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(54) **Title:** USE OF ASCORBIC ACID AS STABILIZING AGENT FOR ANTI B7-H3 ANTIBODIES

(57) **Abstract:** The present invention relates to pharmaceutical compositions comprising a radiolabeled B7H3 antibody or antigen binding fragment thereof and ascorbic acid, methods for stabilizing pharmaceutical compositions and use of ascorbic acid as a stabilizing agent and/or a scavenger agent.

The present specification comprises a sequence listing in computer readable format, submitted together with the application. The sequence listing forms part of the disclosure and is incorporated in the specification in its entirety.

The present invention relates to pharmaceutical compositions comprising a radiolabeled B7H3 antibody or antigen binding fragment thereof and ascorbic acid, methods for stabilizing pharmaceutical compositions and use of ascorbic acid as a stabilizing agent and/or a scavenger agent.

Technical Background

The interest for the use of antibodies for radioimmune therapy (RIT) has increased within the last years and decades. Of particular importance is the final stability of radiolabeled antibodies with regards to radiolysis by the emitted β- and/or γ-radiation. It is well known that radiolabeled antibodies might be damaged during labeling and storage.

Chakrabarti M. et al. 1996 relates to a method for protecting the murine monoclonal anti-CD5 antibody, T101, during the labeling procedure with ^{121}I or ^{90}Y by using various radioprotectants, such as human serum albumin, cysteamine, glycerol and ascorbic acid.

WO0180884 with the title "Intrathecal administration of Rituximab for treatment of central nervous system lymphomas" discloses a radiolabeled anti-CD20 antibody, Rituximab, which might be administered intrathecally for treating central nervous system (CNS) lymphomas.

WO03101495 with the title "Methods and compositions for radioimmunotherapy of brain and CNS tumors" discloses a method of treating a brain tumor administering a multispecific antibody with one targeting arm binding a cancer antigen and a capture arm that binds a radionuclide carrier. The multispecific antibody can be administered intrathecally.

WO0232375 with the title "Uses of Monoclonal Antibody 8H9" discloses a composition comprising an effective amount of monoclonal antibody 8H9 or a derivative thereof and a suitable carrier. Other antibodies comprising the complementary determining regions of

monoclonal antibody 8H9 or a derivative thereof, capable of binding to the same antigen as the monoclonal antibody 8H9 are also disclosed.

Summary of the invention

The final stability of radiolabeled antibodies with regards to radiolysis by the emitted β- and/or γ-radiation is of particular importance. Thus, there is a need for providing stable pharmaceutical compositions comprising radiolabeled antibodies.

Radiolabeled antibodies might be damaged during labeling, storage and/or in use. Thus, there is a need for providing methods for stabilizing pharmaceutical compositions comprising radiolabeled antibodies and processes for effectively producing such pharmaceutical compositions.

According to an aspect, the invention concerns a pharmaceutical composition comprising:

(i) A radiolabeled B7H3 antibody or antigen binding fragment thereof, and

(ii) Ascorbic acid.

According to another aspect, the invention concerns a method of stabilizing a pharmaceutical composition comprising a radiolabeled B7H3 antibody or antigen binding fragment thereof, comprising:

a. Producing said B7H3 antibody or antigen binding fragment thereof,

b. Radiolabeling said B7H3 antibody or antigen binding fragment thereof,

c. Formulating said radiolabeled B7H3 antibody or antigen binding fragment thereof into a pharmaceutical composition,

d. Stabilizing said pharmaceutical composition by adding ascorbic acid.

According to another aspect, the invention concerns a method of stabilizing a pharmaceutical composition comprising a radiolabeled B7H3 antibody or antigen binding fragment thereof, comprising:

a. Producing said B7H3 antibody or antigen binding fragment thereof,

b. Radiolabeling said B7H3 antibody or antigen binding fragment thereof,

c. Providing a stabilized pharmaceutical composition by adding ascorbic acid and optionally additional excipients.

According to another aspect, the invention concerns a process for producing a pharmaceutical composition comprising a radiolabeled B7H3 antibody or antigen binding fragment thereof, comprising:

a. Producing said B7H3 antibody or antigen binding fragment thereof,

b. Radiolabeling said B7H3 antibody or antigen binding fragment thereof,

c. Formulating said radiolabeled B7H3 antibody or antigen binding fragment thereof into a pharmaceutical composition,

d. Adding ascorbic acid to said pharmaceutical composition.

According to another aspect, the invention concerns a process for producing a pharmaceutical composition comprising a radiolabeled B7H3 antibody or antigen binding fragment thereof, comprising:

a. Producing said B7H3 antibody or antigen binding fragment thereof,

b. Radiolabeling said B7H3 antibody or antigen binding fragment thereof,

c. Providing a pharmaceutical composition by adding ascorbic acid and optionally additional excipients.

According to another aspect, the invention concerns use of ascorbic acid as a stabilizing agent and/or a scavenger agent.

According to another aspect, the invention concerns use of ascorbic acid as a stabilizing agent and/or a scavenger agent for a radiolabeled B7H3 antibody or antigen binding fragment thereof.

According to another aspect, the invention concerns use of ascorbic acid as a stabilizing agent and/or a scavenger agent for a pharmaceutical composition comprising a radiolabeled B7H3 antibody or antigen binding fragment thereof.

According to another aspect, the invention concerns use of ascorbic acid as a stabilizing agent and/or a scavenger agent for a pharmaceutical composition according to the invention.

According to another aspect, the invention concerns a method of treating cancer in an individual, wherein the method comprises a step of administering a therapeutically effective amount of a pharmaceutical composition according to the invention.

According to another aspect, the invention concerns a method for treating, preventing and/or alleviating the symptoms of a disorder affecting the central nervous system (CNS), such as a neurodegenerative condition and/or disease, an inflammatory disease or cancer, in particular a metastatic cancer, in a subject, wherein said method comprises a step of administration to said subject of a therapeutically effective amount of a pharmaceutical composition according to the invention, and wherein said pharmaceutical composition is delivered into CNS using a device allowing or adapted to provide intra-cerebroventricular administration.

According to another aspect, the invention concerns a method for treating, preventing and/or alleviating the symptoms of a condition in a subject, wherein said condition is characterized by B7H3 antigen or B7H3 antigen expression, and wherein said method comprises a step of administering a therapeutically effective amount of a pharmaceutical composition according to the invention and wherein said pharmaceutical composition is delivered into the central nervous system (CNS) using a device allowing or adapted to provide intra-cerebroventricular administration.

According to another aspect, the invention concerns a method for treating, preventing and/or alleviating the symptoms of a disorder affecting the central nervous system (CNS), such as a neurodegenerative condition and/or disease, an inflammatory disease or cancer, in particular a metastatic cancer, in a subject, wherein said method comprises a step of administration to said subject of a therapeutically effective amount of a pharmaceutical composition according to the invention, and wherein said pharmaceutical composition is delivered into CNS using convection-enhanced delivery (CED).

According to another aspect, the invention concerns a method for treating, preventing and/or alleviating the symptoms of a condition in a subject, wherein said condition is characterized by B7H3 antigen or B7H3 antigen expression, and wherein said method comprises a step of administering a therapeutically effective amount of a pharmaceutical composition according to the invention, and wherein said pharmaceutical composition is delivered into the central nervous system (CNS) using convection-enhanced delivery (CED).

According to an aspect, the invention concerns the pharmaceutical composition of the invention for use as a medicament.

According to an aspect, the invention concerns the pharmaceutical composition of the invention for use in the treatment of cancer.

According to an aspect, the invention concerns the pharmaceutical composition of the invention for use in a treatment comprising intracerebroventricular, intrathecal, intracerebral or intraventricular administration.

According to an aspect, the invention concerns the pharmaceutical composition of the invention for use in a treatment comprising convection-enhanced delivery (CED).

According to another aspect, the invention concerns a kit of parts comprising a pharmaceutical composition comprising a radiolabeled B7H3 antibody or antigen binding fragment thereof and ascorbic acid.

According to another aspect, the invention concerns a kit of parts comprising a pharmaceutical composition according to the invention and ascorbic acid.

Detailed Disclosure

According to an embodiment, the invention concerns a pharmaceutical composition comprising:

(i) A radiolabeled B7H3 antibody or antigen binding fragment thereof, and

(ii) Ascorbic acid.

B7H3 is in the present application and claims intended to mean a B7H3 antigen, and a B7H3 antibody is intended to mean an antibody capable of binding the B7H3 antigen.

According to an embodiment, the invention concerns the pharmaceutical composition, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof is for delivery to the central nervous system (CNS).

According to an embodiment, the invention concerns the pharmaceutical composition, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof is for intracerebroventricular (ICV), intrathecal, intracerebral or intraventricular administration.

According to an embodiment, the invention concerns the pharmaceutical composition, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof is for convection-enhanced delivery (CED).

According to an embodiment, the invention concerns the pharmaceutical composition, wherein said ascorbic acid is a stabilizing agent and/or a scavenger agent.

It is known that radiation may lead to radiolysis of e.g., water, forming several highly reactive species, and it is speculated that ascorbic acid may, at least in part, exert its action by scavenging these formed reactive species. However, the present invention is not limited by any particular mechanism. On the contrary, what is important is the ability of ascorbic acid to stabilize radiolabeled B7H3 antibody or antigen binding fragment thereof and avoid or reduce formation of high molecular weight aggregates (HMW) and/or low molecular weight fragments (LMW).

According to an embodiment, the invention concerns the pharmaceutical composition, wherein the amount of said ascorbic acid is at least 0.001% (w/w), alternatively 0.005% (w/w), alternatively 0.01% (w/w), alternatively 0.02% (w/w), alternatively 0.03% (w/w), alternatively 0.04% (w/w), alternatively 0.05% (w/w), alternatively 0.06% (w/w), alternatively 0.07% (w/w), alternatively 0.08% (w/w), alternatively 0.09% (w/w), alternatively 0.1% (w/w).

According to an embodiment, the invention concerns the pharmaceutical composition, wherein the amount of said ascorbic acid is at most 10% (w/w), alternatively 9.5% (w/w), alternatively 9% (w/w), alternatively 8.5% (w/w), alternatively 8% (w/w), alternatively 7.5% (w/w), alternatively 7% (w/w), alternatively 6.5% (w/w), alternatively 6% (w/w), alternatively 5.5% (w/w), alternatively 5% (w/w).

According to an embodiment, the invention concerns the pharmaceutical composition, wherein the amount of said ascorbic acid is selected from 0.001-10% (w/w), 0.01-10% (w/w), 0.05-10% (w/w), 0.05-9% (w/w), 0.05-8% (w/w), 0.05-7% (w/w), 0.05-6% (w/w), 0.05-5% (w/w), 0.05-4% (w/w), 0.05-3% (w/w), 0.05-2% (w/w), 0.05-1.5% (w/w) and 0.05-1.3% (w/w).

According to an embodiment, the invention concerns the pharmaceutical composition, wherein the amount of said ascorbic acid is selected from 0.05-0.2% (w/w), 0.05-0.1% (w/w) and 1-1.5% (w/w).

According to an embodiment, the invention concerns the pharmaceutical composition, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof comprises light chain CDR sequences according to SEQ ID NO: 1-3 and/or heavy chain CDR sequences according to SEQ ID NO: 4-6.

According to an embodiment, the invention concerns the pharmaceutical composition, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof comprises a VL sequence according to SEQ ID NO: 7 and/or a VH sequence according to SEQ ID NO: 8.

According to an embodiment, the invention concerns the pharmaceutical composition, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof comprises a light chain sequence according to SEQ ID NO: 9 and/or a heavy chain sequence according to SEQ ID NO: 10.

According to an embodiment, the invention concerns the pharmaceutical composition, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof is Omburtamab or derived from Omburtamab.

According to an embodiment, the invention concerns the pharmaceutical composition, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof comprises or is an scFv.

According to an embodiment, the invention concerns the pharmaceutical composition, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof comprises or is a SADA (a self-assembly disassembly) construct. SADA domains and techniques for using SADA compounds, comprising an antigen binding site in addition to a SADA domain, is disclosed in WO2018/204873, and the disclosure thereof may also be used according to the present invention.

According to an embodiment, the invention concerns the pharmaceutical composition, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof comprises or is linked to a chelating agent, such as a bifunctional chelating agent.

According to an embodiment, the invention concerns the pharmaceutical composition, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof is, comprises or is linked to a functional group capable of binding radioisotopes, which exists as metallic ions. Examples of such functional groups include DOTA-groups, DTPA-groups, and HEHA-groups, such as DOTA-hapten, DTPA-hapten, DOTA/HEHA-hapten and/or a HEHA-hapten.

DOTA, or 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, contains a central 12-membered tetraaza ring. The DOTA ring structure may be substituted with different organic groups as known in the art and such substituted compounds comprising the DOTA ring structure may also be used according to the invention provided that the substituted compounds retain the ability of binding radioisotopes which exists as metallic ions. One example of such a compound comprising a DOTA ring structure substituted with an organic group is p- aminobenzyl-DOTA (Bn-DOTA).

