeutic or surrogate). The blood is then analyzed for platelet count and/or levels of AST and/or ALT. Decreased blood pressure may also be determined this way; if the blood pressure is decreased, it will not be possible to draw blood from the mouse during the period during which the macroscopic symptoms are displayed. To determine if the platelet count is decreased and/or if the level of AST and/or ALT is elevated, it is possible to compare either with a blood sample drawn from the mouse prior to administration of the therapeutic antibody molecule or surrogate antibody or with a sample drawn from a control mouse. The decreased blood pressure will be restored within the same period as the macroscopic symptoms. The platelet count, AST level and ALT level will take a bit longer to be restored; it is normalized within 6-10 hours, such as within 8 hours.

The predictive method described herein in these further aspects of the invention can be used to predict if a therapeutic antibody molecule binding specifically to a human target will be associated with a tolerability issue in connection with intravenous administration to a human.

Moreover, the predictive method described herein in these further aspects of the invention can be used to test strategies for overcoming such a tolerability issue. More precisely, it can be used to predict if a specific strategy can prevent or mitigate a tolerability issue associated with intravenous administration to a human of a therapeutic antibody molecule binding specifically to a human target. This is useful for example for a therapeutic antibody molecule that is being clinically developed or is already used in the clinic for which tolerability issues have been observed.

Furthermore, the predictive method described herein In these further aspects of the invention can be used both to predict if a therapeutic antibody molecule binding specifically

to a human target will be associated with a tolerability issue in connection with intravenous administration to a human and to predict if a specific strategy can prevent or mitigate the tolerability issue. This may be of interest for example when developing a drug since it enables both identification of a potential problems and means of finding a solution to the problem.

If the predictive method described herein in these further aspects of the invention is to be used only to predict if a therapeutic antibody molecule binding specifically to a human target will be associated with a tolerability issue in connection with intravenous administration to a human, the method is performed as described above, with administration of the therapeutic or surrogate antibody followed by observance of the mouse. Normally, not only one mouse would be used, but instead a test group of several mice, such as 5-10, would be used and the experiment would be repeated to ascertain that any change observed is representative, reproducible and statistically significant.

If the predictive method described herein in these further aspects of the invention is to be used only to, or in addition to, predict if a specific strategy can prevent or mitigate a tolerability issue associated with intravenous administration to a human of a therapeutic antibody molecule binding specifically to a human target, the method described above is performed on a control mouse, or preferably on a control group of mice, such as 5-10 mice. In addition, a second mouse, or preferably a second group of mice, such as 5-10 mice, is treated in accordance with the specific strategy that is to be tested. The results for the second mouse, or second group of mice, are compared to the results for the control mouse, or control group of mice.

Examples of strategies for overcoming tolerability issue arising in connection with intravenous administration of a therapeutic antibody molecule to a human are different prophylactic treatments, different therapeutic treatments, altered administration routes and/or modifications of the therapeutic antibody molecule. By testing such strategies as described herein, data will be obtained that can be used to predict if that particular strategy can be used to prevent or mitigate a tolerability issue that would be associated with intravenous administration of a specific therapeutic antibody molecule to a human. Thus, it is possible to obtain reliable data without having to test the effect of different strategies on humans that first have to experience the tolerability issue(s).

When the strategy for overcoming a tolerability issue is a prophylactic treatment, a prophylactic agent is administered to the second mouse, or second group of mice, prior to the intravenous or intraperitoneal administration of the therapeutic or surrogate antibody

to the mouse, or group of mice. This strategy is thus pre-treatment with the prophylactic agent. The second mouse, or second group of mice, is observed during a period following immediately after the administration of the therapeutic or surrogate antibody The results for the second mouse, or second group of mice, are compared to the results for the control mouse, or control group of mice, which has not received the prophylactic agent. A decreased display of the macroscopic symptoms for the second mouse, or the second group of mice, compared to the control mouse, or control group of mice, or no display of the macroscopic symptoms at all for the second mouse, or second group of mice, during the period is an indication that administration of the prophylactic agent can be used to prevent or mitigate the tolerability issue that would be associated with intravenous administration of the therapeutic antibody molecule to a human.

The prophylactic agent tested this way may be any agent that is known to prevent or mitigate tolerability issues, or is hypothesized, or screened, for its ability to help mitigate tolerability issues.

In some embodiments of these further aspects of the invention, the prophylactic treatment is pre-treatment with a corticosteroid. In some such embodiments, the pre-treatment comprises two administrations of a corticosteroid. The corticosteroid is preferably a potent corticosteroid, and more preferably a corticosteroid with as high potency as possible or as available. Examples of such corticosteroids are dexamethasone and betamethasone.

When a pre-treatment with a corticosteroid, such as dexamethasone or betamethasone, is used it may comprise two administrations of the corticosteroid prior to administration of the therapeutic or surrogate antibody. In some such embodiments, one dose of corticosteroid is administered 10-48 hours prior to administration of the therapeutic or surrogate antibody, and the other is administered 5 minutes - 5 hours prior to administration of the therapeutic or surrogate antibody. In some such embodiments, one dose of corticosteroid is administered 6-36 hours prior to administration of the therapeutic or surrogate antibody, and the other is administered 15-120 minutes prior to administration of the therapeutic or surrogate antibody. In some such embodiments, the first dose of corticosteroid is administered 16-24 hours prior to administration of the therapeutic or surrogate antibody. In some such embodiments, the second dose of corticosteroid is administered 30-60 minutes prior to administration of the therapeutic or surrogate antibody.

When the strategy for overcoming a tolerability issue is a therapeutic treatment, this may be done by administering a therapeutic agent to the second mouse, or second group of

mice, in conjunction with the intravenous or intraperitoneal administration of the therapeutic or surrogate antibody to the mouse, or group of mice. In this context, in conjunction means essentially at the same time or shortly after. The second mouse, or second group of mice, is observed during a period following immediately after the administration of the therapeutic or surrogate antibody The results for the second mouse, or second group of mice, are compared to the results for the control mouse, or control group of mice, which has not received the therapeutic agent. A decreased display of the macroscopic symptoms for the second mouse, or the second group of mice, compared to the control mouse, or control group of mice, or no display of the macroscopic symptoms at all for the second mouse, or second group of mice, during the period is an indication that administration of the therapeutic agent can be used to prevent or mitigate the tolerability issue that would be associated with intravenous administration of the therapeutic antibody molecule to a human.

The therapeutic agent tested this way may be any agent or drug that is known to reverse or manage adverse events. Immune modulatory agents, such as antibodies, for example an anti-IL-6 antibody, known for use against cytokine release syndrome (Frey NV, Porter DL. Cytokine release syndrome with novel therapeutics for acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program. 2016;2016:567-572), or immune suppressive and/or anti-inflammatory agents, such as corticosteroids or anti-histamine.

When the strategy for overcoming a tolerability issue is a different route of administration, the therapeutic or surrogate antibody is administered to the second mouse, or second group of mice, by a route of administration other than intravenous or intraperitoneal administration. The second mouse, or second group of mice, is observed during a period following immediately after the administration of the therapeutic or surrogate antibody The results for the second mouse, or second group of mice, are compared to the results for the control mouse, or control group of mice, which has received therapeutic or surrogate antibody by intravenous or intraperitoneal administration. A decreased display of the macroscopic symptoms for the second mouse, or the second group of mice, compared to the control mouse, or control group of mice, or no display of the macroscopic symptoms at all for the second mouse, or second group of mice, during the period is an indication that administration of the therapeutic antibody molecule to a human by a route of administration other than intravenous or intraperitoneal can be used to prevent or mitigate the tolerability issue that would be associated with intravenous administration of the therapeutic antibody molecule to a human.

The administration route tested this way may be any route that is known to the skilled person and that is suitable for administration of the therapeutic antibody molecule to humans and also workable for administration of the therapeutic or surrogate antibody to mice.

In some embodiments of these further aspects of the invention, the different route of administration, i.e. the route of administration other than intravenous or intraperitoneal administration, is subcutaneous administration. The therapeutic or surrogate antibody should then be prepared or formulated for subcutaneous administration to the second mouse, or second group of mice.

When the strategy for overcoming a tolerability issue is using a modified format of the therapeutic or surrogate antibody, this modified format of the therapeutic or surrogate antibody is administered intravenous or intraperitoneal to the second mouse. The second mouse, or second group of mice, is observed during a period following immediately after the administration of the modified therapeutic or surrogate antibody The results for the second mouse, or second group of mice, are compared to the results for the control mouse, or control group of mice, which has received the unmodified therapeutic or surrogate antibody by intravenous or intraperitoneal administration. A decreased display of the macroscopic symptoms for the second mouse, or the second group of mice, compared to the control mouse, or control group of mice, or no display of the macroscopic symptoms at all for the second mouse, or second group of mice, during the period is an indication that administration of the modified therapeutic antibody molecule to a human can be used to prevent or mitigate the tolerability issue that would be associated with intravenous administration of the therapeutic antibody molecule to a human.

The modification of the therapeutic antibody molecule tested this way may be any modification known or unknown to give rise to less or less severe toxic events in humans. For example, if a therapeutic antibody molecule that is found to be associated with a tolerability issue in connection with intravenous administration to a human is an antibody that engages Fc receptors, such a modification may be to alter the antibody so that it does not engage Fc receptors or so that it has impaired or abrogated FcγR binding compared to the therapeutic non-modified antibody, while the Fv variable sequence of the modified antibody remains the same as the therapeutic antibody molecule. As mentioned above, the Fc of the surrogate antibody should be chosen to match the therapeutic antibody molecule's Fc with respect to binding/non-binding (or engagement/non- engagement) of FcγR-binding and function.

In some embodiments of these further aspects of the invention, the modification is one that leads to increased engagement of Fc receptors.

It is possible to test more than one of the above strategies, or several variants of one or more than one of the above strategies, at the same time by including further mice, or groups of mice, which one mouse, or group of mice for each strategy or each variant of a strategy.

Described herein in these further aspects of the invention is also a corticosteroid for use in a dosing regimen to prevent or mitigate a tolerability issue in connection with intravenous administration of a therapeutic antibody molecule to a subject, as well as a method for preventing or mitigating a tolerability issue in connection with intravenous administration of a therapeutic antibody molecule to a subject comprising a dosing regimen for administration of a corticosteroid to the subject.

The therapeutic antibody molecule in these further aspects of the invention may be one that has been predicted to be associated with a tolerability issue in connection with intravenous administration to a human using the predictive method described above. In addition, or alternatively, the predictive method described above may have been used to predict that pre-treatment with a corticosteroid in combination with administration of the therapeutic antibody molecule to a human is likely to prevent or mitigate the tolerability issue that otherwise would be associated with intravenous administration of the therapeutic antibody molecule to a human.

The dosing regimen comprises administration of the corticosteroid to a subject in at least two doses prior to intravenous administration of the therapeutic antibody molecule. One dose ("the first dose") of the corticosteroid is administered 10-48 hours prior to start of the administration of therapeutic antibody molecule and one dose ("the second dose")of the corticosteroid is administered 5 minutes - 5 hours prior to the start of administration of the therapeutic antibody molecule .In addition to these two doses, it is possible to use further doses, such as one dose prior to "the first dose", and/or one dose between "the first dose" and "the second dose". Often, a patient is given several administrations of a therapeutic antibody molecule during a whole therapy. The two doses of corticosteroid may then be administered to the patient in connection with one or several administrations of the therapeutic antibody molecule. Preferably, the two doses are given to the patient in connection with each administration of the therapeutic antibody molecule.

In some cases, the first dose of corticosteroid is given 6-36 hours prior to start of administration of the therapeutic antibody molecule and the second dose of corticosteroid is given immediately prior to start of administration of the therapeutic antibody molecule. In this context, immediately prior means approximately 15-120 minutes prior to start of administration of the therapeutic antibody molecule.

In some cases, the first dose of corticosteroid is given 8-30 hours prior to start of administration of the therapeutic antibody molecule.

In some cases, the first dose of corticosteroid is given 16-24 hours prior to start of administration of the therapeutic antibody molecule.

In some cases, the second dose of corticosteroid is given 30-60 minutes prior to start of administration of the therapeutic antibody molecule.

In some cases, the first dose of corticosteroid is given 16-24 hours prior to start of administration of the therapeutic antibody molecule and the second dose of corticosteroid is given 30-60 minutes prior to start of administration of the therapeutic antibody molecule.

In some case, the dosing regimen comprises administration of at least two doses of the corticosteroid prior to each infusion of the antibody during the course of antibody therapy.

The corticosteroid used is preferably a potent corticosteroid, and more preferably a corticosteroid with as high potency as possible or as available. Examples of such corticosteroids are dexamethasone and betamethasone. It is possible to use either dexamethasone or betamethasone, or a a combination of dexamethasone and betamethasone.

In some cases when dexamethasone is used, the first dose is 4-20 mg. In some cases when dexamethasone is used, the second dose is 4-25 mg. In some cases when dexamethasone is used, the first dose is 4-20 mg and second dose is 4-25 mg. In some cases when dexamethasone is used, the first dose is 10-12 mg.

In some cases when dexamethasone is used, the second dose is 20 mg. In some cases when dexamethasone is used, the first dose is 10-12 mg and the second dose is 20 mg. In some cases when betamethasone is used, the first dose is 3.2-16 mg. In some cases when betamethasone is used, the second dose is 3.2-20 mg.

In some cases when betamethasone is used, the first dose is 3.2-16 mg and the second dose is 3.2-20 mg. In some cases when betamethasone is used, the first dose is 8-9.6 mg. In some cases when betamethasone is used, the second dose is 16 mg. In some cases when betamethasone is used, the first dose is 8-9.6 mg and the second dose is 16 mg.

In some cases, the dosing regimen comprises administration of an antihistamine in addition to the at least two administrations of a corticosteroid. In some cases, the antihistamine is administered 10 minutes – 24 hours prior to start of administration of the therapeutic antibody molecule. In some cases, the antihistamine is administered 30-60 minutes prior to start of administration of the therapeutic antibody molecule.

The therapeutic antibody molecule, for with the corticosteroid is used to prevent or mitigate a tolerability issue in connection with intravenous administration is in some cases an Fc receptor binding antibody. In some cases, it is an anti-FcγRIIB antibody. In some cases, it is the anti-FcγRIIB antibody is the antibody having a light chain with SEQ ID No: 1 and a heavy chain with SEQ ID No: 2.

In a thirteenth aspect of the invention, described herein is also a therapeutic antibody molecule for use in the treatment of cancer, wherein the therapeutic antibody molecule is formulated for subcutaneous administration in order to prevent or mitigate a tolerability issue that would occur in connection with intravenous administration of the therapeutic antibody molecule to a subject, as well as a method for treatment of cancer comprising subcutaneous administration of a therapeutic antibody instead of intravenous administration in order to prevent or mitigate a tolerability issue.

In some cases, the therapeutic antibody molecule formulated for subcutaneous administration is an anti-FcγRIIB antibody. In some such cases, the therapeutic antibody molecule is the antibody having a light chain with SEQ ID No: 1 and a heavy chain with SEQ ID No: 2.

In a fourteenth aspect of the invention, described herein is also a modified format of a therapeutic antibody molecule for use in the treatment of cancer, wherein the modification of the therapeutic antibody molecule is made in order to prevent or mitigate a tolerability issue that would occur in connection with intravenous administration of the therapeutic antibody molecule to a subject, as well as a method for treatment of cancer comprising administration of such a modified format of a therapeutic antibody.

The modification of the therapeutic antibody molecule used may be any modification known to give rise to less or less severe toxic events in humans.

As mentioned above, the modification of the therapeutic antibody may also be a modification previously unknown to give rise to less or less severe toxic events in humans that has been tested with the predictive model described herein and found to be useful in order to prevent or mitigate a tolerability issue that would occur in connection with intravenous administration of the therapeutic antibody molecule to a subject.

As mentioned above, one example is that if a therapeutic antibody molecule that is found to be associated with a tolerability issue in connection with intravenous administration to a human is an antibody that engages Fc receptors, a modification used in the present context may be to alter the antibody so that it does not engage Fc receptors or so that it has impaired or abrogated FcγR binding compared to the therapeutic non-modified antibody, while the Fv variable sequence of the modified antibody remains the same as the therapeutic antibody molecule.

Thus, in some such cases, the therapeutic antibody molecule is an Fc receptor binding antibody and the modified format is an antibody having the same Fv variable sequence but having impaired or abrogated FcγR binding compared with the therapeutic antibody molecule. In some case, the therapeutic antibody is an Fc receptor binding antibody anti-FcγRIIB antibody, and in some such cases, the modified format is anti-FcγRIIB antibody is the antibody having a light chain with SEQ ID No: 1 and a heavy chain with SEQ ID No: 195.

In some cases the anti-FcgRIIB antibody is used as single agent. In other cases it is used to enhance activity, or overcome resistance, to other therapeutic antibodies whose activity is modulated by FcgRs e.g. anti-CD20 or anti-PD-1.

With reference to combined treatment anti-CD20 antibodies, anti-FcgRIIB may be used to in treatment of both cancer and inflammatory/autoimmune disease where anti-CD20 antibodies have been approved for therapy. The term subject used herein refers to a human who has been diagnosed as having a specific disease. Herein, the terms subject and patient are used interchangeably.

In some cases, the subject has been diagnosed with a cancer. In some such cases, the cancer is a B-cell malignancy. In some such cases, the cancer is selected from the group

consisting of non-Hodgkin lymphoma, such as follicular lymphoma, diffuse large B cell lymphoma, mantle cell lymphoma, or chronic lymphocytic leukemia.

In some cases, the tolerability issue that is prevented or mitigated is thrombocytopenia (decrease of platelets). In some such cases, it is transient thrombocytopenia.

In some cases, the tolerability issue that is prevented or mitigated is cytokine release syndrome. In some such cases, it is transient cytokine release.

In some cases, the tolerability issue that is prevented or mitigated is elevated liver enzymes. In some such cases, it is elevated levels of aspartate aminotransferase (AST) and/or elevated levels of alanine aminotransferase (ALT).

In a fifteenth aspect of the invention, there is provided a therapeutic antibody molecule for use in the treatment of cancer, an autoimmune disease, an inflammatory disease, an immunological disease, and/or an infectious disease, wherein the therapeutic antibody molecule is an anti-FcγRIIB antibody, and wherein the therapeutic antibody molecule is formulated for subcutaneous administration.

In a sixteenth aspect of the invention, there is provided a therapeutic antibody molecule in the manufacture of a medicament for use in the treatment of cancer, an autoimmune disease, an inflammatory disease, an immunological disease, and/or an infectious disease, wherein the therapeutic antibody molecule is an anti-FcγRIIB antibody having a light chain with SEQ ID No: 1 and a heavy chain with SEQ ID No: 2, and wherein the medicament is formulated for subcutaneous administration.

In a seventeenth aspect of the invention, there is provided a pharmaceutical formulation comprising a therapeutic antibody molecule, wherein the therapeutic antibody molecule is an anti-FcγRIIB antibody having a light chain with SEQ ID No: 1 and a heavy chain with SEQ ID No: 2, and wherein the pharmaceutical formulation comprises a pharmaceutically acceptable diluent or excipient, and is formulated for subcutaneous administration.

Preferably, the therapeutic antibody in these aspects of the invention is an Fc receptor binding antibody. More preferably, the therapeutic antibody is an anti-FcγRIIB antibody.

In alternative embodiments of these aspects of the invention, the therapeutic antibody molecule is as described herein in any of the previous aspects of the invention herein.

However, in a preferred embodiment, the pharmaceutical composition comprises a therapeutic antibody molecule having a light chain with SEQ ID No:1 and a heavy chain with SEQ ID No:2 (which antibody is denoted as BI-1206, as described herein). Preferably, the therapeutic antibody molecule comprises a light chain with SEQ ID No:1, and a heavy chain with SEQ ID No:2, and constant regions with SEQ ID No:202 and 203.

Thus, the invention also provides the following:

- a therapeutic antibody molecule for use in the treatment of cancer, wherein the therapeutic antibody molecule is an anti-FcγRIIB antibody having a light chain with SEQ ID No: 1 and a heavy chain with SEQ ID No: 2, and wherein the therapeutic antibody molecule is formulated for subcutaneous administration;

- use of a therapeutic antibody molecule in the manufacture of a medicament for use in the treatment of cancer, wherein the therapeutic antibody molecule is an anti-FcγRIIB antibody having a light chain with SEQ ID No: 1 and a heavy chain with SEQ ID No: 2, and wherein the therapeutic antibody molecule and/or medicament is formulated for subcutaneous administration;

- a pharmaceutical formulation comprising a therapeutic antibody molecule, wherein the therapeutic antibody molecule is an anti-FcγRIIB antibody as defined herein (and is preferably an anti-FcγRIIB antibody having a light chain with SEQ ID No: 1 and a heavy chain with SEQ ID No: 2), and wherein the pharmaceutical formulation comprises a pharmaceutically acceptable diluent or excipient, and is formulated for subcutaneous administration.

Preferably, the therapeutic antibody molecule for use, the use of a therapeutic antibody molecule, or the pharmaceutical formulation according to the above aspects of the invention (including the fifteenth, sixteenth and seventeenth aspects of the invention) are for treatment of cancer.

It will be appreciated that the pharmaceutical formulation of these aspects of the invention comprises a therapeutically effective amount of the therapeutic antibody. Preferably, the therapeutic antibody is present at a concentration of between about 90mg/mL and about 220mg/mL. For example, the therapeutic antibody may be present at a concentration of about 90mg/mL, or about 100mg/mL, or about 110mg/mL, or about 120mg/mL, or about 130mg/mL, or about 140mg/mL, about 150mg/mL, or about 160mg/mL, or about 170mg/mL, about 180mg/mL, or about 190mg/mL, or about 200mg/mL, about

210mg/mL, or about 220mg/mL. Particularly preferred is a concentration of about 150mg/mL.

It is preferred that the pharmaceutical formulation of these aspects of the invention is sterile.

In a preferred embodiment, the pharmaceutical formulation of these aspects of the invention further comprises between about 5mM and about 20mM acetate, for example, about 10mM acetate, or about 15mM acetate. Particularly preferred is about 5mM acetate.

In a preferred embodiment, the pharmaceutical formulation of these aspects of the invention further comprises between about 50mM and about 250mM NaCl, for example, about 60mM NaCl, or about 70mM NaCl, or about 80mM NaCl, or about 90mM NaCl, or about 100mM NaCl, or about 110mM NaCl, or about 120mM NaCl, or about 130mM NaCl, or about 140mM NaCl, or about 150mM NaCl, or about 160mM NaCl, or about 170mM NaCl, or about 180mM NaCl, or about 190mM NaCl, or about 200mM NaCl, or about 210mM NaCl, or about 220mM NaCl. Particularly preferred is about 110mM NaCl.

In a preferred embodiment, the pharmaceutical formulation of these aspects of the invention further comprises about 0.05% (w/v) Polysorbate 20, such as Tween 20 (Polysorbate) EMPROVE® ESSENTIAL Ph Eur,JPE,NF from Merck/Sigma Aldrich with catalogue No. 8.17072.1000.

In a preferred embodiment, the pharmaceutical formulation of these aspects of the invention is at a pH of between about pH 5.0 and about pH 5.8, for example about pH 5.1, or about pH 5.2, or about pH 5.3, or about pH 5.4, or about pH 5.5, or about pH 5.6, or about pH 5.7. Particularly preferred is a pH of about pH 5.8.

In a particularly preferred embodiment, the pharmaceutical formulation of these aspects of the invention comprises or consists of:

- the therapeutic antibody at a concentration of 150mg/mL;
- 5mM acetate;
- 110mM NaCl;
- 0.05% (w/v) Polysorbate 20; and
- pH 5.8.

In an eighteenth aspect of the invention, there is provided a method for the treatment of cancer, an autoimmune disease, an inflammatory disease, an immunological disease, and/or an infectious disease in a subject, the method comprising the step of administering to the subject a therapeutic antibody molecule, wherein the therapeutic antibody molecule is an Fc receptor binding antibody, and wherein the therapeutic antibody molecule is formulated for subcutaneous administration.

Preferably, in the eighteenth aspect of the invention, the Fc receptor binding antibody is an anti-FcγRIIB antibody. More preferably, the Fc receptor binding antibody is an anti-FcγRIIB antibody having a light chain with SEQ ID No: 1 and a heavy chain with SEQ ID No: 2.

Thus, in a preferred embodiment, the invention provides:

- a method for the treatment of cancer, an autoimmune disease, an inflammatory disease, an immunological disease, and/or an infectious disease in a subject, the method comprising the step of administering to the subject a therapeutic antibody molecule, wherein the therapeutic antibody molecule is an anti-FcγRIIB antibody having a light chain with SEQ ID No: 1 and a heavy chain with SEQ ID No: 2, and wherein the therapeutic antibody molecule is formulated for subcutaneous administration. It will be appreciated that, in the eighteenth aspect of the invention, the therapeutic antibody is preferably administered to the subject by a subcutaneous route of administration.

In a nineteenth aspect of the invention, there is provided a method for the treatment of of cancer, an autoimmune disease, an inflammatory disease, an immunological disease, and/or an infectious disease in a subject, the method comprising the step of administering to the subject a pharmaceutical formulation of the seventeenth aspect of the invention. It will be appreciated that, in the nineteenth aspect of the invention, the pharmaceutical formulation is preferably administered to the subject by a subcutaneous route of administration. It is preferred that the method is for the treatment of cancer.

Preferred, non-limiting examples which embody certain aspects of the invention will now be described, with reference to the following figures and examples:

DESCRIPTION OF THE FIGURES

Figure 1: A mouse model that recapitulates BI-1206 tolerability profile. When the murine surrogate anti-CD32b antibody (AT-130-2 IgG2a) is injected into wildtype C57/BL6 mice intravenously (i.v.) or intraperitoneally (i.p.) the mice display reactions that recapitulates the BI-1206 tolerability profile in the clinic. **A.** shows the % of mice displaying macroscopic IRRs such as, isolation, decreased activity, impaired balance, piloerection, hunching followed by un-natural body posture after injection. When titrating the i.v. dose the same timing and severity of macroscopic symptoms is seen down to 10mg (0.5 mg/kg). However, at 4mg (0.2 mg/kg) no IRRs were seen. When administrating 200mg (10mg/kg) i.p. a delay in IRRs onset was seen in comparison with i.v. injection with the IRRs appearing 20-30 minutes post injection. When increasing the i.p. dose to 400mg (20mg/kg) the onset of IRRs was still delayed compared to the i.v. injection route however, all mice displayed IRRs to the same extent and grade as 200mg i.v. All mice had fully recovered 1h post injection. **B.** PLT (platelet counts in blood) were analysed in fresh blood using a Vetscan shows that mice displaying IRRs (gray bars) also display a decrease in platelet counts. **C.** Blood samples were also analyzed for AST showing an increase in the group receiving 200ug anti-CD32b antibody i.v. **D.** shows IL6 levels in blood of mice injected i.p. with 200ug anti-CD32b antibody over time post injection. A peak is seen 1h post injection and levels are back to normal 8h post injection (gray area). A similar pattern was seen for IL-5, IL-10, KC/GRO, TNF-α.

