CLAIMS

1. Therapeutic combination for use as a medicament, wherein the therapeutic combination comprises:

(a) a first pharmaceutical composition comprising a first proteinaceous molecule comprising a first binding site for binding to a first cell-surface molecule and at least one saponin covalently bound to said first proteinaceous molecule preferably covalently bound to an amino-acid residue of said first proteinaceous molecule, the first pharmaceutical composition optionally further comprising a pharmaceutically acceptable excipient; and

(b) a second pharmaceutical composition comprising a second proteinaceous molecule different from the first proteinaceous molecule, the second proteinaceous molecule comprising a second binding site for binding to a second cell-surface molecule different from the first cell-surface molecule and an effector moiety defined as a pharmaceutically active substance, the second pharmaceutical composition optionally further comprising a pharmaceutically acceptable excipient,

wherein the at least one saponin is a triterpenoid saponin or a bisdesmosidic triterpene saponin, belonging to the type of a 12,13-dehydrooleanane with an aldehyde function in position C-23, and wherein the first binding site of the first proteinaceous molecule comprises or consists of an immunoglobulin or at least one binding fragment or –domain of said immunoglobulin for binding to the first cell-surface molecule, such as any one or more of an antibody, an IgG, a molecule comprising or consisting of a Vhh domain or Vh domain, a Fab, an scFv, an Fv, a dAb, an F(ab)2, Fcab fragment, and/or comprises or consists of at least one ligand, preferably at least one ligand for binding to the first cell-surface molecule such as EGF or a cytokine, and wherein and the second binding site of the second proteinaceous molecule comprises or consists of an immunoglobulin or at least one binding fragment or –domain of said immunoglobulin for binding to the first cell-surface molecule, such as any one or more of an antibody, an IgG, a molecule comprising or consisting of a Vhh domain or Vh domain, a Fab, an scFv, an Fv, a dAb, an F(ab)2, Fcab fragment, and/or comprises or consists of at least one ligand, preferably at least one ligand for binding to the first cell-surface molecule such as EGF or a cytokine.

2. The therapeutic combination of claim 1, wherein the second pharmaceutical composition and the first pharmaceutical composition are to be administered to a patient in need thereof, wherein the first cell-surface molecule is a first tumor cell-surface molecule, preferably first tumor cell-specific surface molecule, and the second cell-surface molecule is a second tumor cell-surface molecule, preferably second tumor cell-specific surface molecule, and wherein the second tumor cell-surface molecule is different from the first tumor cell-surface molecule, preferably the second tumor cell-specific surface molecule is different from the first tumor cell-specific surface molecule.

3. The therapeutic combination for use of claim 2, wherein the first binding site for binding to the first tumor cell-surface molecule, preferably a tumor cell-specific surface molecule, is a first binding site for a first cell-surface receptor present at a tumor cell, preferably specifically present at a tumor cell.

4. The therapeutic combination for use of any one of the preceding claims, wherein the at least one saponin is a triterpenoid saponin or a bisdesmosidic triterpene saponin, belonging to the type of a 12,13-dehydrooleanane with an aldehyde function in position C-23 and comprising a glucuronic acid function in a carbohydrate substituent at the C-3beta-OH group of the saponin, and/or a saponin isolated from a *Gypsophila* species and/or a *Saponaria* species and/or an *Agrostemma* species and/or a *Quillaja* species such as *Quillaja saponaria*.

5. The therapeutic combination for use of any one of the preceding claims, wherein the at least one saponin is SO1861 and/or QS-21.

6. The therapeutic combination for use of any one of the preceding claims, wherein the at least one saponin is a bisdesmosidic triterpene saponin belonging to the type of a 12,13-dehydrooleanane with an aldehyde function in position C-23 , wherein the saponin is covalently coupled the first proteinaceous molecule, preferably covalently coupled to an amino-acid residue of the first proteinaceous molecule, via an aldehyde function in the saponin, preferably said aldehyde function in position C-23, preferably via at least one linker, and/or via at least one cleavable linker, wherein the amino-acid residue preferably is selected from cysteine and lysine.

7. The therapeutic combination for use of claim 6, wherein the aldehyde function in position C-23 of the at least one saponin is covalently coupled to linker N-ε-maleimidocaproic acid hydrazide, which linker is covalently coupled via a thio-ether bond to a sulfhydryl group in the first proteinaceous molecule, such as a sulfhydryl group of a cysteine.

