

the risk that a patient will develop an immune response to the active protein monomer, resulting in the formation of neutralizing antibodies and drug resistance, or other adverse side effects (Mahler J Pharm Sci. 2009 Sep;98(9):2909-34.

5 **[10]** In general, several efforts have been reported in the literature to minimize protein aggregation by various mechanisms. Proteins can be stabilized and thus protected from aggregate formation and other chemical changes by modifying their primary structure, thereby increasing interior hydrophobicity and reducing outer hydrophobicity. However, genetic engineering of proteins may result in impaired functionality and/or increased immunogenicity. Another approach focuses on the dissociation of aggregates (referred to as
10 “disaggregation”) to recover functional, native monomers by using various mechanisms such as temperature, pressure, pH, and salts. Currently, protein aggregates are removed as impurities mainly in the polishing steps of downstream processing. However, in cases of high levels of high-molecular weight (HMW), removing significant amount of HMW not only results in substantial yield loss but also makes the design of a robust downstream process
15 challenging (Chi et al., Pharm Res, Vol. 20, No. 9, Sept 2003, pp. 1325-1336).

[11] Preserving a bispecific antibody construct formulation over a wide concentration range while maintaining its stability and ensuring its quantitative recovery from the administration container poses serious challenges. There is a need in the art for optimized pharmaceutical compositions that provide for enhanced stabilization of preserved therapeutic
20 protein formulations. It is the object of the present invention to comply with this need, both with regard to non half-life extended bispecific antibody constructs and half-life extended bispecific antibody constructs such as of bispecific T cell engagers comprising a half-life extending modality such as Fc-molecules.

SUMMARY

25 **[12]** The safe, quantitative and optionally prolonged administration of protein-based pharmaceuticals such as bispecific antibody constructs including bispecific T cell engaging antibody constructs, typically via the i.v. route, is challenging. To this end, in the context of the present disclosure, a pharmaceutical composition is provided, comprising

- 30 i. a bispecific antibody construct, binding to a target cell surface antigen via a first binding domain and to the T cell surface antigen CD3 via a second binding domain, wherein the chain antibody construct is present in a concentration in the range from 0.5 $\mu\text{g/ml}$ to 20 mg/ml, preferably 0.5 $\mu\text{g/ml}$ to 10 or 5 mg/ml.

- ii. at least one preservative selected from benzyl alcohol, chlorobutanol, phenol, meta-cresol, methylparaben, phenoxyethanol, propylparaben and thiomerosal at a concentration effective to inhibit the growth of microbes,
- iii. a diluent, wherein the bispecific antibody construct is stable.

5 **[12a]** In one aspect, the present disclosure refers to a pharmaceutical composition comprising

- i. a bispecific antibody construct, binding to a target cell surface antigen via a first binding domain and to the T cell surface antigen CD3 via a second binding domain, wherein the chain antibody construct is present in a concentration in the range from 0.5 µg/ml to 20 mg/ml, preferably 0.5 µg/ml to 10 or 5 mg/ml.

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- ii. at least one preservative selected from benzyl alcohol, chlorobutanol, meta-cresol, methylparaben, phenoxyethanol, propylparaben and thiomerosal at a concentration effective to inhibit the growth of microbes, wherein the at least one preservative is present in a concentration in the range 0.009 to 0.9% (w/v), preferably 0.11 to 0.9% or 0.5 to 0.75% (w/v).

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- iii. a diluent, wherein the diluent is a buffer comprising a salt selected from the group consisting of phosphate, acetate, citrate, succinate and tartrate, and/or wherein the buffer comprises histidine, glycine, TRIS glycine, Tris, or mixtures thereof, wherein the bispecific antibody construct is stable.

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[12b] In another aspect, the present disclosure refers to a method of preparing the pharmaceutical composition as described herein, wherein the bispecific antibody construct is provided as a lyophilisate, the lyophilisate preferably comprising a lyoprotector, a buffer and/or a surfactant, and wherein the lyophilisate is reconstituted by a diluent, comprising a preservative and preferably comprising a buffer and/or an excipient as described herein.

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[12c] In yet another aspect, the present disclosure refers to the use of the pharmaceutical composition as described herein, in the manufacture of a medicament for treating of a malignant disease.