DTPA, or diethylenetriaminepentaacetic acid, consists of a diethylenetriamine backbone with five carboxymethyl groups, having the molecular formula $C_{14}H_{23}N_3O_{10}$. The DTPA structure may be substituted with different organic groups as known in the art and such substituted compounds comprising the DTPA structure may also be used according to the invention provided that the substituted compounds retain the ability of binding radioisotopes which exists as metallic ions.

HEHA, or 1,4,7,10,13,16-hexaazacyclooctodecan-1,4,7,10,13,16-hexaacetic acid, contains a central 24 membered ring structure. The HEHA structure may be substituted with different organic groups as known in the art and such substituted compounds comprising the HEHA ring structure may also be used according to the invention provided that the substituted compounds retain the ability of binding radioisotopes which exists as metallic ions.

According to an embodiment, the invention concerns the pharmaceutical composition, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof is, comprises or is linked to a DOTA-hapten, DTPA-hapten, DOTA/HEHA-hapten and/or a HEHA-hapten.

Techniques for conjugating or binding a functional group capable of binding radioisotopes which exists as metallic ions are known in the art and the present invention is not limited the any particular conjugation technique, on the contrary, techniques for conjugating such functional groups as known in the art may also be applied to the present invention.

According to an embodiment, the invention concerns the pharmaceutical composition, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof comprises an Fc part.

According to an embodiment, the invention concerns the pharmaceutical composition, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof does not comprise a Fc part or comprises an inactive or null Fc part.

According to an embodiment, the invention concerns the pharmaceutical composition, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof is IgG1 with inactive Fc or IgG4.

According to an embodiment, the invention concerns the pharmaceutical composition, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof is an IgG1 heterodimer with inactive Fc.

According to an embodiment, the invention concerns the pharmaceutical composition, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof is labeled with a radioisotope.

According to an embodiment, the invention concerns the pharmaceutical composition, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof is labeled with a radioisotope selected from the group consisting of ^{124}I, ^{131}I, ^{177}Lu, ^{99}mTc, ^{64}Cu, ^{86}Y, ^{90}Y, ^{225}Ac and ^{89}Zr.

According to an embodiment, the invention concerns the pharmaceutical composition, comprising at least one pharmaceutically acceptable excipient.

According to an embodiment, the invention concerns the pharmaceutical composition, wherein said pharmaceutically acceptable excipient is selected from the group consisting of diluents, carriers, preservatives, buffers and surfactants.

According to an embodiment, the invention concerns the pharmaceutical composition, wherein the pharmaceutically acceptable excipient is selected from the group consisting of sodium phosphate, human serum albumin, sodium chloride, sodium citrate dihydrate, sodium acetate, sodium ascorbate and hydrochloric acid.

According to an embodiment, the invention concerns the pharmaceutical composition comprising sodium phosphate solution, preferably in a concentration of 0.005-5 M, alternatively 0.01-1 M, alternatively 0.02-2 M, alternatively 0.05 M - 0.5 M, alternatively 0.05 M - 0.4 M, alternatively 0.1 M - 0.4 M, alternatively 0.1 M - 0.3 M, alternatively 0.15 M - 0.3 M, alternatively 0.15 M - 0.25 M, alternatively around 0.2 M.

According to an embodiment, the invention concerns the pharmaceutical composition, wherein the sodium phosphate solution is $NaH_2PO_4xH_2O$ and/or Na_2HPO_4.

According to an embodiment, the invention concerns the pharmaceutical composition comprising human serum albumin, preferably in a concentration of 0.001-10% w/w, alternatively 0.01-5% w/w, alternatively 0.05-5% w/w, alternatively 0.05-4% w/w, alternatively 0.1-4% w/w, alternatively 0.1-3.5% w/w, alternatively 0.1-3% w/w, alternatively 0.1-2.5% w/w, alternatively 0.2-2.5% w/w, alternatively 0.5-2.5% w/w.

According to an embodiment, the invention concerns the pharmaceutical composition comprising an amount of human serum albumin selected from about 1% w/w, 1.1% w/w, 1.2% w/w, 1.3% w/w, 1.4% w/w, 1.5% w/w, 1.6% w/w, 1.7% w/w, 1.8% w/w, 1.9% w/w, 2.0% w/w, 2.1% w/w, 2.2% w/w, 2.3% w/w, 2.4% w/w, and 2.5% w/w.

According to an embodiment, the human serum albumin is recombinant human serum albumin.

According to an embodiment, the invention concerns the pharmaceutical composition comprising sodium chloride, preferably in a concentration of 0.1-200 mM, alternatively 1-100 mM, alternatively 5-95 mM, alternatively 10-90 mM, alternatively 15-85 mM, alternatively 20-80 mM, alternatively 25-75 mM, alternatively 30-70 mM, alternatively 35-65 mM, alternatively around 60 mM.

According to an embodiment, the invention concerns the pharmaceutical composition comprising sodium citrate dihydrate, preferably in a concentration of 0.01-100 mM, alternatively 0.1-50 mM, 0.1-30 mM, alternatively 1-25 mM, alternatively 2-20 mM, alternatively 3-18 mM, alternatively 4-17 mM, alternatively 5-15 mM, alternatively 8-15 mM, alternatively 10-15 mM, alternatively 11-14 mM, alternatively around 12.5 mM.

According to an embodiment, the invention concerns the pharmaceutical composition comprising sodium acetate, preferably in a concentration of 0.01-100 mM, alternatively 1-70

mM, alternatively 2-60 mM, alternatively 5-60 mM, alternatively 5-50 mM, alternatively 10-50 mM, alternatively 15-45 mM, alternatively 20-40 mM, alternatively 25-35 mM, alternatively around 30 mM.

According to an embodiment, the invention concerns the pharmaceutical composition comprising sodium ascorbate, preferably in a concentration of 0.1-200 mM, alternatively 1-100 mM, alternatively 5-95 mM, alternatively 10-90 mM, alternatively 15-85 mM, alternatively 20-80 mM, alternatively 25-75 mM, alternatively 30-70 mM, alternatively 35-65 mM, alternatively around 60 mM.

According to an embodiment, the invention concerns the pharmaceutical composition comprising hydrochloric acid. Hydrochloric acid may be added for adjusting pH.

According to an embodiment, the invention concerns the pharmaceutical composition having a pH between 3-9, alternatively 4-8, alternatively 4.5-8.5, alternatively 5-7, alternatively 5-8, alternatively 5.5-7.5, alternatively 5.5-7, alternatively 6-7, alternatively 6.5-7, alternatively 6.5-6.8.

According to an embodiment, the invention concerns the pharmaceutical composition, wherein said pharmaceutical composition has an increased stability compared to a pharmaceutical composition not comprising ascorbic acid.

According to an embodiment, the invention concerns the pharmaceutical composition, wherein said stability is increased during labeling, during storage and/or in use.

According to an embodiment, the invention concerns the pharmaceutical composition, wherein the amount of high molecular weight aggregates (HMW) and/or low molecular weight fragments (LMW) is reduced compared to a pharmaceutical composition not comprising ascorbic acid.

According to an embodiment, the invention concerns the pharmaceutical composition, wherein the amount of HMW and/or LMW is reduced at least by a factor 1.5 compared to a pharmaceutical composition not comprising ascorbic acid.

According to an embodiment, the invention concerns the pharmaceutical composition, wherein the amount of HMW is below 10%, alternatively 9%, alternatively 8%, alternatively 7%.

According to an embodiment, the invention concerns the pharmaceutical composition, wherein the amount of LMW is below 10%, alternatively 9%, alternatively 8%, alternatively 7%, alternatively 6%, alternatively 5%.

According to an embodiment, the invention concerns the pharmaceutical composition, wherein the amount of HMW and/or LMW is measured after a storage period of 96 hours at -80 °C or after a storage period of 120 h at 2 - 8 °C.

According to an embodiment, the invention concerns the pharmaceutical composition, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof is the sole active ingredient.

According to an embodiment, the invention concerns the pharmaceutical composition, which is a pharmaceutically acceptable composition.

According to an embodiment, the invention concerns a method of stabilizing a pharmaceutical composition comprising a radiolabeled B7H3 antibody or antigen binding fragment thereof, comprising:

a. Producing said B7H3 antibody or antigen binding fragment thereof,
b. Radiolabeling said B7H3 antibody or antigen binding fragment thereof,
c. Formulating said radiolabeled B7H3 antibody or antigen binding fragment thereof into a pharmaceutical composition,
d. Stabilizing said pharmaceutical composition by adding ascorbic acid.

According to an embodiment, the invention concerns a method of stabilizing a pharmaceutical composition comprising a radiolabeled B7H3 antibody or antigen binding fragment thereof, comprising:

a. Producing said B7H3 antibody or antigen binding fragment thereof,
b. Radiolabeling said B7H3 antibody or antigen binding fragment thereof,
c. Providing a stabilized pharmaceutical composition by adding ascorbic acid and optionally additional excipients.

According to an embodiment, the invention concerns the method, wherein the stabilized pharmaceutical composition is a pharmaceutical composition according to the invention.

According to an embodiment, the invention concerns a process for producing a pharmaceutical composition comprising a radiolabeled B7H3 antibody or antigen binding fragment thereof, comprising:

a. Producing said B7H3 antibody or antigen binding fragment thereof,
b. Radiolabeling said B7H3 antibody or antigen binding fragment thereof,
c. Formulating said radiolabeled B7H3 antibody or antigen binding fragment thereof into a pharmaceutical composition,
d. Adding ascorbic acid to said pharmaceutical composition.

According to an embodiment, the invention concerns a process for producing a pharmaceutical composition comprising a radiolabeled B7H3 antibody or antigen binding fragment thereof, comprising:

a. Producing said B7H3 antibody or antigen binding fragment thereof,
b. Radiolabeling said B7H3 antibody or antigen binding fragment thereof,
c. Providing a pharmaceutical composition by adding ascorbic acid and optionally additional excipients.

According to an embodiment, the invention concerns the process, wherein the pharmaceutical composition is a pharmaceutical composition according to the invention.

According to an embodiment, the invention concerns the method or the process, wherein the amount of said ascorbic acid is at least 0.001% (w/w), alternatively 0.005% (w/w), alternatively 0.01% (w/w), alternatively 0.02% (w/w), alternatively 0.03% (w/w), alternatively 0.04% (w/w), alternatively 0.05% (w/w), alternatively 0.06% (w/w), alternatively 0.07% (w/w), alternatively 0.08% (w/w), alternatively 0.09% (w/w), alternatively 0.1% (w/w).

According to an embodiment, the invention concerns the method or the process, wherein the amount of said ascorbic acid is at most 10% (w/w), alternatively 9.5% (w/w), alternatively 9% (w/w), alternatively 8.5% (w/w), alternatively 8% (w/w), alternatively 7.5% (w/w), alternatively 7% (w/w), alternatively 6.5% (w/w), alternatively 6% (w/w), alternatively 5.5% (w/w), alternatively 5% (w/w).

According to an embodiment, the invention concerns the method or the process, wherein the amount of said ascorbic acid is selected from 0.001-10% (w/w), 0.01-10% (w/w), 0.05-10% (w/w), 0.05-9% (w/w), 0.05-8% (w/w), 0.05-7% (w/w), 0.05-6% (w/w), 0.05-5% (w/w), 0.05-4% (w/w), 0.05-3% (w/w), 0.05-2% (w/w), 0.05-1.5% (w/w) and 0.05-1.3% (w/w).

According to an embodiment, the invention concerns the method or the process, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof comprises light chain CDR sequences according to SEQ ID NO: 1-3 and/or heavy chain CDR sequences according to SEQ ID NO: 4-6.

According to an embodiment, the invention concerns the method or the process, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof comprises a VL sequence according to SEQ ID NO: 7 and/or a VH sequence according to SEQ ID NO: 8.

According to an embodiment, the invention concerns the method or the process, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof comprises a light chain sequence according to SEQ ID NO: 9 and/or a heavy chain sequence according to SEQ ID NO: 10.

According to an embodiment, the invention concerns the method or the process, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof is Omburtamab or derived from Omburtamab.

According to an embodiment, the invention concerns the method or the process, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof comprises or is an scFv.

According to an embodiment, the invention concerns the method or the process, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof comprises or is a SADA construct.

According to an embodiment, the invention concerns the method or the process, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof comprises or is linked to a chelating agent, such as a bifunctional chelating agent.

According to an embodiment, the invention concerns the method or the process, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof is, comprises or is

linked to a DOTA-group, DTPA-group, DOTA/HEHA-group and/or a HEHA-group, such as DOTA-hapten, DTPA-hapten, DOTA/HEHA-hapten and/or a HEHA-hapten.

According to an embodiment, the invention concerns the method or the process, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof is labeled with a radioisotope.

According to an embodiment, the invention concerns the method or the process, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof is labeled with a radioisotope selected from the group consisting of ^{124}I, ^{131}I, ^{177}Lu, ^{99}mTc, ^{64}Cu, ^{86}Y, ^{90}Y, ^{225}Ac and ^{89}Zr.

According to an embodiment, the invention concerns the method or the process, wherein said pharmaceutical composition comprises at least one pharmaceutically acceptable excipient.

According to an embodiment, the invention concerns the method or the process, wherein said pharmaceutical composition comprises a pharmaceutically acceptable excipient selected from the group consisting of diluents, carriers, preservatives, buffers and surfactants.