Figure 2: Pre-medication with two doses of corticosteroids dose-dependently block or reduce IRRs in vivo. Mice were either pretreated with: **A** 40 mg/kg or **B** 10 mg/kg Betamethasone 24h and 1h (premed) pre i.v. injection of 10 mg/kg AT-130-2 IgG2a. Mice were bled 20 minutes post injection. The blood was analyzed for platelet counts. Premedication with 10 mg/kg Betamethasone did not completely inhibited IRRs or decrease in platelet count B (striped bars) indicating that lowering the dose of premedication might reduce its potential to inhibit IRRs and platelet decreases.

Figure 3: Split dose – a small pre-dose of Ab lowers the severity of IRRs and platelet decrease. A. Split-dosing was initiated with 8ug/mouse of mouse anti-CD32B AT-130-2 IgG2a i.v. followed by a bulk-dose of 200ug/mouse 1h later. In parallel mice were injected with only the bulk-dose. IRRs were studied (and visualized in the figure according to the grading system in **B**) and platelet counts, and body temperature was measured and compared. A small pre-dose of AT-130 (8ug) lowers the severity/protects against IRR's, platelet decrease, and body temperature decrease when giving a large/main dose (200ug). Gray area indicates normal range of PLT (platelet counts in blood) and body temperature. The pre-dose needs to be 8ug (a dose where IRRs are seen in 50% of the mice **C**), lower doses are not protective.

Figure 4: Combined pre-medication with steroids and antibody split-dosing is needed for full (antibody) tolerance and protection against IRRs. Split-dosing was initiated either: **A** 24h post suboptimal corticosteroid treatment (10mg/kg) or **B** without corticosteroid pretreatment with 8ug/mouse of mouse anti-CD32B AT-130-2 IgG2a i.v. followed by a bulk-dose of 200ug/mouse 1h later. In parallel, mice were injected with only the bulk-dose. IRRs were studied and platelet counts, and body temperature was measured and compared. The small pre-dose of AT-130 (8ug) is well tolerated if a "low" dose of corticosteroids (10mg/kg) is given 24h before. The suboptimal pre-med together with the small pre-dose of AT-130 (8ug) fully protects against IRR's and platelet decrease associated with a large Ab dose (200ug). Suboptimal dose corticosteroids (10mg/kg) is not protective itself. Gray area indicates normal range of PLT and body temperature.

Figure 5: Pre-medication with several different clinically relevant substances does not inhibit IRRs associated with AT-130-2 IgG2a administration. In order to evaluate if pre-treatment with substances generally used in the clinic to treat IRRs could inhibit IRRs in this model, mice were pre-treated with anti-PAF, anti-IL6, anti-histamine or with a leukotriene-antagonist. These pre-medications were given i.p 1h prior to injection i.v of mouse anti-CD32B AT-130-2 IgG2a as a bulk dose of 200 ug/mouse. Mice were observed for macroscopic IRRs such as isolation, mobility, and fur condition. None of these pre-medications could inhibit IRRs.

Figure 6: Tolerability profile seen in human subjects with non-hodgkins B-cell lymphoma after administration of BI-1206 at doses of 70-100mg. (A) Platelet decrease following treatment with BI-1206. The decrease is transient and most episodes have been resolved within a week and never serious or associated with bleeding. Each dot denotes a measurement and the line median. Vertical striped line indicates BI-1206 administration. (B) Platelet decrease is associated with ALT elevations. Though ALT/AST elevations have only been significant in 3/14 patients. (C) Frequency of detected cytokine elevations following treatment with BI-1206. A transient cytokine release has been detected in 7 of 8 subjects where serum/plasma has been available for analysis. The peak cytokine release is seen immediately after infusion and always gone within 24h. (D) Kinetics of platelet decrease, ALT and cytokine elevations is exemplified by individual 504-001. Cytokines are here exemplified by IL-6.

Figure 7: FcgRIIb receptor occupancy translates into B cell depletion. Clinical data is in line with pre-clinical data from *in vivo* models using hFcgRIIB transgenic mice where it has been demonstrated that a sustained receptor

saturation is necessary to achieve sustained B lymphocyte depletion. Two doses of corticosteroids prior to administration anti-FcgRIIb mAb and a small pre-dose of mAb (split dose) improves tolerability (IRRs). FcgRIIb receptor occupancy on peripheral B cells (A) and peripheral B cell levels (B) in human subjects with non-hodgkins B-cell lymphoma treated with 100mg BI-1206 monotherapy. FcgRIIb receptor occupancy (E) and peripheral B cell depletion (F) in hFcgRIIB transgenic mice after i.v. administration of increasing doses of BI-1206. (C) Grade of infusion related reactions (IRRs) in human subjects with non-hodgkins B-cell lymphoma treated with 70-100mg BI-1206. Dark grey bars with black symbols denotes administrations without pre-medication with two doses of corticosteroids; light grey bars and open white symbols denotes administrations with pre-medication with two doses of corticosteroids. On the X-axis subject id and antibody dose is indicated. (D) Significantly lower frequency and severity of IRRs are seen after implementation of premedication with two doses of corticosteroids in the clinical protocol; black symbols dosing without two doses of corticosteroids, grey symbols dosing with two doses of corticosteroids; $P<0.0001$ using Mann Whitney U-test. (G) Infusion related reactions after i.v. administration of anti-FcgRIIb mAb (AT-130-2 mIgG2a) in wild type mice. Dose titration shows that at 0.4mg/kg Ab IRRs appear in approximately 50% of the animals and at i.v. administrated doses above IRRs are seen in 100% of the animals. Pre-medication with two 40mg/kg doses of betapred completely block IRRs whereas two 40mg/kg doses of betapred partly block IRRs. Adding split dos to the suboptimal 10mg/kg betapred blocks IRRs. The split dose is a small pre-dose of 0.4mg/kg Ab followed by a large dose of 10mg/kg Ab. (H) Improved tolerability and sustained efficacy is seen after implementation of premedication with two doses of corticosteroids in the clinical protocol. CR: complete response; PR: partial response; SD: stable disease; DLT: dose limiting toxicity.

Figure 8. Transient FcγRIIB receptor occupancy and peripheral lymphocyte depletion after BI-1206 infusion. Fig. 8 A) FcγRIIB receptor occupancy on peripheral B cells after BI-1206 infusion followed over time in subjects having received 100 mg BI-1206 (n=8). Vertical dashed lines denote BI-1206 infusions. At second and third BI-1206 infusion receptor occupancy data is only available pre-infusion. Line denotes the median. Based on preliminary data. Fig. 8 B) Peripheral lymphocytes after BI-1206 infusion followed over time in subjects having received 100 mg BI-1206 (n=9). Vertical dashed lines denote BI-1206 infusions. Line denotes the median. Based on preliminary data.

Figure 9. Transient decrease of platelets associates with increase in ALT after BI-1206 infusion. Fig. 9 A) Platelet count after BI-1206 infusion followed over time in subjects having received 70-100 mg BI-1206 (n=16). Vertical dashed lines denote BI-

1206 infusions. Line denotes the median. Based on preliminary data. Fig. 9 B) Fold increase of ALT versus percent platelet depletion (n=16). Changes are calculated in relation to day 1, pre-BI-1206-infusion. Based on preliminary data.

Figure 10. Cytokine release after BI-1206 infusion. Number of patients with plasma/serum increase of different cytokines detected at end of BI-1206 infusion. To be considered as positive the value should be >10-fold increased as compared to pre-infusion and >10-fold above the upper limit of normal range (ULN). Samples for analysis have been available from 5 subjects receiving ≥70 mg BI-1206. Based on preliminary data.

Figure 11. Two doses of dexamethasone relieved IRRs, platelet decrease, and transaminase increase in two subjects receiving BI-1206. Platelet count and ALT in subjects 501-001 (Fig. 11 A) and 503-002 (Fig. 11 B). Vertical dashed lines denote antibody infusions. The first infusion in each subject was rituximab alone and the following BI-1206 and rituximab. Grade of IRR at each antibody infusion is indicated. 501-001 and 503-002 received 12 mg and 4 mg dexamethasone, respectively, the evening before and again 20 mg dexamethasone 30 minutes prior to the third administration of BI-1206 (70 mg) during induction therapy. None of the subjects suffered any IRRs after this premedication regimen with two doses of dexamethasone. During the previous two infusions with BI-1206, where dexamethasone (20 mg) was given only 30 minutes prior to infusion, IRRs (grade 2-3) had been experienced. In addition, in subject 501-001 and 503-002 no/low platelet decrease, and no ALT/AST increase was seen after BI-1206 administration when premedicating with two doses of dexamethasone.

Figure 12. Macroscopic symptoms after injection of murine surrogate anti-CD32b (AT-130-2 IgG2a). The murine surrogate anti-CD32b (AT-130-2 IgG2a) was injected into wildtype C57/BL6 mice through 3 different injection routes, intravenously i.v., intraperitoneally i.p. or subcutaneously s.c. Macroscopic symptoms were seen after i.v. and i.p. injection. These macroscopic symptoms included isolation, decreased activity, impaired balance, piloerection, hunching followed by un-natural body posture and the macroscopic symptoms were scored from 0-2 based on the observations. When titrating the i.v. dose a rapid onset of IRRs was seen 5-7 minutes post injection. The same timing and severity of macroscopic symptoms was seen down to 10 µg (0.5 mg/kg). However, at 1 µg (0.05 mg/kg) no macroscopic symptoms were seen. When administrating 200 µg (10 mg/kg) i.p. a delay in onset of macroscopic symptoms was seen in comparison with i.v. injection with the macroscopic symptoms appearing 20-30 minutes post injection. In contrast to the i.v. injection route all mice in this group did not display macroscopic

symptoms and the macroscopic symptoms were less severe in several mice. When increasing the i.p. dose to 400 µg (20 mg/kg) the onset of macroscopic symptoms was still delayed compared to the i.v. injection route however, all mice displayed macroscopic symptoms to the same extent and grade as 200 µg i.v. All mice had fully recovered 1 hour post injection. Finally, when administrating 200 µg to mice s.c., no macroscopic symptoms were seen (up to 24 hours post injection). When increasing the s.c. dose to 400 µg the mice remained unaffected.

Figure 13. Pharmacokinetic profiles of AT-130-2 IgG2a in C57BL/6 mice. Observed AT-130-2 serum concentrations in mice treated with AT-130 via three different administrations routes; 200 µg AT-130-2 via i.v. injection, 200 µg AT-130-2 via i.p. injection and 400 µg AT-130-2 via s.c. injection. Presented data are the mean of 1-4 mice/dose groups. Abbreviations: h=hour(s); i.p. intraperitoneal, i.v. intravenous, s.c. subcutaneous. Note that complete and sustained FcgRIIB receptor is achieved with following s.c. dosing of AT130, although s.c. C_{Max} is lower and kinetics to obtain full saturation is slower compared with i.v. or i.p. dosing.

Figure 14. Correlation between macroscopic symptoms (denoted IRRs in this figure) and high, rapid exposure of AT-130-2 rather than time of FcγRIIB saturation. The serum concentration of AT-130-2 IgG2a (line with dots) is plotted against the grade of macroscopic symptoms (line with squares) for the different administration routes (A: i.v., B: i.p. and C: s.c.). When comparing the serum concentration of AT-130-2 and the presumed receptor occupancy (RO) (dotted line, 10 mg/ml gives 100% receptor saturation) with the onset, severity and duration of IRRs it is clear that there is a correlation between high and rapid exposure of AT-130-2, rather than time of FcγRIIB saturation. Tolerability showing a clear pattern of s.c. > i.p. > i.v. with RO being sustained for a long period of time post recovery from macroscopic symptoms.

Figure 15A. Timing of platelet (PLT) nadir is correlated to the route of administration and time to FcγRIIB saturation. Mice were bled at different time points post injection of AT-130-2 IgG2a and the blood was analyzed for blood platelet count (PLT) in an automated Vetcount. A nadir in platelet count was seen at the same time as onset of macroscopic symptoms after injection of AT-130-2 through both the i.v. and i.p. administration route. For the s.c. administration route where no macroscopic symptoms are seen, a moderate drop was seen 10 hours post injection correlating with the time to FcγRIIB saturation according to PK. In all cases the PLT decrease was transient and was restored to values in the normal range within 8 hours post injection. Mice presenting macroscopic symptoms are shown with filled bars.

Figure 15B shows that transaminase increase following injection of AT-130-2 IgG2a is circumvented when using the s.c. administration route. Mice were bled post injection of AT-130-2 IgG2a and the blood was analyzed for transaminases. For the i.v. administration route an increase is seen in transaminases (AST) 1h post onset of macroscopic symptoms (previously established as time point for a peak value in transaminases). For the s.c. administration route where no macroscopic symptoms are seen, no increase in transaminases was seen 11 hours post injection (1h post the time of FcγRIIB saturation according to PK (10h)).

Figure 16: Transient platelet decrease, transaminase increase and cytokine release, after administration of AT-130-2 IgG2a. Mice were bled at different time points after i.p. injection of 200 µg AT-130-2 and the blood was analyzed for platelet counts (Fig. 16 A), transaminases (Fig. 16 B) and cytokines (Fig. 16 C). A transient PLT decrease was seen with the PLT counts fully restored 8 hours post injection (Fig. 16 A). An increase in transaminases (AST and ALT) with a peak 1h post injection was the only clinical chemistry parameter affected by AT-130-2 injection (Fig. 16 B). These increases were just like the PLT decrease transient. The same transient increase was seen when AT-130-2 was injected i.v. and no increase in transaminases was detected when AT-130-2 was injected s.c. (data not shown). A panel of cytokines including the analytes IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12p70, KC/GRO, TNF-α were analyzed at different time points post injection of 200 mg i.p. Of the analyzed cytokines IL-5, IL-6, IL-10, KC/GRO, TNF-α showed a transient increase with them all except for IL-5 peaking 1-3 hours post injection (Fig. 16 C). IL-5 showed a delayed peak 3-8 hours post injection (Fig. 16 C). These are the same cytokines that have been indicated to increase in some patients in the clinical studies with BI-1206.

Figure 17. Premedication with 2 doses of corticosteroids inhibits macroscopic symptoms associated with AT-130-2 IgG2a administration. Mice were either pretreated with 40 mg/kg betamethasone 24 hours and 1 hour or left untreated pre i.v. injection of 10 mg/kg AT-130-2 IgG2a. Mice were observed for macroscopic symptoms (Fig. 17 A) and bleed 20 minutes post injection. The blood was analyzed for (Fig. 17 B) platelet counts, (Fig. 17 C) transaminases and cytokines. Premedication with betamethasone completely inhibited the macroscopic symptoms (Fig. 17 A), decrease in platelet count (Fig. 17 B) and reduced the transaminases increase (Fig. 17 C). The transient cytokine release seen after i.v. injection of AT-130-2 was also inhibited by the premedication (data not shown). The same results were seen when using dexamethasone (data not shown).

Figure 18. The dose of premedication is of importance. Mice were either pretreated with 40 mg/kg or 10 mg/kg Betamethasone 24 hours and 1 hour (premed) pre i.v. injection of 10 mg/kg AT-130-2 IgG2a. Mice were observed for macroscopic symptoms (Fig. 18 A) and bleed 20 minutes post injection. The blood was analyzed for (Fig. 18 B) platelet counts. Premedication with 10 mg/kg Betamethasone did not completely inhibited macroscopic symptoms (Fig. 18 A) or decrease in platelet count (Fig. 18 B) indicating that lowering the dose of premedication might reduce its potential to inhibit macroscopic symptoms and platelet decreases.

Figure 19. Steroid premedication 1 hour prior to infusion is not sufficient to inhibit IRRs. Mice were either pretreated with 40 mg/kg Betamethasone 24 hours, 1 hour or 24 hours + 1 hour pre i.v. injection of 10 mg/kg AT-130-2 IgG2a. Mice were observed for macroscopic symptoms (Fig. 19 A) and bleed 10-20 minutes post injection. The blood was analyzed for platelet counts (Fig. 19 B). Single premedication with betamethasone 1 hour post injection of AT-130-2 did not inhibited macroscopic symptoms (Fig. 19 A) or platelet decrease (Fig. 19 B) and single premedication with betamethasone 24 hours post injection of AT-130-2 did only reduce the macroscopic symptoms to a grade 1. This indicates that two doses of steroid treatment are needed to completely inhibit tolerability issues.

Figure 20. Premedication with anti-histamine is not enough to inhibit tolerability issues associated with AT-130-2 IgG2a administration. Mice were either pretreated with anti-histamine alone or with 40 mg/kg Betamethasone (24 hours and 1 hour) +/- anti-histamine pre i.v. injection of 10 mg/kg AT-130-2 IgG2a. Mice were observed for macroscopic symptoms (Fig. 20 A) and bleed approximately 20 minutes post injection. The blood was analyzed for platelet counts (Fig. 20 B). Premedication with anti-histamine alone did not inhibit macroscopic symptoms (Fig. 20 A) but did seem to improve decrease in platelet counts (Fig. 20 B). The addition of anti-histamine to 40 mg/kg Betamethasone (24 hours and 1 hour) pre i.v. injection of 10 mg/kg AT-130-2 IgG2a did not affect macroscopic symptoms or platelet counts. The same results were seen when using three different types of anti-histamines (Zyrlex, Zantac or Au, data not shown).

Figure 21 shows that several but not all murine surrogate antibodies induce IRRs. The murine surrogates anti-CD32b antibody (AT-130-2 mIgG2a), anti-CSFR1 (AFS98 rIgG2a), anti-EGFR (7A7 mIgG2a), anti-CD40 (FGK4.5 rIgG2a) and anti-FcγRIII (AT154-2 mIgG2a) were injected into wildtype C57/BL6 mice intravenously i.v. IRRs was seen after injection of anti-CD32b, anti-CD40 and anti-FcγRIII. The IRRs included

isolation, decreased activity, impaired balance, piloerection, hunching followed by un-natural body posture and the IRRs were scored from 0-2 based on the observations. No IRRs were seen for anti-EGFR or anti-CFSR1. When mice were pretreated with 40 mg/kg betamethasone 24h and 1h pre-injection of anti-CD32b or anti-CD40 no IRRs were seen (anti-FcγRIII was not evaluated with premedication). Indicating that premedication can inhibit IRRs related to different antibodies and targets.

Figure 22 shows that antibodies inducing IRRs also induce platelet decrease. The murine surrogates anti-CD32b antibody (AT-130-2 mIgG2a), anti-CD40 (FGK4.5 rIgG2a) and anti-FcγRIII (AT154-2 mIgG2a) were injected into wildtype C57/BL6 mice intravenously i.v. Platelet counts were analyzed in fresh blood 20 min post injection using a Vetscan (Vetscan HM5 Abaxis, Triolab). A decrease in platelet counts was seen after injection of anti-CD32b, anti-CD40 and anti-FcγRIII. When mice were pretreated with 40 mg/kg betamethasone 24h and 1h pre-injection of anti-CD32b or anti-CD40 no platelet decrease were seen (anti-FcγRIII was not evaluated with premedication). Indicating that premedication can inhibit platelet decrease related to different antibodies and targets.

Specific, non-limiting examples which embody certain aspects of the invention will now be described. These examples should be read together with the brief description of the drawings provided above.

EXAMPLES

EXAMPLE 1

Summary

A split dosing regimen in combination with corticosteroid pre-treatment was evaluated in an *in vivo* model recapitulating the tolerability profile seen with BI-1206 using the BI-1206 murine surrogate AT-130-2 IgG2a. The split dosing regimen in combination with corticosteroid pre-treatment improves the tolerability profile of anti-FCγRIIb treatment. Macroscopic IRRs, and platelet counts are improved with split dosing. The time span between the first dose and the second dose does not seem to be of importance while the correct timing of pre-treatment with corticosteroids appears to be important for complete tolerance of the first dose.

Materials & Methods

Test substance

The anti-mouse CD32B IgG2a clone AT130-2 was transiently expressed in HEK293 cells. The specificity of the purified research batch was demonstrated in a luminescence-based ELISA or in FACS analyses. Endotoxin-levels of antibodies were found to be <0.1 IU/mL as determined by the LAL-Amoebocyte test.

Antibody clone	**Description**	**Reference**
AT-130-2 IgG2a	Mouse surrogate of BI-1206	mIgG2aK-AT130 ref: uct, 2019-06-07, 1443:65

Mice

Six to eight weeks-old (17-20 g) female C57/BL6 and Balb C mice were obtained from Taconic or Janvier. Mice were injected i.v with mouse anti-CD32B AT-130-2 IgG2a either as a bulk dose of 200 ug/mouse or as a split-dose with 8 ug/mouse followed by 200 ug/mouse.

Premedication

For the corticosteroid treatment, Betapred (betamethasone, VNR: 008938, Alfasigma S.P.A.) was used at 10 mg/kg which is a suboptimal dose in these mouse models.

Split-dosing

Split-dosing was initiated 24h post corticosteroid treatment with 8ug/mouse of mouse

anti-CD32B AT-130-2 IgG2a i.v. followed by a bulk-dose of 200ug/mouse 20-40 minutes later. In parallel mice were injected with only the bulk-dose.

Animal monitoring

Mice were monitored post injection with regards to changes in behavior and macroscopic symptoms such as isolation, mobility, and fur condition. Macroscopic IRRs scoring system of 0-2 was set up based on the observations.

Scoring	Macroscopic symptoms
0	No visible symptoms
1	Isolation, decreased activity
2	Isolation, decreased activity, impaired balance, piloerection, hunching followed by un-natural body posture

Body temperature

Body temperature was measured 20 min post injection of bulk dose with a mouse thermometer.

Blood sampling

Blood samples were collected from vena saphena 20 min post injection of bulk dose of anti-CD32B for instant blood count analysis. For liver enzyme and cytokine analysis, the mice were bled from the aorta under isoflurane anesthesia just prior to sacrifice. Samples for liver enzymes and cytokines were collected 1h and respectively 3h after bulk dose.

Platelet count

Platelet counts were analyzed in fresh blood using a Vetscan (Vetscan HM5 Abaxis, Triolab).

Transaminases

Transaminases were analyzed shipping of frozen serum samples to (IDEXX BioResearch Vet Med Labor GmbH).

Results and Discussion

A split dosing regimen in combination with corticosteroid pre-treatment improves the tolerability profile of anti-CD32b treatment. The tolerability profile of anti-CD32b treatment alone can be seen in Figure 1. Macroscopic IRRs and platelet counts are

improved with split dosing in combination with an initial dose of corticosteroid (Figures 2, 3 and 4). This was evaluated in an *in vivo* model recapitulating the tolerability profile seen with BI-1206 using the BI-1206 murine surrogate AT-130-2 IgG2a. The time span between the first dose and the second dose does not seem to be of importance however, the correct timing of pre-treatment with corticosteroids appears important for complete tolerance of the first dose.

EXAMPLE 2

Summary

In order to evaluate if pre-treatment with other substances (aside from corticosteroids) generally used in the clinic to treat IRRs could inhibit IRRs in this model, the inventors pre-treated mice with several other clinically relevant substances. None of the tested pre-mediciations could inhibit IRRs in this model, suggesting they are not useful in preventing adverse effects associated with BI-1206 administration.

Materials and Methods

Test substance

The anti-mouse CD32B IgG2a clone AT130-2 was transiently expressed in HEK293 cells. The specificity of the purified research batch was demonstrated in a luminescence-based ELISA or in FACS analyses. Endotoxin-levels of antibodies were found to be <0.1 IU/mL as determined by the LAL-Amoebocyte test.

Antibody clone	**Description**	**Reference**
AT-130-2 IgG2a	Mouse surrogate of BI-1206	mIgG2aK-AT130 ref: uct, 2019-06-07, 1443:65

Mice

Six to eight week-old (17-20 g) female C57/BL6 and Balb C mice were obtained from Taconic or Janvier. Mice were injected i.v with mouse anti-CD32B AT-130-2 IgG2a either as a bulk dose of 200 ug/mouse or as a split-dose with 8 ug/mouse followed by 200 ug/mouse.

Premedication

For the corticosteroid treatment, Betapred (betamethasone, VNR: 008938, Alfasigma S.P.A.) was used at 10 mg/kg which is a suboptimal dose in these mouse models.

Other premedications evaluated were anti-PAF (CV3988, sc-201015, Santa Cruz 20mg/kg), anti-IL6 (clone 15A7, BE0047, Bioxcell, 10mg/kg), anti-histamine (Zantac, VNR: 077875, GlaxoSmithKline AB, 5 mg/kg) or a leukotriene-antagonist (131064, Apoex, 4mg/kg). These premedications were given i.p 1h prior to injection i.v of mouse anti-CD32B AT-130-2 IgG2a as a bulk dose of 200 ug/mouse.

Split-dosing

Split-dosing was initiated 24h post corticosteroid treatment with 8ug/mouse of mouse anti-CD32B AT-130-2 IgG2a i.v followd by a bulk-dose of 200ug/mouse 20-40 minutes later. In parallel mice were injected with only the bulk-dose.

Animal monitoring

Mice were monitored post injection with regards to changes in behavior and macroscopic symptoms such as isolation, mobility, and fur condition. A macroscopic IRR scoring system of 0-2 was set up based on the observations.

Scoring	Macroscopic symptoms
0	No visible symptoms
1	Isolation, decreased activity
2	Isolation, decreased activity, impaired balance, piloerection, hunching followed by un-natural body posture

Body temperature

Body temperature was measured 20 minutes post injection of bulk dose with a mouse thermometer.

Blood sampling

Blood samples were collected from vena saphena 20 minutes post injection of bulk dose of anti-CD32B for instant blood count analysis. For liver enzyme and cytokine analysis, the mice were bled from the aorta under isoflurane anesthesia just prior to sacrifice. Samples for liver enzymes and cytokines were collected 1h and respectively 3h after bulk dose.

