

COMBINATION TREATMENT

FIELD OF THE INVENTION

[0001] The present invention relates to a pharmaceutical composition comprising a first multispecific antibody (MA1) comprising one binding domain, which specifically binds to CD137 (CD137-BD), and one binding domain, which specifically binds to PDL1 (PDL1-BD); a second multispecific antibody (MA2) comprising at least one binding domain, which specifically binds to a tumor cell associated antigen (TAA-BD), and one binding domain, which specifically binds to CD3 (CD3-BD); and a pharmaceutically acceptable carrier. The present invention further relates to a kit comprising said first multispecific antibody MA1 and said second multispecific antibody MA2. The present invention further relates to the use as well as to methods of use of said pharmaceutical composition or said kit. Finally, the present invention relates to a method for treating a patient suffering from cancer, comprising the step of administering a first multispecific antibody (MA1) comprising one binding domain, which specifically binds to CD137 (CD137-BD), and one binding domain, which specifically binds to PDL1 (PDL1-BD), and a second multispecific antibody (MA2) comprising at least one binding domain, which specifically binds to a tumor cell associated antigen (TAA-BD), and one binding domain, which specifically binds to CD3 (CD3-BD).

BACKGROUND OF THE INVENTION

[0002] Cancer continues to pose a major unmet medical need, despite the considerable progress made in its treatment. Some of the most substantial progress made in cancer treatment in recent years has come with the advent of immunotherapies of various molecular classes, including, but not limited to: monoclonal antibodies (mAbs), bispecific antibodies (bsAbs), recombinant proteins, and chimeric antigen receptor-T cell (CAR-T cell) therapies. Such therapies induce anti-tumor immunity by: a) actively directing immune-effector cells to tumor-resident cells and/or b) stimulating immune-effector cells and/or c) relieving tumor-mediated immune-suppression. These immunotherapies commonly exploit the overexpression

of specific antigens by tumor-resident cells (*e. g.*, malignant cells, cells of the tumor vasculature, stromal cells, immune cells, etc.) – as compared to extratumoral loci – to target their pharmacological activity to tumors. Among these antigens, tumor-associated antigens (TAAs) comprise cell-surface proteins selectively overexpressed by malignant cells. By binding to TAAs with high affinity, immunotherapies can restrict their immunomodulatory activity to immunological synapses between tumor cells and immune effector cells to a degree.

[0003] A common class of TAA-binding immunotherapeutics are mAbs that elicit anti-tumor immunity by opsonizing tumor-cells and by triggering antibody-dependent cell-mediated cytotoxicity (ADCC) by Fcγ receptor (FcγR)-expressing cells, primarily natural killer (NK) cells. Other TAA-binding immunotherapies leverage cytotoxic T lymphocytes (CTLs) to induce targeted depletion of malignant cells, such as CAR-T cells as well as bsAbs that simultaneously engage the T cell antigen CD3 (TAA/CD3 bsAbs).

[0004] While the therapeutic utility of TAA-(re)directed CTLs and conventional TAA/CD3 bsAbs have been clinically validated, dose-limiting toxicities (DLTs) often preclude administration at maximally effective doses (MEDs) or lead to discontinuation of treatment, resulting in limited efficacy.

[0005] One reason for the DLTs is that conventional TAA/CD3 bsAbs are also commonly associated with cytokine release syndrome (CRS), putatively due to excessive activity of anti-CD3 domains. Extratumoral activity of immunotherapies results in the secretion of pro-inflammatory cytokines in healthy tissues, which can result in undesirable safety profiles. Furthermore, while TAA/CD3 bsAbs potentially deplete TAA-overexpressing cells, they do so by recruiting and stimulating CTLs regardless of whether such cells express a T cell receptor (TCR) that recognizes a tumor-antigen(s) (*i. e.*, tumor-reactive T cell). Therefore, rather than stimulating or reactivating the host's native anti-tumor immunity, TAA/CD3 bsAbs somewhat indiscriminately stimulate CTLs, potentially posing safety risks.

[0006] Although the exact pathways by which such DLTs arise can vary, the risk of immunotherapy-related toxicities can typically be minimized or eliminated by enhancing the tumor-localization of pharmacological activity.

[0007] TAAs that are almost exclusively expressed on cancer cells, such as oncofetal tumor antigens, are referred to as clean TAAs. TAA that are also

expressed on normal, non-cancer cells – typically at lower levels compared to cancer cells – are considered non-clean TAAs. Due to the very high potency of TAA/CD3 bsAbs approaches, non-clean TAAs are a challenge as they damage non-tumor cells that also express the TAA. Mesothelin (MSLN), EGFR, EpCAM and HER2 are examples of non-clean TAAs; they are not only expressed on tumor cells but also in various other tissues, albeit at a lower level. Therefore, when targeting non-clean TAAs, novel therapies that improve the selectivity of TAA/CD3 bsAb approaches for tumor tissues and minimize off-tumor/on-target effects are needed. This particularly applies to MSLN/CD3 bsAb and HER2/CD3 bsAb approaches.

[0008] Different strategies are pursued to increase the efficiency and selectivity of TAA/CD3 bsAb approaches.

[0009] One strategy involves the use of avidity effects by providing multispecific T-cell engaging antibodies that are bivalent for the desired TAA, i.e. T-cell engaging multispecific antibodies having two or more binding domains that are specific for the same TAA (TAA-BDs), e.g. two MSLN-BDs or two HER2-BDs, and one binding domain that specifically binds to CD3 (CD3-BD), wherein the binding affinity of the two or more TAA-BDs are in a well-balanced range. This bivalent binding strategy allows the efficient avidity driven targeting of tumor cells with high TAA expression levels, while healthy, i.e. low TAA expressing cells, are much less affected. Such multispecific antibodies are theoretically capable of eliciting a high tumor localization and improved selectivity, which could provide safer and more effective therapies for a variety of cancers. However, implementation of multispecific antibodies for therapeutic use has been complicated due to issues with their molecular architecture, the properties of their component antigen-binding domains, their producibility and/or poor biophysical properties. Thus, only a limited number of such multispecific molecules have been developed so far.

[0010] WO 2019/157308 for example describes bispecific 1Fab-IgG-based antibodies having two low-affinity anti-HER2 binding domains and one anti-CD3 ϵ binding domain, which exhibit improved in vitro selectivity for high HER2-expressing cell lines.

[0011] Yoon et al. (Biomolecules, 2020,10(3), 399) describe a bispecific antibody having two low-affinity anti-MSLN binding domains and one anti-CD3 ϵ binding domain. This bispecific antibody is IgG-based having two scFab arms, with

specificity for MSLN and CD3 ϵ , and one additional MSLN-specific scFab fragment fused to the N-terminus of the CD3 ϵ -specific scFab.