According to an embodiment, the invention concerns the method or the process, wherein said pharmaceutical composition has an increased stability compared to a pharmaceutical composition not comprising ascorbic acid.

According to an embodiment, the invention concerns the method or the process, wherein the stability of said pharmaceutical composition is increased during labeling, during storage and/or in use.

According to an embodiment, the invention concerns the method or the process, wherein the amount of HMW and/or LMW in said pharmaceutical composition is reduced compared to a pharmaceutical composition not comprising ascorbic acid.

According to an embodiment, the invention concerns the method or the process, wherein the amount of HMW and/or LMW in said pharmaceutical composition is reduced at least by a factor 1.5 compared to a pharmaceutical composition not comprising ascorbic acid.

According to an embodiment, the invention concerns the method or the process, wherein the amount of HMW in said pharmaceutical composition is below 10%, alternatively 9%, alternatively 8%, alternatively 7%.

According to an embodiment, the invention concerns the method or the process, wherein the amount of LMW in said pharmaceutical composition is below 10%, alternatively 9%, alternatively 8%, alternatively 7%, alternatively 6%, alternatively 5%.

According to an embodiment, the invention concerns the method or the process, wherein the amount of HMW and/or LMW in said pharmaceutical composition is measured after a storage period of 96 hours at -80 °C or after a storage period of 120 h at 2 - 8 °C.

According to an embodiment, the invention concerns the method or the process, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof is the sole active ingredient in said pharmaceutical composition.

According to an embodiment, the invention concerns the method or the process, wherein in said pharmaceutical composition is a pharmaceutically acceptable composition.

According to an embodiment, the invention concerns use of ascorbic acid as a stabilizing agent and/or a scavenger agent.

According to an embodiment, the invention concerns use of ascorbic acid as a stabilizing agent and/or a scavenger agent for a radiolabeled B7H3 antibody or antigen binding fragment thereof.

According to an embodiment, the invention concerns use of ascorbic acid as a stabilizing agent and/or a scavenger agent for a pharmaceutical composition comprising a radiolabeled B7H3 antibody or antigen binding fragment thereof.

According to an embodiment, the invention concerns use of ascorbic acid as a stabilizing agent and/or a scavenger agent for a pharmaceutical composition according to the invention.

According to an embodiment, the invention concerns a method of treating cancer in an individual, wherein the method comprises a step of administering a therapeutically effective amount of a pharmaceutical composition according to the invention.

According to an embodiment, the invention concerns a method for treating, preventing and/or alleviating the symptoms of a disorder affecting the central nervous system (CNS), such as a neurodegenerative condition and/or disease, an inflammatory disease or cancer, in particular a metastatic cancer, in a subject, wherein said method comprises a step of administration to said subject of a therapeutically effective amount of a pharmaceutical composition according to the invention, and wherein said pharmaceutical composition is delivered into CNS using a device allowing or adapted to provide intra-cerebroventricular administration.

According to an embodiment, the invention concerns a method for treating, preventing and/or alleviating the symptoms of a condition in a subject, wherein said condition is characterized by B7H3 antigen or B7H3 antigen expression, and wherein said method comprises a step of administering a therapeutically effective amount of a pharmaceutical composition according to the invention and wherein said pharmaceutical composition is delivered into the central nervous system (CNS) using a device allowing or adapted to provide intra-cerebroventricular administration.

According to an embodiment, the invention concerns a method for treating, preventing and/or alleviating the symptoms of a disorder affecting the central nervous system (CNS), such as a neurodegenerative condition and/or disease, an inflammatory disease or cancer, in particular a metastatic cancer, in a subject, wherein said method comprises a step of administration to said subject of a therapeutically effective amount of a pharmaceutical composition according to the invention, and wherein said pharmaceutical composition is delivered into CNS using convection-enhanced delivery (CED).

According to an embodiment, the invention concerns a method for treating, preventing and/or alleviating the symptoms of a condition in a subject, wherein said condition is characterized by B7H3 antigen or B7H3 antigen expression, and wherein said method comprises a step of administering a therapeutically effective amount of a pharmaceutical composition according to the invention and wherein said pharmaceutical composition is delivered into the central nervous system (CNS) using convection-enhanced delivery (CED).

According to an embodiment, the invention concerns the method, wherein said device comprises a catheter.

According to an embodiment, the invention concerns the method, wherein said device comprises a reservoir, such as an Ommaya reservoir.

According to an embodiment, the invention concerns the method, wherein said cancer is a brain cancer, a central nervous system (CNS) lymphoma or a CNS cancer.

According to an embodiment, the invention concerns the method, wherein said cancer is selected among a carcinoma, a sarcoma, a lymphoma and a leukemia.

According to an embodiment, the invention concerns the method, wherein said cancer is selected among neuroblastoma, medulloblastoma, glioblastoma, small cell lung cancer, non-small cell carcinoma, a pediatric sarcoma, an adult sarcoma, breast cancer, liver cancer, melanoma, non-small cell lung carcinoma, lung adenocarcinoma or a gastrointestinal cancer.

According to an embodiment, the invention concerns the method, wherein said cancer is an ovarian cancer or gastric cancer.

According to an embodiment, the invention concerns the method, wherein said pharmaceutical composition is administered intracerebroventricularly, intrathecally, intracerebrally or intraventricularly.

According to an embodiment, the invention concerns the method, wherein said condition or cancer is characterized by overexpression of B7H3.

According to an embodiment, the invention concerns the pharmaceutical composition for use as a medicament.

According to an embodiment, the invention concerns the pharmaceutical composition for use in the treatment of cancer.

According to an embodiment, the invention concerns the pharmaceutical composition for use in a method of treating according to the invention.

According to an embodiment, the invention concerns the pharmaceutical composition for use according to the invention, wherein said cancer is a brain cancer, a central nervous system (CNS) lymphoma or a CNS cancer.

According to an embodiment, the invention concerns the pharmaceutical composition for use according to the invention, wherein said cancer is selected among a carcinoma, a sarcoma, a lymphoma and a leukemia.

According to an embodiment, the invention concerns the pharmaceutical composition for use according to the invention, wherein said cancer is selected among neuroblastoma, medulloblastoma, glioblastoma, small cell lung cancer, non-small cell carcinoma, a pediatric sarcoma, an adult sarcoma, breast cancer, liver cancer, melanoma, non-small cell lung carcinoma, lung adenocarcinoma or a gastrointestinal cancer.

According to an embodiment, the invention concerns the pharmaceutical composition for use according to the invention, wherein said cancer is an ovarian cancer or gastric cancer.

According to an embodiment, the invention concerns the pharmaceutical composition for use according to the invention, wherein said pharmaceutical composition is administered intracerebroventricularly, intrathecally, intracerebrally or intraventricularly.

According to an embodiment, the invention concerns the pharmaceutical composition for use in a treatment comprising intracerebroventricular, intrathecal, intracerebral or intraventricular administration.

According to an embodiment, the invention concerns the pharmaceutical composition for use according to the invention, wherein said pharmaceutical composition is administered using convection-enhanced delivery (CED).

According to an embodiment, the invention concerns the pharmaceutical composition for use in a treatment comprising convection-enhanced delivery (CED).

According to an embodiment, the invention concerns a kit of parts comprising a pharmaceutical composition comprising a radiolabeled B7H3 antibody or antigen binding fragment thereof and ascorbic acid.

According to an embodiment, the invention concerns a kit of parts comprising a pharmaceutical composition according to the invention and ascorbic acid.

According to an embodiment, the invention concerns the kit of parts, further comprising instructions for use.

Ascorbic acid is an organic acid with a ring structure similar to glucose. It may exist in two forms in humans, L-ascorbate (reduced form) and Dehydroascorbate (oxidized form). Ascorbic acid might be provided in mineral ascorbate form, such as sodium ascorbate, calcium ascorbate or other mineral ascorbates.

A potential antibody used in clinical trials for brain cancer treatment in children is the radiolabeled omburtamab (^{131}I-omburtamab) targeting the B7-H3 antigen. The application of the radiolabeled compound may be performed via intracerebral injection into the cerebrospinal fluid (CSF). After complete administration, the ^{131}I-omburtamab apparently distributes via the CSF and accumulates in the tumor tissue leading to a precise radiation damage of the tumor tissue. In the same manner the antibody may be used for further studies with the radiometal ^{177}Lu and the antibody conjugate DTPA-omburtamab.

Examples of antigen binding fragments encompassed within the term "antigen binding fragment thereof" of an antibody include (i) a Fab fragment, a monovalent fragment consisting of the VH, VL, CH1 and CL domains; (ii) a F(ab')2 fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the VH and CH1 domains; (iv) a Fv fragment consisting of the VH and VL domains of a single arm of an antibody, (v) a dAb fragment, which comprises a single variable domain; and (vi) an isolated complementarity determining region (CDR). Furthermore, although the two domains of the Fv fragment, VH and VL, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the VH and VL regions pair to form monovalent molecules, known as single chain Fv (scFv). In some embodiments, an "antigen binding fragment", as described herein, is or comprises such a single chain antibody. In some embodiments, an "antigen binding fragment" is or comprises a diabody. Diabodies are bivalent, bispecific antibodies in which VH and VL domains are expressed on a single polypeptide chain, but using a linker that is too short to allow for pairing between the two domains on the same chain, thereby forcing the domains to pair with complementary domains of another chain and creating two antigen binding sites. Such antibody binding portions are known in the art. In some embodiments, an antigen binding fragment is or comprises a single chain "linear antibody" comprising a pair of tandem Fv segments (VH-CHT -VH-CH1) which, together with complementary light chain polypeptides, form a pair of antigen binding regions. In some embodiments, an antigen binding fragment may have structural elements characteristic of chimeric or humanized antibodies. In general, humanized antibodies are human.

A SADA construct may be defined as a polypeptide conjugate comprising:

(i) a self-assembly disassembly (SADA) domain or SADA polypeptide and

(ii) at least a first binding domain that binds to a first target and is linked to the SADA polypeptide.

In some embodiments, the SADA construct further comprises a second binding domain that binds to a second target, which is different from or identical to the first target.

In some embodiments, the first and/or second binding domain is or comprises an antibody, antibody component, or antigen binding fragment.

In some embodiments, the first and second binding domains are part of a bispecific antibody agent. In some embodiments, the bispecific antibody agent comprises a first binding domain that binds a tumor target and a second binding domain that binds a metal-Bn-DOTA.

In some embodiments, the SADA construct may be characterized by one or more multimerization dissociation constants (KD).

In some embodiments, the SADA construct may be constructed and arranged so that it adopts a first multimerization state and one or more higher-order multimerization states, wherein:

the first multimerization state is less than about 70 kDa in size, at least one of the higher-order multimerization states is a homo-tetramer or higher-order homo-multimer greater than 150 kDa in size,

wherein the higher-order homo-multimerized conjugate is stable in aqueous solution when the conjugate is present at a concentration above the SADA polypeptide KD, and

the conjugate transitions from the higher-order multimerization state(s) to the first multimerization state under physiological conditions when the concentration of the conjugate is below the SADA polypeptide KD.

In some embodiments, a SADA domain is composed of multimerization domains which are each composed of helical bundles that associate in a parallel or anti-parallel orientation. In some embodiments, a SADA domain is selected from the group of one of the following human proteins: p53, p63, p73, heterogeneous nuclear Ribonucleoprotein (hnRNPC) C, or N-terminal domain of Synaptosomal-associated protein 23 (SNAP-23), Stefin B (Cystatin B),

Potassium voltage-gated channel subfamily KQT member 4 (KCNQ4), Cyclin-D-related protein (CBFA2T1), or variants or fragments thereof.

In some embodiments, a SADA polypeptide is or comprises a tetramerization domain of p53, p63, p73, hnRNPC, SNAP-23, Stefin B, KCNQ4, or CBFA2T1. In some embodiments, a SADA polypeptide is or comprises a sequence that is at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to a sequence of p53, p63, p73, hnRNPC, SNAP-23, Stefin B, KCNQ4, or CBFA2T1.

Among other things, the present disclosure provides various conjugates comprising a SADA domain linked to one or more binding domains. In some embodiments, such conjugates are characterized in that they multimerize to form a complex of a desired size under relevant conditions (e.g., in a solution in which the conjugate is present above a threshold concentration or pH and/or when present at a target site characterized by a relevant level or density of receptors for the payload), and disassemble to a smaller form under other conditions (e.g., absent the relevant environmental multimerization trigger). SADA constructs, SADA domains and SADA polypeptides are further described and exemplified in WO2018204873.

In some embodiments, the antibody or antigen binding fragment thereof comprises a chelating agent, such as a bifunctional chelating agent. In some embodiments, the antibody or antigen binding fragment thereof is or comprises a DOTA-group, DTPA-group, DOTA/HEHA-group and/or a HEHA-group, such as DOTA-hapten, DTPA-hapten, DOTA/HEHA-hapten and/or a HEHA-hapten. In some embodiments, the antibody or antigen binding fragment thereof is linked to a chelating agent, such as a bifunctional chelating agent. In some embodiments, the antibody or antigen binding fragment thereof is linked to a DOTA-group, DTPA-group, DOTA/HEHA-group and/or a HEHA-group, such as DOTA-hapten, hapten, DOTA/HEHA-hapten and/or a HEHA-hapten. Examples of suitable chelating agents, groups and haptens are described in WO2019010299, WO0059896 and WO0168618.