Platelet count

Platelet counts were analyzed in fresh blood using a Vetscan (Vetscan HM5 Abaxis, Triolab).

Transaminases

Transaminases were analysed by shipping of frozen serum samples to (IDEXX BioResearch Vet Med Labor GmbH).

Results and Discussion

As shown in Figure 5, none of the tested substances (anti-PAF, anti-IL-6, anti-histamine and a leukotrien-antagonist) could prevent the IRRs associated with AT-130-2 administration in this mouse model. This suggests that only corticosteroids as a pre-treatment are capable of providing the protective effect described in Example 1. This finding is surprising considering all of these substances are generally used in clinic to treat IRRs associated with other therapeutic antibodies.

EXAMPLE 3

Summary

It is apparent that iv administration of BI-1206 is frequently associated with IRRs, thrombocytopenia, transient spikes in cytokines, and less frequently but in the most severe cases, increases in liver enzymes (Figure 6). It it therefore advantageous if a dosage regimen can be used which can prevent or mitigate these adverse effects. It is also apparent that in non-Hodgkin lymphoma patients, FcγRIIb receptor occupancy translates to B cell depletion (which correlates with *in vivo* data from mouse models), and sustained receptor satuation is therefore important for sustained B lymphocyte depletion, however achieving such sustained high receptor occupancy required for therapeutic benefit by i.v. injection is associated with high levels of IRRs (Figure 7).

Materials and Methods

Platelet counts, ALT concentrations and IRR grading

Platelet counts, ALT concentrations and IRR grading were obtained from clinical sites where anayzed and reported according local standard procedures. All described data from the clinical studies is preliminary, only partially quality controlled and should be considered as illustrative of the pharmacodynamic effects and tolerability associated with BI-1206.

FcgRIIb receptor occupancy

The FcgRIIb receptor occupancy in humans and hFcgRIIb transgenic mice was analyzed using flow cytometry. Whole blood from was incubated with either 005-C05 antibody (targeting hFcgRIIb) or anti-hCD32-AF647 antibody. 005-C05 binds the same epitope as BI-1206 but with much lower affinity. In the analysis, the Geo Mean of respectively mAb

(005-C05 and anti-human CD32) was acquired on the CD19+ cell population. Receptor occupancy (RO) was calculated using the following equations: RO (%) = ((Total Receptors-Normalized Free Receptors) *100) / Total Receptors. All replicates of 005-C05 geo mean of CD19+ cells were then multiplied by the Normalization factor.

Cytokine analysis

For cytokine concentrations, frozen plasma samples were thawed and diluted x2 and x8. Two parallel set of cytokines were analyzed, the proinflammatory assay with IL-6, IL-8, TNF-α, IFN-γ, IL-10, IL-2 and IL-4 (MesoScale Discovery (MSD) #K15049), and the chemokine assay with MIP-1β, IL-1β, IL-23, IL-12p70, TARC and VEGF (MSD #K15067). The assays followed the manufacturer's protocol as outlined briefly: 50 µL of sample and calibration standard were added to the appropriate MSD plates and incubated. Following washing, 25 µL of SULFO-TAG detection antibody mixture were added to each well of the corresponding plate. The plates were analyzed on a QuickPlex SQ120 Reader instrument (MSD) and cytokine concentration was calculated using the MSD software (Discovery Workbench, 2013; version LSR-4-0-12).

B cell depletion in hFcgRIIb transgenic mice

B cell depletion in hFcgRIIb transgenic mice was analyzed using flow cytometry using commercially available anitobodies.

Results and Discussion

As shown in Figure 6 it is apparent that iv administration of BI-1206 is frequently associated with IRRs, thrombocytopenia, transient spikes in cytokines, and less frequently but in the most severe cases, increases in liver enzymes. As shown in Figure 7, achieving such sustained high receptor occupancy is required for therapeutic benefit is associated with high levels of IRRs.

EXAMPLE 4

In Example 4A and Example 4B, an antibody denoted BI-1206 is used. This antibody has the following light and heavy chains:

Light chain:
QSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYADDHRPSGVPDRFSG
SKSGTSASLAISGLRSEDEADYYCASWDDSQRAVIFGGGTKLTVLGQPKAAPSVTLFPPSSEELQAN
KATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQ
VTHEGSTVEKTVAPTECS (SEQ. ID. No: 1)

Heavy chain:
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWMAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARELYDAFDIWGQGTLVTVSSASTKGPSVFPLAPSS
KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI
CNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV
SHEDPEVKFNWYVDGVEVHNAKTKPREEQY**N**STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI
EKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD
SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ. ID. No: 2)

A modified format of BI-1206 is format wherein the glycosylation site at N297 (marked in bold above) is mutated to a Q (marked in bold below), i.e. an N297Q mutation, resulting in the following heavy chain:

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWMAVISYDGSNKYYADSVK
GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARELYDAFDIWGQGTLVTVSSASTKGPSVFPLAPSS
KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYI
CNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV
SHEDPEVKFNWYVDGVEVHNAKTKPREEQY**Q**STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI
EKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD
SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ. ID. No: 195)

As surrogate antibody and control antibody, the anti-mouse CD32B antibody AT130-2 as IgG2a isotype and the control antibody AT130-2 N297A as IgG1 isotype are used below. AT130-2 as IgG2a isotype is commercially available, for example from ThermoFisher Scientific as Catalog # 12-0321-82, however # 12-0321-82 is a PE conjugate so the antibody then should be modified so that it is not a conjugate. AT130-2 N297A as IgG1

isotype may be produced by any known method including substituting N in position 297 (as identified above) with A.

Example 4A – Target: FcγRIIB

Background

BioInvent International AB has developed the therapeutic monoclonal antibody BI-1206 with anti-tumor activity that can be used as single therapy or in combination with anti-CD20 targeting therapeutics or other clinically validated checkpoints inhibitors. BI-1206 binds with high specificity to CD32B (FcγRIIB) and is currently evaluated in two clinical phase I/IIa studies, CRUKD/16/001 and 17-BI-1206-02, treating patients with chronic lymphocytic leukemia (CLL) and B-cell non-Hodgkin's lymphoma (B-cell NHL). All below described data from the clinical studies is preliminary, only partially quality controlled and should be considered as illustrative of the pharmacodynamic effects and tolerability associated with BI-1206. Part of the data is based on personal communication with individual investigators.

To date up to 100 mg of BI-1206 have been administrated, as monotherapy or in combination with rituximab, to 24 human subjects. 100 mg BI-1206 shows transient receptor saturation on peripheral B cells with 100%, or close to 100%, receptor occupancy for up to 48 hours (Figure 8). Correspondingly a transient depletion of peripheral B lymphocytes is seen, recovered within approximately 7 days (Figure 8). This is in line with pre-clinical in vivo models using hFcγRIIB mice where it has been demonstrated that a sustained receptor saturation is necessary to achieve sustained B lymphocyte depletion.

Frequent infusion related reactions (IRRs) have been seen during BI-1206 infusions in human subjects (Figure 7A). Administration of ≥50 mg BI-1206 is also associated with a transient decrease in platelets (Figure 9). Thrombocytopenia has not been serious nor associated with bleeding and most episodes resolved within a week. There appears to be a connection between platelet decrease and elevated transaminases (i.e. alanine transaminase (ALT) and aspartate transaminase (AST)), where the ALT and AST increase has been significant in 3 out of 16 subjects receiving ≥70 mg BI-1206 (Figure 9).

Moreover, a transient cytokine release has been observed in 5 out 5 subjects receiving ≥70 mg BI-1206 where plasma or serum has been available for analysis. The cytokine release includes macrophage inflammatory protein (MIP)-1β, tumor necrosis factor (TNF)-α, interleukin (IL)-10, IL-8, IL-6, and IL-4, and the peak is seen immediately after infusion

and cytokines are always normalized within 24 hours (Figure 10). The cytokine release has not been associated with clinical symptoms.

In the clinical study 17-BI-1206-02, 16 subjects have recieved 70-100mg BI-1206, altogether there have been 58 BI-1206 adminstrations at these dose levels. 46 of these administrations were given following implementation of the in vivo protective corticosteroid-based premedication regimen identified in the animal model, (Figure 7C and 7H). Implementation of the in vivo animal model identified premedication regimen into the clinic resulted in statistically significant reduced severity and frequency of IRRs in human cancer patients (Figure 7D and 7H).

Subjects 501-001 and 503-002 received 12 mg and 4 mg dexamethasone, respectively, the evening before and again 20 mg dexamethasone 30 minutes prior to the third administration of BI-1206 (70 mg) during induction therapy. Both subjects did not suffer IRRs after this premedication regimen using two doses of dexamethasone. During the previous two infusions with BI-1206, where dexamethasone (20 mg) was given only 30 minutes prior to infusion, IRRs (grade 2-3) had been experienced. In addition, in subject 501-001 and 503-002 no/low platelet decrease, and no ALT/AST increase was seen after BI-1206 administration when premedicating with two doses of dexamethasone (Figure 11). The third subject (201-003) had received 9 administrations of 30mg of BI-1206 (4 doses during induction phase and 5 doses during maintenance phase) and repeatedly experienced IRR's. At the 10th BI-1206 administration premedication with two doses of dexamethasone was used, and IRR's were improved to grade 1. In subject 201-003 which received a lower dose of BI-1206 (30 mg) platelet decrease or ALT/AST increase had never been seen. Importantly, and consistent with FcgRIIB receptor saturation determining therapeutic efficacy, therapeutic efficacy was maintained following implementation of the premedication regimen in the clinic. Both complete and partial responses have been observed in patients following incorporation of the premedication regimen into the clinical protocol (Figure 7H).

Materials & Methods

Test and control substances

The anti-mouse CD32B IgG2a clone AT130-2 and the control antibody (AT130-2 N297A) were transiently expressed in HEK293 cells. The specificity of the purified research batches was demonstrated in a luminescence-based enzyme linked immunosorbent assay (ELISA) or in flow cytometry analyses. Endotoxin-levels of antibodies were found to be <0.1 IU/mL as determined by the LAL-Amoebocyte test.

Antibody clone	Description
AT-130-2 IgG2a	Mouse surrogate of BI-1206 as described above
AT-130-2 IgG1 N297A	Fc null version of mouse surrogate of BI-1206 as described above

Mice

Six to eight weeks-old (17-20 g) female C57/BL6 mice were obtained from Taconic. Mice were injected either intra-venous (i.v.), intra-perinatal (i.p.) or sub-cutaneous (s.c.) with mouse anti-CD32B AT-130-2 IgG2a in doses ranging from 1 µg – 400 µg/mouse.

Premedication

For the corticosteroid treatment, Betapred (betamethasone, VNR: 008938, Alfasigma S.P.A.) or Dexamethasone (Cat. No: S1322, batch no: 02, Selleckchem) was used. For the anti-histamine treatment Zyrlex (10 mg/ml, VNR: 523084, MACURE PHARMA ApS), Zantac (25 mg/ml, VNR: 077875, GlaxoSmithKline AB) or Aeurius (0.5 mg/ml, VNR: 097288, Merck Sharp & Dohme BV) was used.

Animal monitoring

Mice were monitored post injection with regard to changes in behavior and macroscopic symptoms such as isolation, mobility, and fur condition. Macroscopic IRRs scoring system of 0-2 was set up based on the observations:

Scoring	Macroscopic symptoms
0	No visible symptoms
1	Isolation, decreased activity
2	Isolation, decreased activity, impaired balance, piloerection, hunching followed by un-natural body posture

Blood sampling

Blood samples were collected from vena saphena for instant blood count analysis. For serum concentrations of AT130-2, liver enzyme and cytokine analysis, the mice were bled from the aorta under isoflurane anesthesia just prior to sacrifice.

Serum concentrations of AT130-2

Serum concentrations of AT130-2 mAb has been was quantified using a sandwich ELISA. Briefly, recombinant CD32B protein (Sino Biological #50030-M08H) was used as coating. Diluted samples were added to the ELISA plate, and following incubation and washing steps, detection was conducted via an HRP conjugated polyclonal donkey-anti-mouse-IgG Ab (Jackson #715-035-151). Subsequently the Pico Chemiluminescent Substrate (ThermoFisher #37069) were used and plate reading was performed with a Tecan Ultra Microplate reader.

Platelet count

Platelet counts were analyzed in fresh blood using a Vetscan (Vetscan HM5 Abaxis, Triolab).

Transaminases

Transaminases were analyzed shipping of frozen serum samples to (IDEXX BioResearch Vet Med Labor GmbH).

Cytokines

To study the potential contributors of infusion-related reactions (IRRs) in the mice, cytokine release has been evaluated at selected timepoints in association with i.p. injection of AT-130-2 mAb. Serum samples frozen once were thawed and diluted x2 or x4. Cytokines were analyzed with the V-plex Proinflammatory Panel 1 Mouse kit (MesoScale Discovery #K15048D), including the analytes interferon(IFN)-γ, interleukin(IL)-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12p70, KC/GRO, tumor necrosis factor (TNF)-α. The assay followed the manufacturer's protocol as outlined briefly: 50 µL of sample and calibration standard were added to the MSD plates and incubated. Following washing, 25 µL of SULFO-TAG detection antibody mixture were added to each well of the corresponding plate. The plates were analyzed on a QuickPlex SQ120 Reader instrument (MSD) and cytokine concentration was calculated using the MSD software (Discovery Workbench, 2013; version LSR-4-0-12).

Results

Macroscopic symptoms after murine surrogate anti-CD32b IgG2a (AT-130-2)

The murine surrogate anti-CD32b (AT-130-2 IgG2a) was injected into wildtype C57/BL6 mice through 3 different injection routes, intravenously (i.v.), intraperitoneally (i.p.) or subcutaneously (s.c.). At 200 µg (corresponding to 10 mg/kg) a rapid onset of infusion-related reactions (IRRs) was seen 5-7 minutes after i.v. injection. These IRRs included isolation, decreased activity, impaired balance, piloerection, hunching followed by un-natural body posture. Blood sampling of these mice indicated reduced blood pressure. 10-

15 minutes post IRRs onset these mice started to recover and 1h post injection no macroscopic symptoms were seen.

When titrating the i.v. dose, the same timing and severity of macroscopic symptoms was seen down to 10 µg (0.5 mg/kg). However, at 1 µg (0.05 mg/kg) no IRRs were seen (Figure 12).

When administrating the same dose 200 µg (10mg/kg) i.p. a delay in IRRs onset was seen with the IRRs appearing 20-30 minutes post injection. In contrast to the i.v. injection route all mice in this group did not display IRRs and the IRRs were less severe in several mice (Figure 12).

When increasing the i.p. dose to 400 µg (20mg/kg) the onset of IRRs was still delayed compared to the i.v. injection route however, all mice displayed IRRs to the same extent and grade as 200 µg i.v. (Figure 12). All mice had fully recovered 1h post injection.

Finally, when administrating 200 µg to mice s.c. no IRRs were seen (up to 24h post injection). When increasing the s.c. dose to 400 µg the mice remained unaffected (Figure 12).

When administrating the Fc-null version of AT-130-2, AT-130-2 IgG1 N297A i.v. no IRRs were seen, indicating that Fc-binding is necessary to incite the symptoms associated with AT-130-2.

The pharmacokinetic profiles of AT-130-2 was assessed for i.v., i.p., and s.c. injection (Figure 13).

When comparing the PK and the presumed receptor occupancy (RO, based on separate experiments not shown here where it was shown that 10 µg/ml gives 100% receptor saturation) with the onset, severity and duration of IRRs it is clear that there is a correlation between high and rapid exposure of AT-130-2, rather than time of FcγRIIB saturation. Tolerability showing a clear pattern of s.c. > i.p. > i.v. with RO being sustained for a long period of time post IRRs recovery (Figure14).

Platelets, transaminases and cytokines

To investigate if the IRRs seen in these mice were associated with other parameters seen in the clinical studies with BI-1206 mice were bled at the onset of IRRs and the blood was analyzed for blood cell count, clinical chemistry parameters and cytokines. In the case of

s.c. injection where no IRRs occurred, mice were bled at different timepoints post injection. A decrease in platelet count (PLT) was seen at the same time as IRRs onset after injection of AT-130-2 through both the i.v. and i.p. administration route (Figure 15A). For the s.c. administration route only a moderate drop was seen 10h post injection (Figure 15A). In all cases the PLT decrease was transient and was restored to values in the normal range within 8h post injection (data for 200 µg AT-130-2 injected i.p. is shown in Figure 16A). When administering AT-130-2 IgG2a s.c. the transaminase increase seen following i.v. injection is circumvented. For the i.v. administration route an increase is seen in transaminases (AST) 1h post onset of macroscopic symptoms (previously established as time point for a peak value in transaminases). However, for the s.c. administration route no macroscopic symptoms were seen. More specifically, no increase in transaminases was seen 11 hours post injection (1h post the time of FcγRIIB saturation according to PK (10h)), as shown in Figure 15B.

With regard to clinical chemistry parameters an increase in transaminases (AST and ALT) with a peak 1h post injection was the only parameter affected by AT-130-2 injection. These increases were just like the PLT decrease transient (Figure 16B). The same transient increase was seen when AT-130-2 was injected i.v. and no increase in transaminases was detected when AT-130-2 was injected s.c.

A panel of cytokines including the analytes IFN-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12p70, KC/GRO, TNF-α were analyzed at different time points post injection of 200 µg i.p. Of all the analyzed cytokines IL-5, IL-6, IL-10, KC/GRO, TNF-α showed a transient increase, all peaking 1-3 hours post injection, except for IL-5 (Figure 16C). IL-5 showed a delayed peak 3-8 hours post injection (Figure 16C). These were the same cytokines that have been indicated to increase in some patients in the clinical studies with BI-1206.

Premedication

In order to investigate if premedication with corticosteroids could inhibit the IRRs and associated toxicities of AT-130-2, mice were premedicated with 40 mg/kg betamethasone 16-24h and 1h pre injection of AT-130-2. Both the IRRs and the platelet decrease seen with AT-130-2 was completely inhibited with premedication (Figure 17A-B). Also, the increase in liver transaminases and cytokine release was less profound (Figure 17C and data not shown). The same effect was seen when another corticosteroid, dexamethasone was assessed (data not shown).

To assess the importance of the dose of corticosteroid treatment the dose of betamethasone was decreased from 40 mg/kg to 10 mg/kg in the following experiment

(Figure 18). At 10 mg/kg both IRRs and a decrease in platelet count were seen in half of the mice indicating that a high dose of corticosteroids is needed to completely block the IRRs and associated toxicities (Figure 18).

Further, the importance of the two doses of corticosteroid treatment was investigated by comparing the protective effect of only early (1 hours pre injection) or only late (24 hours pre injection) premedication with the two doses of corticosteroid treatment. Premedication only 1 hour pre injection could not inhibit the IRRs nor the decrease in platelet count (Figure 19). Premedication 24h pre injection diminished the IRRs and the platelet decrease but could not completely block these symptoms (Figure 19), indicating that two doses of corticosteroids is needed to fully block IRRs.

Finally, the impact of antihistamine, which is a standard premedication in the clinical trials, was evaluated. Premedication with antihistamine alone did not inhibit IRRs or platelet decrease. When combining the two doses of corticosteroid treatment with antihistamine pretreatment the protective effect was retained (Figure 20). These results were confirmed for three different types of antihistamines (Zyrlex, Zantac and Aeurius).

Conclusions

Our data demonstrates an in vivo model using intra-venous (i.v.) or intra-perinatal (i.p.) administration of anti-FcγRIIB mIgG2a surrogate (AT-130-2) in wild type mice recapitulates the tolerability profile seen with BI-1206, including IRR's, decreased platelet count, elevated transaminases (i.e. ALT and AST) and transient cytokine release. The IRR's appear 5-20 minutes after AT-130-2 injection with macroscopic symptoms including isolation, decreased activity, impaired balance, piloerection, hunching followed by un-natural body posture and decreased blood pressure. The visual physical reaction is transient, and the animals are fully recovered 1h after the antibody administration. The macroscopic symptoms are accompanied by a decrease in platelet count and elevated transaminases which are normalized within 8 hours. The cytokine release is acute and transient and includes IL-6, IL-5, IL-10, TNFα and KC/GRO (rodent homolog of human IL-8). The cytokine profile and kinetics is equivalent to what is seen after BI-1206 in human subjects. In the mouse model there is an apparent correlation between the IRR's and high and rapid exposure, rather than time of FcγRIIB saturation, where sub-cutaneous (s.c.) administration of AT-130-2 is better tolerated than i.p. and i.v. administration. The timing of onset of symptoms correlates with the serum concentration where receptor saturation is achieved. However, also when administrating an antibody dose that achieves receptor saturation for 6 days or longer the animals recover from all symptoms within 24h. Sustained FcγRIIB blockade per se does not appear to be the causative of IRRs.

In this model premedication with two doses of corticosteroids (dexamethasone or betamethasone) inhibits the macroscopic IRRs as well as platelet decrease and transaminase elevation. The two doses are given s.c. 16-24 hours and i.v. 30-60 minutes prior to antibody administration. The prevention of macroscopic symptoms in the mice by corticosteroids is dose-dependent and importantly the timing of premedication is crucial. The dose 16-24 hours prior to antibody administration is imperative in order to gain the protective effect. If corticosteroids are only given 30-60 minutes prior to antibody administration no protective effect with regard to the macroscopic symptoms is seen, whereas the dose16-24 hours prior to antibody administration alone partially improves tolerability. When both doses are given, inhibition of the macroscopic symptoms, platelet decrease, transaminase elevation, and cytokine release is achieved.

Dosing of human patients according to the corticosteroid-based regimen identified in the mouse model protected against IRRs and allowed for administration of higher doses, which are likely to be associated with stronger antitumor activity, of the studied anti-FcgRIIB antibody.

Example 4B – Other targets

Materials & Methods

Test and control substances

The anti-mouse CD32b clone was transiently expressed in HEK293 cells. The specificity of the batch was demonstrated in a luminescence-based enzyme linked immunosorbent assay (ELISA) or in flow cytometry analyses. Endotoxin-levels of antibodies were found to be <0.1 IU/mL as determined by the LAL-Amoebocyte test. The anti-mouse CD40, EGFR and CSFR1 antibodies were purchased from BioXcell or Absolute Antibody (see table below) and the anti-mouse FcγRIII antibody AT154-2 was a gift from University of Southampton. Alternatively, AT154-2 as rat IgG2b isotype may be purchased from, for example, BioRad, Argio Biolaboratories (ARG23942) or LSBio (LS-C745656) which is then converted into IgG2a format using any well-known method.

Antibody clone	**Description**	**Reference**
AT-130-2 Mouse IgG2a	anti-mouse CD32b	*(See comments above Example 1)*
FGK4.5/ FGK45 Rat IgG2a	anti-mouse CD40	BP0016-2, BioXcell,

7A7 Mouse IgG2a	anti-mouse EGFR	Ab00134-2.0, Absolute Antibody
AFS98 Rat IgG2a	anti-mouse CSFR1	BE0213, BioXcell
AT154-2 Mouse IgG2a	anti-mouse FcγRIII	*(See comments above the table)*

Mice

Six to eight weeks-old (17-20 g) female C57/BL6 mice were obtained from Taconic. Mice were injected intra-venous (i.v.), with 200 µg/mouse of the different antibodies.

Premedication

For the corticosteroid treatment, Betapred (betamethasone, VNR: 008938, Alfasigma S.P.A.) or Dexamethasone (Cat. No: S1322, Batch No: 02, Selleckchem) was used.

Animal monitoring

Mice were monitored post injection with regard to changes in behavior and macroscopic symptoms such as isolation, mobility, and fur condition. Macroscopic IRRs scoring system of 0-2 was set up based on the observations:

Scoring	**Macroscopic symptoms**
0	No visible symptoms
1	Isolation, decreased activity
2	Isolation, decreased activity, impaired balance, piloerection, hunching followed by un-natural body posture

Blood sampling

Blood samples were collected from vena saphena for instant blood count analysis.

Platelet count

Platelet counts were analyzed in fresh blood using a Vetscan (Vetscan HM5 Abaxis, Triolab).

Conclusions

This example shows that the model described herein can distinguish between antibody molecules that induce tolerability issues and those that do not. It further shows that premedication can inhibit IRRs related to different antibodies and targets.

This example also shows that antibodies that induce IRRs also induce thrombocytopenia. Furthermore, it demonstrates that premedication can inhibit thrombocytopenia related to different antibodies and targets.

Embodiments of the invention

Certain embodiments of the invention will be described with reference to the following numbered paragraphs:

1. A therapeutic system for use in improving tolerability of an antibody molecule that specifically binds to FcyRIIb in a subject, wherein the therapeutic system comprises:

   (i) an antibody molecule that specifically binds to FcyRIIb, wherein the antibody molecule is administered to the subject as at least a first dose and a second dose; and

   (ii) a corticosteroid,

   wherein the first dose of the antibody molecule is lower than the maximum therapeutically effective dose of the antibody molecule; and
   wherein the corticosteroid is administered to the subject before the first dose of the antibody molecule.

2. A combination comprising an antibody molecule and a corticosteroid for use in a dosage regimen for improving tolerability of an antibody molecule that specifically binds to FcyRIIb in a subject, wherein the dosage regimen comprises the following steps:

   (i) administration of a corticosteroid before administration of a first dose of the antibody molecule;
   (ii) administration of the first dose of the antibody molecule that specifically binds to FcyRIIb that is lower than the maximum therapeutically effective dose; and
   (iii) administration of a second dose of the antibody molecule that specifically binds to FcyRIIb, wherein the first dose of the antibody molecule is administered prior to the second dose.

3. Use of:

   (i) an antibody molecule that specifically binds to FcyRIIb; and
   (ii) a corticosteroid,

in the manufacture of a medicament for improving tolerability of an antibody molecule that specifically binds to FcyRIIb in a subject, wherein the medicament comprises at least a first dose and a second dose of the antibody molecule; and
wherein the first dose of the antibody molecule is lower than the maximum therapeutically effective dose of the antibody molecule; and
wherein the corticosteroid is administered before the first dose of the antibody molecule.

4. A method for improving tolerability of an antibody molecule that specifically binds to FcyRIIb in a subject comprising:

(i) administration of a corticosteroid before administration of a first dose of the antibody molecule;
(ii) administration of the first dose of the antibody molecule that specifically binds to FcyRIIb that is lower than the maximum therapeutically effective dose; and
(iii) administration of a second dose of the antibody molecule that specifically binds to FcyRIIb, wherein the first dose of the antibody molecule is administered prior to the second dose.