[0012] Another strategy involves co-administration of additional immunotherapeutic antibodies with the aim to enhance patient response to the TAA-(re)directed immunotherapy, e.g. by relieving tumor-mediated immune-suppression and/or by increasing the immune response by further activating co-stimulating receptors, but without increasing side effects. Ideally, this approach should allow a reduction of the effective dose level of the DLT-critical TAA/CD3 bispecific antibody component, resulting in broadening the therapeutic window.

[0013] Tumor-mediated immune-suppression is often induced by the expression of immune-checkpoint ligands/receptors (e. g., PD-1, PDL1, CTLA-4). Immune checkpoints are regulators of the immune system and are involved in processes such as self-tolerance or immune suppression in cancer. Monoclonal antibodies that block immune-suppressive antigens, such as CTLA-4 (e. g., ipilimumab), PD-1 (e. g., nivolumab, pembrolizumab) and PDL1 (e. g., avelumab, atezolizumab), have elicited impressive response rates in patients exhibiting a variety of tumor histology phenotypes.

[0014] PDL1 (CD274, B7-H1) is a 40 kDa type I transmembrane protein. PDL1 is a surface glycoprotein ligand for PD-1, a key immune checkpoint receptor expressed by activated T and B cells, and mediates immunosuppression. PDL1 is implicated in the suppression of immune system responses during chronic infections, pregnancy, tissue allografts, autoimmune diseases, and cancer. PDL1 is found on both antigen-presenting cells and human cancer cells, such as squamous cell carcinoma of the head and neck, melanoma, and brain, thyroid, thymus, esophagus, lung, breast, gastrointestinal tract, colorectum, liver, pancreas, kidney, adrenal cortex, bladder, urothelium, ovary, and skin tumors (Katsuya Y, et al., *Lung Cancer*.88(2):154–159 (2015); Nakanishi J, et al., *Cancer Immunol Immunother*. 56(8):1173–1182 (2007); Nomi T, et al., *Clin Cancer Res*. 13(7):2151–2157 (2007); Fay AP, et al., *J Immunother Cancer*. 3:3 (2015); Strome SE, et al., *Cancer Res*. 63(19):6501–6505 (2003); Jacobs JF, et al. *Neuro Oncol*.11(4):394–402 (2009); Wilmotte R, et al. *Neuroreport*. 16(10):1081–1085 (2005)). PDL1 is rarely expressed on normal tissues but inducibly expressed on tumor sites (Dong H, et al., *Nat Med*. 8(8):793–800 (2002); Wang et al., *Onco Targets Ther*. 9: 5023–5039 (2016)). PDL1 downregulates

T cell activation and cytokine secretion by binding to PD-1 (Freeman et al., 2000; Latchman et al, 2001). PD-1, activated by PDL1, potentially provides an immune-tolerant environment for tumor development and growth. PDL1 also negatively regulates T cell function through interaction with another receptor, B7.1 (B7-1, CD80).

[0015] A number of antibodies that disrupt PD-1 signaling have entered clinical development. These antibodies belong to the following two main categories: those that target PD-1 (nivolumab, Bristol-Myers Squibb; pembrolizumab, Merck, Whitehouse Station, NJ; pidilizumab, CureTech, Yavne, Israel) and those that target PDL1 (MPDL3280A, Genentech, South San Francisco, CA; MEDI4736, MedImmune/AstraZeneca; BMS-936559, Bristol-Myers Squibb; MSB0010718C, EMD Serono, Rockland, MA) (for review see Postow MA et al., J Clin Oncol. Jun 10;33(17):1974-82 (2015)). Targeting PDL1 versus targeting PD-1 may result in different biologic effects. PD-1 antibodies prevent interaction of PD-1 with both its ligands, PDL1 and PDL2. PDL1 antibodies do not prevent PD-1 from interacting with PDL2, although the effect of this interaction remains unknown. PDL1 antibodies however prevent interaction of PDL1 with not only PD-1, but also B7-1 (Butte MJ, et al., Immunity 27:111-122, (2007)), which is believed to exert negative signals on T cells. Blocking PDL1 has demonstrated promising early data, and currently, four clinical anti-PDL1 mAbs are in the testing: atezolizumab and MEDI4736 (both are Fc null variants of human IgG1), MSB001078C (IgG1), and BMS-936559 (IgG4) (Chester C., et al., Cancer Immunol Immunother Oct;65(10):1243-8 (2016)).

[0016] New and emerging co-administration treatments frequently combine anti-PDL1/PD1 antibodies with TAA-(re)directed CTL-based immunotherapies.

[0017] WO 2017/112775, for example, describes a method for treating or inhibiting the growth of a tumor, comprising the administering of an anti PD-1 antibody in combination with a bispecific antibody comprising a first antigen-binding arm that specifically binds CD20 and a second antigen-binding arm that specifically binds CD3.

[0018] WO 2015/095418 describes a method for treating HER2-positive cancers, comprising the administering of an anti PD-1 antibody in combination with a bispecific antibody that specifically binds HER2 and CD3.

[0019] In addition, T cell co-stimulatory receptors (e. g., CD137, OX40, ICOS, GITR) are currently being clinically evaluated as targets for therapeutic stimulation of T cells in cancer. One putative advantage of anti-tumor T cell stimulation via such targets is that they are transiently expressed upon TCR signaling. As such, their expression tends to be selectively increased in inflamed tumor microenvironments (TMEs), particularly on tumor-reactive T cells, whose TCRs are receiving consistent stimulation through interaction with major histocompatibility complexes (MHCs) expressed by malignant cells and antigen-presenting cells (APCs). Therefore, targeting co-stimulatory receptors with, e. g., mAbs and bsAbs, should more selectively stimulate and expand pre-existing anti-tumor T cells than e.g. CD3-targeting approaches, potentially rendering such biologics safer and their effects more durable.

[0020] Among co-stimulatory receptors, CD137 (4-1BB, TNF-receptor superfamily 9, TNFRSF9) has emerged as especially promising due to its expression profile and its role as a multipotent mediator of anti-tumor immunity (Bartkowiak and Curran, *Front Oncol.* 2015, 5, 117; Yonezawa et al., *Clin Cancer Res.* 2015, 21, 3113-20). CD137 is an inducible T cell co-stimulatory receptor. Its expression is activation-dependent and encompasses a broad subset of immune cells, including activated CD8⁺ T cells, CD4⁺ T cells, NK cells, NKT cells, Tregs, dendritic cells (DC), including follicular DC, stimulated mast cells, differentiating myeloid cells, monocytes, neutrophils, eosinophils (Wang et al, *Immunol Rev.* 229(1): 192-215 (2009)), and activated B cells (Zhang et al, *J Immunol.* 184(2):787-795 (2010)). In addition, CD137 expression has also been demonstrated on tumor vasculature (Broil K et al., *Am J Clin Pathol.* 115(4):543-549 (2001); Seaman et al, *Cancer Cell* 11(6):539-554 (2007)) and atherosclerotic endothelium (Olofsson et al, *Circulation* 117(10): 1292 1301 (2008)).