Convection-enhanced delivery (CED) is a form of direct delivery that bypasses the blood–brain barrier, producing high local drug concentrations with limited systemic exposure. Convection-enhanced delivery (CED) generates a pressure gradient at the tip of an infusion catheter to deliver therapeutics directly through the interstitial spaces of the central nervous system.

Intracerebroventricular (ICV) administration is an injection technique of substances directly into the cerebrospinal fluid in cerebral ventricles in order to bypass the blood brain barrier.

Intracerebroventricular (ICV) administration helps bypass the blood–brain barrier by permitting high concentrations of a drug to directly reach the central compartment of the brain. For ICV administration, an external drug reservoir may be used or a drug reservoir may be implanted subcutaneously in the scalp. A catheter may be used to connect the reservoir to the ventricular space in the brain.

Figures

Fig. 1 shows high molecular weight aggregates (HMW) and low molecular weight fragments (LMW) content in compositions comprising ^{131}I-omburtamab, rHSA and no ascorbic acid stored at -80 °C at time 0 hours.

Fig. 2 shows HMW and LMW content in compositions comprising ^{131}I-omburtamab, rHSA and no ascorbic acid stored at -80 °C at time 96 hours.

Fig. 3 shows HMW and LMW content in compositions comprising ^{131}I-omburtamab, rHSA and 0.1% ascorbic acid stored at -80 °C at time 0 hours.

Fig. 4 shows HMW and LMW content in compositions comprising ^{131}I-omburtamab, rHSA and 0.1% ascorbic acid stored at -80 °C at time 96 hours.

Fig. 5 shows LMW content in a composition comprising ^{177}Lu-DTPA-omburtamab, HSA and 0.8% ascorbic acid stored at 2 - 8°C at time 0 hours.

Fig. 6 shows LMW content in a composition comprising ^{177}Lu-DTPA-omburtamab, HSA and 0.8% ascorbic acid stored at 2 - 8°C at time 120 hours.

Fig. 7 shows HMW and LMW content in a composition comprising ^{177}Lu-DTPA-omburtamab and 1.2% ascorbic acid stored at -80°C at time 0 hours.

Fig. 8 shows HMW and LMW content in a composition comprising ^{177}Lu-DTPA-omburtamab and 1.2% ascorbic acid stored at -80°C at time 124 hours.

All cited references are incorporated by reference.

The accompanying Figures and Examples are provided to explain rather than limit the present invention. It will be clear to the person skilled in the art that aspects, embodiments, claims and any items of the present invention may be combined.

Unless otherwise mentioned, all percentages are in weight/weight. Unless otherwise mentioned, all measurements are conducted under standard conditions (ambient temperature and pressure). Unless otherwise mentioned, test conditions are according to European Pharmacopoeia 8.0.

Examples

Example 1: ^{131}I-omburtamab for intracerebroventricular (ICV) administration

Stability of composition comprising ^{131}I-omburtamab drug product with and without ascorbic acid was measured and compared. Content of ^{131}I-omburtamab drug product is shown in Table 1.

Component	Composition per Batch
^{131}I-omburtamab	≥ 16.3 mCi/mL 0.08 – 0.35 mg/mL
Buffer (Sodium phosphate solution, 0.2 M)	4.46 mL (m($NaH_2PO_4xH_2O$) = 24.8 mg m(Na_2HPO_4) = 105.1 mg)
20% Recombinant Human Serum Albumin (rHSA), USP	0.45 mL (1.8%; v/v)
	4.9 mL Total Volume

Table 1: Content of ^{131}I-omburtamab drug product for ICV administration.

Two compositions comprising ^{131}I-omburtamab ICV drug product were prepared. Composition 1 comprised ^{131}I-omburtamab drug product with 2% (w/w) recombinant human serum albumin (rHSA) as stabilizing agent. Composition 2 comprised ^{131}I-omburtamab drug product with 2% (w/w) rHSA as stabilizing agent and 0.1% (w/w) ascorbic acid. The stability of these compositions was compared and analyzed after a storage time of 96 h at -80°C. The results are summarized in Table 2 and Figures 1-4.

t / h	2 % rHSA			2 % rHSA + 0.1 % ascorbic acid		
	Product purity / %	HMW / %	LMW / %	Product purity / %	HMW / %	LMW / %
0 (EOS)	92.6	5.8	1.6	93.1	5.6	1.3
96	81.2	12.9	5.9	89.4	6.4	4.2

Table 2: Summary of stability studies of ^{131}I-omburtamab including ascorbic acid in final drug product formulation. EOS: End of Synthesis; HMW: High molecular weight aggregates; LMW: Low molecular weight fragments.

Addition of ascorbic acid shows a clear effect regarding the evolution of by-products. The evolving by-products are high molecular weight aggregates (HMW) as well as low molecular weight fragments (LMW). The increase of HMW for Composition 1 (no ascorbic acid) was 7.1% and the increase of LMW was 4.3%. When adding ascorbic acid to the composition (Composition 2) the in-growth of by-products after 96 h could be reduced. The development of both HMW and the LMW were reduced. The increase was reduced to 0.8% for HMW and 2.9% for LMW, respectively.

Based on these results a positive effect of ascorbic acid on stabilizing the product composition could be demonstrated. The evolution of the aggregating by-products (HMW) could be reduced by the factor of 8 compared with a composition containing only rHSA, whereas the fragments (LMW) could be minimized by the factor of 1.5 for ^{131}I-omburtamab.

Example 2: ^{131}I-omburtamab for convection enhanced delivery (CED)

Stability of compositions comprising ^{131}I-omburtamab drug product with and without ascorbic acid was measured and compared. Content of ^{131}I-omburtamab CED drug product is shown in Table 3.

Component	Composition per Batch
^{131}I-omburtamab	0.75 mCi/mL 0.19 mg/mL
Buffer (Sodium phosphate solution, 0.2 M)	3.6 - 7.2 (m($NaH_2PO_4xH_2O$) = 19.4-38.8 mg m(Na_2HPO_4) = 82.3-164.6 mg)
20% Recombinant Human Serum Albumin (rHSA), USP	0.4 – 0.8 mL (1.8 %; v/v)

Ascorbic Acid	5.2-5.5 mM (m(Ascorbic acid) = 3.8-7.4 mg)
	4.0 – 8.0 mL Total Volume

Table 3: Content of ^{131}I-omburtamab drug product for CED

Comparative studies (pre-liminary) show that a higher stability could be achieved for a 6 mCi batch for the CED administration after 48 h at 2-8 °C, when ascorbic acid is included in the dilution buffer. The purity of the product including the ascorbic acid was 94 %, whereas the product purity was 88 %, when the ascorbic acid was excluded. After 144 hours the product purity was still above 89 % for the formulation including ascorbic acid, whereas 82 % product purity was observed even after only 72 h for the formulation without ascorbic acid.

Example 3: ^{177}Lu-DTPA-omburtamab for intracerebroventricular (ICV) administration

Stability of compositions comprising ^{177}Lu-DTPA-omburtamab drug product and different amounts of ascorbic acid was measured and compared. Content of ^{177}Lu-DTPA-omburtamab drug product is shown in Table 4.

Component	Composition per Batch
^{177}Lu-DTPA-omburtamab	0.13–0.38 mg/mL 0.13 mCi/mL (dosimetry dose) 2.50–21.25 mCi/mL (therapeutic dose)
Sodium chloride	60 mM (m = 14.0 mg)
Sodium citrate dihydrate	12.5 mM (m = 12.9 mg)
Sodium acetate	30 mM (m = 9.8 mg)
Sodium ascorbate	60 mM (m = 47.6 mg)
Hydrochloric Acid	Adjust pH 6.5–6.8
	4.0 mL Total Volume

Table 4: Content of ^{177}Lu-DTPA-omburtamab drug product for ICV

Ascorbic acid with HSA:

Composition A comprising ^{177}Lu-DTPA-omburtamab was prepared. Composition A comprised ^{177}Lu-DTPA-omburtamab drug product with 5% (w/w) human serum albumin (HSA) as stabilizing agent and 0.8% (w/w) ascorbic acid. The stability of the product was evaluated

over a storage period of 120 h at 2 - 8°C. The results are summarized in Table 5 and Figures 5-6.

The combination of HSA and ascorbic acid showed a positive effect on the stability of the product with respect to radiolysis. After 120 h the fraction of LMWs raised up to 8.8% at temperature of 2-8°C which is below the upper value of the specification limits (10% LMW/HMW).

	Composition A
t / h	LMW / %
0 (EOS)	2.0
120	8.8

Table 5: Summary of stability studies of ^{177}Lu-DTPA-omburtamab including HSA and ascorbic acid in final drug product formulation. EOS: End of Synthesis; LMW: Low molecular weight fragments.

Ascorbic acid without HSA:

Composition B comprising ^{177}Lu-DTPA-omburtamab was prepared. Composition B comprised ^{177}Lu-DTPA-omburtamab drug product with 1.2% (w/w) ascorbic acid. The stability of the product was evaluated over a storage period of 124 h at -80°C. The results are summarized in Table 6 and Figures 7-8.

	Composition B		
t / h	Product purity / %	HMW / %	LMW / %
0 (EOS)	97.2	2.3	0.5
124	91.5	4.4	4.1

Table 6: Summary of stability studies of ^{177}Lu-DTPA-omburtamab including ascorbic acid in final drug product formulation. EOS: End of Synthesis; HMW: High molecular weight aggregates; LMW: Low molecular weight fragments

After 124 h an increase from 2.3% to 4.4% for HMW was detected, whereas the evolving LMW reached 4.1%. These values are below the upper value of the specification limits (10 % LMW/HMW).

The stabilizing/scavenging effect of ascorbic acid seem to be present for compositions comprising ^{177}Lu-DTPA-omburtamab as well. Addition of ascorbic acid leads to a low evolution of HMWs and LMWs in the tested compositions. The amount of HMWs and LMWs does not reaches the upper value of the specification limits (10% LMW/HMW).

Comparing the different amounts of ascorbic acid in the final composition for ^{177}Lu-DTPA-omburtamab the 1.2% seems to have a great impact on the stability of the product. While for the composition with 0.8% ascorbic acid the total increase of LMWs was 6.8%, the increase in the LMWs for the 1.2% ascorbic acid composition was 4.1% with even no LMWs at the end of the synthesis.

SEQUENCES

SEQ ID NO. 1: Anti-B7H3 Light chain CDR-1

Arg Ala Ser Gln Ser Ile Ser Asp Tyr Leu His

SEQ ID NO. 2: Anti-B7H3 Light chain CDR-2

Tyr Ala Ser Gln Ser Ile Ser

SEQ ID NO. 3: Anti-B7H3 Light chain CDR-3

Gln Asn Gly His Ser Phe Pro Leu Thr

SEQ ID NO. 4: Anti-B7H3 Heavy chain CDR-1

Asn Tyr Asp Ile Asn

SEQ ID NO. 5: Anti-B7H3 Heavy chain CDR-2

Trp Ile Phe Pro Gly Asp Gly Ser Thr Gln Tyr Asn Glu Lys Phe Lys Gly

SEQ ID NO. 6: Anti-B7H3 Heavy chain CDR-3

Gln Thr Thr Ala Thr Trp Phe Ala Tyr

SEQ ID NO. 7: Anti-B7H3 VL

Asp Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Thr Pro Gly Asp Arg Val Ser Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Asp Tyr Leu His Trp Tyr Gln Gln Lys Ser His Glu Ser Pro Arg Leu Leu Ile Lys Tyr Ala Ser Gln Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Ser Asp Phe Thr Leu Ser Ile Asn Ser Val Glu Pro Glu Asp Val Gly Val Tyr Tyr Cys Gln Asn Gly His Ser Phe Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys

SEQ ID NO. 8: Anti-B7H3 VH

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Lys Pro Gly Ala Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Asp Ile Asn Trp Val Arg Gln Arg Pro Glu Gln Gly Leu Glu Trp Ile Gly Trp Ile Phe Pro Gly Asp Gly Ser Thr Gln Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Thr Asp Thr Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Arg Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg Gln Thr Thr Ala Thr Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala

SEQ ID NO. 9: Anti-B7H3 Light chain

Asp Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Thr Pro Gly Asp Arg Val Ser Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Asp Tyr Leu His Trp Tyr Gln Gln Lys Ser His Glu Ser Pro Arg Leu Leu Ile Lys Tyr Ala Ser Gln Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Ser Asp Phe Thr Leu Ser Ile Asn Ser Val Glu Pro Glu Asp Val Gly Val Tyr Tyr Cys Gln Asn Gly His Ser Phe Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro Ile Val Lys Ser Phe Asn Arg Asn Glu Cys

SEQ ID NO. 10: Anti-B7H3 Heavy chain

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Lys Pro Gly Ala Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr Asp Ile Asn Trp Val Arg Gln Arg Pro Glu Gln Gly Leu Glu Trp Ile Gly Trp Ile Phe Pro Gly Asp Gly Ser Thr Gln Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Thr Asp Thr Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Arg Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys Ala Arg Gln Thr Thr Ala Thr Trp Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Ala Lys Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu Ser Ser Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys Ile Val Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro Glu Val Ser Ser Val Phe Ile Phe Pro Pro Lys Pro Lys Asp Val Leu Thr Ile Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser Lys Asp Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu Val His Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn Gly Lys Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln Val Tyr Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val Ser Leu Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val Glu Trp Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln Pro Ile Met Asp Thr Asp Gly Ser Tyr Phe Val Tyr Ser Lys Leu Asn Val Gln Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val Leu His Glu Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His Ser Pro Gly Lys

Claims

1. A pharmaceutical composition comprising:

   (i) A radiolabeled B7H3 antibody or antigen binding fragment thereof, and

   (ii) Ascorbic acid.