5. The system, combination for use, use, or method of paragraphs 1-4, wherein the system, combination for use, use, or method further comprises administration of one or more therapeutic antibodies for the treatment of cancer in a subject.

6. The system, combination for use, use, or method of paragraph 5, wherein the therapeutic antibody is selected from: rituximab; pembrolizumab; nivolumab; cemiplimab; camrelizumab; dostarlimab; obinutuzumab; ofatumumab, and biosimilars or equivalents thereof.

7. The system, combination for use, use, or method of paragraphs 1-6, wherein the corticosteroid is administered to the subject at a time point from 10 minutes to 48 hours before the first dose of the antibody molecule that specifically binds to FcyRIIb.

8. The system, combination for use, use, or method of paragraph 7, wherein the corticosteroid is administered to the subject at a time point from 10 minutes to 24 hours before the first dose of the antibody molecule that specifically binds to FcyRIIb.

9. The system, combination for use, use, or method of paragraphs 1-6, wherein the corticosteroid is administered as a first dose and a second dose, and wherein the first dose of the corticosteroid is administered at a time point from 16 hours to 48 hours before the first dose of the antibody molecule that specifically binds to FcγRIIb, and wherein the second dose of the corticosteroid is administered at a time point from 10 minutes to 2 hours before the first dose of the antibody molecule that binds specifically to FcγRIIb.

10. The system, combination for use, use, or method of paragraph 9, wherein a further dose of corticosteroid is administered at a time point from 16 hours to 48 hours before the second dose of the antibody molecule that specifically binds to FcγRIIb.

11. The system, combination for use, use, or method of paragraphs 1-10, wherein the first dose of the antibody molecule that specifically binds to FcγRIIb is administered at a time point from one to 24 hours before the second dose of the antibody molecule that specifically binds to FcγRIIb.

12. The system, combination for use, use, or method of paragraphs 1-10, wherein the first dose of the antibody molecule that specifically binds to FcγRIIb is administered about one hour before the second dose of the antibody molecule that specifically binds to FcγRIIb.

13. The system, combination for use, use, or method of paragraphs 1-10, wherein the first dose of the antibody molecule that specifically binds to FcγRIIb is administered about 24 hours before the second dose of the antibody molecule that specifically binds to FcγRIIb.

14. The system, combination for use, use, or method of paragraphs 1-10, wherein the first dose of the antibody molecule that specifically binds to FcγRIIb is administered from 24 hours to 48 hours before the second dose of the antibody molecule that specifically binds to FcγRIIb.

15. The system, combination for use, use, or method of paragraphs 1-14, wherein the corticosteroid is administered at a dose of 4 mg or greater.

16. The system, combination for use, use, or method of paragraphs 1-15, wherein the corticosteroid is administered at a dose of 12 mg or greater.

17. The system, combination for use, use, or method of paragraphs 1-14, wherein the corticosteroid is administered at a dose of from 4 mg to 20 mg.

18. The system, combination for use, use, or method of paragraph 17, wherein the corticosteroid is administered at a dose of from 12 mg to 20 mg.

19. The system, combination for use, use, or method of paragraph 17, wherein the corticosteroid is administered at a dose of from 4 mg to 12 mg.

20. The system, combination for use, use, or method of paragraphs 1-19, wherein the corticosteroid is dexamethasone or betamethasone or a combination of dexamethasone and betamethasone.

21. The system, combination for use, use, or method of paragraphs 1-20, wherein the first dose of the antibody molecule that specifically binds to FcyRIIb is lower than the maximum tolerated therapeutic dose.

22. The system, combination for use, use, or method of paragraphs 1-21, wherein the first dose of the antibody molecule that specifically binds to FcyRIIb is at least 50% lower than the maximum therapeutically effective dose.

23. The system, combination for use, use, or method of paragraphs 1-22, wherein the first dose of the antibody molecule that specifically binds to FcyRIIb is administered at a dose of from 0.2 mg/kg to 0.6 mg/kg.

24. The system, combination for use, use, or method of paragraph 23, wherein the first dose of the antibody molecule that specifically binds to FcyRIIb is administered at a dose of from 0.3 mg/kg to 0.5 mg/kg.

25. The system, combination for use, use, or method of paragraphs 1-24, wherein the first dose of the antibody molecule that specifically binds to FcyRIIb is administered at a dose of from 20 mg to 40 mg.

26. The system, combination for use, use, or method of paragraph 25, wherein the first dose of the antibody molecule that specifically binds to FcyRIIb is administered at a dose of about 30 mg.

27. The system, combination for use, use, or method of paragraphs 1-26, wherein the second dose of the antibody molecule that specifically binds to FcyRIIb is a therapeutically effective dose.

28. The system, combination for use, use, or method of paragraphs 1-27, wherein the second dose of the antibody molecule that specifically binds to FcyRIIb is the maximum tolerated therapeutic dose or the maximum feasible therapeutic dose.

29. The system, combination for use, use, or method of paragraphs 1-27, wherein the second dose of the antibody molecule that specifically binds to FcyRIIb is lower than a therapeutically effective dose.

30. The system, combination for use, use, or method of paragraphs 1-29, wherein further additional doses of the antibody molecule that specifically binds to FcyRIIb are administered to the subject following the second dose of the antibody molecule that specifically binds to FcyRIIb.

31. The system, combination for use, use, or method of paragraphs 1-30, wherein infusion related reactions associated with the administration of the antibody molecule that specifically binds to FcyRIIb are reduced or eliminated.

32. The system, combination for use, use, or method of paragraphs 1-31, wherein changes to the body temperature and/or platelet count and/or blood levels of liver enzymes of the subject are reduced (and are preferably reduced to acceptable levels) for at least 24 hours following administration of the second dose of the antibody molecule that specifically binds to FcyRIIb.

33. The system, combination for use, use, or method of paragraphs 1-32, wherein the antibody molecule that specifically binds to FcyRIIb is capable of binding one or more Fcy receptors via its Fc region.

34. The system, combination for use, use, or method of paragraphs 1-33, wherein the antibody molecule that specifically binds to FcyRIIb has a light chain sequence of SEQ ID No: 1 and a heavy chain of SEQ ID No: 2.

35. The system, combination for use, use, or method of paragraphs 1-34, wherein the first and second doses of the antibody molecule that specifically binds to FcyRIIb are formulated for intravenous delivery to the subject.

36. The system, combination for use, use, or method of paragraphs 1-35, wherein the corticosteroid is formulated for intravenous or oral delivery to the subject.

37. A kit comprising:

(i) an antibody molecule that specifically binds to FcγRIIb, optionally as defined in paragraphs 33 and/or 34;
(ii) a corticosteroid, optionally as defined in any one of paragraphs 15-20; and
(iii) optionally, instructions for use,

wherein the antibody molecule is provided as a first dose and a second dose, wherein the first dose of the antibody molecule is lower than the maximum therapeutically effective dose of the antibody molecule, further optionally wherein the first dose is as defined in paragraphs 11-14 and 21-26, further optionally wherein the second dose is as defined in paragraphs 27-29.

38. The kit of paragraph 37, wherein the kit is for improving the tolerability of the antibody molecule in a subject.

39. The kit of paragraph 37 or 38, wherein the corticosteroid is provided in a dose as defined in any one of paragraphs 12-17.

40. The kit of paragraphs 37-39, wherein the kit further comprises one or more therapeutic antibodies.

41. The kit of paragraph 40, wherein the therapeutic antibody is selected from: rituximab; pembrolizumab; nivolumab; cemiplimab; camrelizumab; dostarlimab; obinutuzumab; ofatumumab, and biosimilars or equivalents thereof.

42. The kit of paragraph 40 or 41, wherein the kit is for use in treating cancer in a subject.

43. The system, combination for use, use, method, or kit substantially as described herein with reference to the description and drawings.

44. A method for predicting if a therapeutic antibody molecule binding specifically to a human target will be associated with a tolerability issue in connection with intravenous administration to a human, comprising the following step:

(i) intravenous or intraperitoneal administration of the therapeutic antibody molecule, if cross-reactive with murine target, or a surrogate antibody, to a mouse and observation of the mouse during a period following immediately after the administration of the therapeutic or surrogate antibody, wherein a display of the macroscopic symptoms isolation and decreased activity during the period followed by restoration of the state of the mouse to the normal state is an indication that the intravenous administration of the therapeutic antibody molecule to a human will be associated with a tolerability issue,
and/or for predicting if a prophylactic or therapeutic treatment, an altered administration route and/or a modification of the therapeutic antibody molecule can prevent or mitigate a tolerability issue associated with intravenous administration to a human of a therapeutic antibody molecule binding specifically to a human target,
comprising the following step(s) in addition to (i) as set out above:

(ii) administration of a prophylactic or therapeutic agent to a mouse in conjunction with intravenous or intraperitoneal administration of the therapeutic or surrogate antibody to a mouse, and observation of the mouse during a period following immediately after the administration of the therapeutic or surrogate antibody, wherein a decreased display of the macroscopic symptoms compared to the macroscopic symptoms displayed by the mouse in (i) or no display of the macroscopic symptoms during the period is an indication that pre-treatment with the prophylactic or therapeutic agent in combination with administration of the therapeutic antibody molecule to a human can prevent or mitigate the tolerability issue that otherwise would be associated with intravenous administration of the therapeutic antibody molecule to a human;

(iii) administration of the therapeutic or surrogate antibody to a mouse by a route of administration other than intravenous or intraperitoneal administration, and observation of the mouse during a period following immediately after the administration of the therapeutic or surrogate antibody, wherein a decreased display of the macroscopic symptoms compared to the macroscopic symptoms displayed by the mouse in (i) or no display of the macroscopic symptoms during the period is an indication that the other route of administration can be used for

administration of the therapeutic antibody molecule to a human to prevent or mitigate the tolerability issue that would be associated with intravenous administration of the therapeutic antibody molecule to a human; and/or

(iv) intravenous or intraperitoneal administration of a modified format of the therapeutic or surrogate antibody to a mouse by a route of administration other than intravenous or intraperitoneal administration, and observation of the mouse during a period following immediately after the administration of the modified therapeutic or surrogate antibody, wherein a decreased display of the macroscopic symptoms compared to the macroscopic symptoms displayed by the mouse in (i) or no display of the macroscopic symptoms during the period is an indication that administration of the therapeutic antibody molecule in the modified format to a human can be used to prevent or mitigate the tolerability issue that would be associated with intravenous administration of the therapeutic antibody molecule to a human.

45. A method according to paragraph 44, wherein a display in (i) of 1-3 additional macroscopic symptoms selected from impaired balance, piloerection, and hunching followed by un-natural body posture during the period in (i) where after the state of the mouse is restored to the normal state further strengthens the indication that the intravenous administration of the therapeutic antibody molecule to the human will be associated with a tolerability issue.

46. A method according to paragraph 44 or 45, wherein the period during which the macroscopic symptoms are displayed in (i) starts 5-10 minutes after administration of the therapeutic or surrogate antibody and ends 45-90 minutes after administration of the therapeutic or surrogate antibody, and wherein the observation period in (ii), (iii) and/or (iv) is of the same length.

47. A method according to any one of the paragraphs 44-46, wherein at least one of the following additional parameters:
- decreased blood pressure
- decreased platelet count, and or
- increased liver enzymes (AST/ALT).

observed during the period in (i) further strengthens the indication that the intravenous administration of the therapeutic antibody molecule to a human will be associated with a tolerability issue.

48. A method for predicting if a prophylactic or therapeutic treatment can prevent or mitigate a tolerability issue associated with intravenous administration to a human of a therapeutic antibody molecule binding specifically to a human target according to any one of the claims 1-4 comprising at least steps (i) and (ii), wherein pre-treatment is used in (ii) and wherein this pre-treatment is administration of a corticosteroid to the mouse prior to injection of the therapeutic or surrogate antibody.

49. A method according to paragraph 48, wherein the pre-treatment comprises two administrations of a corticosteroid, wherein one is given 10-48 hours prior to administration of the therapeutic or surrogate antibody and the other is given 5 minutes - 5 hours prior to administration of the therapeutic or surrogate antibody.

50. A method according to paragraph 49, wherein the corticosteroid is dexamethasone or betamethasone.

51. A method for predicting if an altered administration route can prevent or mitigate a tolerability issue associated with intravenous administration to a human of a therapeutic antibody molecule binding specifically to a human target according to any one of the paragraphs 44-50 comprising at least steps (i) and (iii), wherein the route of administration used in (iii) is subcutaneous administration.

52. A method for predicting if a modification of the therapeutic antibody molecule can prevent or mitigate a tolerability issue associated with intravenous administration to a human of a therapeutic antibody molecule binding specifically to a human target according to any one of the paragraphs 44-51 comprising at least steps (i) and (iv), wherein the modified format of the therapeutic or surrogate antibody used in (iv) is a modification that leads to decreased or abolished engagement of Fc receptors.

53. A method according to any one of the paragraphs 44-52, wherein the human target is selected from the group consisting of FcγRIIB, FcγRIIA and CD40.

54. A method according to paragraph 53, wherein the therapeutic antibody molecule is a human anti-FcγRIIB antibody capable of binding a human FcγR via its Fc domain and wherein the mouse surrogate antibody is an anti-FcγRIIb antibody capable of binding a mouse FcγR via its Fc domain.

55. A method according to paragraph 54, wherein the therapeutic antibody molecule is a human anti-FcγRIIB IgG1 antibody and wherein the mouse surrogate antibody is an anti-FcγRIIb mIgG2a.

56. A corticosteroid for use in a dosing regimen to prevent or mitigate a tolerability issue in connection with intravenous administration of a therapeutic antibody molecule to a subject,
wherein the therapeutic antibody molecule has been predicted to be associated with a tolerability issue in connection with intravenous administration to a human using the method of any one of the paragraphs 44-56 , and/or wherein pre-treatment with the corticosteroid combination with administration of the therapeutic antibody molecule to a human has been predicted to prevent or mitigate the tolerability issue that otherwise would be associated with intravenous administration of the therapeutic antibody molecule to a human using the method of any one of the paragraphs 48-50, or any one of the paragraphs 53-55 when referring to any one of the paragraphs 48-50,
and wherein the dosing regimen comprises administration of the corticosteroid to the subject in at least two doses prior to intravenous administration of the therapeutic antibody molecule, wherein one dose of the corticosteroid is administered 10-48 hours prior to start of the administration of therapeutic antibody molecule ("the first dose") and one dose of the corticosteroid is administered 5 minutes - 5 hours prior to the start of administration of the therapeutic antibody molecule ("the second dose").

57. A corticosteroid for use in a dosing regimen to prevent or mitigate a tolerability issue in connection with intravenous administration of a therapeutic antibody molecule to a subject,
wherein the therapeutic antibody molecule is an anti-FcγRIIB antibody,
and wherein the dosing regimen comprises administration of the corticosteroid to the subject in at least two doses prior to intravenous administration of the therapeutic antibody molecule, wherein one dose of the corticosteroid is administered 10-48 hours prior to start of the administration of therapeutic antibody molecule ("the first dose") and one dose of the corticosteroid is administered 5 minutes - 5 hours prior to the start of administration of the therapeutic antibody molecule ("the second dose").

58. A corticosteroid for use according to paragraph 56 or 57, wherein the first dose is given 6-36 hours prior to start of administration of the therapeutic antibody

molecule and the second dose is given 15-120 minutes prior to start of administration of the therapeutic antibody molecule.

59. A corticosteroid for use according to paragraph 56-58, wherein the first dose is given 16-24 hours prior to start of administration of the therapeutic antibody molecule.

60. A corticosteroid for use according to any one of the paragraphs 56-59, wherein the second dose is given 30-60 minutes prior to start of administration of the therapeutic antibody molecule.

61. A corticosteroid for use according to any one of the paragraphs 56-60, wherein the dosing regimen comprises administration of the at least two doses of the corticosteroid prior to each infusion of the antibody during the course of antibody therapy.

62. A corticosteroid for use according to claim any one of the paragraphs 56-61, wherein the corticosteroid is dexamethasone or betamethasone or a combination of dexamethasone and betamethasone.

63. A corticosteroid for use according to any one of the paragraphs 56-62, wherein the corticosteroid is dexamethasone and wherein the first dose is 4-20 mg and the second dose is 4-25 mg.

64. A corticosteroid for use according to paragraph 63, wherein the first dose is 10-12 mg and the second dose is 20 mg.

65. A corticosteroid for use according to any one of the paragraphs 56-62, wherein the corticosteroid is betamethasone and wherein the first dose is 3.2-16 mg and the second dose is 3.2-20 mg.

66. A corticosteroid for use according to paragraph 65, wherein the first dose is 8-9.6 mg and the second dose is 16 mg.

67. A corticosteroid for use according to claim any one of the paragraphs 56-66, wherein the dosing regimen further comprises administration of an antihistamine 10 minutes – 24 hours prior to start of administration of the therapeutic antibody molecule.

68. A corticosteroid for use according to any one of the paragraphs 56-67, wherein the therapeutic antibody is an Fc receptor binding antibody.

69. A corticosteroid for use according to any one of the paragraphs 56-68, wherein the therapeutic antibody is an anti-FcγRIIB antibody.

70. A corticosteroid for use according to paragraph 69, wherein the anti-FcγRIIB antibody is the antibody having a light chain with SEQ ID No: 1 and a heavy chain with SEQ ID No: 2.

71. A therapeutic antibody molecule for use in the treatment of cancer, wherein the therapeutic antibody molecule has been predicted to be associated with a tolerability issue in connection with intravenous administration to a human using the method of any one of the paragraphs 44-55 and/or wherein the subcutaneous route of administration of therapeutic antibody molecule to a human has been predicted to prevent or mitigate the tolerability issue that otherwise would be associated with intravenous administration of the therapeutic antibody molecule to a human using the method of paragraph 51, or any one of the paragraphs 53-55 when referring to paragraph 51,
and wherein the therapeutic antibody is formulated for subcutaneous administration.

72. A therapeutic antibody molecule for use according to paragraph 71, wherein the therapeutic antibody is an anti-FcγRIIB antibody.

73. A therapeutic antibody molecule for use according to paragraph 72, wherein the anti-FcγRIIB antibody is the antibody having a light chain with SEQ ID No: 1 and a heavy chain with SEQ ID No: 2.

74. A modified format of a therapeutic antibody molecule for use in the treatment of cancer, wherein the therapeutic antibody molecule has been predicted to be associated with a tolerability issue in connection with intravenous administration to a human using the method of any one of the paragraphs 44-55 and/or wherein administration of the therapeutic antibody molecule in the modified format to a human has been predicted to prevent or mitigate the tolerability issue that otherwise would be associated with intravenous administration of the therapeutic

antibody molecule to a human using the method of paragraph 52, or any one of the paragraph 53-55 when referring to paragraph 52,
and wherein the therapeutic antibody molecule is an Fc receptor binding antibody and the modified format is an antibody having the same Fv variable sequence but having impaired or abrogated FcγR binding compared with the therapeutic antibody molecule.

75. A modified format of a therapeutic antibody molecule for use according to paragraph 74, wherein the therapeutic antibody is an anti-FcγRIIB antibody.

76. A modified format of a therapeutic antibody molecule for use according to paragraph 75, wherein the modified format of the anti-FcγRIIB antibody is the antibody having a light chain with SEQ ID No: 1 and a heavy chain with SEQ ID No: 295.

77. A method for preventing or mitigating a tolerability issue in connection with intravenous administration of a therapeutic antibody molecule to a subject comprising a corticosteroid dosing regimen,
wherein the therapeutic antibody molecule has been predicted to be associated with a tolerability issue in connection with intravenous administration to a human using the method of any one of the paragraphs 44-56, and/or wherein pre-treatment with the corticosteroid combination with administration of the therapeutic antibody molecule to a human has been predicted to prevent or mitigate the tolerability issue that otherwise would be associated with intravenous administration of the therapeutic antibody molecule to a human using the method of any one of the paragraphs 48-50, or any one of the paragraphs 53-56 when referring to any one of the paragraphs 48-50,
and wherein the dosing regimen comprises administration of the corticosteroid to the subject in at least two doses prior to intravenous administration of the therapeutic antibody molecule, wherein one dose of the corticosteroid is administered 10-48 hours prior to start of the administration of therapeutic antibody molecule ("the first dose") and one dose of the corticosteroid is administered 5 minutes - 5 hours prior to the start of administration of the therapeutic antibody molecule ("the second dose").

78. A method according to paragraph 77, wherein the first dose is given 6-36 hours prior to start of administration of the therapeutic antibody molecule and the second

dose is given 15-120 minutes prior to start of administration of the therapeutic antibody molecule.

79. A method according to paragraph 77 or 78, wherein the first dose is given 16-24 hours prior to start of administration of the therapeutic antibody molecule.

80. A method according to any one of the paragraphs 77-79, wherein the second dose is given 30-60 minutes prior to start of administration of the therapeutic antibody molecule.

81. A method according to any one of the paragraphs 77-80, wherein the dosing regimen comprises administration of the at least two doses of the corticosteroid prior to each infusion of the antibody during the course of antibody therapy.

82. A method according to any one of the paragraphs 77-81, wherein the corticosteroid is dexamethasone or betamethasone or a combination of dexamethasone and betamethasone.

83. A method according to any one of the paragraphs 77-82, wherein the corticosteroid is dexamethasone and wherein the first dose is 4-20 mg and the second dose is 4-25 mg.

84. A method according to paragraph 83, wherein the first dose is 10-12 mg and the second dose is 20 mg.

85. A method according to any one of the paragraphs 77-82, wherein the corticosteroid is betamethasone and wherein the first dose is 3.2-16 mg and the second dose is 3.2-20 mg.

86. A method according to paragraph 85, wherein the first dose is 8-9.6 mg and the second dose is 16 mg.

87. A method according to claim any one of the paragraphs 77-86, wherein the dosing regimen further comprises administration of an antihistamine 10 minutes – 24 hours prior to start of administration of the therapeutic antibody molecule.

88. A method according to any one of the paragraphs 76-86, wherein the antibody is an Fc receptor binding antibody.

89. A method according to any one of the paragraphs 77-88, wherein the antibody is an anti-FcγRIIB antibody.

90. A method according to paragraph 89, wherein the anti-FcγRIIB antibody is the antibody having a light chain with SEQ ID No: 1 and a heavy chain with SEQ ID No: 2.

91. A method for treatment of cancer comprising subcutaneous administration of a therapeutically active amount of a therapeutic antibody molecule which has been predicted to be associated with a tolerability issue in connection with intravenous administration to a human using the method of any one of the paragraphs 44-56 and/or wherein the subcutaneous route of administration of therapeutic antibody molecule to a human has been predicted to prevent or mitigate the tolerability issue that otherwise would be associated with intravenous administration of the therapeutic antibody molecule to a human using the method of paragraph 51, or any one of the paragraphs 53-56 when referring to paragraph 51.

92. A method according to paragraph 91, wherein the antibody is an anti-FcγRIIB antibody.

93. A method according to paragraph 92, wherein the anti-FcγRIIB antibody is the antibody having a light chain with SEQ ID No: 1 and a heavy chain with SEQ ID No: 2.

94. A method for treatment of cancer comprising administration of a therapeutically active amount of a modified format of a therapeutic antibody, wherein the therapeutic antibody molecule has been predicted to be associated with a tolerability issue in connection with intravenous administration to a human using the method of any one of the paragraphs 44-56 and/or wherein administration of the therapeutic antibody molecule in the modified format to a human has been predicted to prevent or mitigate the tolerability issue that otherwise would be associated with intravenous administration of the therapeutic antibody molecule to a human using the method of paragraph 52, or any one of the paragraphs 53-56 when referring to paragraph 52,
and wherein the therapeutic antibody molecule is an Fc receptor binding antibody and the modified format is an antibody having the same Fv variable sequence but

having impaired or abrogated FcγR binding compared with the therapeutic antibody molecule.

95. A method according to paragraph 94, wherein the antibody is an anti-FcγRIIB antibody.

96. A method according to paragraph 95, wherein the anti-FcγRIIB antibody is the antibody having a light chain with SEQ ID No: 1 and a heavy chain with SEQ ID No: 2 with a N297Q mutation in the heavy chain.

97. A therapeutic antibody molecule for use in the treatment of cancer, an autoimmune disease, an inflammatory disease, an immunological disease, and/or an infectious disease, wherein the therapeutic antibody molecule is an anti-FcγRIIB antibody, and wherein the therapeutic antibody molecule is formulated for subcutaneous administration.

98. Use of a therapeutic antibody molecule in the manufacture of a medicament for use in the treatment of cancer, an autoimmune disease, an inflammatory disease, an immunological disease, and/or an infectious disease, wherein the therapeutic antibody molecule is an anti-FcγRIIB antibody having a light chain with SEQ ID No: 1 and a heavy chain with SEQ ID No: 2, and wherein the medicament is formulated for subcutaneous administration.

99. A pharmaceutical formulation comprising a therapeutic antibody molecule, wherein the therapeutic antibody molecule is an anti-FcγRIIB antibody having a light chain with SEQ ID No: 1 and a heavy chain with SEQ ID No: 2, and wherein the pharmaceutical formulation comprises a pharmaceutically acceptable diluent or excipient, and is formulated for subcutaneous administration.

100. A therapeutic antibody molecule for use according to paragraph 97, use of a therapeutic antibody molecule according to paragraph 98, or a pharmaceutical formulation according to paragraph 99, wherein the therapeutic antibody is an Fc receptor binding antibody.

101. A therapeutic antibody molecule for use according to paragraph 97 or 100, use of a therapeutic antibody molecule according to paragraph 98 or 100, or a pharmaceutical formulation according to paragraph 99 or 100, wherein the therapeutic antibody is an anti-FcγRIIB antibody.

102. A therapeutic antibody molecule for use according to paragraph 101, use of a therapeutic antibody molecule according to paragraph 101, or a pharmaceutical formulation according to paragraph 101, wherein the therapeutic antibody has a light chain with SEQ ID No: 1 and a heavy chain with SEQ ID No: 2.

103. A therapeutic antibody molecule for use according to paragraph 101 or 102, use of a therapeutic antibody molecule according to paragraph 101 or 102, or a pharmaceutical formulation according to paragraph 101 or 102, for treatment of cancer.

104. The pharmaceutical formulation according to any one of the paragraphs 99-103, wherein the therapeutic antibody is present at a concentration of between about 90mg/mL and about 220 mg/mL.