[0021] CD137 co-stimulates T cells to carry out effector functions such as eradication of established tumors, broadening primary CD8⁺ T cell responses, and enhancing the memory pool of antigen-specific CD8⁺ T cells. *In vivo* efficacy studies in mice have revealed that CD137-agonistic mAbs, administered both as a monotherapy and as a component of combination regimens, leads to anti-tumor protective T cell memory responses and tumor regression in multiple tumor models.

[0022] Thus, several co-administration treatments are currently under investigation that combine CD137-agonistic mAbs with TAA-(re)directed CTLs immunotherapies.

[0023] WO 2018/114754 and WO 2018/114748 for example describe methods for treating or delaying progression of cancer, wherein a CD137-agonistic antibody is applied in combination with a bispecific antibody that specifically binds to a TAA and CD3, particularly to CD20 and CD3.

[0024] Although utilization of CD137-agonistic mAbs is a very promising treatment strategy, clinical data collected thus far suggest that a mAb-based approach to CD137 stimulation results in a trade-off between efficacy and safety. Namely, highly active CD137-agonistic mAbs elicit dose limiting toxicities (DLTs) that attenuate treatment efficacy, whereas weakly active CD137-agonistic mAbs are well tolerated but do not seem to be highly efficacious, including at their predicted minimum effective dose (MED).

[0025] Highly active CD137-agonistic mAbs lead to alterations in the immune system and organ function, increasing risks of toxicities. High doses of such mAbs in naïve and tumor-bearing mice have been reported to induce T cell infiltration to the liver and elevations of aspartate aminotransferase and alanine aminotransferase, consistent with liver inflammation (Niu L, et al. *J Immunol* 178(7):4194–4213 (2007); Dubrot J, et al., *Int J Cancer* 128(1):105–118 (2011); Segal NH et al. *Clin Canc Res*: 1929-1936 (2016)), as well as FcγR induced immune cell accumulation in the liver of wild-type mice (Claus et al. *Sci Transl Med* (11): 1-12 (2019)). Initial clinical studies into the human therapeutic use of CD137-agonistic mAbs have also demonstrated elevation of liver enzymes and increased incidence of hepatitis (Sznol M., et al., *J Clin Oncol* 26(115S):3007 (2008); Ascierto PA, et al., *Semin Oncol* 37(5):508–516 (2010); Chester C., et al., *Cancer Immunol Immunother* Oct;65(10):1243-8 (2016)). Potentially fatal hepatitis was observed in a Bristol-Myers Squibb (BMS) phase II anti-CD137 study for previously treated stage III/IV melanoma, National Clinical Trial (NCT) 00612664. This study and several others (NCT00803374, NCT00309023, NCT00461110, NCT00351325) were terminated due to adverse events (Chester C., et al., *Cancer Immunol Immunother* Oct;65(10):1243-8 (2016)). Such adverse events are most probably due to systemic overstimulation of T cells. CD137-mediated liver toxicity is believed to be caused by on-target activation of the myeloid cells in the

liver, followed by recruitment of CD4⁺/CD8⁺ T cells, which are activated and cause damage.

[0026] To gain additional cross-linking function and achieve certain levels of TNRSF, in particular CD137, activation, it has recently been suggested to use multivalent and multispecific fusion polypeptides that bind PDL1 and TNRSF members, or folate receptor alpha (FR α) and TNRSF members, wherein the binding to PDL1 or FR α is capable of providing additional crosslinking function (WO 2017/123650). Eckelman et al. have demonstrated that bivalent engagement of CD137, as in the case of INBRX-105, a multispecific and multivalent polypeptide having two PDL1 binding domains, two CD137 binding domains and an Fc region, is insufficient to effectively cluster and mediate productive CD137 signaling in absence of an exogenous clustering event, using an assay isolating the effects of the molecule on a reporter T cell-line. In contrast, engagement for a second cell surface antigen PDL1 in the presence of PDL1-positive cells enables further clustering of CD137 and productive signaling (WO 2017/123650).

[0027] Recently, the effect of multivalent and multispecific fusion polypeptides that bind PDL1 and CD137 on T cell activation and proliferation has been evaluated *in vitro*. Using an autologous *in vitro* co-culture system implementing immature DC and donor matched T cells, it has been demonstrated that INBRX-105, a multispecific and multivalent polypeptide having two PDL1 binding domains, two CD137 binding domains and an Fc region, is superior in inducing interferon-gamma (INF γ) production or mediating CD8⁺ T cell proliferation and activation, when compared to the monospecific PDL1 sd-Ab-Fc fusion protein, the CD137 sdAb-Fc fusion protein, the combination of the two, the anti-PDL1 antibody atezolizumab, the anti-CD137 antibody utomilumab (PF-05082566), or the anti-PDL1 antibody pembrolizumab, and combinations thereof (WO 2017/123650).

[0028] Such multivalent CD137-agonistic and PD-1/PDL1-antagonistic bispecific antibodies have recently been tested in combination with TAA/CD3 bsAbs.

[0029] Berezhnoy et al., poster PB-067 presented at the 30th EORTC/AACR/NCI Symposium, 2018, Dublin, describe the co-administration of a trivalent bispecific TRIDENT® antibody, which has one PDL1 binding domain, two CD137 binding domains and an Fc region, with a bivalent bispecific anti-5T4 x CD3 dual-affinity re-targeting (DART®) antibody comprising an Fc region in a RKO tumor mouse model.

It has been demonstrated that the combined administration of these two bispecific antibodies results in a strong improvement of T-cell mediated cancer cell killing when compared to the administration of the individual bispecific components alone.

[0030] The data disclosed in the above mentioned studies relating to the single application and/or the co-application of CD137-agonizing and PDL1-antagonizing bispecific antibodies implies that it is highly favorable – or even required – that these bispecific antibodies comprise at least two CD137 binding domains in order to ensure efficient clustering of CD137 and productive signaling and, in turn, a reasonably high increase in the efficacy of TAA-(re)directed T-cell mediated killing of cancer cells. Also, all CD137-agonizing and PDL1-antagonizing bispecific antibodies developed so far have an immunoglobulin Fc region. However, the combination of bispecific antibodies that target CD3 with multispecific antibodies having two CD137 binding domains raises concerns about the safety of such co-treatment approaches. These concerns are further fortified by the presence of Fc regions in the applied molecules, which generally cause off-tumor effects such as systematic activation of T-cells. This holds particularly true in cases, where the TAA/CD3 bsAbs are directed to non-clean TAAs, i.e. TAAs that are also expressed in healthy cells albeit to a lower extent than in the particular tumor cells.