8. The therapeutic combination for use of any one of the preceding claims, wherein the at least one saponin is a bisdesmosidic triterpene saponin belonging to the type of a 12,13-dehydrooleanane with an aldehyde function in position C-23 and comprising a glucuronic acid function in a carbohydrate substituent at the C-3beta-OH group of the saponin, wherein the saponin is covalently coupled to an amino-acid residue of the first proteinaceous molecule via the glucuronic acid function in the carbohydrate substituent at the C-3beta-OH group of the saponin, preferably via at least one linker, wherein the amino-acid residue preferably is selected from cysteine and lysine.

9. The therapeutic combination for use of claim 8, wherein the glucuronic acid function in the carbohydrate substituent at the C-3beta-OH group of the at least one saponin is covalently coupled to linker 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate, which linker is covalently coupled via an amide bond to an amine group in the first proteinaceous molecule, such as an amine group of a lysine or an N-terminus of the first proteinaceous molecule.

10. The therapeutic combination for use of claim 2, wherein the second binding site for binding to the second tumor cell-surface molecule, preferably the second tumor cell-specific surface molecule, is a

second binding site for a second cell-surface receptor present at a tumor cell, preferably specifically present at a tumor cell.

11. The therapeutic combination for use of any one of the preceding claims, wherein the first binding site and the second binding site are binding sites for binding to a first and second tumor-cell receptor respectively, preferably for binding to a first and second tumor-cell specific receptor respectively, preferably present at the same tumor cell, and wherein the first and second tumor-cell receptor are preferably tumor-cell specific receptors, and/or are selected from CD71, CA125, EpCAM(17-1A), CD52, CEA, CD44v6, FAP, EGF-IR, integrin, syndecan-1, vascular integrin alpha-V beta-3, HER2, EGFR, CD20, CD22, Folate receptor 1, CD146, CD56, CD19, CD138, CD27L receptor, PSMA, CanAg, integrin-alphaV, CA6, CD33, mesothelin, Cripto, CD3, CD30, CD239, CD70, CD123, CD352, DLL3, CD25, ephrinA4, MUC1, Trop2, CEACAM5, CEACAM6, HER3, CD74, PTK7, Notch3, FGF2, C4.4A, FLT3, CD38, FGFR3, CD7, PD-L1, CTLA4, CD52, PDGFRA, VEGFR1, VEGFR2, more preferably selected from HER2, CD71 and EGFR, with the proviso that the first binding site is different from the second binding site and with the proviso that the first and second tumor-cell specific receptor, preferably the first and second tumor-cell specific receptor, are different receptors.

12. The therapeutic combination for use of any one of the preceding claims, wherein the first proteinaceous molecule and the second proteinaceous molecule comprise or consist of cetuximab, daratumumab, gemtuzumab, trastuzumab, panitumumab, brentuximab, inotuzumab, moxetumomab, polatuzumab, obinutuzumab, OKT-9 anti-CD71 monoclonal antibody of the IgG type, pertuzumab, rituximab, ofatumumab, Herceptin, alemtuzumab, pinatuzumab, OKT-10 anti-CD38 monoclonal antibody, an antibody of Table A2 or Table A3 or Table A4, preferably cetuximab or trastuzumab or OKT-9, or at least one tumor-cell receptor binding-domain thereof and/or at least one tumor-cell receptor binding-fragment thereof, with the proviso that the first binding site is different from the second binding site.

13. The therapeutic combination for use of any one of the preceding claims, wherein the effector moiety, comprised by the second proteinaceous molecule, comprises or consists of at least one of an oligonucleotide, a nucleic acid and a xeno nucleic acid, preferably selected from any one or more of a vector, a gene, a cell suicide inducing transgene, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), anti-sense oligonucleotide (ASO, AON), short interfering RNA (siRNA), microRNA (miRNA), DNA aptamer, RNA aptamer, mRNA, mini-circle DNA, peptide nucleic acid (PNA), phosphoramidate morpholino oligomer (PMO), locked nucleic acid (LNA), bridged nucleic acid (BNA), 2’-deoxy-2’-fluoroarabino nucleic acid (FANA), 2’-O-methoxyethyl-RNA (MOE), 2'-O,4'-aminoethylene bridged nucleic acid, 3’-fluoro hexitol nucleic acid (FHNA), a plasmid, glycol nucleic acid (GNA) and threose nucleic acid (TNA), or a derivative thereof, more preferably a BNA, for example a BNA for silencing HSP27 protein expression.

14. The therapeutic combination for use of any one of the preceding claims, wherein the effector moiety that is comprised by the second proteinaceous molecule comprises or consists of at least one proteinaceous molecule selected from any one or more of an enzyme such as urease and Cre-recombinase, a protein toxin, a ribosome-inactivating protein, a protein toxin selected from Table A5 and/or a bacterial toxin and a plant toxin.