[12d] In yet another aspect, the present disclosure refers to a kit comprising the bispecific antibody construct as a lyophilisate, the lyophilisate preferably comprising a lyoprotector, a buffer and/or a surfactant, and a diluent, comprising a preservative and preferably comprising a buffer and/or an excipient as described herein.

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[13] It is envisaged in the context of the present disclosure that the bispecific antibody construct is present at a concentration in the range selected from the list consisting of

(a) 0.5 to 200 µg/ml at a pH of 6.5 to 7.5, or

(b) 0.5 to 1000 µg/ml at a pH of 4.0 to 6.0, or

5 (c) 0.5 µg to 2 mg in the presence of a CD3 binding domain stabilizing agent, preferably citrate, at a pH of 4.0 to 7.5 or

(d) 0.5 µg to 20 mg, preferably 0.5 µg to 10 or 5 mg/ml at a pH of 4.0 to 7.5, wherein the bispecific antibody comprises a third binding domain which comprises two polypeptide monomers, each comprising a hinge, a CH2 and a CH3 domain, wherein
10 said two polypeptide monomers are fused to each other via a peptide linker, and wherein said third binding domain comprises in an amino to carboxyl order:

[14] hinge-CH2-CH3-linker-hinge-CH2-CH3.

[15] It is also envisaged in the context of the present disclosure that the pharmaceutical composition comprises a bispecific antibody construct which is a bispecific single chain
15 antibody construct.

[16] It is further envisaged in the context of the present disclosure that the bispecific antibody construct is present in a concentration in the range of 1.0 to 20 mg/ml, or 1.0 to 10 mg/ml, or 1.0 µg/ml to 5 mg/ml or 1.0 µg/ml to 4 mg/ml or 1.0 µg/ml to 3 mg/ml, or 1.0 µg/ml to 2 mg/ml or 1.0 µg/ml to 1 mg/ml or 1.5 to 5 mg/ml or 1.5 µg/ml to 4 mg/ml or 1.5 µg/ml to
20 3 mg/ml, or 1.5 µg/ml to 2 mg/ml or 1.5 µg/ml to 1 mg/ml or 1.5 to 200 µg/ml.

[17] It is also envisaged in the context of the present disclosure that the at least one preservative is present in a concentration in the range from 0.001 to 1.0% (w/v).

[18] It is even more envisaged in the context of the present disclosure that the preservative is present in a concentration in the range from 0.009 to 0.9% (w/v), preferably
25 0.11 to 0.9%, or 0.5 to 0.75% (w/v) or 0.6 to 0.74% (w/v).

[19] It is envisaged in the context of the present disclosure that the diluent is a buffer comprising a salt selected from the group consisting of phosphate, acetate, citrate, succinate and tartrate, and/or wherein the buffer comprises histidine, glycine, TRIS glycine, Tris, or mixtures thereof.

[20] It is further envisaged in the context of the present disclosure that the diluent is a buffer selected from the group consisting of potassium phosphate, acetic acid/sodium acetate, citric acid/sodium citrate, succinic acid/sodium succinate, tartaric acid/sodium tartrate, and histidine/histidine HCl or mixtures thereof.

5 **[21]** It is also envisaged in the context of the present disclosure that the diluent is a buffer present at a concentration in the range of 0.1 to 150 mM, preferably in the range of 0.25 to 50 mM.

[22] It is even more envisaged in the context of the present disclosure that the diluent is a buffer comprising citrate at a concentration the range of 0.25 to 50 mM.

10 **[23]** It is envisaged in the context of the present disclosure that the pH of the composition is in the range of 4.0 to 8.0, preferably in the range of pH 4.0 to 5.0 or pH 6.5 to 7.5, or preferably at pH 7.0.

[24] It is further envisaged in the context of the present disclosure that the pharmaceutical composition further comprises one or more excipients selected from the group consisting of
15 sucrose, trehalose, mannitol, sorbitol, arginine, lysine, polysorbate 20, polysorbate 80, poloxamer 188, pluronic and combinations thereof.

[25] It is also envisaged in the context of the present disclosure that the pharmaceutical composition further comprises polysorbate, preferably polysorbate 80, and/or lysine HCL.