[0031] Apart from that, the development of such co-treatment approaches is a challenging task. The biophysical and functional characterization as well as the biological testing of the multispecific antibodies applied therein, be it alone or in combination, are typically difficult and laborious, due to their multispecific architecture and the complexity of their interaction in biological systems. Thus, such co-treatment strategies generally have significant economic and commercial drawbacks over single component therapies, due to their higher development, approval and production costs. Consequently, even for those co-treatment strategies where a gain in risk-to-benefit can be achieved, such improvement must surpass the drawbacks of higher development efforts and development costs.

[0032] In summary, there remains a clear need for novel TAA-(re)directed immunotherapies with increased tumor cell localization and effective T cell activation, which at the same time have a tolerable toxicological profile, i.e. immunotherapies with an improved risk-to-benefit ratio, in particular for novel TAA-(re)directed immunotherapies that target non-clean TAAs.

SUMMARY OF THE INVENTION

[0033] It is an object of the present invention to provide a medicament to improve treatment of a proliferative disease, particularly a cancer. More specifically, it was an object of the present invention to provide novel TAA-(re)directed immunotherapies with increased on target efficacy and a tolerable toxicological profile.

[0034] The inventors could previously identify a series of multispecific antibodies comprising one CD137 binding domain (CD137-BD) and one PDL1 binding domain (PDL1-BD). Said multispecific antibodies are able to cluster and to agonize CD137 signaling in a targeted manner, i.e. solely in the presence of PDL1-positive cells such as in PDL1-positive tumor microenvironment, thus avoiding systemic activation of CD137. At the same time, said multispecific antibodies block the binding of PDL1 to PDL. These multispecific antibodies as well as pharmaceutical compositions and methods of use thereof are disclosed in the patent application WO 2019/072868, which is herewith incorporated by reference in its entirety.

[0035] The inventors have now surprisingly found that the combined application of such a CD137-agonizing and PDL1-blocking multispecific antibody, as defined herein, with a multispecific antibody that specifically targets TAAs and CD3 results in a significantly greater efficacy in TAA-(re)directed target cell killing (*in vitro*) and a substantially increased tumor growth inhibition (*in vivo*) relative to the application of said individual multispecific antibodies alone, despite of the fact that these CD137-agonizing and PDL1-blocking multispecific antibodies have only one CD137 binding domain, only one PDL1 binding domain and also do not comprise a immunoglobulin Fc region.

[0036] At the same time, the toxicological profile of the combined application of the PDL1-/CD137-binding multispecific antibodies, as described herein, with anti-TAAxCD3 multispecific antibodies is not worse than the toxicological profile of the application of the TAAxCD3 multispecific antibodies alone.

[0037] Accordingly, in a first aspect, the present invention relates to a pharmaceutical composition comprising:

- 1) a first multispecific antibody (MA1) comprising
 - a) one binding domain, which specifically binds to CD137 (CD137-BD), and

- b) one binding domain, which specifically binds to PDL1 (PDL1-BD),
- 2) a second multispecific antibody (MA2) comprising
 - a) at least one binding domain, which specifically bind(s) to a tumor cell associated antigen (TAA-BD),
 - b) one binding domain, which specifically binds to CD3 (CD3-BD),
- 3) a pharmaceutically acceptable carrier.

[0038] In a second aspect, the present invention relates to a kit comprising:

- 1) a first multispecific antibody (MA1) comprising
 - a) one binding domain, which specifically binds to CD137 (CD137-BD), and
 - b) one binding domain, which specifically binds to PDL1 (PDL1-BD), and
- 2) a second multispecific antibody (MA2) comprising
 - a) at least one binding domain, which specifically binds to a tumor cell associated antigen (TAA-BD), and
 - b) one binding domain, which specifically binds to CD3 (CD3-BD).

[0039] In a third aspect, the present invention relates to a pharmaceutical composition or a kit of the present invention for use as a medicament.

[0040] In a fourth aspect, the present invention relates to a pharmaceutical composition or a kit of the present invention for use in the treatment of a disease, particularly a human disease, more particularly a human disease selected from cancers.

[0041] In a fifth aspect, the present invention relates to a method for the treatment of a disease, particularly a human disease, more particularly a human disease selected from cancers, comprising the step of administering the pharmaceutical composition or the kit of the present invention.

[0042] In a sixth aspect, the present invention relates to a method for treating a patient suffering from cancer, comprising the step of administering a first multispecific antibody (MA1) comprising one binding domain, which specifically binds to CD137 (CD137-BD), and one binding domain, which specifically binds to PDL1 (PDL1-BD), and a second multispecific antibody (MA2) comprising at least one binding domain, which specifically binds to a tumor cell associated antigen (TAA-BD), and one binding domain, which specifically binds to CD3 (CD3-BD).

[0043] In a seventh aspect, the present invention relates to a multispecific antibody MA1 comprising one binding domain, which specifically binds to CD137 (CD137-BD), and one binding domain, which specifically binds to PDL1 (PDL1-BD) for use in

the treatment of a subject suffering from a proliferative disease, particularly a cancer, wherein said multispecific antibody MA1 is administered to said subject in combination with a multispecific antibody MA2 comprising at least one binding domain, which specifically binds to a tumor cell associated antigen (TAA-BD), and one binding domain, which specifically binds to CD3 (CD3-BD).

[0044] In an eight aspect, the present invention relates to a multispecific antibody MA2 comprising at least one binding domain, which specifically binds to a tumor cell associated antigen (TAA-BD), and one binding domain, which specifically binds to CD3 (CD3-BD) for use in the treatment of a subject suffering from a proliferative disease, particularly a cancer, wherein said multispecific antibody MA2 is administered to said subject in combination with a multispecific antibody MA1 comprising one binding domain, which specifically binds to CD137 (CD137-BD), and one binding domain, which specifically binds to PDL1 (PDL1-BD).

[0045] The aspects, advantageous features and preferred embodiments of the present invention summarized in the following items, respectively alone or in combination, further contribute to solving the object of the invention:

1. A pharmaceutical composition comprising:
 - 1) a first multispecific antibody (MA1) comprising
 - a) one binding domain, which specifically binds to CD137 (CD137-BD), and
 - b) one binding domain, which specifically binds to PDL1 (PDL1-BD),
 - 2) a second multispecific antibody (MA2) comprising
 - a) at least one binding domain, which specifically bind(s) to a tumor cell associated antigen (TAA-BD),
 - b) one binding domain, which specifically binds to CD3 (CD3-BD),
 - 3) a pharmaceutically acceptable carrier.
2. A kit comprising:
 - 1) a first multispecific antibody (MA1) comprising
 - a) one binding domain, which specifically binds to CD137 (CD137-BD), and
 - b) one binding domain, which specifically binds to PDL1 (PDL1-BD), and
 - 2) a second multispecific antibody (MA2) comprising
 - a) at least one binding domain, which specifically binds to a tumor cell associated antigen (TAA-BD), and
 - b) one binding domain, which specifically binds to CD3 (CD3-BD).