105. The pharmaceutical formulation according to any one of the paragraphs 99-104, further comprising between about 5 mM and about 20 mM acetate, and/or between about 50mM and about 250mM NaCl, and/or about 0.05% Polysorbate 20, and/or wherein the pharmaceutical formulation is at a pH of between about pH 5.0 and about pH 5.8.

106. The pharmaceutical formulation according to any one of the paragraphs 99-105, wherein the formulation comprises:
- the therapeutic antibody at a concentration of 150 mg/mL;
- 5mM acetate;
- 110mM NaCl;
- 0.05% (w/v) Polysorbate 20; and
- wherein the formulation is at a pH 5.8.

107. A method for the treatment of cancer, an autoimmune disease, an inflammatory disease, an immunological disease, and/or an infectious disease in a subject, the method comprising the step of administering to the subject a therapeutic antibody molecule, wherein the therapeutic antibody molecule is an Fc receptor binding antibody, and wherein the therapeutic antibody molecule is formulated for subcutaneous administration.

108. The method of paragraph 107, wherein the Fc receptor binding antibody is an anti-FcγRIIB antibody.

109. The method of paragraph 107 or 108, wherein the Fc receptor binding antibody is an anti-FcγRIIB antibody having a light chain with SEQ ID No: 1 and a heavy chain with SEQ ID No: 2.

110. A method for the treatment of cancer, an autoimmune disease, an inflammatory disease, an immunological disease, and/or an infectious disease in a subject, the method comprising the step of subcutaneously administering to the subject a pharmaceutical formulation as defined in any one of the paragraphs 99-106.

111. The method of paragraph 109 or 110 for the treatment of cancer.

CLAIMS

1. A therapeutic system for use in improving tolerability of an antibody molecule that specifically binds to FcyRIIb in a subject, wherein the therapeutic system comprises:

   (i) an antibody molecule that specifically binds to FcyRIIb, wherein the antibody molecule is administered to the subject as at least a first dose and a second dose; and

   (ii) a corticosteroid,

   wherein the first dose of the antibody molecule is lower than the maximum therapeutically effective dose of the antibody molecule; and
   wherein the corticosteroid is administered to the subject before the first dose of the antibody molecule.

2. A combination comprising an antibody molecule and a corticosteroid for use in a dosage regimen for improving tolerability of an antibody molecule that specifically binds to FcyRIIb in a subject, wherein the dosage regimen comprises the following steps:
   (i) administration of a corticosteroid before administration of a first dose of the antibody molecule;
   (ii) administration of the first dose of the antibody molecule that specifically binds to FcyRIIb that is lower than the maximum therapeutically effective dose; and
   (iii) administration of a second dose of the antibody molecule that specifically binds to FcyRIIb, wherein the first dose of the antibody molecule is administered prior to the second dose.

3. Use of:
   (i) an antibody molecule that specifically binds to FcyRIIb; and
   (ii) a corticosteroid,

   in the manufacture of a medicament for improving tolerability of an antibody molecule that specifically binds to FcyRIIb in a subject, wherein the medicament comprises at least a first dose and a second dose of the antibody molecule; and
   wherein the first dose of the antibody molecule is lower than the maximum therapeutically effective dose of the antibody molecule; and

wherein the corticosteroid is administered before the first dose of the antibody molecule.

4. A method for improving tolerability of an antibody molecule that specifically binds to FcγRIIb in a subject comprising:

(i) administration of a corticosteroid before administration of a first dose of the antibody molecule;
(ii) administration of the first dose of the antibody molecule that specifically binds to FcγRIIb that is lower than the maximum therapeutically effective dose; and
(iii) administration of a second dose of the antibody molecule that specifically binds to FcγRIIb, wherein the first dose of the antibody molecule is administered prior to the second dose.

5. The system, combination for use, use, or method of claims 1-4, wherein the system, combination for use, use, or method further comprises administration of one or more therapeutic antibodies for the treatment of cancer in a subject,
optionally wherein the therapeutic antibody is selected from: rituximab; pembrolizumab; nivolumab; cemiplimab; camrelizumab; dostarlimab; obinutuzumab; ofatumumab, and biosimilars or equivalents thereof.

6. The system, combination for use, use, or method of claims 1-5, wherein the corticosteroid is administered to the subject at a time point from 10 minutes to 48 hours before the first dose of the antibody molecule that specifically binds to FcγRIIb,
optionally wherein the corticosteroid is administered to the subject at a time point from 10 minutes to 24 hours before the first dose of the antibody molecule that specifically binds to FcγRIIb.

7. The system, combination for use, use, or method of claims 1-5, wherein the corticosteroid is administered as a first dose and a second dose, and wherein the first dose of the corticosteroid is administered at a time point from 16 hours to 48 hours before the first dose of the antibody molecule that specifically binds to FcγRIIb, and wherein the second dose of the corticosteroid is administered at a time point from 10 minutes to 2 hours before the first dose of the antibody molecule that binds specifically to FcγRIIb,

optionally wherein a further dose of corticosteroid is administered at a time point from 16 hours to 48 hours before the second dose of the antibody molecule that specifically binds to FcγRIIb.

8. The system, combination for use, use, or method of claims 1-7, wherein the first dose of the antibody molecule that specifically binds to FcγRIIb is administered at a time point from one to 24 hours before the second dose of the antibody molecule that specifically binds to FcγRIIb.

9. The system, combination for use, use, or method of claims 1-7, wherein the first dose of the antibody molecule that specifically binds to FcγRIIb is administered about one hour before the second dose of the antibody molecule that specifically binds to FcγRIIb.

10. The system, combination for use, use, or method of claims 1-7, wherein the first dose of the antibody molecule that specifically binds to FcγRIIb is administered about 24 hours before the second dose of the antibody molecule that specifically binds to FcγRIIb.

11. The system, combination for use, use, or method of claims 1-7, wherein the first dose of the antibody molecule that specifically binds to FcγRIIb is administered from 24 hours to 48 hours before the second dose of the antibody molecule that specifically binds to FcγRIIb.

12. The system, combination for use, use, or method of claims 1-11, wherein the corticosteroid is administered at a dose of 4 mg or greater, and/or wherein the corticosteroid is administered at a dose of 12 mg or greater.

13. The system, combination for use, use, or method of claims 1-11, wherein the corticosteroid is administered at a dose of from 4 mg to 20 mg, optionally wherein the corticosteroid is administered at a dose of from 12 mg to 20 mg, or wherein the corticosteroid is administered at a dose of from 4 mg to 12 mg.

14. The system, combination for use, use, or method of claims 1-13, wherein the corticosteroid is dexamethasone or betamethasone or a combination of dexamethasone and betamethasone.

15. The system, combination for use, use, or method of claims 1-14, wherein the first dose of the antibody molecule that specifically binds to FcγRIIb is lower than the maximum tolerated therapeutic dose.

16. The system, combination for use, use, or method of claims 1-15, wherein the first dose of the antibody molecule that specifically binds to FcγRIIb is at least 50% lower than the maximum therapeutically effective dose.

17. The system, combination for use, use, or method of claims 1-16, wherein the first dose of the antibody molecule that specifically binds to FcγRIIb is administered at a dose of from 0.2 mg/kg to 0.6 mg/kg, optionally wherein the first dose of the antibody molecule that specifically binds to FcγRIIb is administered at a dose of from 0.3 mg/kg to 0.5 mg/kg.

18. The system, combination for use, use, or method of claims 1-17, wherein the first dose of the antibody molecule that specifically binds to FcγRIIb is administered at a dose of from 20 mg to 40 mg, optionally wherein the first dose of the antibody molecule that specifically binds to FcγRIIb is administered at a dose of about 30 mg.

19. The system, combination for use, use, or method of claims 1-18, wherein the second dose of the antibody molecule that specifically binds to FcγRIIb is a therapeutically effective dose.

20. The system, combination for use, use, or method of claims 1-19, wherein the second dose of the antibody molecule that specifically binds to FcγRIIb is the maximum tolerated therapeutic dose or the maximum feasible therapeutic dose; or wherein the second dose of the antibody molecule that specifically binds to FcγRIIb is lower than a therapeutically effective dose.

21. The system, combination for use, use, or method of claims 1-20, wherein further additional doses of the antibody molecule that specifically binds to FcγRIIb are administered to the subject following the second dose of the antibody molecule that specifically binds to FcγRIIb.

22. The system, combination for use, use, or method of claims 1-21, wherein infusion related reactions associated with the administration of the antibody molecule that specifically binds to FcγRIIb are reduced or eliminated; and/or wherein changes to

the body temperature and/or platelet count and/or blood levels of liver enzymes of the subject are reduced (and are preferably reduced to acceptable levels) for at least 24 hours following administration of the second dose of the antibody molecule that specifically binds to FcγRIIb.

23. The system, combination for use, use, or method of claims 1-22, wherein the antibody molecule that specifically binds to FcγRIIb is capable of binding one or more Fcγ receptors via its Fc region.

24. The system, combination for use, use, or method of claims 1-23, wherein the antibody molecule that specifically binds to FcγRIIb has a light chain sequence of SEQ ID No: 1 and a heavy chain of SEQ ID No: 2.

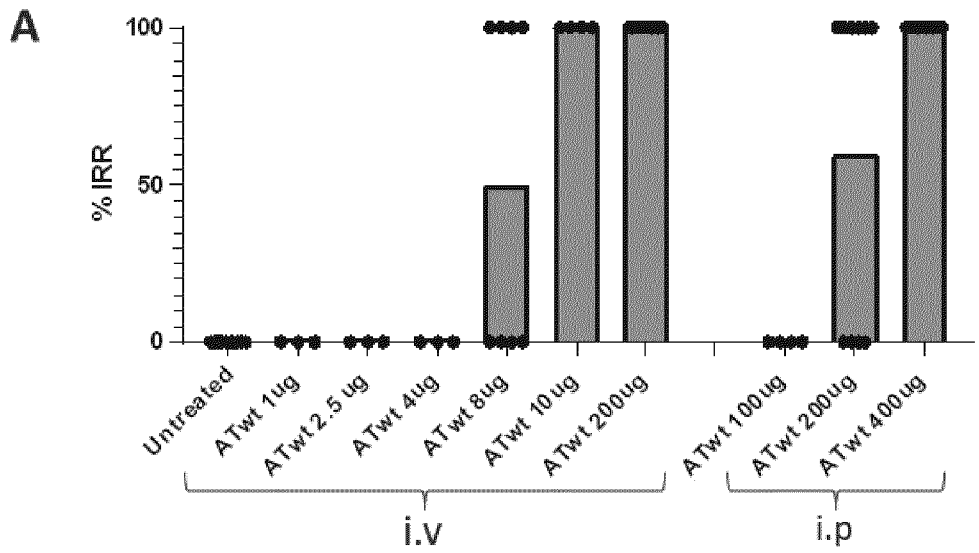
25. The system, combination for use, use, or method of claims 1-24, wherein the first and second doses of the antibody molecule that specifically binds to FcγRIIb are formulated for intravenous delivery to the subject; and/or wherein the corticosteroid is formulated for intravenous or oral delivery to the subject.

26. A kit comprising:
(i) an antibody molecule that specifically binds to FcγRIIb, optionally as defined in claims 23 and/or 24;
(ii) a corticosteroid, optionally as defined in any one of claims 12-14; and
(iii) optionally, instructions for use,

wherein the antibody molecule is provided as a first dose and a second dose, wherein the first dose of the antibody molecule is lower than the maximum therapeutically effective dose of the antibody molecule, further optionally wherein the first dose is as defined in claims 8-11 and 15-18, further optionally wherein the second dose is as defined in claims 19-20.

27. The kit of claim 26, wherein the kit is for improving the tolerability of the antibody molecule in a subject; and/or wherein the corticosteroid is provided in a dose as defined in any one of claims 9-13; and/or wherein the kit further comprises one or more therapeutic antibodies,
optionally wherein the therapeutic antibody is selected from: rituximab; pembrolizumab; nivolumab; cemiplimab; camrelizumab; dostarlimab; obinutuzumab; ofatumumab, and biosimilars or equivalents thereof; further optionally wherein the kit is for use in treating cancer in a subject.

Figure 1


A
100
50
0
% IRR
Untreated
ATwt 1ug
ATwt 2.5 ug
ATwt 4ug
ATwt 8ug
ATwt 10 ug
ATwt 200ug
ATwt 100ug
ATwt 200ug
ATwt 400ug
i.v
i.p

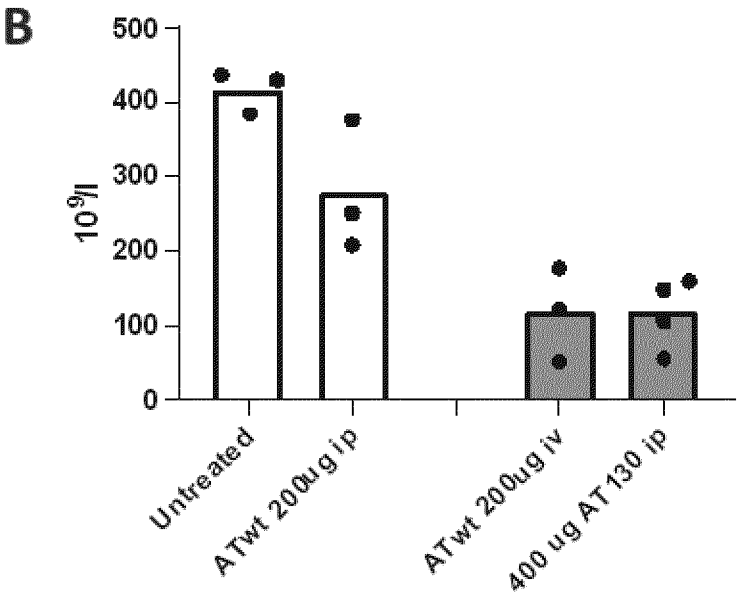
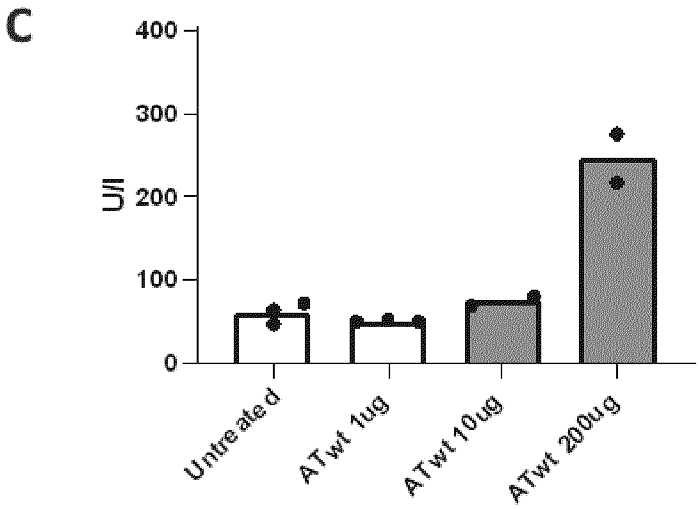

B
500
400
300
200
100
0
10^9/l
Untreated
ATwt 200ug ip
ATwt 200ug iv
400 ug AT130 ip

Figure 1 continued



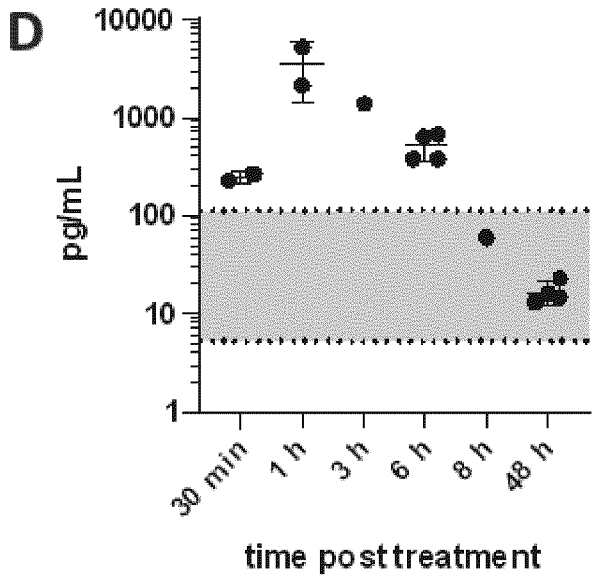


Figure 2

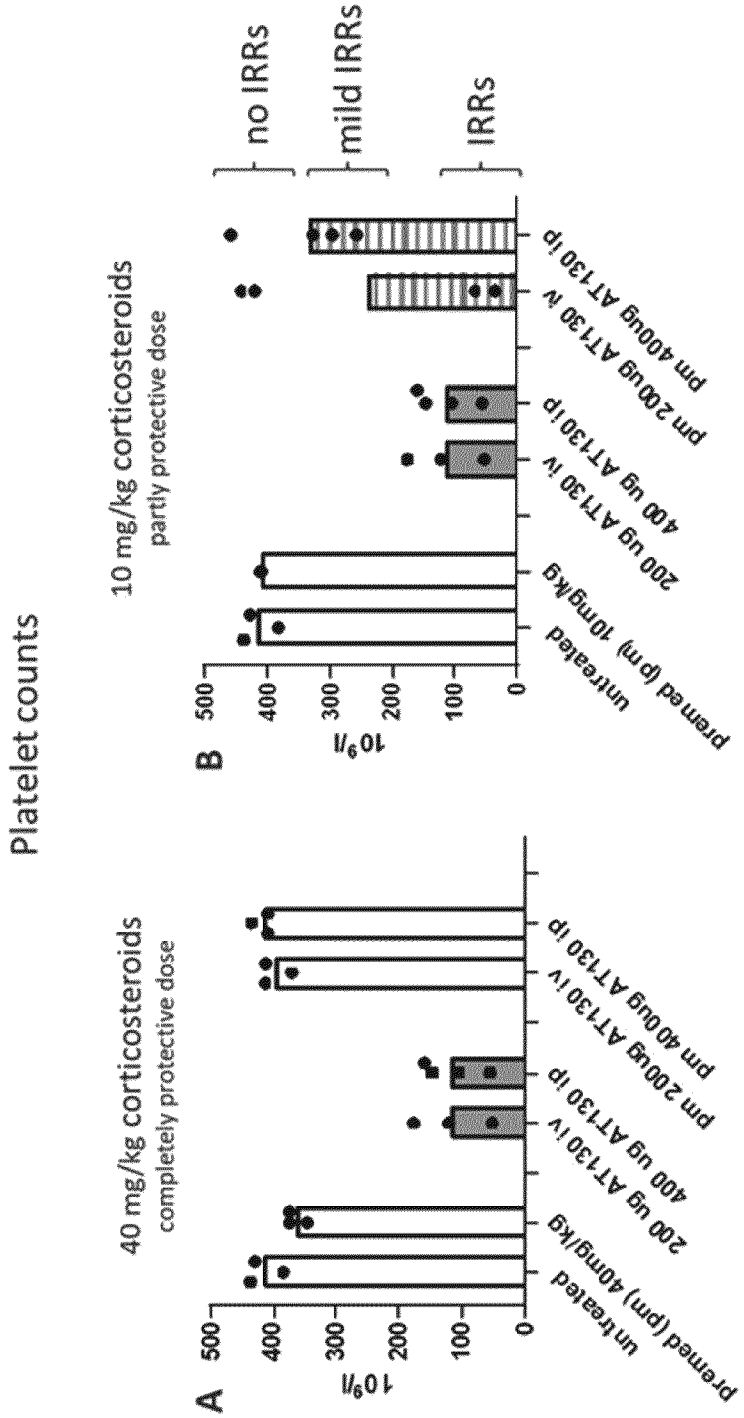

Platelet counts
A
40 mg/kg corticosteroids
completely protective dose
B
10 mg/kg corticosteroids
partly protective dose
no IRRs
mild IRRs
IRRs
10⁹/l
0
100
200
300
400
500
untreated
premed (pm) 10mg/kg
200 ug AT130 iv
400 ug AT130 iv
pm 200ug AT130 ip
pm 400ug AT130 iv
pm 400ug AT130 ip
premed (pm) 40mg/kg

Figure 3

A

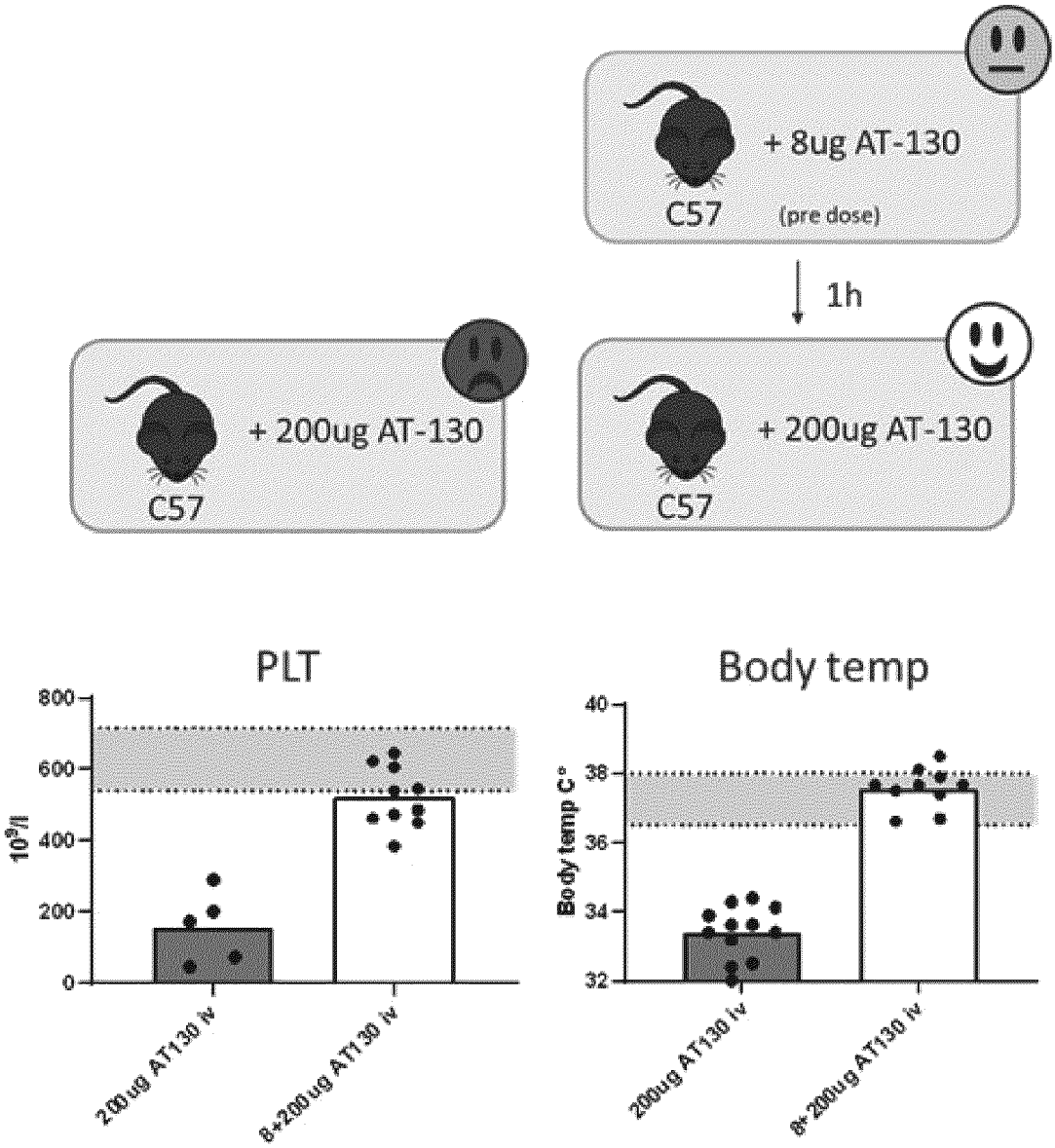

+ 8ug AT-130
C57
(pre dose)
1h
+ 200ug AT-130
C57
+ 200ug AT-130
C57
PLT
800
600
400
200
0
10³/l
200ug AT130 iv
8+200ug AT130 iv
Body temp
40
38
36
34
32
Body temp C°
200ug AT130 iv
8+200ug AT130 iv

Figure 3 continued

B

Scoring	Macroscopic symptoms
0 	No visible symptoms
1 	Isolation, decreased activity
2 	Isolation, decreased activity, impaired balance, piloerection, hunching, un-natural body posture