15. The therapeutic combination for use of any one of the preceding claims wherein the effector moiety that is comprised by the second proteinaceous molecule comprises or consists of at least one proteinaceous molecule selected from any one or more of a viral toxin such as apoptin; a bacterial toxin such as Shiga toxin, Shiga-like toxin, Pseudomonas aeruginosa exotoxin (PE) or exotoxin A of PE, full-length or truncated diphtheria toxin (DT), cholera toxin; a fungal toxin such as alpha-sarcin; a plant toxin including ribosome-inactivating proteins and the A chain of type 2 ribosome-inactivating proteins such as dianthin e.g. dianthin-30 or dianthin-32, saporin e.g. saporin-S3 or saporin-S6, bouganin or de-immunized derivative debouganin of bouganin, shiga-like toxin A, pokeweed antiviral protein, ricin, ricin A chain, modeccin, modeccin A chain, abrin, abrin A chain, volkensin, volkensin A chain, viscumin, viscumin A chain; or an animal or human toxin such as frog RNase, or granzyme B or angiogenin from humans, or any fragment or derivative thereof; preferably the protein toxin is dianthin and/or saporin.

16. The therapeutic combination for use of any one of the claims 1-15, wherein the effector moiety, that is comprised by the second proteinaceous molecule, comprises or consists of at least one payload, preferably selected from any one or more of a toxin targeting ribosomes, a toxin targeting elongation factors, a toxin targeting tubulin, a toxin targeting DNA and a toxin targeting RNA, more preferably any one or more of emtansine, pasudotox, maytansinoid derivative DM1, maytansinoid derivative DM4, monomethyl auristatin E (MMAE, vedotin), monomethyl auristatin F (MMAF, mafodotin), a Calicheamicin, N-Acetyl-γ-calicheamicin, a pyrrolobenzodiazepine (PBD) dimer, a benzodiazepine, a CC-1065 analogue, a duocarmycin, Doxorubicin, paclitaxel, docetaxel, cisplatin, cyclophosphamide, etoposide, docetaxel, 5-fluorouracyl (5-FU), mitoxantrone, a tubulysin, an indolinobenzodiazepine, AZ13599185, a cryptophycin, rhizoxin, methotrexate, an anthracycline, a camptothecin analogue, SN-38, DX-8951f, exatecan mesylate, truncated form of *Pseudomonas aeruginosa* exotoxin (PE38), a Duocarmycin derivative, an amanitin, α-amanitin, a spliceostatin, a thailanstatin, ozogamicin, tesirine, Amberstatin269 and soravtansine, or a derivative thereof.

17. The therapeutic combination for use of any one of the preceding claims, wherein the effector moiety, that is comprised by the second proteinaceous molecule is any one of the effector moieties of claim 13 or any one of the effector moieties of claims 14-16.

18. The therapeutic combination for use of any one of the preceding claims, wherein the second proteinaceous molecule comprises or consists of any one of Gemtuzumab ozogamicin, Brentuximab vedotin, Trastuzumab emtansine, Inotuzumab ozogamicin, Moxetumomab pasudotox and Polatuzumab vedotin and an antibody-drug conjugate of Table A2 and Table A3, or at least one tumor-cell receptor

binding-domain thereof and/or at least one tumor-cell receptor binding-fragment thereof, wherein said domain(s) or fragment(s) comprise(s) the effector moiety and are preferably (a) tumor-cell specific receptor binding-domain(s) and/or (a) tumor-cell specific receptor binding-fragment(s).

19. The therapeutic combination for use of any one of the preceding claims, wherein the first proteinaceous molecule comprises more than one covalently bound saponin, preferably 2, 3, 4, 5, 6, 8, 10, 16, 32, 64, 128 or 1-100 saponins, or any number of saponins therein between, such as 7, 9, 12 saponins.

20. The therapeutic combination for use of claim 19, wherein the more than one covalently bound saponin are covalently bound directly to an amino-acid residue of the first proteinaceous molecule, preferably to a cysteine and/or to a lysine, and/or are covalently bound via at least one linker and/or via at least one cleavable linker and/or via at least one oligomeric or polymeric scaffold, preferably 1-8 of such scaffolds or 2-4 of such scaffolds, wherein the at least one scaffold is optionally based on a dendron, wherein 1-32 saponins, preferably 2, 3, 4, 5, 6, 8, 10, 16, 32 saponins, or any number of saponins therein between, such as 7, 9, 12 saponins, are covalently bound to the at least one scaffold.