2. The pharmaceutical composition according to claim 1, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof is for delivery to the central nervous system (CNS).

3. The pharmaceutical composition according to any of the preceding claims, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof is for intracerebroventricular (ICV), intrathecal, intracerebral or intraventricular administration.

4. The pharmaceutical composition according to any of the preceding claims, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof is for convection-enhanced delivery (CED).

5. The pharmaceutical composition according to any of the preceding claims, wherein said ascorbic acid is a stabilizing agent and/or a scavenger agent.

6. The pharmaceutical composition according to any of the preceding claims, wherein the amount of said ascorbic acid is at least 0.001% (w/w), alternatively 0.005% (w/w), alternatively 0.01% (w/w), alternatively 0.02% (w/w), alternatively 0.03% (w/w), alternatively 0.04% (w/w), alternatively 0.05% (w/w), alternatively 0.06% (w/w), alternatively 0.07% (w/w), alternatively 0.08% (w/w), alternatively 0.09% (w/w), alternatively 0.1% (w/w).

7. The pharmaceutical composition according to any of the preceding claims, wherein the amount of said ascorbic acid is at most 10% (w/w), alternatively 9.5% (w/w), alternatively 9% (w/w), alternatively 8.5% (w/w), alternatively 8% (w/w), alternatively 7.5% (w/w), alternatively 7% (w/w), alternatively 6.5% (w/w), alternatively 6% (w/w), alternatively 5.5% (w/w), alternatively 5% (w/w).

8. The pharmaceutical composition according to any of the preceding claims, wherein the amount of said ascorbic acid is selected from 0.001-10% (w/w), 0.01-10% (w/w), 0.05-10% (w/w), 0.05-9% (w/w), 0.05-8% (w/w), 0.05-7% (w/w), 0.05-6% (w/w), 0.05-5% (w/w), 0.05-4% (w/w), 0.05-3% (w/w), 0.05-2% (w/w), 0.05-1.5% (w/w) and 0.05-1.3% (w/w).

9. The pharmaceutical composition according to any of the preceding claims, wherein the amount of said ascorbic acid is selected from 0.05-0.2% (w/w), 0.05-0.1% (w/w) and 1-1.5% (w/w).

10. The pharmaceutical composition according to any of the preceding claims, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof comprises light chain CDR sequences according to SEQ ID NO: 1-3 and/or heavy chain CDR sequences according to SEQ ID NO: 4-6.

11. The pharmaceutical composition according to any of the preceding claims, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof comprises a VL sequence according to SEQ ID NO: 7 and/or a VH sequence according to SEQ ID NO: 8.

12. The pharmaceutical composition according to any of the preceding claims, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof comprises a

light chain sequence according to SEQ ID NO: 9 and/or a heavy chain sequence according to SEQ ID NO: 10.

13. The pharmaceutical composition according to any of the preceding claims, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof is Omburtamab or derived from Omburtamab.

14. The pharmaceutical composition according to any of the preceding claims, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof comprises or is an scFv.

15. The pharmaceutical composition according to any of the preceding claims, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof comprises or is a SADA construct.

16. The pharmaceutical composition according to any of the preceding claims, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof comprises or is linked to a chelating agent, such as a bifunctional chelating agent.

17. The pharmaceutical composition according to any of the preceding claims, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof is, comprises or is linked to a DOTA-group, DTPA-group, DOTA/HEHA-group and/or a HEHA-group.

18. The pharmaceutical composition according to any of the preceding claims, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof is, comprises or is linked to a DOTA-hapten, DOTA/HEHA-hapten and/or a HEHA-hapten.

19. The pharmaceutical composition according to any of the preceding claims, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof comprises an Fc part.

20. The pharmaceutical composition according to any of the preceding claims, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof does not comprise a Fc part or comprises an inactive or null Fc part.

21. The pharmaceutical composition according to any of the preceding claims, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof is IgG1 with inactive Fc or IgG4.

22. The pharmaceutical composition according to any of the preceding claims, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof is an IgG1 heterodimer with inactive Fc.

23. The pharmaceutical composition according to any of the preceding claims, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof is labeled with a radioisotope.

24. The pharmaceutical composition according to any of the preceding claims, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof is labeled with a radioisotope selected from the group consisting of ^{124}I, ^{131}I, ^{177}Lu, ^{99}mTc, ^{64}Cu, ^{86}Y, ^{90}Y, ^{225}Ac and ^{89}Zr.

25. The pharmaceutical composition according to any of the preceding claims, comprising at least one pharmaceutically acceptable excipient.

26. The pharmaceutical composition according to claim 25, wherein said pharmaceutically acceptable excipient is selected from the group consisting of diluents, carriers, preservatives, buffers and surfactants.

27. The pharmaceutical composition according to claim 25 or 26, wherein said pharmaceutically acceptable excipient is selected from the group consisting of sodium phosphate, human serum albumin, sodium chloride, sodium citrate dihydrate, sodium acetate, sodium ascorbate and hydrochloric acid.

28. The pharmaceutical composition according to any of the preceding claims comprising sodium phosphate solution, preferably in a concentration of 0.005-5 M, alternatively 0.01-1 M, alternatively 0.02-2 M, alternatively 0.05 M - 0.5 M, alternatively 0.05 M - 0.4 M, alternatively 0.1 M - 0.4 M, alternatively 0.1 M - 0.3 M, alternatively 0.15 M - 0.3 M, alternatively 0.15 M - 0.25 M, alternatively around 0.2 M.

29. The pharmaceutical composition according to claim 28, wherein said sodium phosphate solution is $NaH_2PO_4xH_2O$ and/or Na_2HPO_4.

30. The pharmaceutical composition according to any of the preceding claims comprising human serum albumin, preferably in a concentration of 0.001-10% w/w, alternatively 0.01-5% w/w, alternatively 0.05-5% w/w, alternatively 0.05-4% w/w, alternatively 0.1-4% w/w, alternatively 0.1-3.5% w/w, alternatively 0.1-3% w/w, alternatively 0.1-2.5% w/w, alternatively 0.2-2.5% w/w, alternatively 0.5-2.5% w/w.

31. The pharmaceutical composition according to any of the preceding claims comprising an amount of human serum albumin selected from about 1% w/w, 1.1% w/w, 1.2% w/w, 1.3% w/w, 1.4% w/w, 1.5% w/w, 1.6% w/w, 1.7% w/w, 1.8% w/w, 1.9% w/w, 2.0% w/w, 2.1% w/w, 2.2% w/w, 2.3% w/w, 2.4% w/w, and 2.5% w/w.

32. The pharmaceutical composition according to any of the preceding claims wherein said human serum albumin is recombinant.

33. The pharmaceutical composition according to any of the preceding claims comprising sodium chloride, preferably in a concentration of 0.1-200 mM, alternatively 1-100 mM, alternatively 5-95 mM, alternatively 10-90 mM, alternatively 15-85 mM, alternatively 20-80 mM, alternatively 25-75 mM, alternatively 30-70 mM, alternatively 35-65 mM, alternatively around 60 mM.

34. The pharmaceutical composition according to any of the preceding claims comprising sodium citrate dihydrate, preferably in a concentration of 0.01-100 mM, alternatively 0.1-50 mM, 0.1-30 mM, alternatively 1-25 mM, alternatively 2-20 mM, alternatively 3-18 mM, alternatively 4-17 mM, alternatively 5-15 mM, alternatively 8-15 mM, alternatively 10-15 mM, alternatively 11-14 mM, alternatively around 12.5 mM.

35. The pharmaceutical composition according to any of the preceding claims comprising sodium acetate, preferably in a concentration of 0.01-100 mM, alternatively 1-70 mM, alternatively 2-60 mM, alternatively 5-60 mM, alternatively 5-50 mM, alternatively 10-50 mM, alternatively 15-45 mM, alternatively 20-40 mM, alternatively 25-35 mM, alternatively around 30 mM.

36. The pharmaceutical composition according to any of the preceding claims comprising sodium ascorbate, preferably in a concentration of 0.1-200 mM, alternatively 1-100 mM, alternatively 5-95 mM, alternatively 10-90 mM, alternatively 15-85 mM, alternatively 20-80 mM, alternatively 25-75 mM, alternatively 30-70 mM, alternatively 35-65 mM, alternatively around 60 mM.

37. The pharmaceutical composition according to any of the preceding claims comprising hydrochloric acid.

38. The pharmaceutical composition according to any of the preceding claims having a pH between 3-9, alternatively 4-8, alternatively 4.5-8.5, alternatively 5-7, alternatively 5-8, alternatively 5.5-7.5, alternatively 5.5-7, alternatively 6-7, alternatively 6.5-7, alternatively 6.5-6.8.

39. The pharmaceutical composition according to any of the preceding claims, wherein said pharmaceutical composition has an increased stability compared to a pharmaceutical composition not comprising ascorbic acid.

40. The pharmaceutical composition according to claim 39, wherein said stability is increased during labeling, during storage and/or in use.

41. The pharmaceutical composition according to any of the preceding claims, wherein the amount of high molecular weight aggregates (HMW) and/or low molecular weight fragments (LMW) is reduced compared to a pharmaceutical composition not comprising ascorbic acid.

42. The pharmaceutical composition according to any of the preceding claims, wherein the amount of HMW and/or LMW is reduced at least by a factor 1.5 compared to a pharmaceutical composition not comprising ascorbic acid.

43. The pharmaceutical composition according to any of the preceding claims, wherein the amount of HMW is below 10%, alternatively 9%, alternatively 8%, alternatively 7%.

44. The pharmaceutical composition according to any of the preceding claims, wherein the amount of LMW is below 10%, alternatively 9%, alternatively 8%, alternatively 7%, alternatively 6%, alternatively 5%.

45. The pharmaceutical composition according to any of the preceding claims, wherein the amount of HMW and/or LMW is measured after a storage period of 96 hours at -80 °C or after a storage period of 120 h at 2 - 8 °C.

46. The pharmaceutical composition according to any of the preceding claims, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof is the sole active ingredient.

47. The pharmaceutical composition according to any of the preceding claims, which is a pharmaceutically acceptable composition.

48. The pharmaceutical composition according to any of the preceding claims, where the composition is an aqueous composition.

49. A method of stabilizing a pharmaceutical composition comprising a radiolabeled B7H3 antibody or antigen binding fragment thereof, comprising:

a. Producing said B7H3 antibody or antigen binding fragment thereof,

b. Radiolabeling said B7H3 antibody or antigen binding fragment thereof,

c. Formulating said radiolabeled B7H3 antibody or antigen binding fragment thereof into a pharmaceutical composition,

d. Stabilizing said pharmaceutical composition by adding ascorbic acid.

50. A method of stabilizing a pharmaceutical composition comprising a radiolabeled B7H3 antibody or antigen binding fragment thereof, comprising:

a. Producing said B7H3 antibody or antigen binding fragment thereof,

b. Radiolabeling said B7H3 antibody or antigen binding fragment thereof,

c. Providing a stabilized pharmaceutical composition by adding ascorbic acid and optionally additional excipients.

51. The method according to claim 49 or 50, wherein the stabilized pharmaceutical composition is a pharmaceutical composition according to any of claims 1-47.

52. A process for producing a pharmaceutical composition comprising a radiolabeled B7H3 antibody or antigen binding fragment thereof, comprising:

a. Producing said B7H3 antibody or antigen binding fragment thereof,

b. Radiolabeling said B7H3 antibody or antigen binding fragment thereof,

c. Formulating said radiolabeled B7H3 antibody or antigen binding fragment thereof into a pharmaceutical composition,

d. Adding ascorbic acid to said pharmaceutical composition.

53. A process for producing a pharmaceutical composition comprising a radiolabeled B7H3 antibody or antigen binding fragment thereof, comprising:

a. Producing said B7H3 antibody or antigen binding fragment thereof,

b. Radiolabeling said B7H3 antibody or antigen binding fragment thereof,

c. Providing a pharmaceutical composition by adding ascorbic acid and optionally additional excipients.

54. The process according to claim 52 or 53, wherein the pharmaceutical composition is a pharmaceutical composition according to any of claims 1-47.

55. The method or the process according to any of the preceding claims, wherein the amount of said ascorbic acid is at least 0.001% (w/w), alternatively 0.005% (w/w), alternatively 0.01% (w/w), alternatively 0.02% (w/w), alternatively 0.03% (w/w),

alternatively 0.04% (w/w), alternatively 0.05% (w/w), alternatively 0.06% (w/w), alternatively 0.07% (w/w), alternatively 0.08% (w/w), alternatively 0.09% (w/w), alternatively 0.1% (w/w).