3. The pharmaceutical composition of item 1, or the kit of item 2, wherein said MA2 comprises one or two TAA-BD(s).
4. The pharmaceutical composition of item 1 or 3, or the kit of item 2 or 3, wherein said MA1 or said MA2, or both antibodies MA1 and MA2, do not comprise an immunoglobulin Fc region polypeptide.
5. The pharmaceutical composition of any one of the preceding items, wherein said pharmaceutical composition comprises:
 - 1) a first multispecific antibody (MA1) comprising
 - a) one binding domain, which specifically binds to CD137 (CD137-BD), and
 - b) one binding domain, which specifically binds to PDL1 (PDL1-BD),
 - 2) a second multispecific antibody (MA2) comprising
 - a) one or two binding domain(s), which specifically bind(s) to a tumor cell associated antigen (TAA-BD),
 - b) one binding domain, which specifically binds to CD3 (CD3-BD),
 - 3) a pharmaceutically acceptable carrier,wherein said MA1 does not comprise an immunoglobulin Fc region polypeptide.
6. The kit of any one of the preceding items, wherein said kit comprises:
 - 1) a first multispecific antibody (MA1) comprising
 - a) one binding domain, which specifically binds to CD137 (CD137-BD), and
 - b) one binding domain, which specifically binds to PDL1 (PDL1-BD), and
 - 2) a second multispecific antibody (MA2) comprising
 - a) one or two binding domain(s), which specifically bind(s) to a tumor cell associated antigen (TAA-BD), and
 - b) one binding domain, which specifically binds to CD3 (CD3-BD),wherein said MA1 does not comprise an immunoglobulin Fc region polypeptide.
7. The pharmaceutical composition or the kit of any one of the preceding items, wherein said MA1 or MA2, or both antibodies MA1 and MA2, further comprises one human serum albumin binding domain (hSA-BD).

8. The pharmaceutical composition or the kit of any one of the preceding items, wherein the binding domains of said MA1 and MA2, e.g., PDL1-BD, CD137-BD, TAA-BD, CD3-BD or hSA-BD, are independently of each other selected from the group consisting of a Fab, an Fv, an scFv, a dsFv, an sdAb, a STAB, and binding domains based on alternative scaffolds including but not limited to ankyrin-based domains, fynomers, avimers, anticalins, fibronectins, and binding sites being built into constant regions of antibodies (e.g. f-star technology), particularly wherein the binding domains of MA1 and MA2 are independently of each other selected from the group consisting of a Fab, an Fv, an scFv, a dsFv, an sdAb and a STAB, more particularly wherein the binding domains of MA1 and MA2 are independently of each other selected from the group consisting of an Fv, an scFv, a dsFv and a STAB.
9. The pharmaceutical composition or the kit of any one of the preceding items, wherein said MA1 or said MA2, or both antibodies MA1 and MA2, do not comprise CH1 and/or CL regions, in particular wherein said MA1 or said MA2, or both antibodies MA1 and MA2, exclusively comprise immunoglobulin variable domains.
10. The pharmaceutical composition or the kit of any one of the preceding items, wherein each of said binding domains comprised in MA1 and MA2 is independently selected from
 - (a) a cognate pair of a VL domain and a VH domain (Fv fragment); or
 - (b) a cognate pair of a VL domain and a VH domain linked by a polypeptide linker (scFv fragment) and/or a disulfide bond.
11. The pharmaceutical composition or the kit of any one of the preceding items, wherein the binding domains of said MA1 are capable of binding simultaneously to their respective antigens.
12. The pharmaceutical composition or the kit of any one of items 7 to 11, wherein said MA1 consists of one CD137-BD, one PDL1-BD and one hSA-BD.
13. The pharmaceutical composition or the kit of any one of the preceding items, wherein said MA1 acts as an agonist of CD137 in the presence of PDL1-positive cells.

14. The pharmaceutical composition or the kit of any one of the preceding items, wherein said MA1 does not inhibit the interaction between CD137 and its ligand CD137L, in particular as measured by a competition ELISA.
15. The pharmaceutical composition or the kit of any one of the preceding items, wherein said CD137-BD:
- binds to human CD137 with a monovalent dissociation constant (K_D) of less than 50nM, particularly with a monovalent K_D of 0.005 to 50 nM, more particularly of 0.01 to 30 nM, more particularly of 0.01 to 10 nM, more particularly of 0.1 to 5 nM, as measured by surface plasmon resonance (SPR), particularly wherein said CD137-BD is an scFv;
 - binds to human CD137 with a K_{off} rate of 10^{-2} s^{-1} or less, more particularly of 10^{-2} s^{-1} to 10^{-6} s^{-1} more particularly of $5 \times 10^{-3} \text{ s}^{-1}$ to 10^{-5} s^{-1} , more particularly of 10^{-3} s^{-1} to $5 \times 10^{-4} \text{ s}^{-1}$, as measured by SPR;
 - binds to human CD137 with a K_{on} rate of at least $10^4 \text{ M}^{-1} \text{ s}^{-1}$ or greater, more particularly of $10^4 \text{ M}^{-1} \text{ s}^{-1}$ to $10^7 \text{ M}^{-1} \text{ s}^{-1}$, more particularly of $10^5 \text{ M}^{-1} \text{ s}^{-1}$ to $5 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$, as measured by SPR;
 - does not cross-compete with urelumab and utomilumab; and/or
 - is cross-reactive with *Macaca fascicularis* (cynomolgus) CD137, in particular binds to cynomolgus CD137 with a monovalent K_D of less than 50 nM, particularly with a monovalent K_D of 0.005 to 50 nM, more particularly of 0.01 to 30 nM, more particularly of 0.01 to 10 nM, more particularly of 0.1 to 5 nM, as measured by SPR, particularly wherein said CD137-BD is an scFv; and/or
 - when being in scFv format, has a melting temperature (T_m), determined by differential scanning fluorimetry, of at least 50°C, preferably of at least 55°C, more preferably at least 60°C, in particular wherein said antibody or antigen binding fragment thereof is formulated in phosphate citrate buffer at pH 6.4, 150 mM NaCl, in particular wherein said antibody is formulated in 50 mM phosphate citrate buffer with 150 mM NaCl at pH 6.4;
 - when being in scFv format, has a loss in monomer content, after storage for at least two weeks, particularly for at least four weeks, at 4°C, of less than 7 %, e.g. less than 6 %, less than 5 %, less than 4 %, less than 3 %, less than 2 %, preferably less than 1 %, when said antibody is at a starting concentration of 10 mg/ml, and in particular wherein said antibody is formulated in 50 mM phosphate citrate buffer with 150 mM NaCl at pH 6.4;