21. The therapeutic combination for use of any one of the claims 6-20, wherein the cleavable linker is subject to cleavage under acidic conditions, reductive conditions, enzymatic conditions or light-induced conditions, and preferably the cleavable linker comprises a cleavable bond selected from a hydrazone bond and a hydrazide bond subject to cleavage under acidic conditions, and/or a bond susceptible to proteolysis, for example proteolysis by Cathepsin B, and/or a bond susceptible for cleavage under reductive conditions such as a disulphide bond.

22. The therapeutic combination for use of any one of the claims 6-21, wherein the cleavable linker is subject to cleavage *in vivo* under acidic conditions as present in endosomes and/or lysosomes of mammalian cells, preferably human cells, preferably at pH 4.0 – 6.5, and more preferably at pH $\leq$ 5.5.

23. The therapeutic combination for use of any one of the claims 20-22, wherein the oligomeric or polymeric scaffold comprises a polymeric or oligomeric structure and comprises at least one chemical group, the at least one chemical group for covalently coupling of the scaffold to the amino-acid residue of said first proteinaceous molecule.

24. The therapeutic combination for use of any one of the claims 20-23, wherein the at least one saponin is covalently bound to the polymeric or oligomeric structure of the scaffold via a cleavable linker according to any one of the claims 20-23.

25. The therapeutic combination for use of any one of the claims 20-24, wherein the at least one saponin is covalently bound to the polymeric or oligomeric structure of the scaffold via any one or more of an imine bond, a hydrazone bond, a hydrazide bond, an oxime bond, a 1,3-dioxolane bond, a disulphide

bond, a thio-ether bond, an amide bond, a peptide bond or an ester bond, preferably via at least one linker.

26. The therapeutic combination for use of any one of the claims 20-25, wherein the at least one saponin comprises an aldehyde function in position C-23 and optionally a glucuronic acid function in the carbohydrate substituent at the C-3beta-OH group of the at least one saponin, which aldehyde function is involved in the covalent bonding to the polymeric or oligomeric structure of the scaffold, and/or, if present, the glucuronic acid function is involved in the covalent bonding to the polymeric or oligomeric structure of the scaffold, either via direct binding or via at least one linker.

27. The therapeutic combination for use of claim 26, wherein the aldehyde function in position C-23 of the at least one saponin is covalently coupled to linker N-ε-maleimidocaproic acid hydrazide, which linker is covalently coupled via a thio-ether bond to a sulfhydryl group in the polymeric or oligomeric structure of the scaffold, such as a sulfhydryl group of a cysteine.

28. The therapeutic combination for use of claim 26 or 27, wherein the glucuronic acid function in the carbohydrate substituent at the C-3beta-OH group of the at least one saponin is covalently coupled to linker 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate, which linker is covalently coupled via an amide bond to an amine group in the polymeric or oligomeric structure of the scaffold, such as an amine group of a lysine or an N-terminus of a proteinaceous molecule.

29. The therapeutic combination for use of any one of the claims 20-28, wherein the chemical group of the polymeric or oligomeric scaffold, for covalently coupling of the scaffold to the amino-acid residue of the first proteinaceous molecule, is a click chemistry group, preferably selected from a tetrazine, an azide, an alkene or an alkyne, or a cyclic derivative of these groups, more preferably the click chemistry group is an azide.

30. The therapeutic combination for use of any one of the claims 20-29, wherein the polymeric or oligomeric structure of the scaffold comprises a linear, branched and/or cyclic polymer, oligomer, dendrimer, dendron, dendronized polymer, dendronized oligomer, a DNA, a polypeptide, poly-lysine, a poly-ethylene glycol, or an assembly of these polymeric or oligomeric structures which assembly is preferably built up by covalent cross-linking.

31. The therapeutic combination for use of any one of the preceding claims, wherein the first pharmaceutical composition and the second pharmaceutical composition are to be administered to a patient in need thereof.

32. Use of a therapeutic combination in the manufacture of a medicament for the treatment or prevention of cancer in a human subject, wherein the therapeutic combination comprises:

(a) the first pharmaceutical composition as defined in claim 1, wherein the first cell-surface molecule is a first tumor cell-surface molecule, preferably a first tumor cell-specific surface molecule; and

(b) the second pharmaceutical composition as defined in claim 1, wherein the second cell-surface molecule is a second tumor cell-surface molecule different from the first tumor cell-surface molecule, preferably the second cell-surface molecule is a second tumor cell-specific surface molecule different from the first tumor cell-specific surface molecule.