56. The method or the process according to any of the preceding claims, wherein the amount of said ascorbic acid is at most 10% (w/w), alternatively 9.5% (w/w), alternatively 9% (w/w), alternatively 8.5% (w/w), alternatively 8% (w/w), alternatively 7.5% (w/w), alternatively 7% (w/w), alternatively 6.5% (w/w), alternatively 6% (w/w), alternatively 5.5% (w/w), alternatively 5% (w/w).

57. The method or the process according to any of the preceding claims, wherein the amount of said ascorbic acid is selected from 0.001-10% (w/w), 0.01-10% (w/w), 0.05-10% (w/w), 0.05-9% (w/w), 0.05-8% (w/w), 0.05-7% (w/w), 0.05-6% (w/w), 0.05-5% (w/w), 0.05-4% (w/w), 0.05-3% (w/w), 0.05-2% (w/w), 0.05-1.5% (w/w) and 0.05-1.3% (w/w).

58. The method or the process according to any of the preceding claims, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof comprises light chain CDR sequences according to SEQ ID NO: 1-3 and/or heavy chain CDR sequences according to SEQ ID NO: 4-6.

59. The method or the process according to any of the preceding claims, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof comprises a VL sequence according to SEQ ID NO: 7 and/or a VH sequence according to SEQ ID NO: 8.

60. The method or the process according to any of the preceding claims, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof comprises a light

chain sequence according to SEQ ID NO: 9 and/or a heavy chain sequence according to SEQ ID NO: 10.

61. The method or the process according to any of the preceding claims, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof is Omburtamab or derived from Omburtamab.

62. The method or the process according to any of the preceding claims, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof comprises or is an scFv.

63. The method or the process according to any of the preceding claims, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof comprises or is a SADA construct.

64. The method or the process according to any of the preceding claims, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof comprises or is linked to a chelating agent, such as a bifunctional chelating agent.

65. The method or the process according to any of the preceding claims, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof is, comprises or is linked to a DOTA-group, DTPA-group, DOTA/HEHA-group and/or a HEHA-group.

66. The method or the process according to any of the preceding claims, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof is, comprises or is linked to a DOTA-hapten, DOTA/HEHA-hapten and/or a HEHA-hapten.

67. The method or the process according to any of the preceding claims, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof is labeled with a radioisotope.

68. The method or the process according to any of the preceding claims, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof is labeled with a radioisotope selected from the group consisting of ^{124}I, ^{131}I, ^{177}Lu, ^{99}mTc, ^{64}Cu, ^{86}Y, ^{90}Y, ^{225}Ac and ^{89}Zr.

69. The method or the process according to any of the preceding claims, wherein said pharmaceutical composition comprises at least one pharmaceutically acceptable excipient.

70. The method or the process according to any of the preceding claims, wherein said pharmaceutical composition comprises a pharmaceutically acceptable excipient selected from the group consisting of diluents, carriers, preservatives, buffers and surfactants.

71. The method or the process according to any of the preceding claims, wherein said pharmaceutical composition has an increased stability compared to a pharmaceutical composition not comprising ascorbic acid.

72. The method or the process according to any of the preceding claims, wherein the stability of said pharmaceutical composition is increased during labeling, during storage and/or in use.

73. The method or the process according to any of the preceding claims, wherein the amount of HMW and/or LMW in said pharmaceutical composition is reduced compared to a pharmaceutical composition not comprising ascorbic acid.

74. The method or the process according to any of the preceding claims, wherein the amount of HMW and/or LMW in said pharmaceutical composition is reduced at least by a factor 1.5 compared to a pharmaceutical composition not comprising ascorbic acid.

75. The method or the process according to any of the preceding claims, wherein the amount of HMW in said pharmaceutical composition is below 10%, alternatively 9%, alternatively 8%, alternatively 7%.

76. The method or the process according to any of the preceding claims, wherein the amount of LMW in said pharmaceutical composition is below 10%, alternatively 9%, alternatively 8%, alternatively 7%, alternatively 6%, alternatively 5%.

77. The method or the process according to any of the preceding claims, wherein the amount of HMW and/or LMW in said pharmaceutical composition is measured after a storage period of 96 hours at -80 °C or after a storage period of 120 h at 2 - 8 °C.

78. The method or the process according to any of the preceding claims, wherein said radiolabeled B7H3 antibody or antigen binding fragment thereof is the sole active ingredient in said pharmaceutical composition.

79. The method or the process according to any of the preceding claims, wherein in said pharmaceutical composition is a pharmaceutically acceptable composition.

80. Use of ascorbic acid as a stabilizing agent and/or a scavenger agent.

81. Use of ascorbic acid as a stabilizing agent and/or a scavenger agent for a radiolabeled B7H3 antibody or antigen binding fragment thereof.

82. Use of ascorbic acid as a stabilizing agent and/or a scavenger agent for a pharmaceutical composition comprising a radiolabeled B7H3 antibody or antigen binding fragment thereof.

83. Use of ascorbic acid as a stabilizing agent and/or a scavenger agent for a pharmaceutical composition according to any of claims 1-47.

84. A method of treating cancer in an individual, wherein the method comprises a step of administering a therapeutically effective amount of a pharmaceutical composition according to any of claims 1-47.

85. A method for treating, preventing and/or alleviating the symptoms of a disorder affecting the central nervous system (CNS), such as a neurodegenerative condition and/or disease, an inflammatory disease or cancer, in particular a metastatic cancer, in a subject, wherein said method comprises a step of administration to said subject of a therapeutically effective amount of a pharmaceutical composition according to any of claims 1-47, and wherein said pharmaceutical composition is delivered into CNS using a device allowing or adapted to provide intracerebroventricular administration.

86. A method for treating, preventing and/or alleviating the symptoms of a condition in a subject, wherein said condition is characterized by B7H3 antigen or B7H3 antigen expression, and wherein said method comprises a step of administering a therapeutically effective amount of a pharmaceutical composition according to any of claims 1-47 and wherein said pharmaceutical composition is delivered into the

central nervous system (CNS) using a device allowing or adapted to provide intracerebroventricular administration.

87. The method according to claim 85 or 86, wherein said device comprises a catheter.

88. The method according to any of claims 85-87 wherein said device comprises a reservoir, such as an Ommaya reservoir.

89. A method for treating, preventing and/or alleviating the symptoms of a disorder affecting the central nervous system (CNS), such as a neurodegenerative condition and/or disease, an inflammatory disease or cancer, in particular a metastatic cancer, in a subject, wherein said method comprises a step of administration to said subject of a therapeutically effective amount of a pharmaceutical composition according to any of claims 1-47, and wherein said pharmaceutical composition is delivered into CNS using convection-enhanced delivery (CED).

90. A method for treating, preventing and/or alleviating the symptoms of a condition in a subject, wherein said condition is characterized by B7H3 antigen or B7H3 antigen expression, and wherein said method comprises a step of administering a therapeutically effective amount of a pharmaceutical composition according to any of claims 1-47 and wherein said pharmaceutical composition is delivered into the central nervous system (CNS) using convection-enhanced delivery (CED).

91. The method according to any of claims 84-90, wherein said cancer is a brain cancer, a central nervous system (CNS) lymphoma or a CNS cancer.

92. The method according to any of claims 84-91, wherein said cancer is selected among a carcinoma, a sarcoma, a lymphoma and a leukemia.

93. The method according to any of claims 84-92, wherein said cancer is selected among neuroblastoma, medulloblastoma, glioblastoma, small cell lung cancer, non-small cell carcinoma, a pediatric sarcoma, an adult sarcoma, breast cancer, liver cancer, melanoma, non-small cell lung carcinoma, lung adenocarcinoma or a gastrointestinal cancer.

94. The method according to any of claims 84-93, wherein said cancer is an ovarian cancer or gastric cancer.

95. The method according to any of claims 84-94, wherein said pharmaceutical composition is administered intracerebroventricularly, intrathecally, intracerebrally or intraventricularly.

96. The method according to any of claims 84-95, wherein said condition or cancer is characterized by overexpression of B7H3.

97. The pharmaceutical composition according to any of claims 1-47 for use as a medicament.

98. The pharmaceutical composition according to any of claims 1-47 for use in a method of treatment of cancer.

99. The pharmaceutical composition according to any of claims 1-47 for use in a method of treatment according to any of the preceding claims.

100. The pharmaceutical composition for use according to any of the preceding claims, wherein said cancer is a brain cancer, a central nervous system (CNS) lymphoma or a CNS cancer.

101. The pharmaceutical composition for use according to any of the preceding claims, wherein said cancer is selected among a carcinoma, a sarcoma, a lymphoma and a leukemia.

102. The pharmaceutical composition for use according to any of the preceding claims, wherein said cancer is selected among neuroblastoma, medulloblastoma, glioblastoma, small cell lung cancer, non-small cell carcinoma, a pediatric sarcoma, an adult sarcoma, breast cancer, liver cancer, melanoma, non-small cell lung carcinoma, lung adenocarcinoma or a gastrointestinal cancer.

103. The pharmaceutical composition for use according to any of the preceding claims, wherein said cancer is an ovarian cancer or gastric cancer.

104. The pharmaceutical composition for use according to any of the preceding claims, wherein said pharmaceutical composition is administered intracerebroventricularly, intrathecally, intracerebrally or intraventricularly.

105. The pharmaceutical composition for use according to any of the preceding claims, wherein said pharmaceutical composition is administered using convection-enhanced delivery (CED).

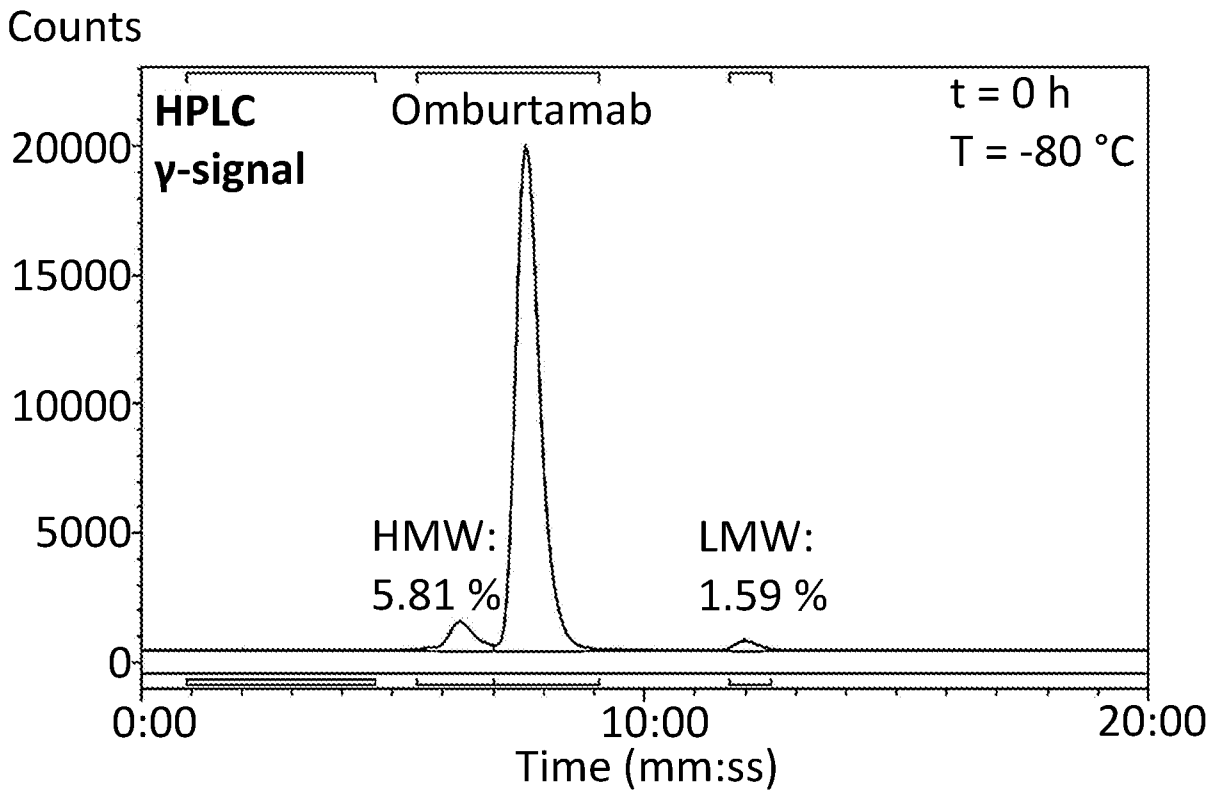
106. The pharmaceutical composition according to any of claims 1-48 for use in a treatment comprising intracerebroventricular, intrathecal, intracerebral or intraventricular administration.

107. The pharmaceutical composition according to any of claims 1-48 for use in a treatment comprising convection-enhanced delivery (CED).

108. A kit of parts comprising a pharmaceutical composition comprising a radiolabeled B7H3 antibody or antigen binding fragment thereof and ascorbic acid.