[26] It is further envisaged in the context of the present disclosure that the pharmaceutical
20 composition does not comprise polysorbate, preferably polysorbate 80, and/or lysine HCL if the concentration of the bispecific antibody construct is at least 10 µg/ml, preferably 15 µg/ml or 20 µg/ml.

[27] It is even more envisaged in the context of the present disclosure that the first binding domain of the bispecific antibody construct binds to at least one target cell surface antigen
25 selected from the group consisting of CD19, CD33, EGFRvIII, MSLN, CDH19, FLT3, DLL3, CDH3, BCMA and PSMA.

[28] It is envisaged in the context of the present disclosure that the first binding domain comprises a VH region comprising CDR-H1, CDR-H2 and CDR-H3 and a VL region comprising CDR-L1, CDR-L2 and CDR-L3 selected from the group consisting of:

30 (a) CDR-H1 as depicted in SEQ ID NO: 1, CDR-H2 as depicted in SEQ ID NO: 2, CDR-H3 as depicted in SEQ ID NO: 3, CDR-L1 as depicted in SEQ ID NO: 4, CDR-L2 as depicted in SEQ ID NO: 5 and CDR-L3 as depicted in SEQ ID NO: 6,

- (b) CDR-H1 as depicted in SEQ ID NO: 29, CDR-H2 as depicted in SEQ ID NO: 30, CDR-H3 as depicted in SEQ ID NO: 31, CDR-L1 as depicted in SEQ ID NO: 34, CDR-L2 as depicted in SEQ ID NO: 35 and CDR-L3 as depicted in SEQ ID NO: 36,
- (c) CDR-H1 as depicted in SEQ ID NO: 42, CDR-H2 as depicted in SEQ ID NO: 43,
5 CDR-H3 as depicted in SEQ ID NO: 44, CDR-L1 as depicted in SEQ ID NO: 45, CDR-L2 as depicted in SEQ ID NO: 46 and CDR-L3 as depicted in SEQ ID NO: 47,
- (d) CDR-H1 as depicted in SEQ ID NO: 53, CDR-H2 as depicted in SEQ ID NO: 54, CDR-H3 as depicted in SEQ ID NO: 55, CDR-L1 as depicted in SEQ ID NO: 56, CDR-L2 as depicted in SEQ ID NO: 57 and CDR-L3 as depicted in SEQ ID NO: 58,
- 10 (e) CDR-H1 as depicted in SEQ ID NO: 65, CDR-H2 as depicted in SEQ ID NO: 66, CDR-H3 as depicted in SEQ ID NO: 67, CDR-L1 as depicted in SEQ ID NO: 68, CDR-L2 as depicted in SEQ ID NO: 69 and CDR-L3 as depicted in SEQ ID NO: 70,
- (f) CDR-H1 as depicted in SEQ ID NO: 83, CDR-H2 as depicted in SEQ ID NO: 84, CDR-H3 as depicted in SEQ ID NO: 85, CDR-L1 as depicted in SEQ ID NO: 86, CDR-L2 as
15 depicted in SEQ ID NO: 87 and CDR-L3 as depicted in SEQ ID NO: 88,
- (g) CDR-H1 as depicted in SEQ ID NO: 94, CDR-H2 as depicted in SEQ ID NO: 95, CDR-H3 as depicted in SEQ ID NO: 96, CDR-L1 as depicted in SEQ ID NO: 97, CDR-L2 as depicted in SEQ ID NO: 98 and CDR-L3 as depicted in SEQ ID NO: 99,
- (h) CDR-H1 as depicted in SEQ ID NO: 105, CDR-H2 as depicted in SEQ ID NO: 106,
20 CDR-H3 as depicted in SEQ ID NO: 107, CDR-L1 as depicted in SEQ ID NO: 109, CDR-L2 as depicted in SEQ ID NO: 110 and CDR-L3 as depicted in SEQ ID NO: 111,
- (i) CDR-H1 as depicted in SEQ ID NO: 115, CDR-H2 as depicted in SEQ ID NO: 116, CDR-H3 as depicted in SEQ ID NO: 117, CDR-L1 as depicted in SEQ ID NO: 118, CDR-L2 as depicted in SEQ ID NO: 119 and CDR-L3 as depicted in SEQ ID NO: 120,
- 25 (j) CDR-H1 as depicted in SEQ ID NO: 126, CDR-H2 as depicted in SEQ ID NO: 127, CDR-H3 as depicted in SEQ ID NO: 128, CDR-L1 as depicted in SEQ ID NO: 129, CDR-L2 as depicted in SEQ ID NO: 130 and CDR-L3 as depicted in SEQ ID NO: 131,
- (k) CDR-H1 as depicted in SEQ ID NO: 137, CDR-H2 as depicted in SEQ ID NO: 138, CDR-H3 as depicted in SEQ ID NO: 139, CDR-L1 as depicted in SEQ ID NO: 140, CDR-L2
30 as depicted in SEQ ID NO: 141 and CDR-L3 as depicted in SEQ ID NO: 142,
- (l) CDR-H1 as depicted in SEQ ID NO: 152, CDR-H2 as depicted in SEQ ID NO: 153, CDR-H3 as depicted in SEQ ID NO: 154, CDR-L1 as depicted in SEQ ID NO: 155, CDR-L2 as depicted in SEQ ID NO: 156 and CDR-L3 as depicted in SEQ ID NO: 157, and