and/or

- h. when being in scFv format, has a loss in monomer content, after storage for at least two weeks, particularly for at least four weeks, at 40°C, of less than 5 %, e.g. less than 4 %, less than 3 %, less than 2 %, preferably less than 1 %, when said antibody is at a starting concentration of 10 mg/ml, and in particular wherein said antibody is formulated in 50 mM phosphate citrate buffer with 150 mM NaCl at pH 6.4.
16. The pharmaceutical composition or the kit of any one of the preceding items, wherein said CD137-BD binds to human CD137 with a monovalent dissociation constant (K_D) which is at least 5 times, preferably at least 10 times, e.g., at least 20, at least 30, at least 50, at least 100 times, higher than the monovalent dissociation constant (K_D) of said PDL1-BD for binding to human PDL1, when measured by SPR.
17. The pharmaceutical composition or the kit of any one of the preceding items, wherein said CD137-BD binds to human CD137 with a monovalent dissociation constant (K_D) that is 20 to 1000 times, preferably 30 to 800 times, in particular 50 to 500 times higher than the monovalent dissociation constant (K_D) of said PDL1-BD for binding to human PDL1, when measured by SPR.
18. The pharmaceutical composition or the kit of any one of the items 13 to 17, wherein said CD137-BD comprises
- (i) the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 1, 2 and 3, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 8, 9 and 10, respectively; and
 - (ii) VH3 or VH4 domain framework sequences FR1 to FR4; particularly VH3 domain framework sequences FR1 to FR4; and
 - (iii) a VL domain comprising a VL framework comprising framework regions FR1, FR2 and FR3, which are selected from V_k subtypes, particularly from the V_{k1} and V_{k3} subtypes, particularly are of the V_{k1} subtype, and a framework FR4, which is selected from a V_k FR4 and a V_λ FR4, particularly is a V_λ FR4 comprising an amino acid sequence having at least 70, 80, 90 percent identity, particularly at least 90 percent identity, to any of SEQ ID NO: 94 to SEQ ID NO: 101, more particularly a V_λ FR4 selected from any of SEQ ID NO: 94 to SEQ ID NO: 101, particularly a V_λ FR4 according to SEQ

ID NO: 94 or 101.

19. The pharmaceutical composition or the kit of item 18, wherein said CD137-BD comprises
 - a) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 1, 2 and 3, respectively,
 - b) LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 8, 9 and 10, respectively,
 - c) a VH sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequences SEQ ID NO: 4, 5, 6 or 7, and
 - d) a VL sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequences SEQ ID NO: 11, 12, 13 or 14.
20. The pharmaceutical composition or the kit of item 18 or 19, wherein said VH domain comprises a cysteine at position 51 (AHO numbering) and said VL domain comprises a cysteine at position 141 (AHO numbering).
21. The pharmaceutical composition or the kit of any one of the items 18 to 20, wherein said CD137-BD comprises: a VH domain comprising an amino acid sequence selected from any of SEQ ID NOs: 4, 5, 6 and 7; and a VL domain comprising an amino acid sequence selected from any of SEQ ID NOs: 11, 12, 13 and 14.
22. The pharmaceutical composition or the kit of item 21, wherein said CD137-BD comprises
 - (a) a VH sequence of SEQ ID NO: 4 and a VL sequence of SEQ ID NO: 11;
 - (b) a VH sequence of SEQ ID NO: 5 and a VL sequence of SEQ ID NO: 12;
 - (c) a VH sequence of SEQ ID NO: 6 and a VL sequence of SEQ ID NO: 13; or
 - (d) a VH sequence of SEQ ID NO: 7 and a VL sequence of SEQ ID NO: 14.
23. The pharmaceutical composition or the kit of any one of items 18 to 20, wherein said CD137-BD comprising: a VH sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 7; and a VL sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 14, wherein said VH domain comprises a cysteine at position 51 (AHO numbering) and said VL domain comprises a cysteine at position 141 (AHO numbering).

24. The pharmaceutical composition or the kit of any one of the items 13 to 17, wherein said CD137-BD comprises
- (i) the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 19, 20 and 21, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 23, 24 and 25, respectively; and
 - (ii) VH3 or VH4 domain framework sequences FR1 to FR4; particularly VH3 domain framework sequences FR1 to FR4; and
 - (iii) a VL domain comprising a VL framework comprising framework regions FR1, FR2 and FR3, which are selected from Vk subtypes, particularly from the Vk1 and Vk3 subtypes, particularly are of the Vk1 subtype, and a framework FR4, which is selected from a Vk FR4 and a Vλ FR4, particularly is a Vλ FR4 comprising an amino acid sequence having at least 70, 80, 90 percent identity, particularly at least 90 percent identity, to any of SEQ ID NO: 94 to SEQ ID NO: 101, more particularly a Vλ FR4 selected from any of SEQ ID NO: 94 to SEQ ID NO: 101, particularly a Vλ FR4 according to SEQ ID NO: 94 or 101.
25. The pharmaceutical composition or the kit of item 24, wherein said CD137-BD comprises: a VH sequence that is at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to an amino acid sequence of SEQ ID NO: 22; and a VL sequence that is at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to an amino acid sequence of SEQ ID NO: 26.
26. The pharmaceutical composition or the kit of item 24 or 25, wherein said VH domain or VH sequence comprises a cysteine at position 51 (AHO numbering) and said VL domain or VL sequence comprises a cysteine at position 141 (AHO numbering).
27. The pharmaceutical composition or the kit of any one of the items 24 to 26, wherein said CD137- BD comprises: a VH sequence of SEQ ID NO: 22 and a VL sequence of SEQ ID NO: 26.
28. The pharmaceutical composition or the kit of any one of items 13 to 17, wherein said CD137-BD comprises