109. A kit of parts comprising a pharmaceutical composition according to any of claims 1-47 and ascorbic acid.

110. The kit of parts according to any of the preceding claims, further comprising instructions for use.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γ-signal
Omburtamab
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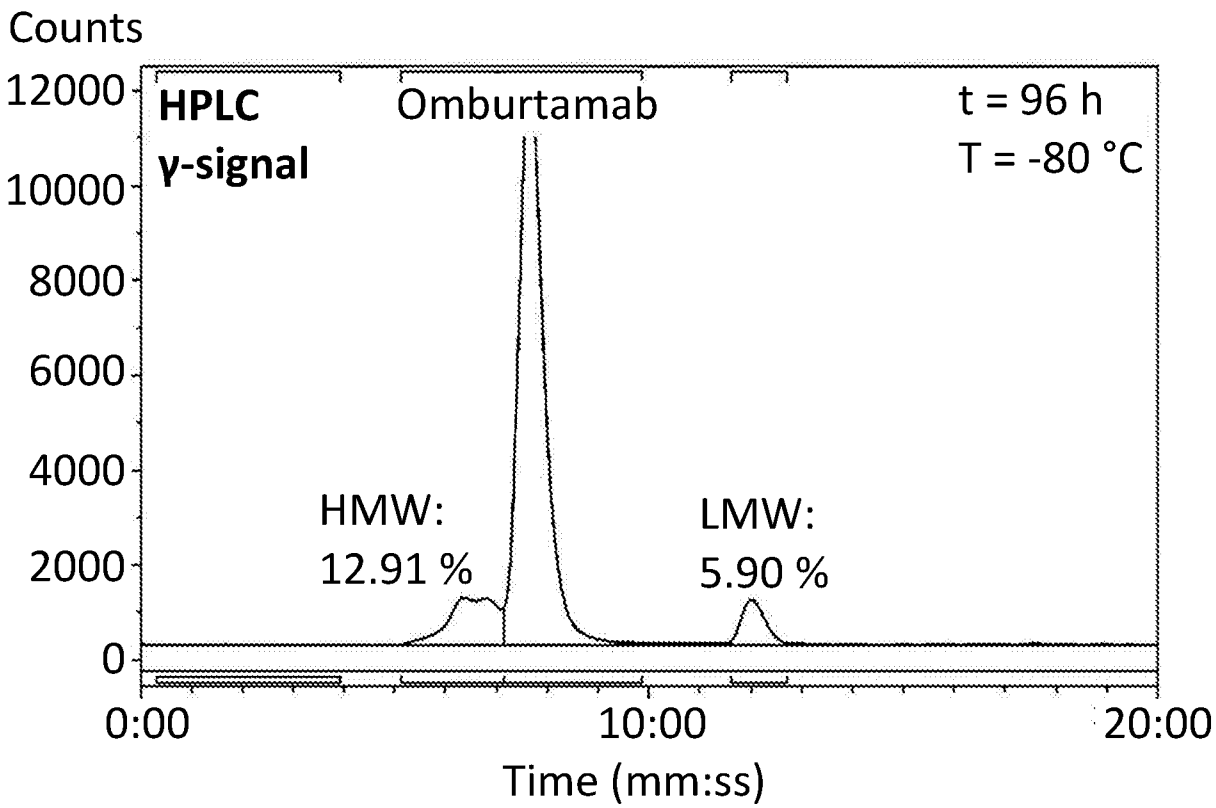
15000
10000
5000
0
HMW:
5.81 %
LMW:
1.59 %
0:00
10:00
20:00
Time (mm:ss)

Fig. 1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HPLC
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Omburtamab
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10000
8000
6000
4000
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LMW:
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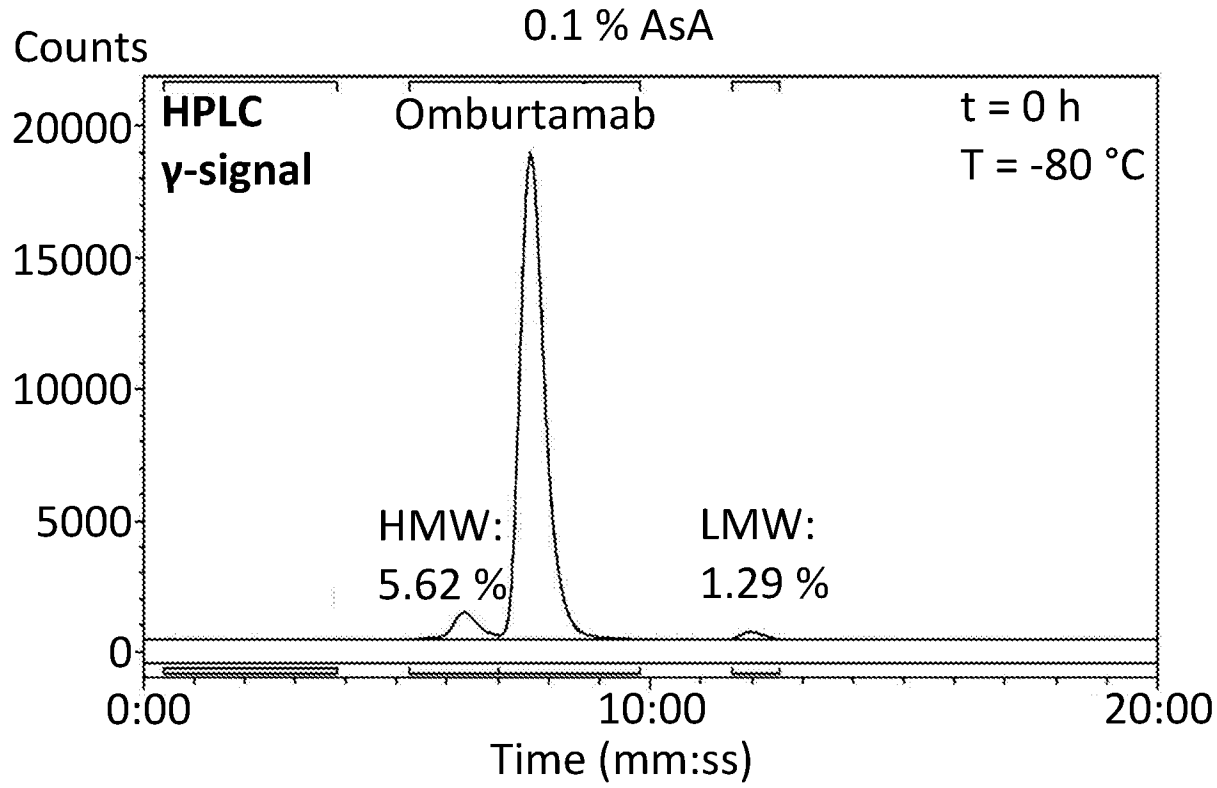
Time (mm:ss)

Fig. 2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Counts
HPLC
γ-signal
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10000
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5.62 %
LMW:
1.29 %
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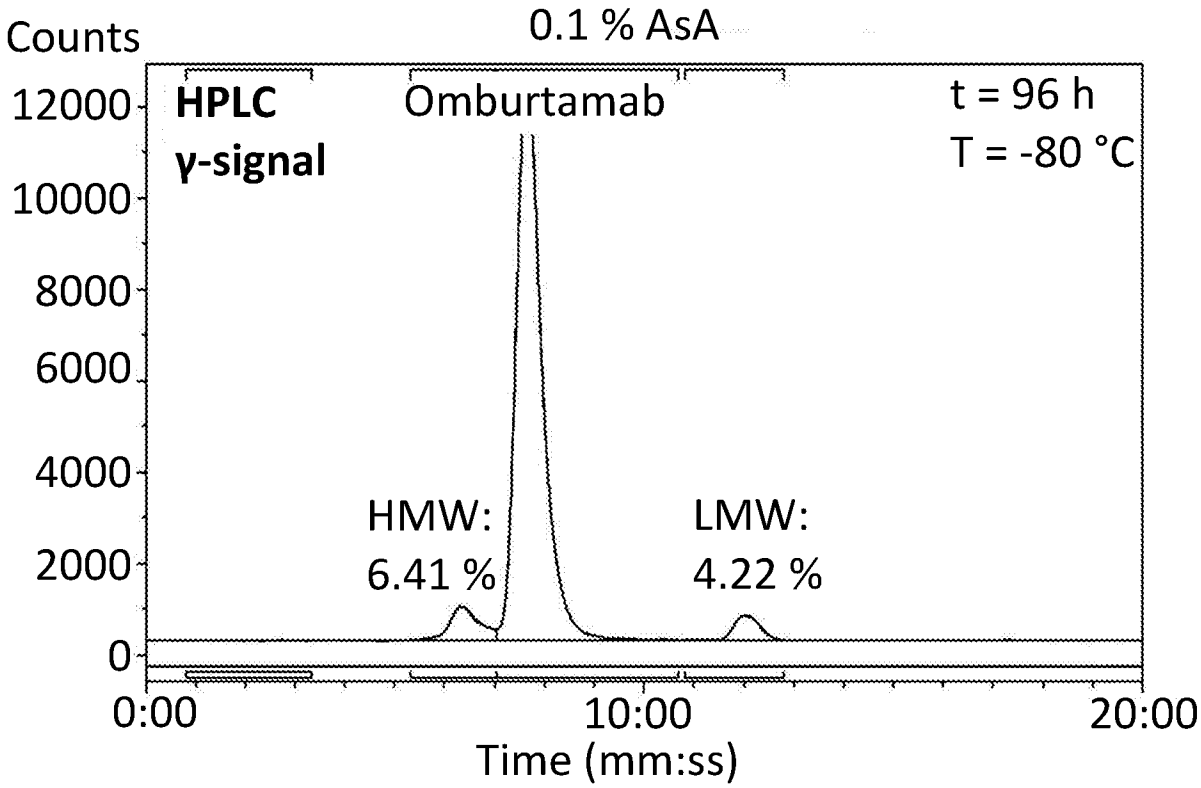
20:00
Time (mm:ss)

Fig. 3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Counts
HPLC
γ-signal
Omburtamab
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10000
8000
6000
4000
2000
0
HMW:
6.41 %
LMW:
4.22 %
0:00
10:00
20:00
Time (mm:ss)

Fig. 4

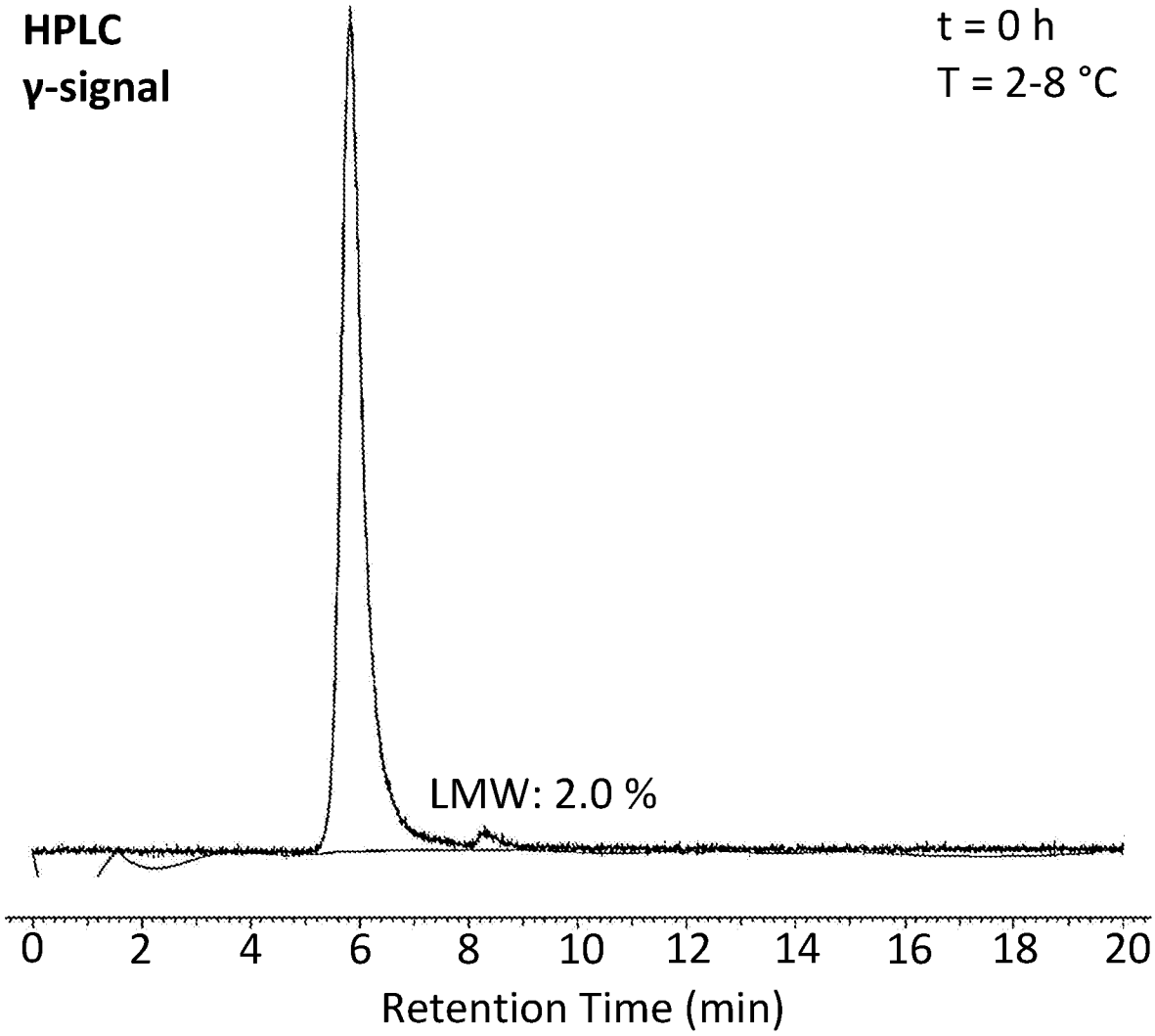

HPLC
γ-signal
t = 0 h
T = 2-8 °C
LMW: 2.0 %
0
2
4
6
8
10
12
14
16
18
20
Retention Time (min)