(m) CDR-H1 as depicted in SEQ ID NO: 167, CDR-H2 as depicted in SEQ ID NO: 168, CDR-H3 as depicted in SEQ ID NO: 169, CDR-L1 as depicted in SEQ ID NO: 107, CDR-L2 as depicted in SEQ ID NO: 171 and CDR-L3 as depicted in SEQ ID NO: 172.

5 **[29]** It is further envisaged in the context of the present disclosure that the bispecific antibody construct is provided with a half-life extending (HLE) moiety, preferably a scFc domain.

[30] It is also envisaged in the context of the present disclosure that the pharmaceutical composition is liquid, lyophilized or frozen liquid.

10 **[31]** It is even more envisaged in the context of the present disclosure that the composition comprises < 5% of multimers of the bispecific antibody construct, preferably < 1%.

[32] It is envisaged in the context of the present disclosure that the multimers are dimers.

15 **[33]** It is further envisaged in the context of the present disclosure that the composition comprises < 5% of multimers of the bispecific antibody construct, preferably < 1% for a time period of at least 4 days, preferably at least 10 days, more preferably at least 14 days at room temperature.

[34] It is also envisaged in the context of the present disclosure that the pharmaceutical composition is filled in a plastic administration container preferably made of EVA, polyolefin, and/or PVC.

20 **[35]** It is even more envisaged in the context of the present disclosure that the bispecific single chain antibody construct is recovered by at least 90%, preferably at least 95, 96, 97, 98 or even at least 99% from the dilution from the plastic administration container comprising at least one of the buffers and/or excipients as described herein.

25 **[36]** It is envisaged in the context of the present disclosure that the pharmaceutical composition comprises at least 0.25 mM citrate, at least 0.0125 mM lysine and/or at least 0.001% polysorbate 80 at a pH of 6.5 to 7.5.

[37] It is further envisaged that the pharmaceutical composition in the context of the present disclosure is a storage solution stored at -50°C, preferably at -40, -30°C or -20°C.

30 **[38]** It is also envisaged in the context of the present disclosure that the pharmaceutical composition provided as a storage solution stored at -50°C, preferably at -40, -30°C or -20°C comprises the bispecific antibody comprising a third binding domain which comprises two

polypeptide monomers, each comprising a hinge, a CH2 and a CH3 domain, wherein said two polypeptide monomers are fused to each other via a peptide linker, and wherein said third binding domain comprises in an amino to carboxyl order:

hinge-CH2-CH3-linker-hinge-CH2-CH3.

5 **[39]** It is further envisaged in the context of the present disclosure that the bispecific antibody construct is provided as a lyophilisate, the lyophilisate preferably comprising a lyoprotector, a buffer and/or a surfactant, and wherein the lyophilisate is reconstituted by a diluent, comprising a preservative and preferably comprising a buffer and/or an excipient.