C

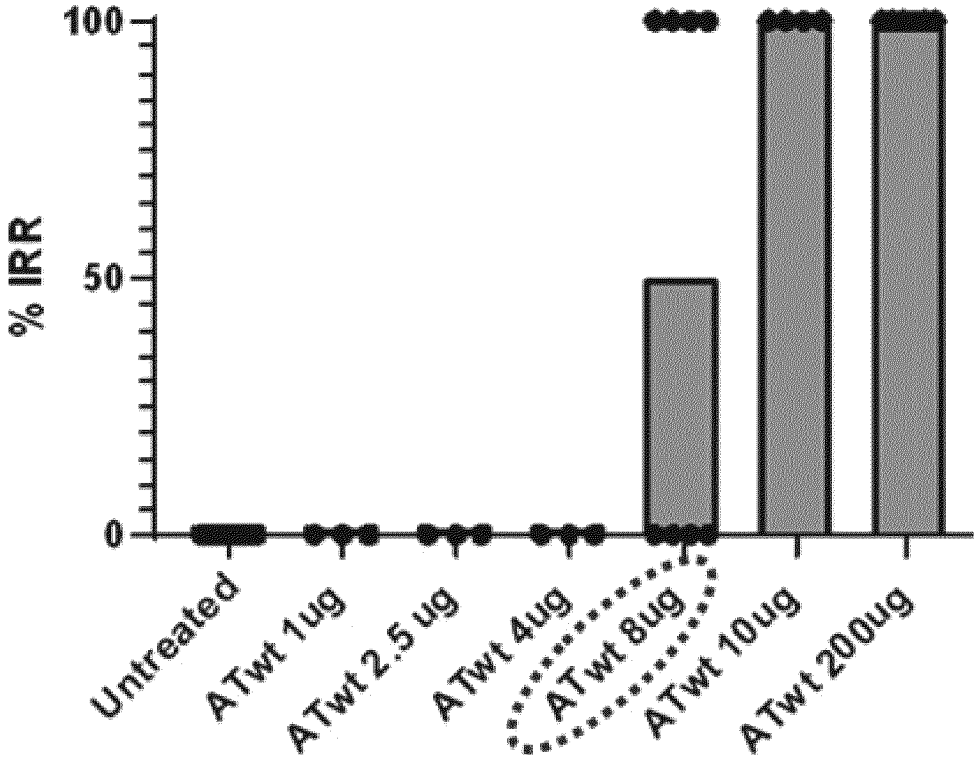


Figure 4

A

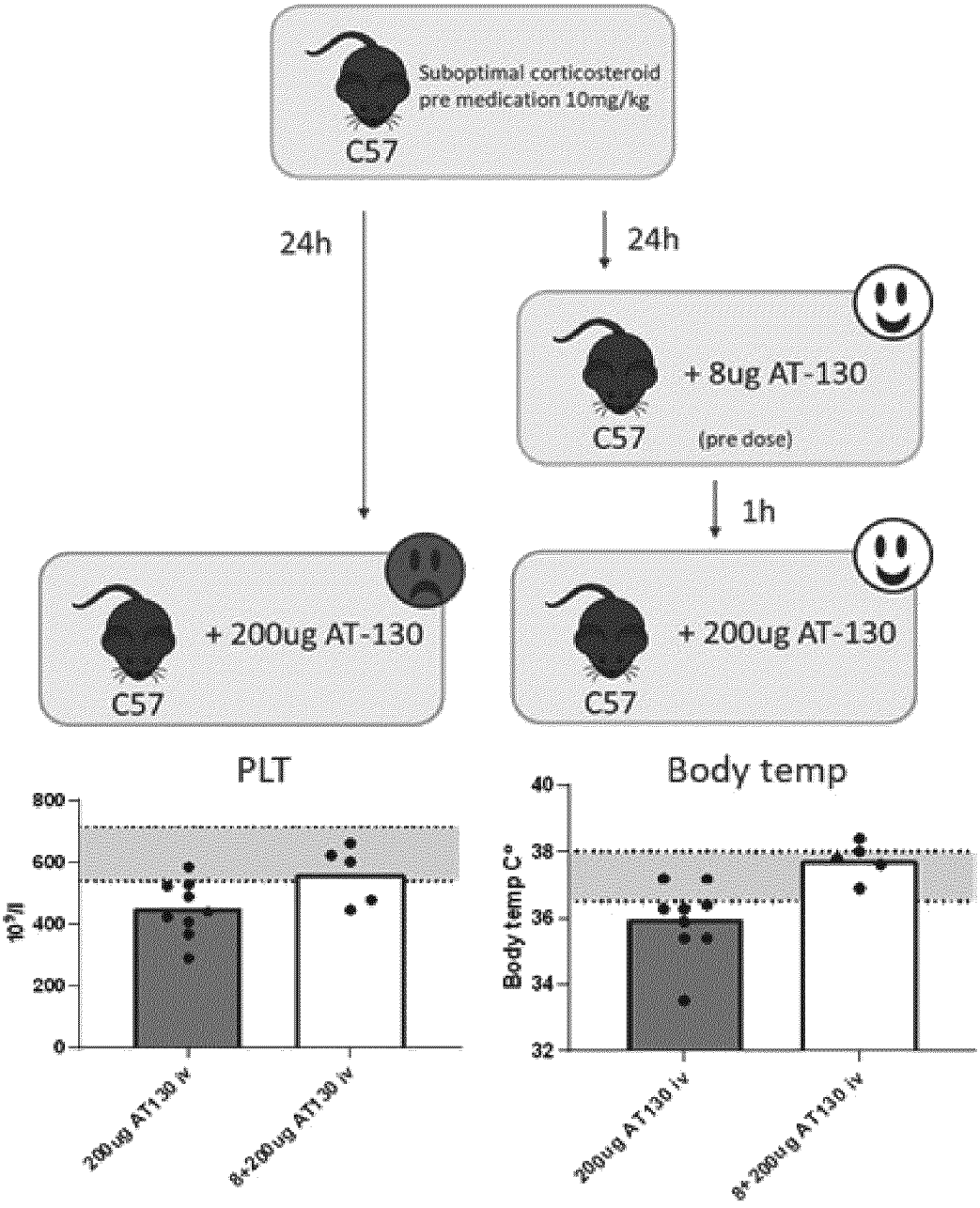

Suboptimal corticosteroid pre medication 10mg/kg
C57
24h
24h
+ 8ug AT-130
C57
(pre dose)
1h
+ 200ug AT-130
C57
+ 200ug AT-130
C57
PLT
800
600
400
200
0
200ug AT130 iv
8+200ug AT130 iv
Body temp
40
38
36
34
32
Body temp C°
200ug AT130 iv
8+200ug AT130 iv

Figure 4 continued

B

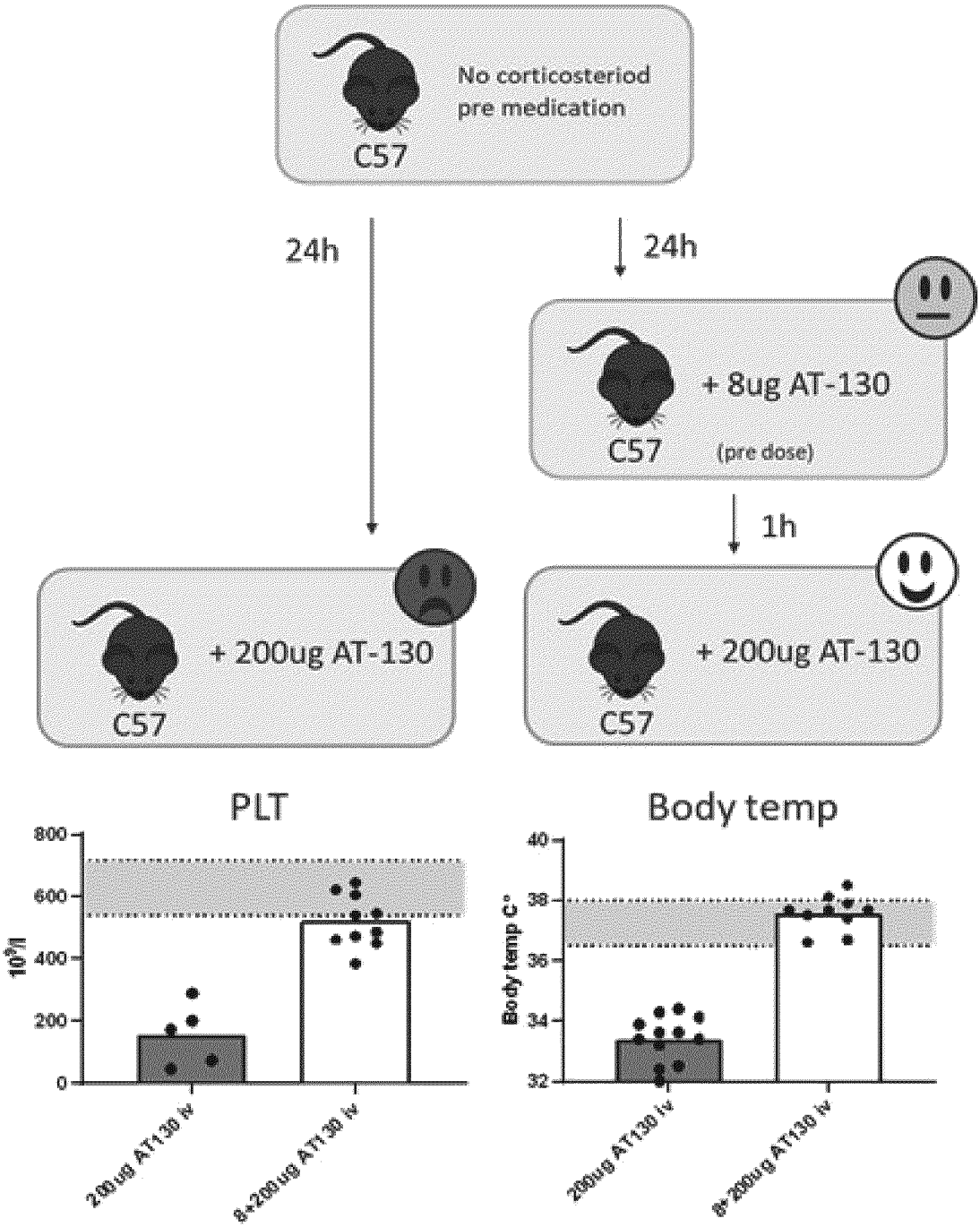


Figure 5

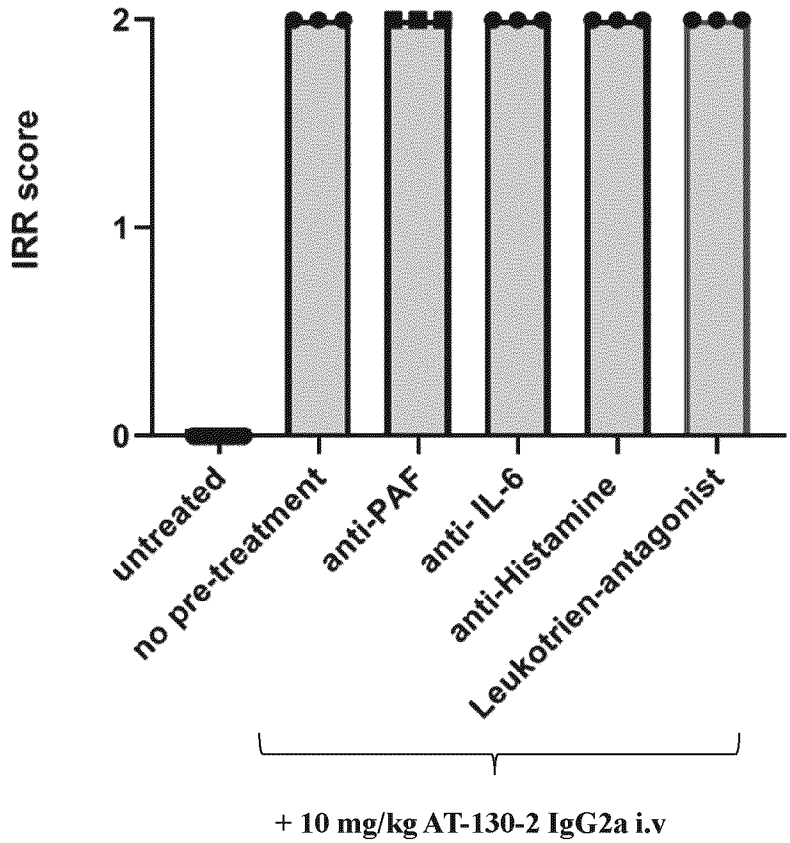

IRR score
2
1
0
untreated
no pre-treatment
anti-PAF
anti- IL-6
anti-Histamine
Leukotrien-antagonist
+ 10 mg/kg AT-130-2 IgG2a i.v

Figure 6

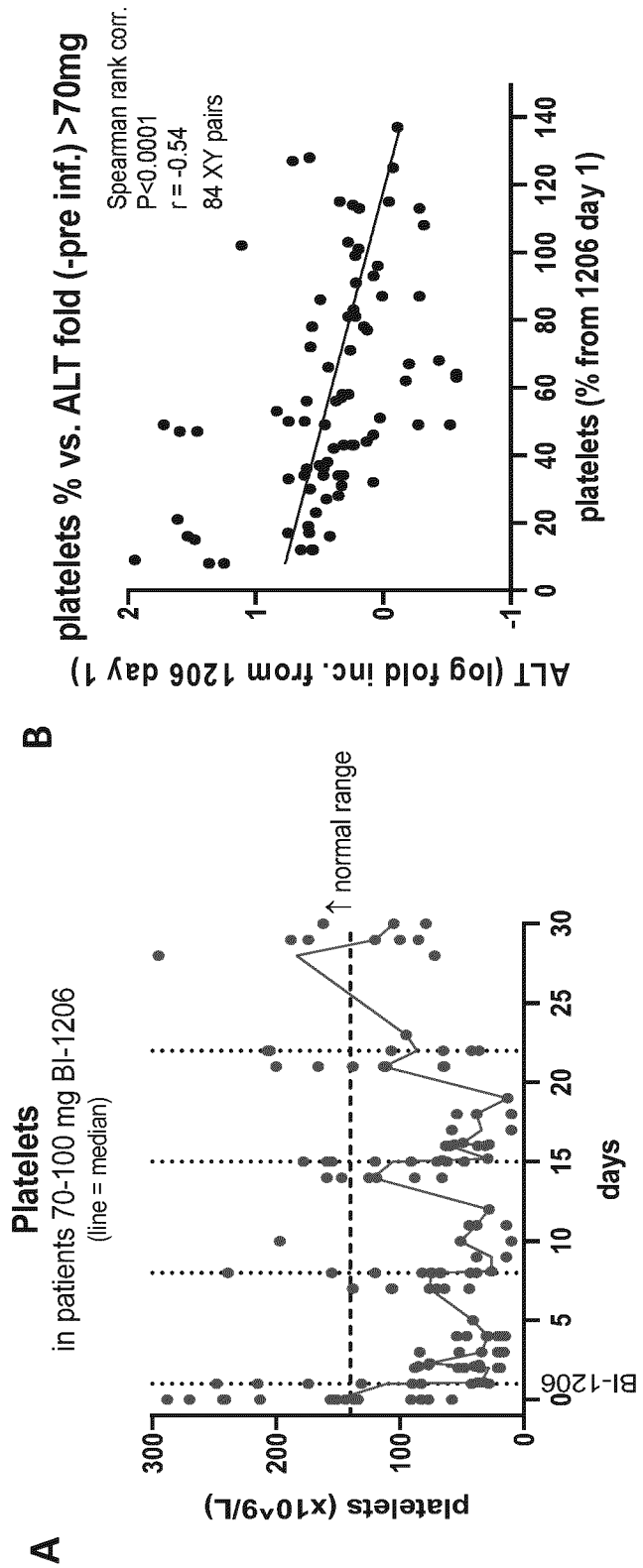

A
Platelets
in patients 70-100 mg BI-1206
(line = median)
normal range
platelets (x10^9/L)
300
200
100
0
BI-1206
0
5
10
15
20
25
30
days
B
platelets % vs. ALT fold (-pre inf.) >70mg
Spearman rank corr.
P<0.0001
r = -0.54
84 XY pairs
ALT (log fold inc. from 1206 day 1)
2
1
0
-1
0
20
40
60
80
100
120
140
platelets (% from 1206 day 1)

Figure 6 continued

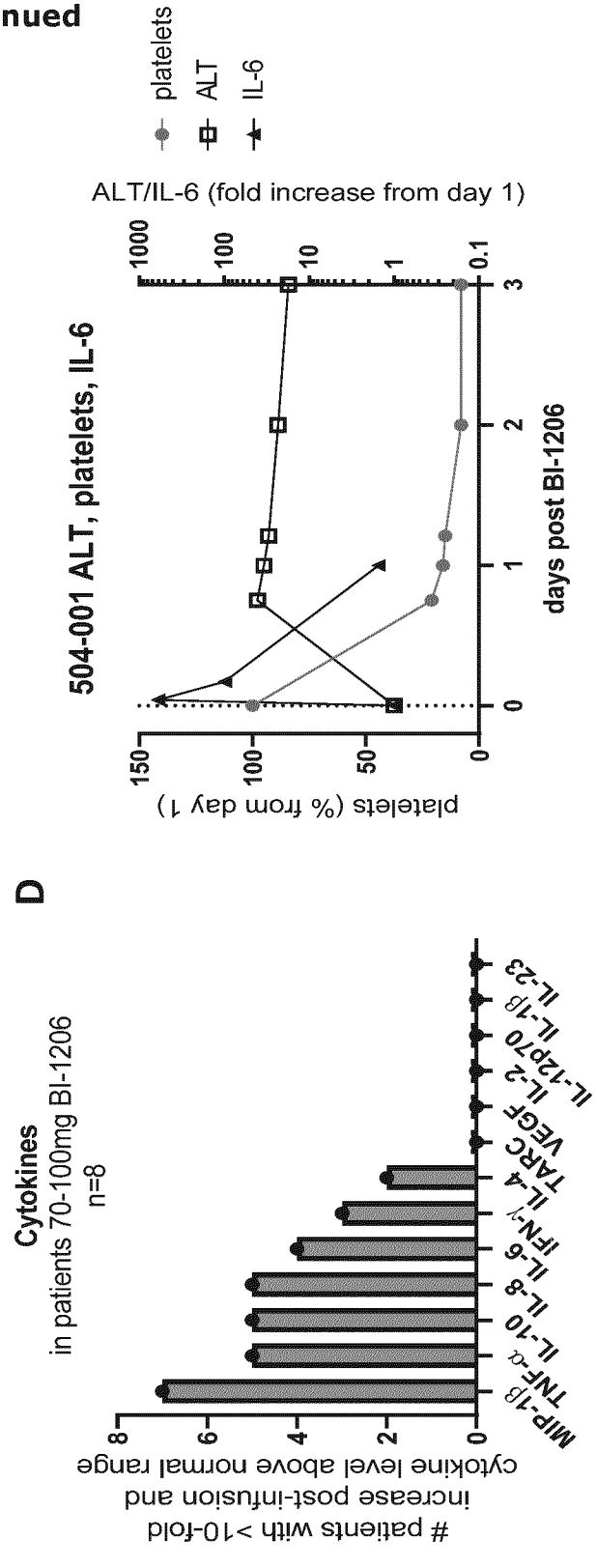


Figure 7

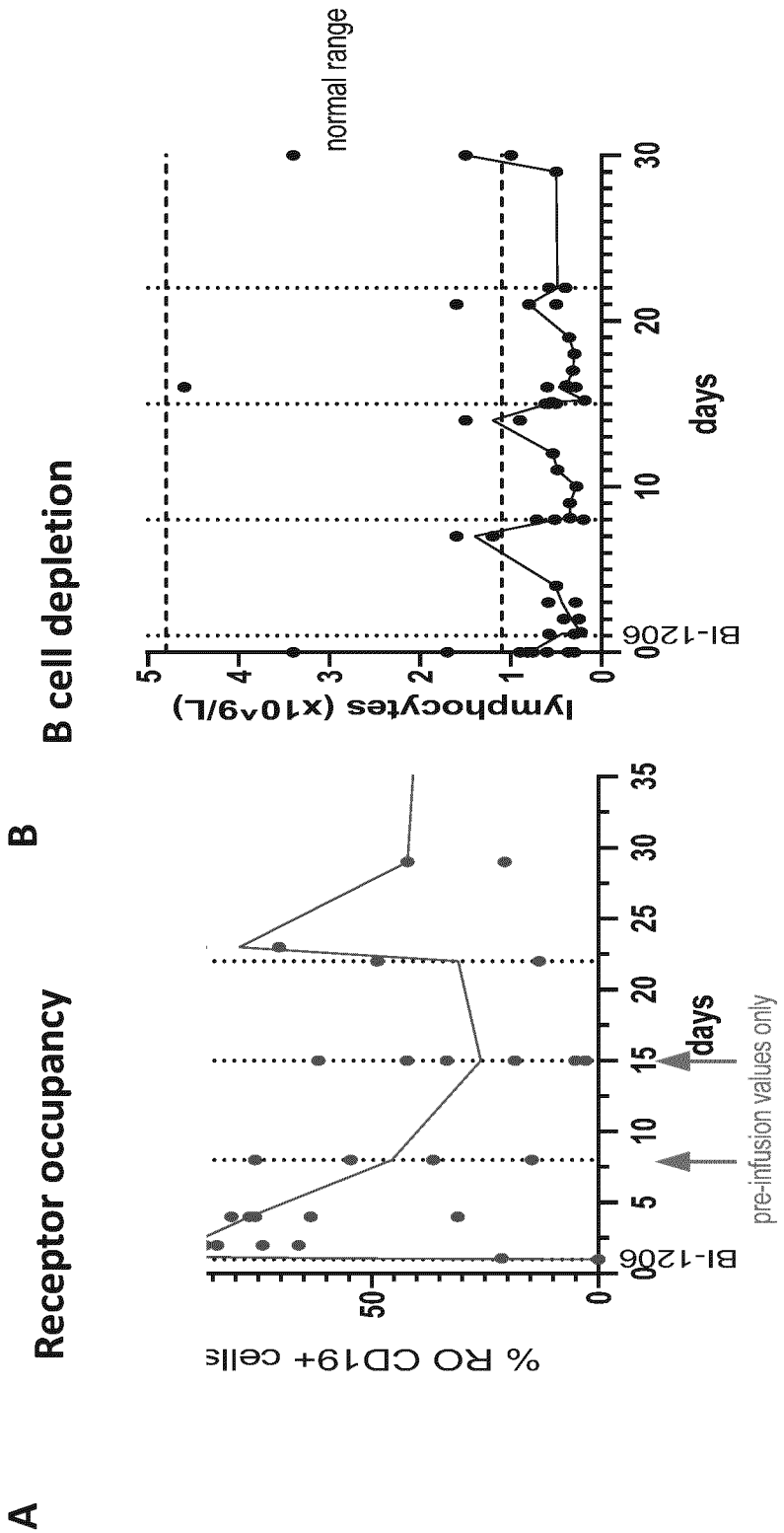

A
Receptor occupancy
% RO CD19+ cells
BI-1206
days
pre-infusion values only
B
B cell depletion
Lymphocytes (x10^9/L)
normal range
BI-1206
days