- (i) the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 28, 29 and 30, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 34, 35 and 36, respectively; and
 - (ii) VH3 or VH4 domain framework sequences FR1 to FR4; particularly VH3 domain framework sequences FR1 to FR4; and
 - (iii) a VL domain comprising a VL framework comprising framework regions FR1, FR2 and FR3, which are selected from Vk subtypes, particularly from the Vk1 and Vk3 subtypes, particularly are of the Vk1 subtype, and a framework FR4, which is selected from a Vk FR4 and a Vλ FR4, particularly is a Vλ FR4 comprising an amino acid sequence having at least 70, 80, 90 percent identity, particularly at least 90 percent identity, to any of SEQ ID NO: 94 to SEQ ID NO: 101, more particularly a Vλ FR4 selected from any of SEQ ID NO: 94 to SEQ ID NO: 101, particularly a Vλ FR4 according to SEQ ID NO: 94 or 101.
29. The pharmaceutical composition or the kit of item 28, wherein said CD137-BD comprises: a VH sequence that is at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 31, 32 and 33; and a VL sequence that is at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 37, 38 and 39.
30. The pharmaceutical composition or the kit of item 28 or 29, wherein said VH sequence or VH domain comprises a cysteine at position 51 (AHO numbering) and said VL domain or VL sequence comprises a cysteine at position 141 (AHO numbering).
31. The pharmaceutical composition or the kit of any one of items 28 to 30, wherein said CD137- BD comprises:
- (a) a VH sequence of SEQ ID NO: 31 and a VL sequence of SEQ ID NO: 37;
 - (b) a VH sequence of SEQ ID NO: 32 and a VL sequence of SEQ ID NO: 38; or
 - (c) a VH sequence of SEQ ID NO: 33 and a VL sequence of SEQ ID NO: 39.
32. The pharmaceutical composition or the kit of any one of the items 28 to 31, wherein said CD137-BD comprises: a VH sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 33; and a VL

sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 39, wherein said VH sequence comprises a cysteine at position 51 (AHO numbering) and said VL sequence comprises a cysteine at position 141 (AHO numbering).

33. The pharmaceutical composition or the kit of any of the preceding items, wherein said PDL1-BD is a blocker of PDL1.
34. The pharmaceutical composition or the kit of item 33, wherein said PDL1-BD:
- binds to human PDL1 with a monovalent dissociation constant (K_D) of less than 10 nM, particularly with a monovalent K_D of 0.05 pM to 10 nM, more particularly of 0.1 pM to 5 nM, more particularly of 0.2 pM to 1 nM, more particularly 0.5 pM to 500 pM, more particularly of 1 pM to 200 pM, more particularly of 1 pM to 100 pM, as measured by SPR;
 - binds to human PDL1 with a K_{off} rate of $5 \times 10^{-3} \text{ s}^{-1}$ or less, more particularly of $5 \times 10^{-3} \text{ s}^{-1}$ to 10^{-7} s^{-1} , more particularly of 10^{-3} s^{-1} to $5 \times 10^{-6} \text{ s}^{-1}$, more particularly of 10^{-3} s^{-1} to 10^{-6} s^{-1} , as measured by SPR;
 - binds to human PDL1 with a K_{on} rate of at least $10^4 \text{ M}^{-1}\text{s}^{-1}$ or greater, more particularly of $10^4 \text{ M}^{-1}\text{s}^{-1}$ to $10^8 \text{ M}^{-1}\text{s}^{-1}$, more particularly of $10^5 \text{ M}^{-1}\text{s}^{-1}$ to $5 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$, more particularly of $5 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ to $10^7 \text{ M}^{-1}\text{s}^{-1}$, as measured by SPR;
 - is cross-reactive with *Macaca fascicularis* (cynomolgus) PDL1;
 - is non-cross reactive to *Mus musculus* PDL1; and/or
 - when being in scFv format, has a melting temperature (T_m), determined by differential scanning fluorimetry, of at least 55°C, e.g. at least 60°C, preferably at least 65°C, more preferably at least 70°C, in particular wherein said antibody or antigen-binding fragment thereof is formulated in phosphate citrate buffer at pH 6.4, 150 mM NaCl, in particular wherein said antibody is formulated in 50 mM phosphate citrate buffer with 150 mM NaCl at pH 6.4;
 - when being in scFv format, has a loss in monomer content, after five consecutive freeze-thaw cycles, of less than 5 %, preferably less than 3 %, more preferably less than 1 %, when said antibody is at a starting concentration of 10 mg/ml, in particular wherein said antibody is formulated in 50 mM phosphate citrate buffer with 150 mM NaCl at pH 6.4; and/or
 - when being in scFv format, has a loss in monomer content, after storage for at least two weeks, particularly for at least four weeks, at 4°C, of less than 15

%, e.g. less than 12 %, less than 10 %, less than 7 %, less than 5 %, less than 4 %, less than 3 %, less than 2 %, preferably less than 1 %, when said antibody is at a starting concentration of 10 mg/ml, and in particular wherein said antibody is formulated in 50 mM phosphate citrate buffer with 150 mM NaCl at pH 6.4.

35. The pharmaceutical composition or the kit of item 33 or 34, wherein said PDL1-BD comprises

- (i) the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 43, 44 and 45, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 49, 50 and 51, respectively; and
- (ii) VH3 or VH4 domain framework sequences FR1 to FR4; particularly VH3 domain framework sequences FR1 to FR4; and
- (iii) a VL domain comprising a VL framework comprising framework regions FR1, FR2 and FR3, which are selected from Vk subtypes, particularly from the Vk1 and Vk3 subtypes, particularly are of the Vk1 subtype, and a framework FR4, which is selected from a Vk FR4 and a Vλ FR4, particularly is a Vλ FR4 comprising an amino acid sequence having at least 70, 80, 90 percent identity, particularly at least 90 percent identity, to any of SEQ ID NO: 94 to SEQ ID NO: 101, more particularly a Vλ FR4 selected from any of SEQ ID NO: 94 to SEQ ID NO: 101, particularly a Vλ FR4 according to SEQ ID NO: 94 or 101.

36. The pharmaceutical composition or the kit of item 33 or 34, wherein said PDL1-BD comprises

- (i) the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 57, 58 and 59, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 63, 64 and 65, respectively; and
- (ii) VH3 or VH4 domain framework sequences FR1 to FR4; particularly VH3 domain framework sequences FR1 to FR4; and
- (iii) a VL domain comprising a VL framework comprising framework regions FR1, FR2 and FR3, which are selected from Vk subtypes, particularly from the Vk1 and Vk3 subtypes, particularly are of the Vk1 subtype, and a framework FR4, which is selected from a Vk FR4 and a Vλ FR4, particularly is a Vλ FR4 comprising an amino acid sequence having at least 70, 80, 90 percent identity, particularly at least 90 percent identity, to any of SEQ ID NO: 94 to SEQ ID NO: 101, more particularly a Vλ FR4 selected from any of

SEQ ID NO: 94 to SEQ ID NO: 101, particularly a V λ FR4 according to SEQ ID NO: 94 or 101.