10 **[40]** It is especially envisaged in the context of the present disclosure that the pharmaceutical composition is stored until use as solution, as solution in frozen state or as lyophilisate, and is then administered, optionally after dilution or reconstitution, without the need of adding further excipients selected from preservatives, stabilizers or surfactants.

[41] It is also envisaged in the context of the present disclosure that the pharmaceutical composition is for use in the treatment of a malignant disease.

15 **[42]** Even more envisaged in the context of the present disclosure is a method for the treatment or amelioration of a malignant disease, comprising the step of administering to a subject in need thereof the pharmaceutical composition according to the present disclosure, or produced according to the method of the present disclosure.

20 **[43]** It is envisaged in the context of the present disclosure that the pharmaceutical composition according to the present disclosure is administered intravenously, preferably continuously, for 1 to 24 hours, preferably 1 to 10 or 2 to 5 hours.

[44] It is further envisaged in the context of the present disclosure that the pharmaceutical composition according to the present disclosure is administered intravenously continuously for 2 to 14 days, preferably for 2 to 10 days, most preferably for 4 to 7 days.

25 **[45]** Also envisaged in the context of the present disclosure is a kit comprising the bispecific antibody construct as a lyophilisate, the lyophilisate preferably comprising a lyoprotector, a buffer and/or a surfactant, and a diluent, comprising a preservative and preferably comprising a buffer and/or an excipient according to the present disclosure.

DESCRIPTION OF THE FIGURES

[46] Figure 1: Stability diagram as per percentile high molecular weight (HMW) species of CD19xCD3 bispecific antibody constructs as determined by SEC-HPLC for preservatives chlorobutanol, methylparaben, phenol and thiomerosal at 25°C and pH 4.

[47] Figure 2: Stability diagram as per percentile high molecular weight (HMW) species of CD19xCD3 bispecific antibody constructs as determined by SEC-HPLC for preservative benzyl alcohol depending on CD19xCD3 bispecific antibody constructs concentration at 25°C and pH 7.

[48] Figure 3: Stability diagram as per percentile main peak (A) and high molecular weight (HMW) species of CD19xCD3 bispecific antibody constructs as determined by SEC-HPLC for preservative benzyl alcohol depending on preservative concentration at 25°C (B), and depending on administration container material (C). Stability diagram as per percentile main peak (monomer) of CD19xCD3 bispecific antibody constructs as determined by SEC-HPLC for preservative benzyl alcohol depending on preservative concentration at 25°C depending on administration container material (D).

[49] Figure 4: Denaturation diagram of CD19xCD3 bispecific antibody constructs at a concentration of 1 mg/ml in presence or absence of preservative benzyl alcohol as determined by fluorescence spectrometry at pH 4.

[50] Figure 5: Microbial growth diagrams for *E. coli* (A), *P. aruginosa* (B), *E. cloace* (C), *S. aureus* (D), *M. luteus* (E) and *C. albicans* (F) in formulations comprising CD19xCD3 bispecific antibody constructs and 0, 0.5, 0.6 or 0.7% benzyl alcohol.

[51] Figure 6: Stabilization effects of citrate –where applicable in the presence of benzyl alcohol- on FAP α (A), anti-CD3 domain wherein the peptide 108-112 in anti-CD3 domain (YISYW) corresponds to the peptide 367-370 in FAP α (B), CD33xCD3 bispecific antibody constructs wherein the peptide 364-368 in CD33xCD3 bispecific antibody constructs (YISYW) corresponds to the peptide 366-370 in FAP α (C), and EGFRvIIIxCD3 bispecific antibody constructs wherein the peptide 365-369 in EGFRvIIIxCD3 bispecific antibody constructs (YISYW) corresponds to the peptide 366-370 in FAP α (D). Figures 6E and F show the effect of citrate and benzyl alcohol individually and Figures 6G and H in combination, each at a bispecific antibody construct or single domain concentration of 600 μ g/ml each. The results are the same for anti-CD3 domain, CD33xCD3 bispecific antibody constructs, FAP α , and EGFRvIIIxCD3 bispecific antibody constructs.