Figure 7 continued

C

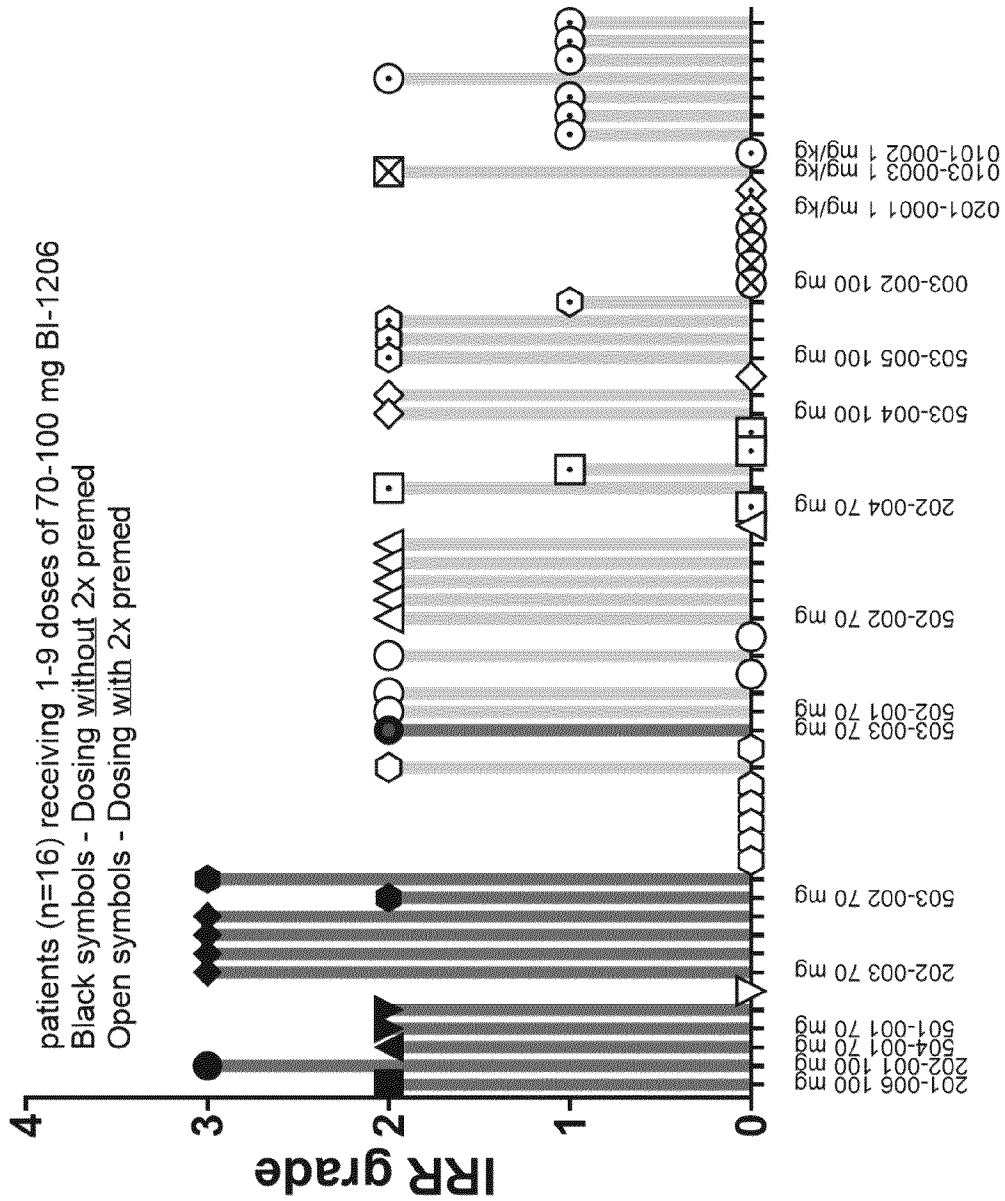


Figure 7 continued

D

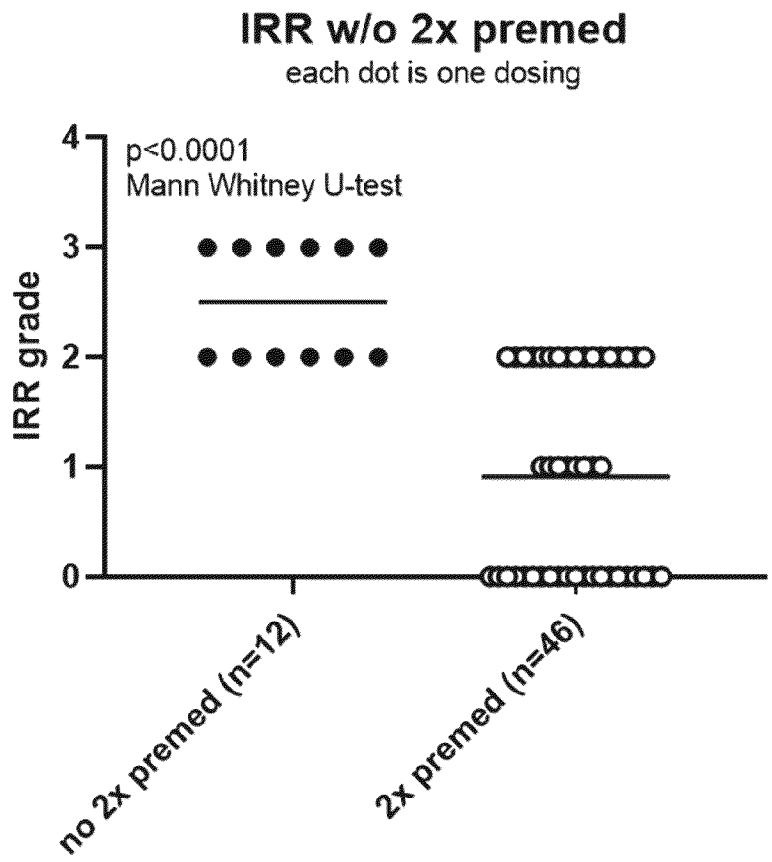


Figure 7 continued

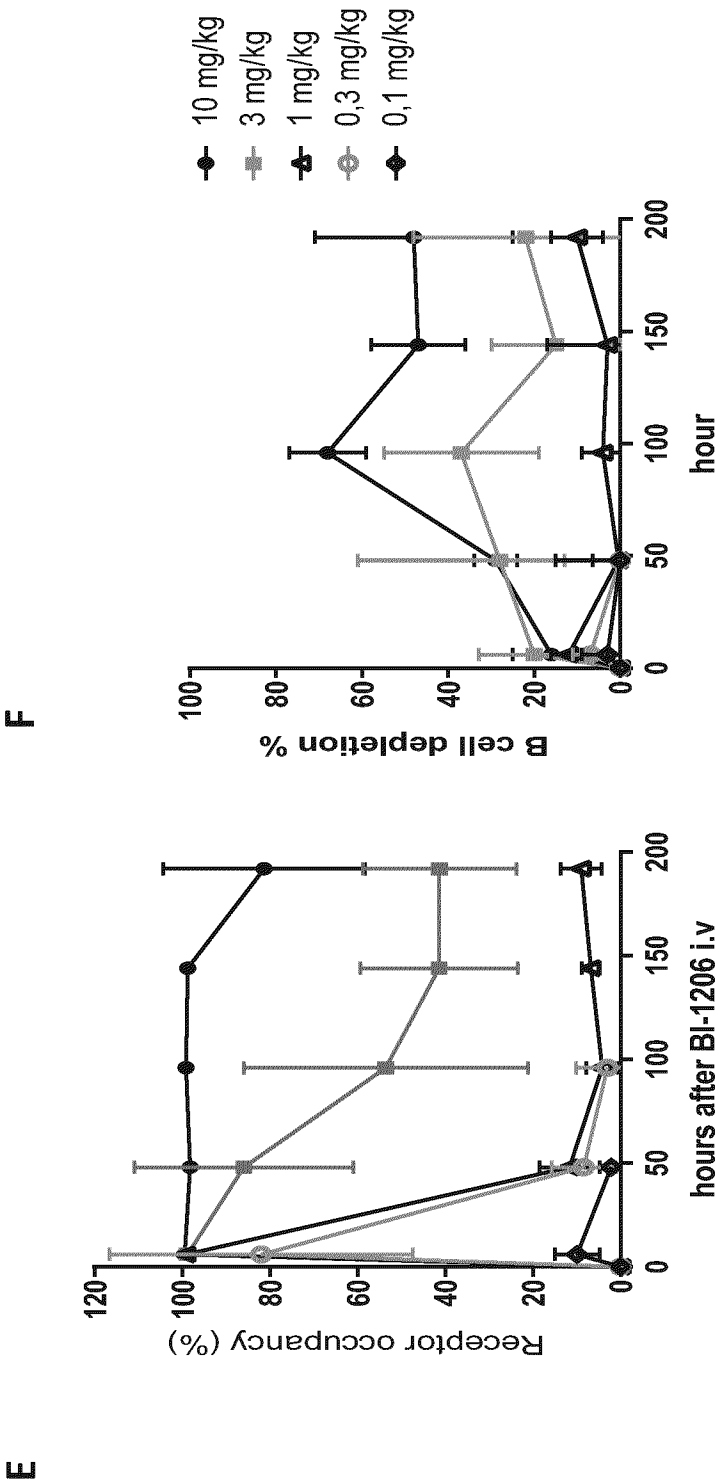


Figure 7 continued

G

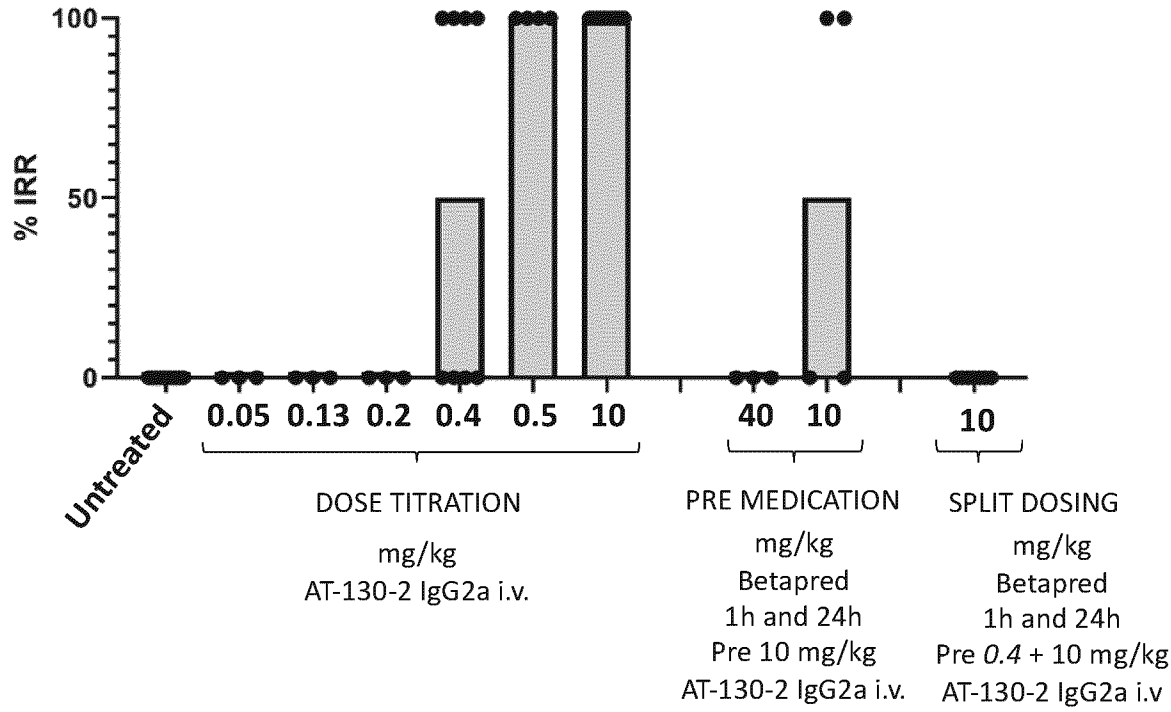


Figure 7 continued

H

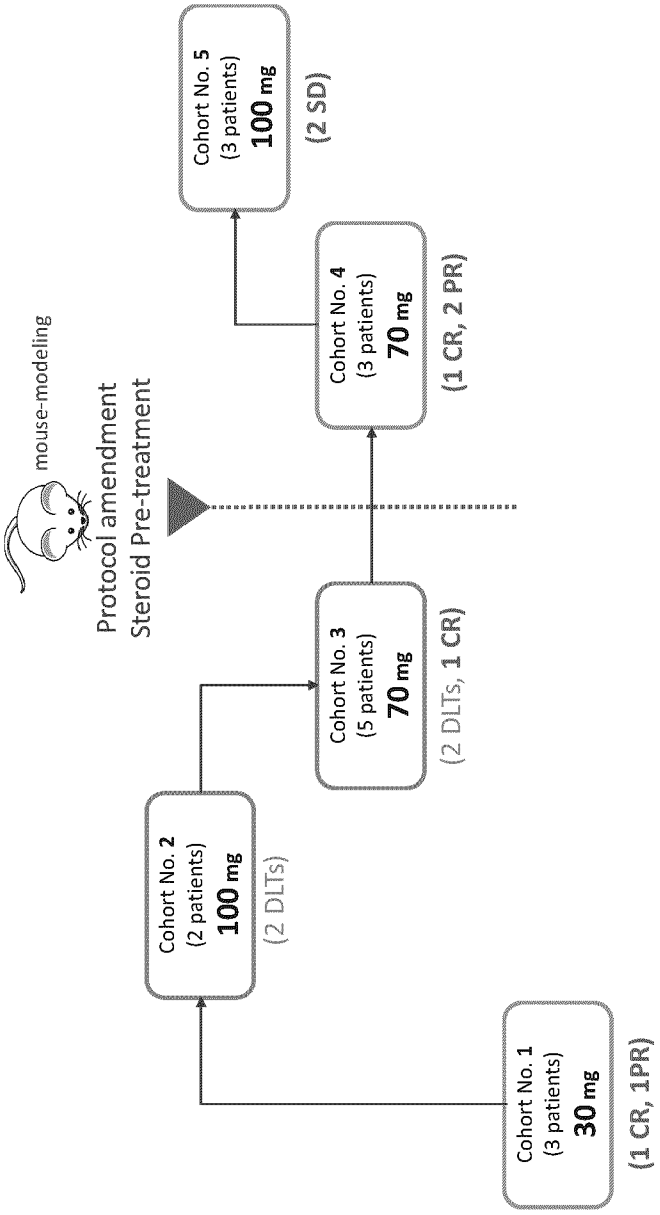
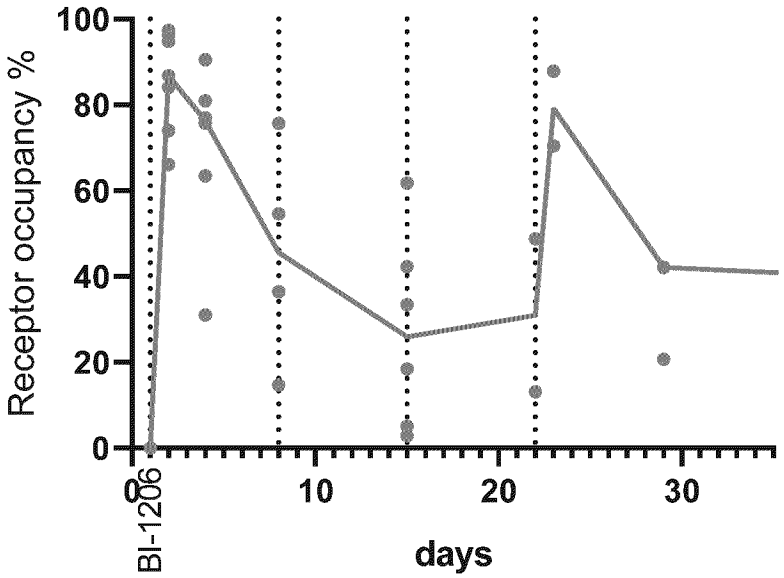


Figure 8

A


Receptor occupancy %
100
80
60
40
20
0
0
10
20
30
BI-1206
days

B

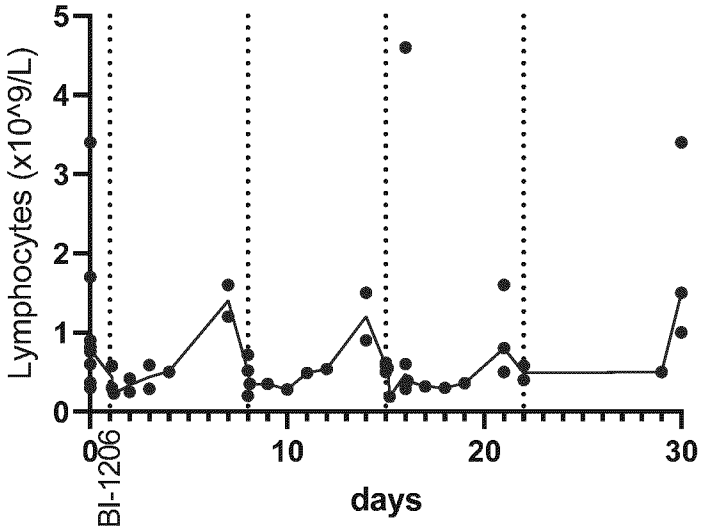
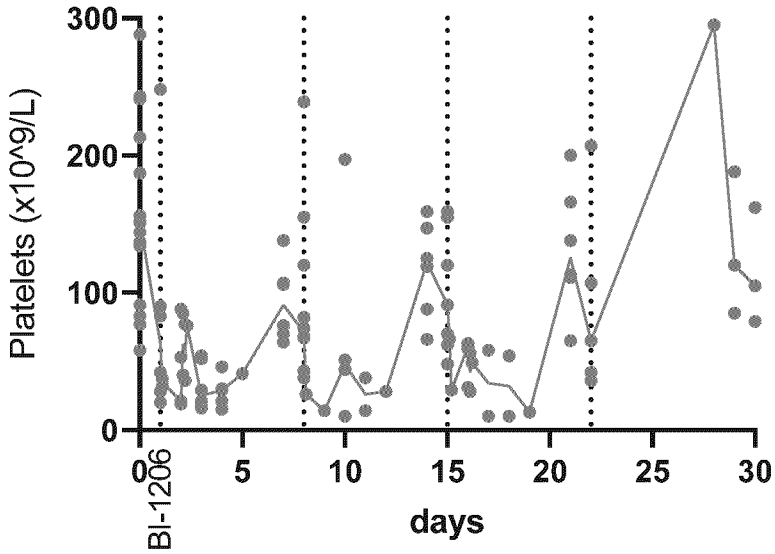

Lymphocytes (x10^9/L)
5
4
3
2
1
0
0
10
20
30
BI-1206
days

Figure 9

A


Platelets (x10^9/L)
300
200
100
0
0
5
10
15
20
25
30
days
BI-1206

B

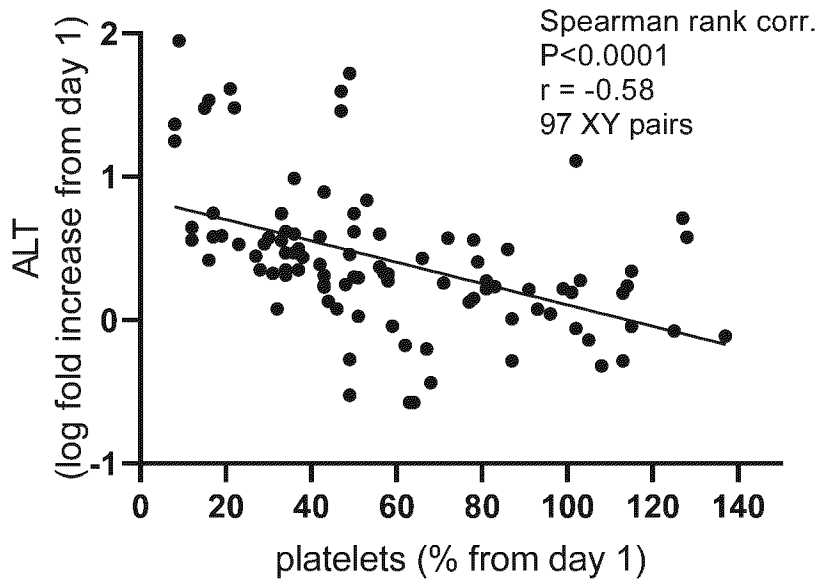

ALT
(log fold increase from day 1)
2
1
0
-1
0
20
40
60
80
100
120
140
platelets (% from day 1)
Spearman rank corr.
P<0.0001
r = -0.58
97 XY pairs

Figure 10

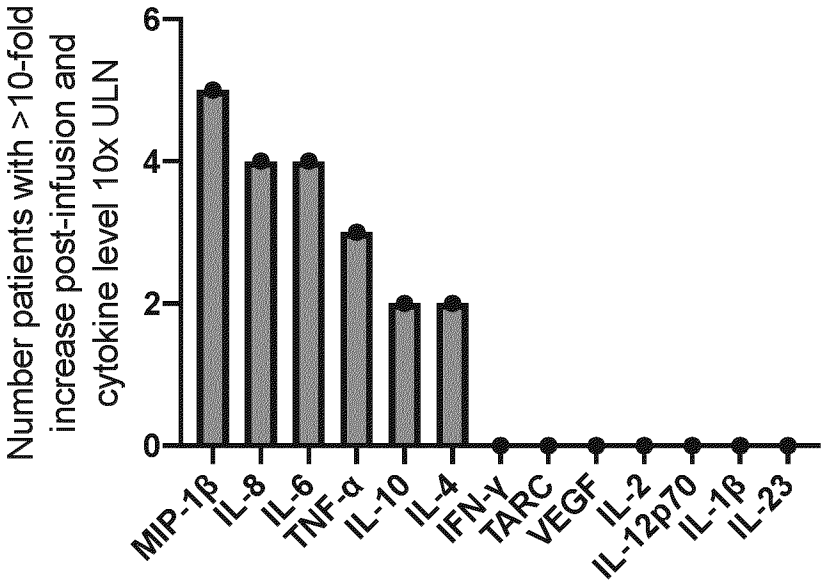
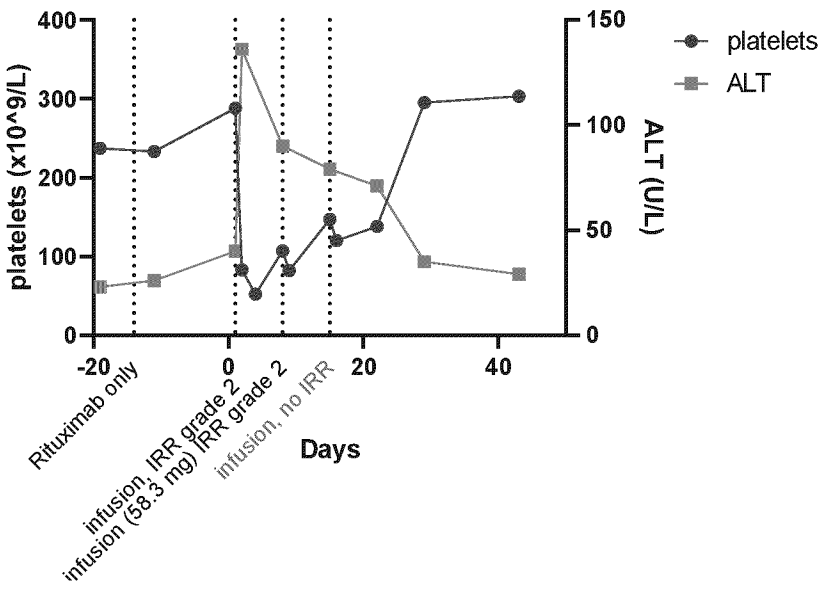

Number patients with >10-fold increase post-infusion and cytokine level 10x ULN
6
4
2
0
MIP-1β
IL-8
IL-6
TNF-α
IL-10
IL-4
IFN-γ
TARC
VEGF
IL-2
IL-12p70
IL-1β
IL-23

Figure 11

A


platelets (x10^9/L)
ALT (U/L)
400
300
200
100
0
150
100
50
0
-20
0
20
40
Days
platelets
ALT
Rituximab only
infusion, IRR grade 2
infusion (58.3 mg)
IRR grade 2
infusion, no IRR

B

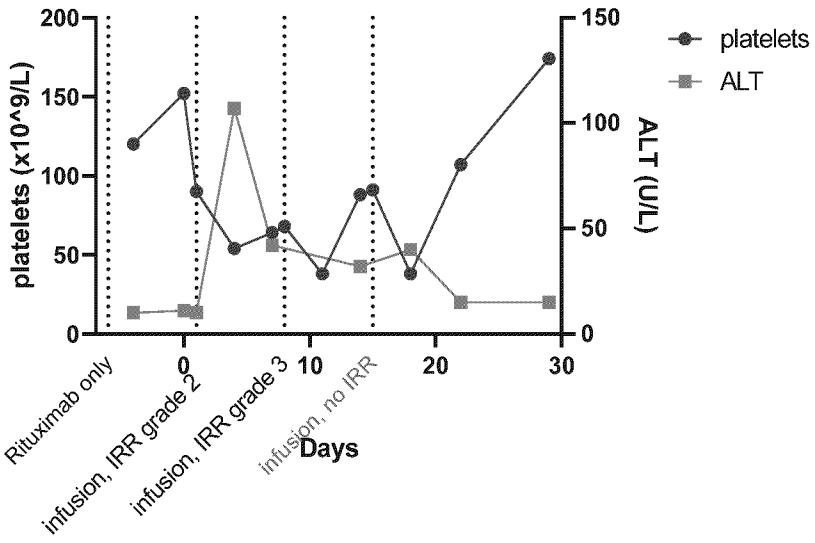

platelets (x10^9/L)
ALT (U/L)
200
150
100
50
0
150
100
50
0
0
10
20
30
Days
platelets
ALT
Rituximab only
infusion, IRR grade 2
infusion, IRR grade 3
infusion, no IRR

Figure 12

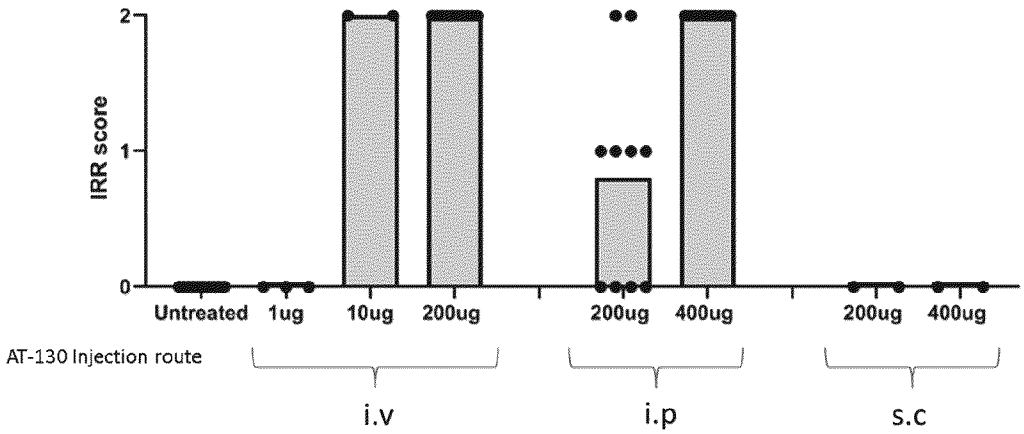


Figure 13

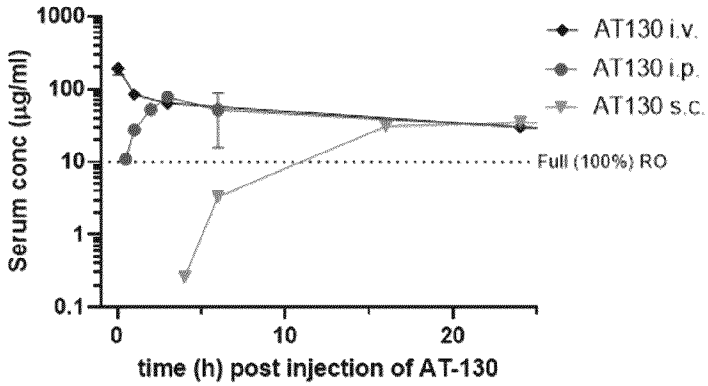


Figure 14

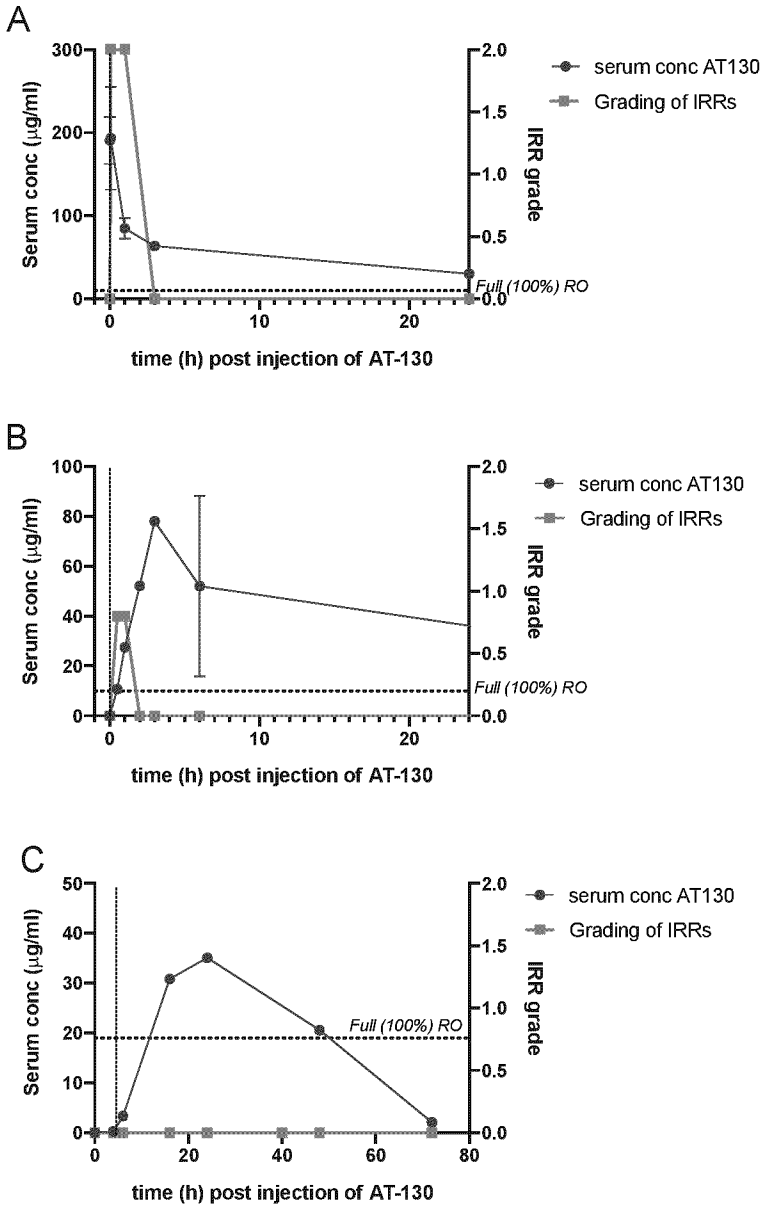
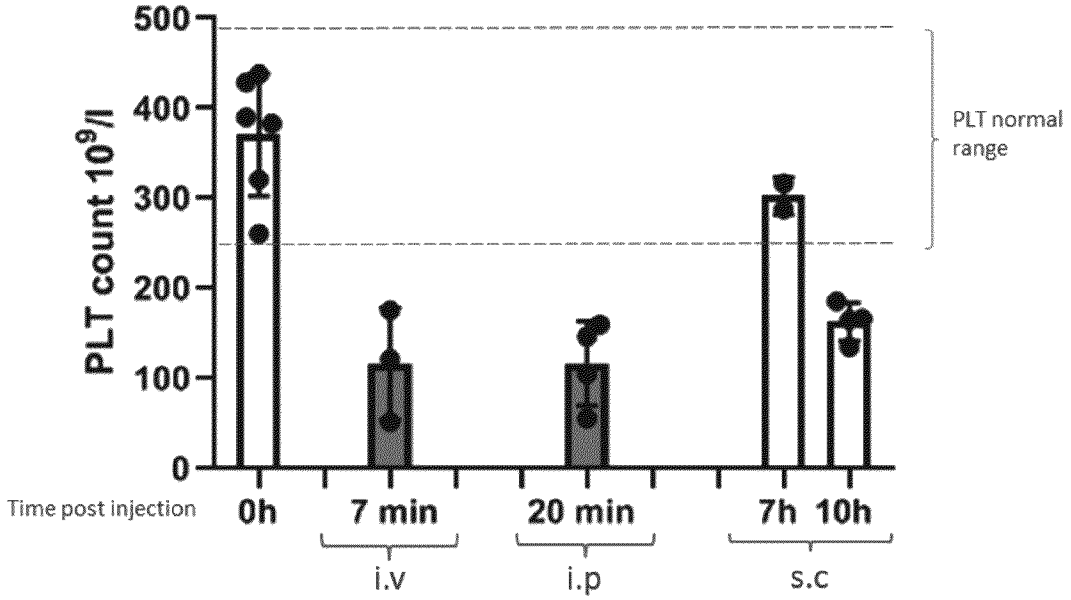