Fig. 5

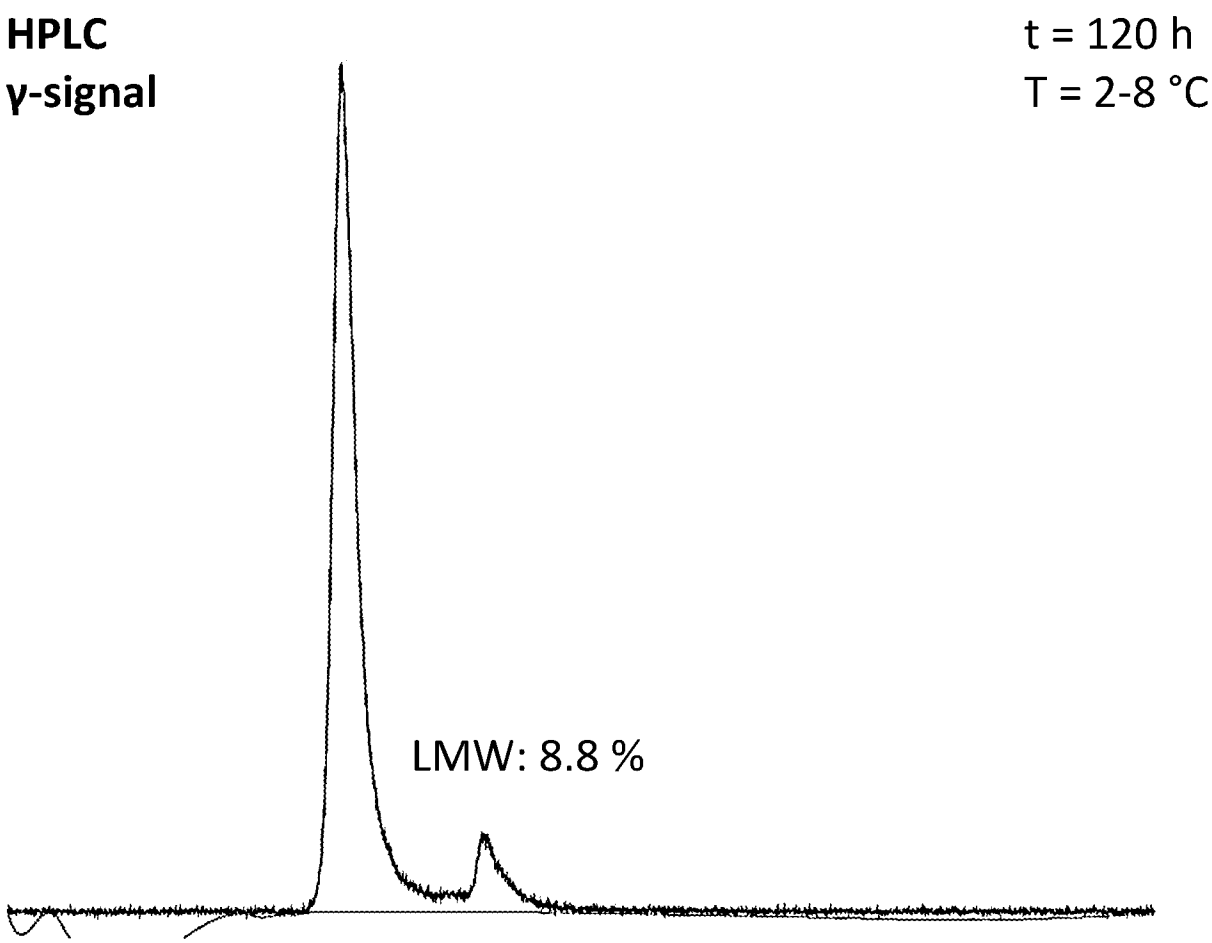
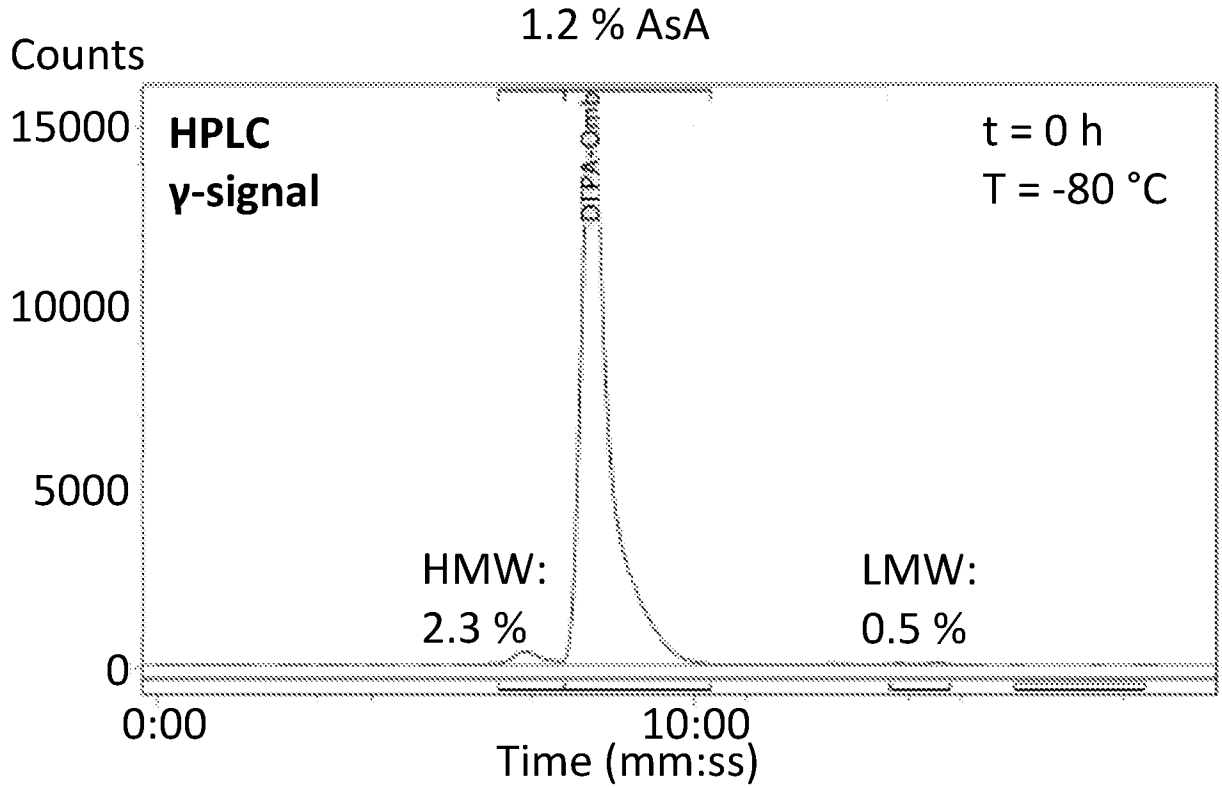


Fig. 6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15000
10000
5000
0
HPLC
γ-signal
DTPA-Omni
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HMW:
2.3 %
LMW:
0.5 %
0:00
10:00
Time (mm:ss)

Fig. 7

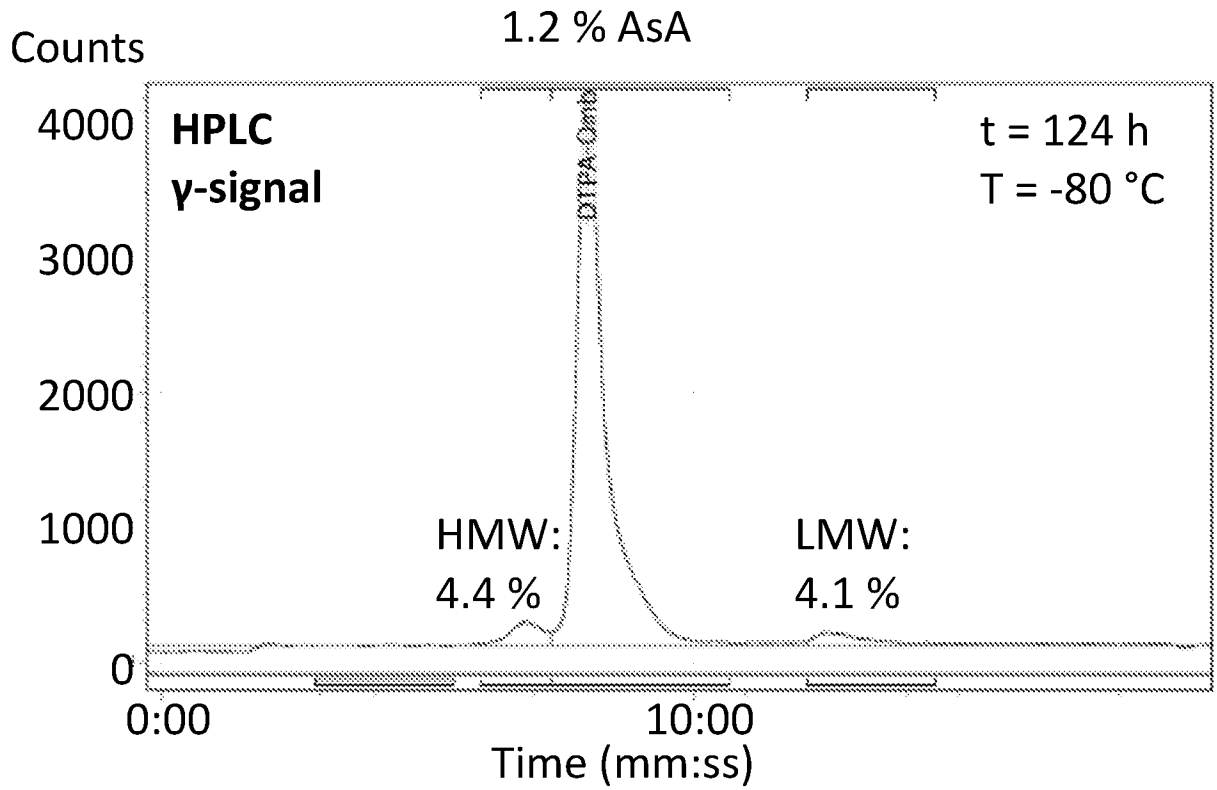
1.2 % AsA
Counts
4000
3000
2000
1000
0
HPLC
γ-signal
DTPA-Omni
t = 124 h
T = -80 °C
HMW:
4.4 %
LMW:
4.1 %
0:00
10:00
Time (mm:ss)

Fig. 8

INTERNATIONAL SEARCH REPORT

International application No
PCT/DK2022/050018

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61P37/00 A61K51/10 C07K16/28
ADD. A61K39/00

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)
A61P A61K 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, CHEM ABS Data, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2017/162663 A1 (BAYER PHARMA AG [DE]) 28 September 2017 (2017-09-28) claims ----- WO 2009/037336 A2 (GE HEALTHCARE LTD [GB]; VEGGELAND JANNE [NO] ET AL.) 26 March 2009 (2009-03-26) claims ----- -/--	1-5, 49-54
Y		1-79, 84-110

[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
17 May 2022	25/05/2022

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	Meyer, Wolfram

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/DK2022/050018

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2018/209346 A1 (MEMORIAL SLOAN KETTERING CANCER CENTER [US]; Y MABS THERAPEUTICS) 15 November 2018 (2018-11-15) line 6 - page 3, line 30 page 4, line 8 - page 5, line 2 page 5, line 3 - page 6, line 9 page 7, line 13 - line 27 page 21, line 17 - line 28 page 23, line 1 - line 5 page 23, line 13 - line 21	1-79, 84-110
X	LIU SHUANG ET AL: "Ascorbic acid: Useful as a buffer agent and radiolytic stabilizer for metalloradiopharmaceuticals", BIOCONJUGATE CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 14, no. 5, 1 September 2003 (2003-09-01), pages 1052-1056, XP002534810, ISSN: 1043-1802, DOI: 10.1021/BC034109I [retrieved on 2003-08-19]	80-83
Y	the whole document	1-79, 84-110

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK2022/050018

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 13ter.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 13ter.1(a)).

      [ ] on paper or in the form of an image file (Rule 13ter.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/DK2022/050018

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