Claims

1. A pharmaceutical composition comprising
 - i. a bispecific antibody construct, binding to a target cell surface antigen via a first binding domain and to the T cell surface antigen CD3 via a second binding domain, wherein the chain antibody construct is present in a concentration in the range from 0.5 µg/ml to 20 mg/ml, preferably 0.5 µg/ml to 10 or 5 mg/ml.
 - ii. at least one preservative selected from benzyl alcohol, chlorobutanol, meta-cresol, methylparaben, phenoxyethanol, propylparaben and thiomerosal at a concentration effective to inhibit the growth of microbes, wherein the at least one preservative is present in a concentration in the range 0.009 to 0.9% (w/v), preferably 0.11 to 0.9% or 0.5 to 0.75% (w/v).
 - iii. a diluent, wherein the diluent is a buffer comprising a salt selected from the group consisting of phosphate, acetate, citrate, succinate and tartrate, and/or wherein the buffer comprises histidine, glycine, TRIS glycine, Tris, or mixtures thereof, wherein the bispecific antibody construct is stable
2. The pharmaceutical composition according to claim 1, wherein the bispecific antibody construct is present at a concentration in the range selected from the group consisting of
 - (a) 0.5 to 200 µg/ml at a pH of 6.5 to 7.5, or
 - (b) 0.5 to 1000 µg/ml at a pH of 4.0 to 6.0, or
 - (c) 0.5 µg to 2 mg in the presence of a CD3 binding domain stabilizing agent, preferably citrate, at a pH of 4.0 to 7.5 or
 - (d) 0.5 µg to 20 mg, preferably 0.05 µg/ml to 10 or 5 mg/ml, at a pH of 4.0 to 7.5,, preferably 4.0 to 6.0, wherein the bispecific antibody comprises a third binding domain which comprises two polypeptide monomers, each comprising a hinge, a CH2 and a CH3 domain, wherein said two polypeptide monomers are fused to each other via a peptide linker, and wherein said third binding domain comprises in an amino to carboxyl order:

hinge-CH2-CH3-linker-hinge-CH2-CH3.
3. The pharmaceutical composition according to claim 1, wherein the bispecific antibody construct is a bispecific single chain antibody construct.

4. The pharmaceutical composition according to claim 1, wherein the diluent is a buffer selected from the group consisting of potassium phosphate, acetic acid/sodium acetate, citric acid/sodium citrate, succinic acid/sodium succinate, tartaric acid/sodium tartrate, and histidine/histidine HCl or mixtures thereof.
5. The pharmaceutical composition according to claim 1, wherein the diluent is a buffer present at a concentration in the range of 0.1 to 150 mM, preferably in the range of 0.25 to 50 mM.
6. The pharmaceutical composition according to claim 1, wherein the diluent is a buffer comprising citrate.
7. The pharmaceutical composition according to claim 1, wherein the diluent is a buffer comprising citrate at a concentration the range of 0.25 to 50 mM.
8. The pharmaceutical composition according to claim 1, wherein the pH of the composition is in the range of 4.0 to 8.0, preferably in the range of pH 4.0 to 5.0 or 6.0 to 7.5, preferably at pH 7.0.
9. The pharmaceutical composition according to claim 1, wherein the pharmaceutical composition further comprises one or more excipients selected from the group consisting of sucrose, trehalose, mannitol, sorbitol, arginine, lysine, polysorbate 20, polysorbate 80, poloxamer 188, pluronic and combinations thereof.
10. The pharmaceutical composition according to claim 9, further comprising polysorbate, preferably polysorbate 80, and/or lysine HCL.
11. The pharmaceutical composition according to claim 9, wherein the composition does not comprise polysorbate, preferably polysorbate 80, and/or lysine HCL if the concentration of bispecific antibody construct is at least 10, 15 or 20 µg/ml, preferably 15 µg/ml.
12. The pharmaceutical composition according to claim 1, wherein the first binding domain of the bispecific antibody construct binds to at least one target cell surface antigen selected from the group consisting of CD19, CD33, EGFRVIII, MSLN, CDH19, FLT3, DLL3, CDH3, BCMA and PSMA.