A
Serum conc (µg/ml)
IRR grade
serum conc AT130
Grading of IRRs
Full (100%) RO
time (h) post injection of AT-130
B
Serum conc (µg/ml)
IRR grade
serum conc AT130
Grading of IRRs
Full (100%) RO
time (h) post injection of AT-130
C
Serum conc (µg/ml)
IRR grade
serum conc AT130
Grading of IRRs
Full (100%) RO
time (h) post injection of AT-130

Figure 15

A


500
400
300
200
100
0
PLT count 10^9/l
PLT normal range
Time post injection
0h
7 min
20 min
7h
10h
i.v
i.p
s.c

B

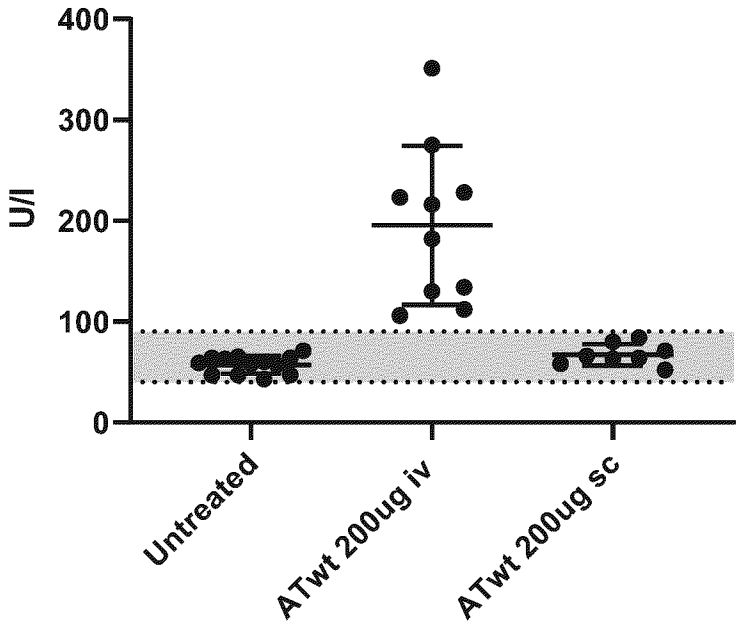

400
300
200
100
0
U/l
Untreated
ATwt 200ug iv
ATwt 200ug sc

Figure 16

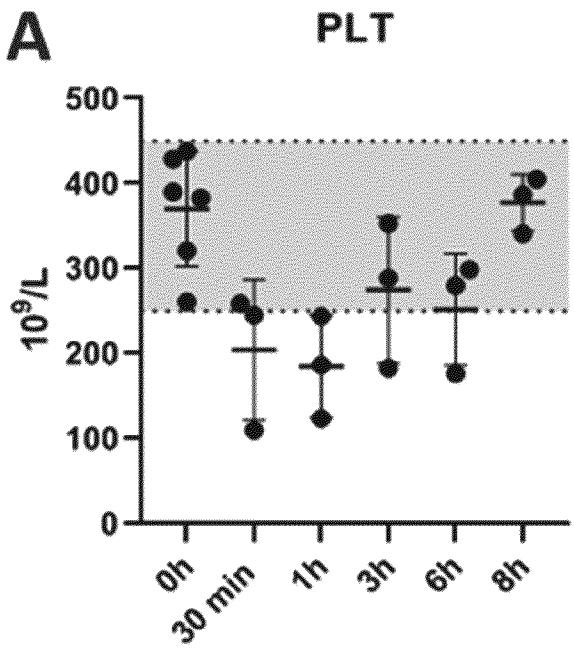


Figure 16 continued

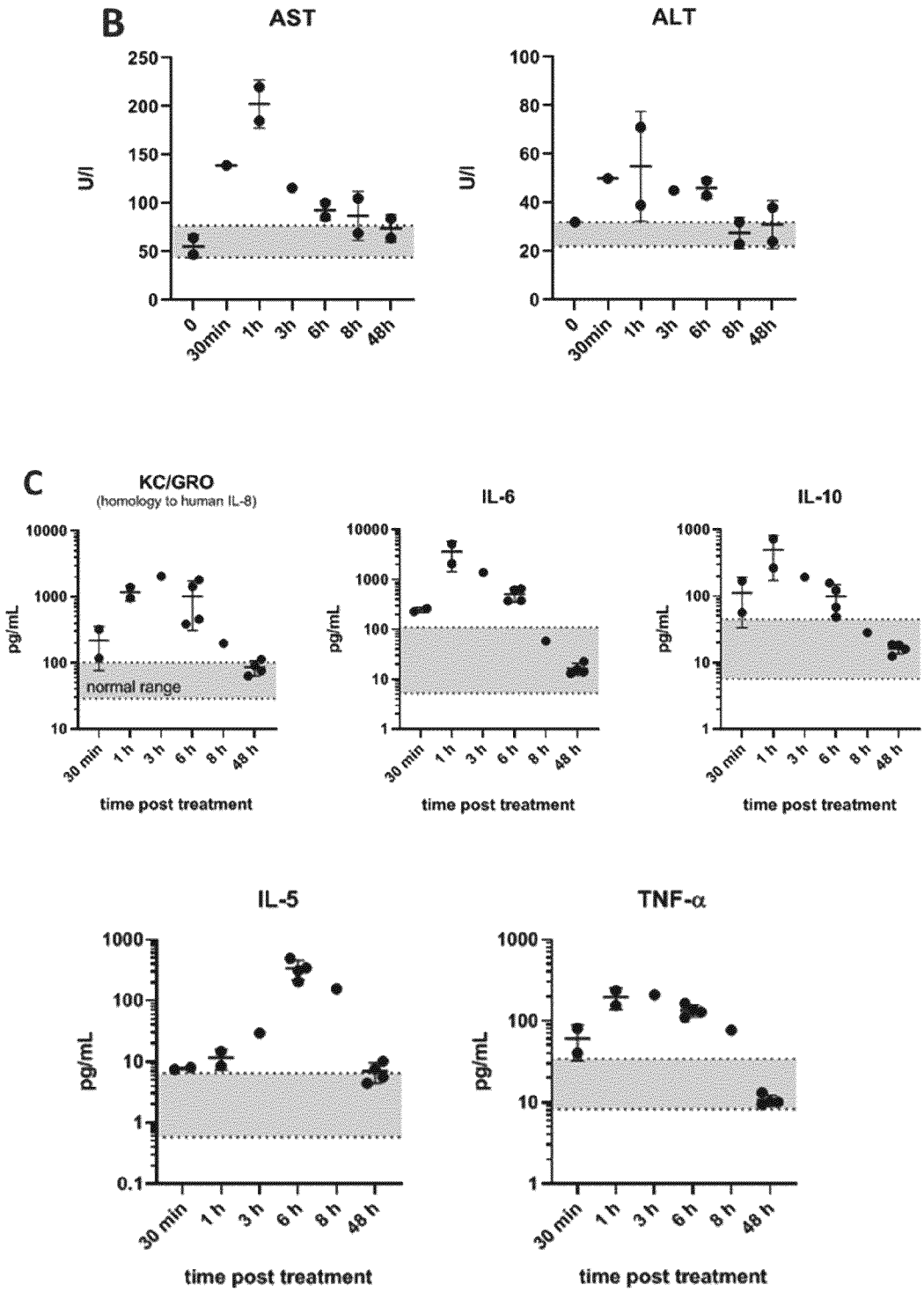


Figure 17

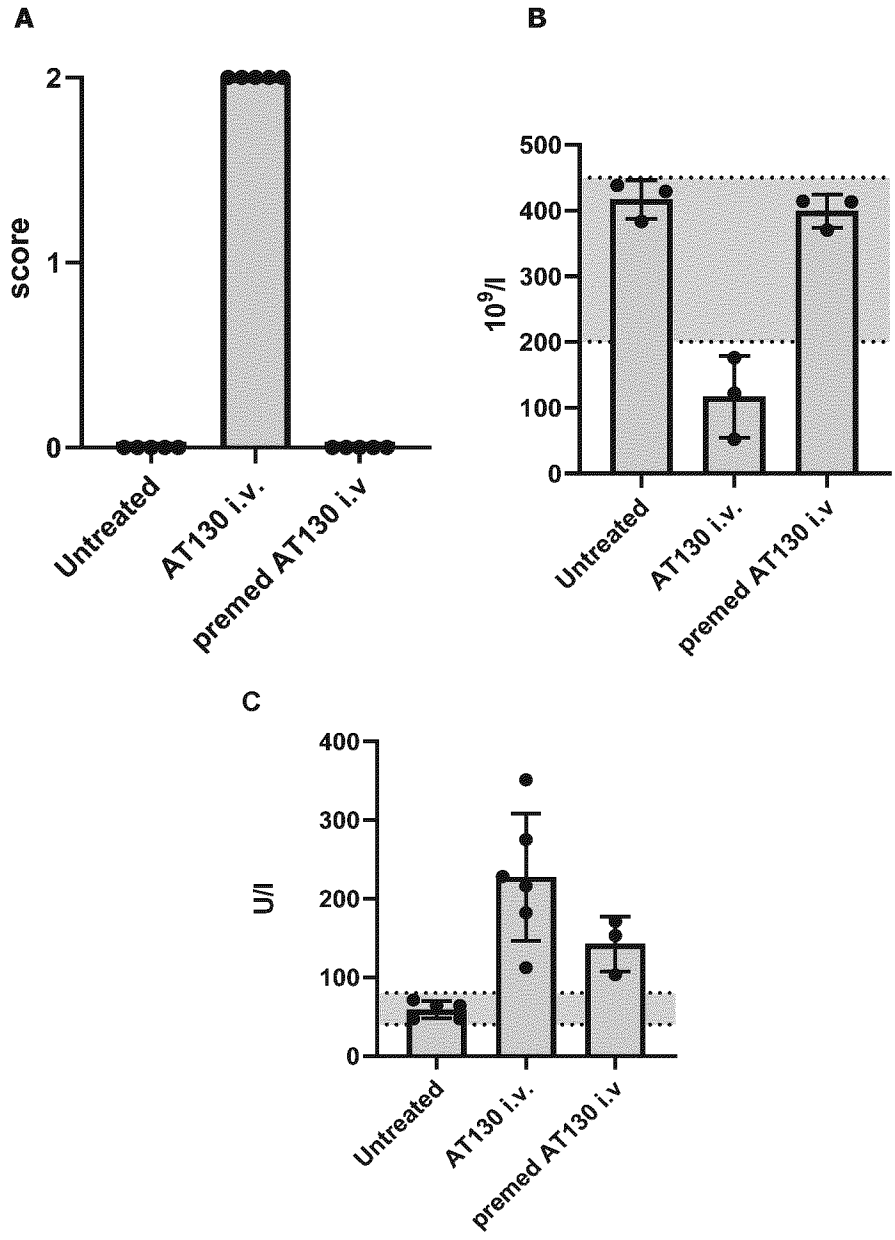
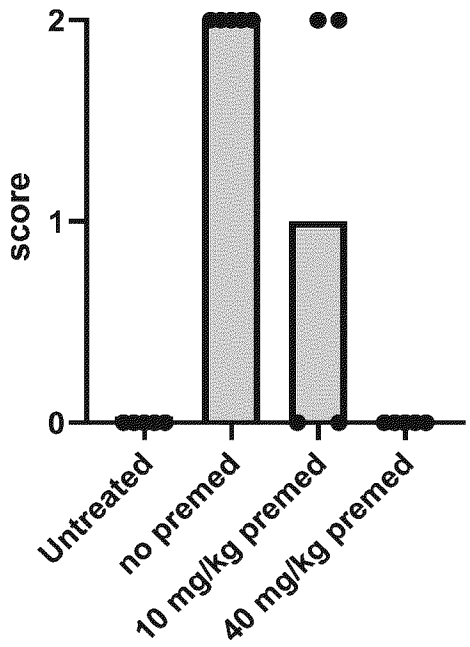

A
score
2
1
0
Untreated
AT130 i.v.
premed AT130 i.v
B
10^9/l
500
400
300
200
100
0
Untreated
AT130 i.v.
premed AT130 i.v
C
U/l
400
300
200
100
0
Untreated
AT130 i.v.
premed AT130 i.v

Figure 18

A


2
1
0
score
Untreated
no premed
10 mg/kg premed
40 mg/kg premed

B

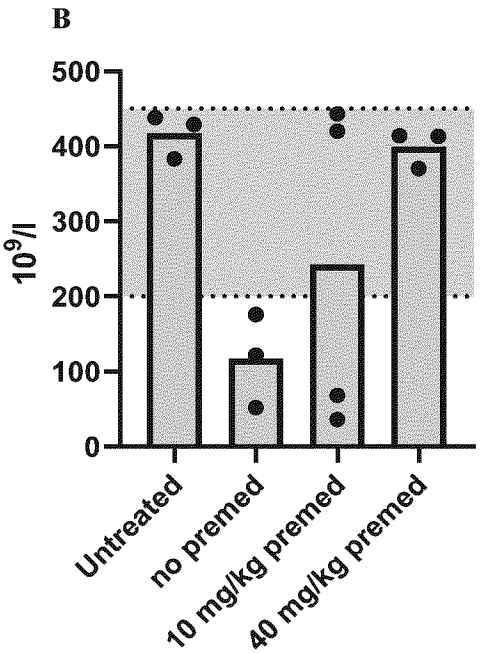
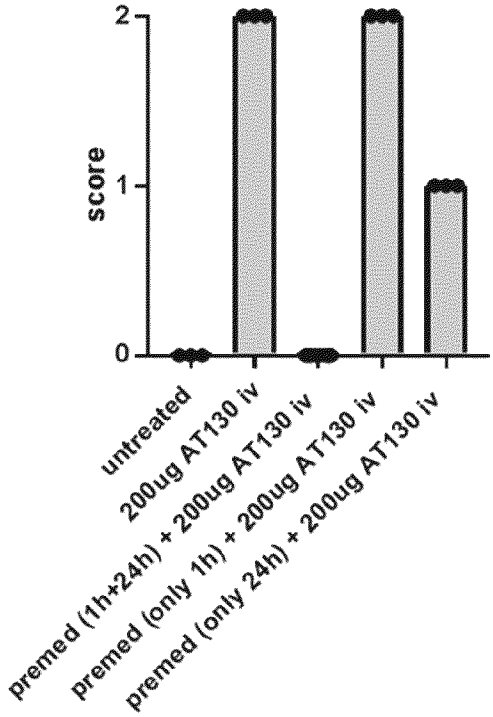

500
400
300
200
100
0
10^9/l
Untreated
no premed
10 mg/kg premed
40 mg/kg premed

Figure 19

A


score
2
1
0
untreated
200ug AT130 iv
premed (1h+24h) + 200ug AT130 iv
premed (only 1h) + 200ug AT130 iv
premed (only 24h) + 200ug AT130 iv

B

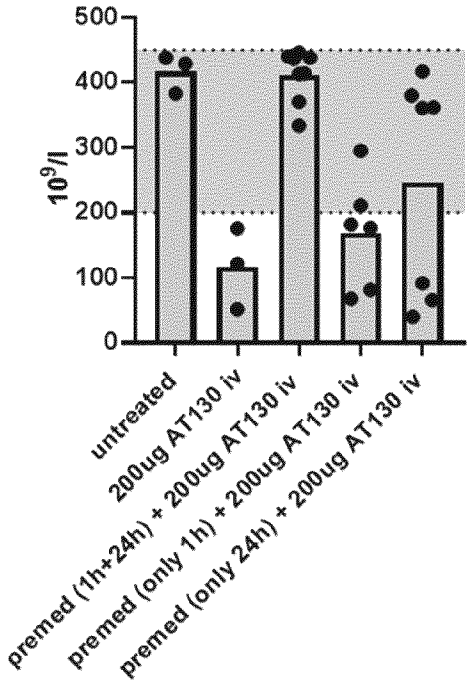
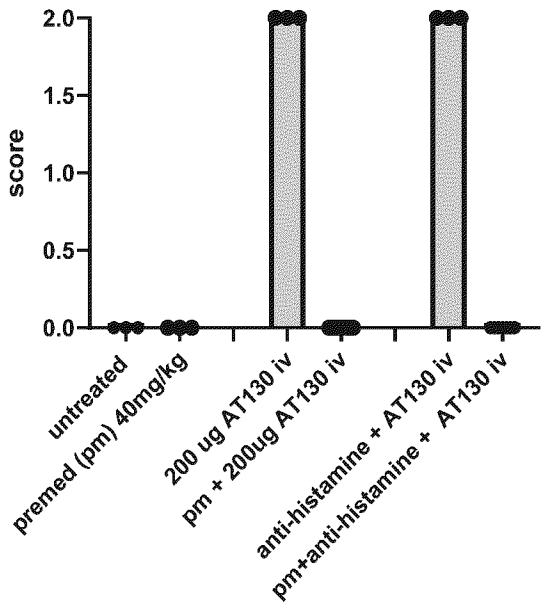

10^9/l
500
400
300
200
100
0
untreated
200ug AT130 iv
premed (1h+24h) + 200ug AT130 iv
premed (only 1h) + 200ug AT130 iv
premed (only 24h) + 200ug AT130 iv

Figure 20

A


2.0
1.5
1.0
0.5
0.0
score
untreated
premed (pm) 40mg/kg
200 ug AT130 iv
pm + 200ug AT130 iv
anti-histamine + AT130 iv
pm+anti-histamine + AT130 iv

B

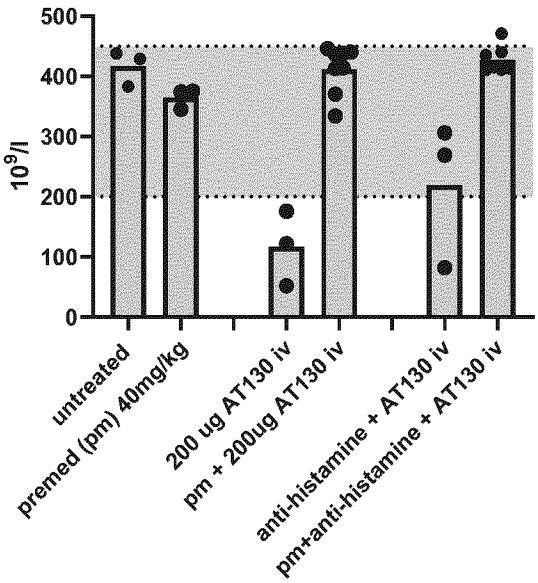

500
400
300
200
100
0
10^9/l
untreated
premed (pm) 40mg/kg
200 ug AT130 iv
pm + 200ug AT130 iv
anti-histamine + AT130 iv
pm+anti-histamine + AT130 iv

Figure 21

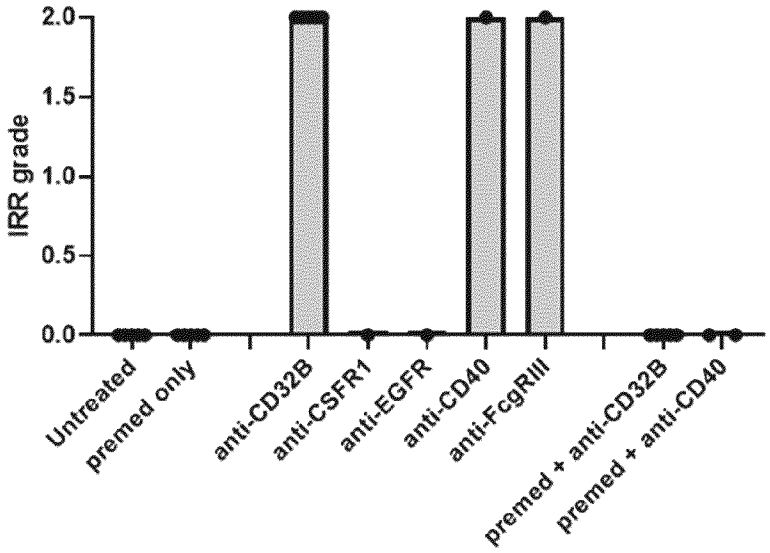
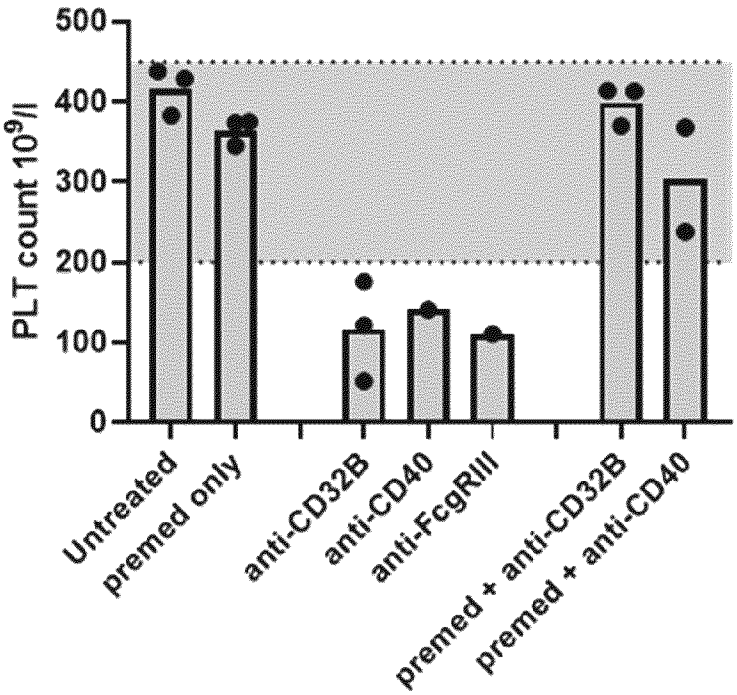


Figure 22



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2021/065005

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K39/395 A61P35/00 A61P37/06 C07K14/575 C07K14/72
C07K16/00 C07K16/28 A61K39/00 A61K47/28
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2019/081983 A1 (NOVARTIS AG [CH]) 2 May 2019 (2019-05-02) page 81 - page 82; example all page 154 - page 155 page 142 ----- -/--	6-11,14, 16-24, 26,27

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 August 2021	06/08/2021

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Fellows, Edward

2

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Clinical Trials . gov archive: "NCT02933320: BI-1206 and an Anti-CD20 Antibody in Patients With CD32b Positive B-cell Lymphoma or Leukaemia", , 1 February 2018 (2018-02-01), XP055827746, Retrieved from the Internet: URL:https://clinicaltrials.gov/ct2/history/NCT02933320?A=2&B=2&C=merged#StudyPageTop [retrieved on 2021-07-26]	1-5,12, 13,15,25
Y	page 2 page 5	6-11,14, 16-24, 26,27

A	Clinical Trials . gov archive: "NCT03571568: A Study of BI-1206 in Combination With Rituximab in Subjects With Indolent B-Cell Non-Hodgkin Lymphoma", , 14 June 2019 (2019-06-14), XP055827749, Retrieved from the Internet: URL:https://clinicaltrials.gov/ct2/history/NCT03571568?A=5&B=5&C=merged#StudyPageTop [retrieved on 2021-07-26] page 2 page 4	1-27

Y	US 2017/174781 A1 (BROWNSTEIN CARRIE [US]) 22 June 2017 (2017-06-22) page 118 - page 121	6-11,14, 16-24, 26,27

Y	US 2011/097345 A1 (LAMBERT JOHN [US] ET AL) 28 April 2011 (2011-04-28) pages 5, 65-70; claim all	6-11,14, 16-24, 26,27

Y	WO 2019/138005 A2 (BIOINVENT INT AB [SE]; UNIV SOUTHAMPTON [GB]) 18 July 2019 (2019-07-18) page 1 - page 4; claim all; example all	6-11,14, 16-24, 26,27

2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2021/065005

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. [X] forming part of the international application as filed:

      [X] in the form of an Annex C/ST.25 text file.

      [ ] on paper or in the form of an image file.

   b. [ ] furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. [ ] furnished subsequent to the international filing date for the purposes of international search only:

      [ ] in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      [ ] on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2021/065005

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2019081983 A1	02-05-2019	EP 3700933 A1	02-09-2020
		US 2021040205 A1	11-02-2021
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US 2017174781 A1	22-06-2017	AU 2016378573 A1	19-07-2018
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		WO 2011050180 A1	28-04-2011
WO 2019138005 A2	18-07-2019	AU 2019207767 A1	09-07-2020
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		CA 3088856 A1	18-07-2019
		CN 111683969 A	18-09-2020
		EP 3737698 A2	18-11-2020
		JP 2021510299 A	22-04-2021
		KR 20200108286 A	17-09-2020
		US 2020362036 A1	19-11-2020
		WO 2019138005 A2	18-07-2019