13. The pharmaceutical composition according to claim 1, wherein the first binding domain comprises a VH region comprising CDR-H1, CDR-H2 and CDR-H3 and a VL region comprising CDR-L1, CDR-L2 and CDR-L3 selected from the group consisting of:
- (a) CDR-H1 as depicted in SEQ ID NO: 1, CDR-H2 as depicted in SEQ ID NO: 2, CDR-H3 as depicted in SEQ ID NO: 3, CDR-L1 as depicted in SEQ ID NO: 4, CDR-L2 as depicted in SEQ ID NO: 5 and CDR-L3 as depicted in SEQ ID NO: 6,
 - (b) CDR-H1 as depicted in SEQ ID NO: 29, CDR-H2 as depicted in SEQ ID NO: 30, CDR-H3 as depicted in SEQ ID NO: 31, CDR-L1 as depicted in SEQ ID NO: 34, CDR-L2 as depicted in SEQ ID NO: 35 and CDR-L3 as depicted in SEQ ID NO: 36,
 - (c) CDR-H1 as depicted in SEQ ID NO: 42, CDR-H2 as depicted in SEQ ID NO: 43, CDR-H3 as depicted in SEQ ID NO: 44, CDR-L1 as depicted in SEQ ID NO: 45, CDR-L2 as depicted in SEQ ID NO: 46 and CDR-L3 as depicted in SEQ ID NO: 47,
 - (d) CDR-H1 as depicted in SEQ ID NO: 53, CDR-H2 as depicted in SEQ ID NO: 54, CDR-H3 as depicted in SEQ ID NO: 55, CDR-L1 as depicted in SEQ ID NO: 56, CDR-L2 as depicted in SEQ ID NO: 57 and CDR-L3 as depicted in SEQ ID NO: 58,
 - (e) CDR-H1 as depicted in SEQ ID NO: 65, CDR-H2 as depicted in SEQ ID NO: 66, CDR-H3 as depicted in SEQ ID NO: 67, CDR-L1 as depicted in SEQ ID NO: 68, CDR-L2 as depicted in SEQ ID NO: 69 and CDR-L3 as depicted in SEQ ID NO: 70,
 - (f) CDR-H1 as depicted in SEQ ID NO: 83, CDR-H2 as depicted in SEQ ID NO: 84, CDR-H3 as depicted in SEQ ID NO: 85, CDR-L1 as depicted in SEQ ID NO: 86, CDR-L2 as depicted in SEQ ID NO: 87 and CDR-L3 as depicted in SEQ ID NO: 88,
 - (g) CDR-H1 as depicted in SEQ ID NO: 94, CDR-H2 as depicted in SEQ ID NO: 95, CDR-H3 as depicted in SEQ ID NO: 96, CDR-L1 as depicted in SEQ ID NO: 97, CDR-L2 as depicted in SEQ ID NO: 98 and CDR-L3 as depicted in SEQ ID NO: 99,
 - (h) CDR-H1 as depicted in SEQ ID NO: 105, CDR-H2 as depicted in SEQ ID NO: 106, CDR-H3 as depicted in SEQ ID NO: 107, CDR-L1 as depicted in SEQ ID NO: 109, CDR-L2 as depicted in SEQ ID NO: 110 and CDR-L3 as depicted in SEQ ID NO: 111,
 - (i) CDR-H1 as depicted in SEQ ID NO: 115, CDR-H2 as depicted in SEQ ID NO: 116, CDR-H3 as depicted in SEQ ID NO: 117, CDR-L1 as depicted in SEQ ID NO: 118, CDR-L2 as depicted in SEQ ID NO: 119 and CDR-L3 as depicted in SEQ ID NO: 120,
 - (j) CDR-H1 as depicted in SEQ ID NO: 126, CDR-H2 as depicted in SEQ ID NO: 127, CDR-H3 as depicted in SEQ ID NO: 128, CDR-L1 as depicted in SEQ ID NO:

- 129, CDR-L2 as depicted in SEQ ID NO: 130 and CDR-L3 as depicted in SEQ ID NO: 131,
- (k) CDR-H1 as depicted in SEQ ID NO: 137, CDR-H2 as depicted in SEQ ID NO: 138, CDR-H3 as depicted in SEQ ID NO: 139, CDR-L1 as depicted in SEQ ID NO: 140, CDR-L2 as depicted in SEQ ID NO: 141 and CDR-L3 as depicted in SEQ ID NO: 142,
- (l) CDR-H1 as depicted in SEQ ID NO: 152, CDR-H2 as depicted in SEQ ID NO: 153, CDR-H3 as depicted in SEQ ID NO: 154, CDR-L1 as depicted in SEQ ID NO: 155, CDR-L2 as depicted in SEQ ID NO: 156 and CDR-L3 as depicted in SEQ ID NO: 157, and
- (m) CDR-H1 as depicted in SEQ ID NO: 167, CDR-H2 as depicted in SEQ ID NO: 168, CDR-H3 as depicted in SEQ ID NO: 169, CDR-L1 as depicted in SEQ ID NO: 170, CDR-L2 as depicted in SEQ ID NO: 171 and CDR-L3 as depicted in SEQ ID NO: 172.
14. The pharmaceutical composition according to claim 1, wherein the pharmaceutical composition is liquid.
15. The pharmaceutical composition according to claim 1, wherein the composition comprises < 5% of multimers of the bispecific antibody construct, preferably < 1%, wherein the multimers are preferably dimers.
16. The pharmaceutical composition according to claim 14, wherein the composition comprises < 5% of multimers of the bispecific antibody construct, preferably < 1% for a time period of at least 4 days, preferably at least 10 days, more preferably at least 14 days at room temperature.
17. The pharmaceutical composition according to claim 1, wherein the pharmaceutical composition is filled in a plastic administration container preferably made of EVA, polyolefin, and/or PVC.
18. The pharmaceutical composition according to claim 17, wherein the bispecific single chain antibody construct is recovered by at least 90%, preferably at least 95, 96, 97, 98 or even at least 99% from the dilution from the plastic administration container comprising at least one of the buffers and/or excipients according to claims 1 or 4 to 10.

19. The pharmaceutical composition according to claim 17, wherein the bispecific single chain antibody construct is recovered by at least 90%, preferably at least 95, 96, 97, 98 or even at least 99% from the dilution from the plastic administration container comprising polysorbate 80.
20. The pharmaceutical composition according to claim 17, wherein the pharmaceutical composition comprises at least 0.25 mM citrate, at least 0.0125 mM lysine and/or at least 0.001% polysorbate 80 at a pH of 6.5 to 7.5.
21. The pharmaceutical composition according to claim 1, wherein the composition is a storage solution stored at -50°C, preferably at -40, -30°C or -20°C.
22. The pharmaceutical composition according to claim 21, wherein the composition comprises the bispecific antibody comprising a third binding domain which comprises two polypeptide monomers, each comprising a hinge, a CH2 and a CH3 domain, wherein said two polypeptide monomers are fused to each other via a peptide linker, and wherein said third binding domain comprises in an amino to carboxyl order:

hinge-CH2-CH3-linker-hinge-CH2-CH3.
23. The pharmaceutical composition according to claim 1, wherein the composition is provided as a lyophilisate for storage.
24. The pharmaceutical composition according to claim 1, wherein said composition is stored until use as solution, as solution in frozen state or as lyophilisate, and is then to be administered, optionally after dilution or reconstitution, without the need of adding further excipients selected from preservatives, stabilizers or surfactants.
25. A method of preparing the pharmaceutical composition according to claim 1, wherein the bispecific antibody construct is provided as a lyophilisate, the lyophilisate preferably comprising a lyoprotector, a buffer and/or a surfactant, and wherein the lyophilisate is reconstituted by a diluent, comprising a preservative and preferably comprising a buffer and/or an excipient according to any of claims 1 or 4 to 10.
26. Use of the pharmaceutical composition according to claim 1, in the manufacture of a medicament for treating of a malignant disease.

27. The pharmaceutical composition according to claim 1, which is to be administered intravenously continuously for 1 to 24 hours, preferably 1 to 10 or 2 to 5 hours, or which is to be administered intravenously continuously for 2 to 14 days, preferably for 2 to 10 days, most preferably for 4 to 7 days.
28. A kit comprising the bispecific antibody construct as a lyophilisate, the lyophilisate preferably comprising a lyoprotector, a buffer and/or a surfactant, and a diluent, comprising a preservative and preferably comprising a buffer and/or an excipient according to any of claims 6 to 13.