37. The pharmaceutical composition or the kit of any one of items 33 to 36, wherein said PDL1-BD comprises: a VH sequence that is at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 46, 47, 48, 60, 61 and 62; and a VL sequence that is at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 52, 53, 66 and 67.
38. The pharmaceutical composition or the kit of any one of items 33 to 36, wherein said PDL1-BD comprises:
- (a) a VH sequence of SEQ ID NO: 46 and a VL sequence of SEQ ID NO: 52;
 - (b) a VH sequence of SEQ ID NO: 47 and a VL sequence of SEQ ID NO: 52;
 - (c) a VH sequence of SEQ ID NO: 48 and a VL sequence of SEQ ID NO: 53;
 - (d) a VH sequence of SEQ ID NO: 60 and a VL sequence of SEQ ID NO: 66;
 - (e) a VH sequence of SEQ ID NO: 61 and a VL sequence of SEQ ID NO: 67; or
 - (f) a VH sequence of SEQ ID NO: 62 and a VL sequence of SEQ ID NO: 66.
39. The pharmaceutical composition or the kit of item 38, wherein said PDL1-BD comprises:
- (a) a VH sequence of SEQ ID NO: 46 and a VL sequence of SEQ ID NO: 52; or
 - (b) a VH sequence of SEQ ID NO: 48 and a VL sequence of SEQ ID NO: 53.
40. The pharmaceutical composition or the kit of item 38, wherein said PDL1-BD comprises:
- (a) a VH sequence of SEQ ID NO: 61 and a VL sequence of SEQ ID NO: 67; or
 - (b) a VH sequence of SEQ ID NO: 62 and a VL sequence of SEQ ID NO: 66.
41. The pharmaceutical composition or the kit of any one of items 7 to 40, wherein said hSA-BD comprises
- (i) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 71, 72 and 73, embedded in an antibody VH framework, particularly in a human antibody VH framework, particularly in a human VH3 framework, and

- (ii) LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 75, 76 and 77, embedded in an antibody VL framework, particularly in a human antibody VL framework, wherein the VL framework comprises framework regions FR1, FR2 and FR3, which are selected from Vk subtypes, particularly from the Vk1 and Vk3 subtypes, particularly are of the Vk1 subtype, and a framework FR4, which is selected from a Vk FR4 and a Vλ FR4, particularly is a Vλ FR4 comprising an amino acid sequence having at least 70, 80, 90 percent identity, particularly at least 90 percent identity, to any of SEQ ID NO: 94 to SEQ ID NO: 101, more particularly a Vλ FR4 selected from any of SEQ ID NO: 94 to SEQ ID NO: 101, particularly a Vλ FR4 according to SEQ ID NO: 94 or 101;

or

- (i) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 80, 81 and 82, embedded in an antibody VH framework, particularly in a human antibody VH framework, particularly in a human VH3 framework, and
- (ii) LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 84, 85 and 86, embedded in an antibody VH framework, particularly in a human antibody VL framework, wherein the VL framework comprises framework regions FR1, FR2 and FR3, which are selected from Vk subtypes, particularly from the Vk1 and Vk3 subtypes, particularly are of the Vk1 subtype, and a framework FR4, which is selected from a Vk FR4 and a Vλ FR4, particularly is a Vλ FR4 comprising an amino acid sequence having at least 70, 80, 90 percent identity, particularly at least 90 percent identity, to any of SEQ ID NO: 94 to SEQ ID NO: 101, more particularly a Vλ FR4 selected from any of SEQ ID NO: 94 to SEQ ID NO: 101, particularly a Vλ FR4 according to SEQ ID NO: 94 or 101.

42. The pharmaceutical composition or the kit of item 41, wherein said hSA-BD comprises: a VH sequence that is at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 74, 83, 189, 190 and 191; and a VL sequence that is at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 78, 87, 192 and 193.

43. The pharmaceutical composition or the kit of any one of items 41 or 42, wherein said hSA-BD comprises:

- (a) a VH sequence of SEQ ID NO: 74 and a VL sequence of SEQ ID NO: 78;
- (b) a VH sequence of SEQ ID NO: 83 and a VL sequence of SEQ ID NO: 87;

- (c) a VH sequence of SEQ ID NO: 190 and a VL sequence of SEQ ID NO: 192;
(d) a VH sequence of SEQ ID NO: 191 and a VL sequence of SEQ ID NO: 192;
or
(e) a VH sequence of SEQ ID NO: 189 and a VL sequence of SEQ ID NO: 193.
44. The pharmaceutical composition or the kit of item 42 or 43, wherein said VH domain comprises a cysteine at position 51 (AHO numbering) and said VL domain comprises a cysteine at position 141 (AHO numbering).
45. The pharmaceutical composition or the kit of any one of the preceding items, wherein said multispecific antibody MA1 is in a format selected from the group consisting of: scDB; a bispecific T cell engager (BiTE; tandem di-scFv), tandem tri-scFv; Fab-(scFv); scFab-dsscFv; tribody (Fab-(scFv)₂); Fab₂; Fab-Fv₂; diabody; triabody; scDb-scFv; a scDb, a tandem tri-scFv, a Fab-(scFv), a scFab-dsscFv, a Fab-(scFv)₂, a Fab₂, a Fab-Fv₂, a diabody or a scDb-scFv fused to the N- and/or the C-terminus of a heterodimerization domain other than heterodimeric Fc domains; and a MATCH.
46. The pharmaceutical composition or the kit of any one of items 1 to 6, wherein said MA1 is an scDb comprising an amino acid sequence selected from any of SEQ ID NOs: 105, 106, 107, 108, 109, 110, and 111.
47. The pharmaceutical composition or the kit of any one of items 1 to 6, wherein said MA1 is an scDb-scFv comprising an amino acid sequence selected from any of SEQ ID NOs: 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129 and 130, preferably wherein said MA1 is an scDb-scFv comprising an amino acid sequence selected from SEQ ID NO: 125, 126, 127 and 130, more preferably wherein said MA1 is an scDb-scFv comprising an amino acid sequence selected from SEQ ID NO: 125, 127 and 130.
48. The pharmaceutical composition or the kit of any one of the preceding items, wherein said CD3-BD of MA2 is binding to CD3 ϵ .
49. The pharmaceutical composition or the kit of item 48, wherein said CD3-BD binds CD3 ϵ with a monovalent K_D of less than 50 nM, particularly with a monovalent K_D

of 0.5 to 50 nM, particularly of 1 to 40 nM, particularly of 2 to 35 nM, particularly of 3 to 30 nM, as measured by SPR.

50. The pharmaceutical composition or the kit of item 48 or 49, wherein said CD3-BD comprises
- (i) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 131, 132 and 133, embedded in an antibody VH framework, particularly in a human antibody VH framework, particularly in a human VH3 framework, and
 - (ii) LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 135, 136 and 137, embedded in an antibody VH framework, particularly in a human antibody VL framework, wherein the VL framework comprises framework regions FR1, FR2 and FR3, which are selected from Vk subtypes, particularly from the Vk1 and Vk3 subtypes, particularly are of the Vk1 subtype, and a framework FR4, which is selected from a Vk FR4 and a Vλ FR4, particularly is a Vλ FR4 comprising an amino acid sequence having at least 70, 80, 90 percent identity, particularly at least 90 percent identity, to any of SEQ ID NO: 94 to SEQ ID NO: 101, more particularly a Vλ FR4 selected from any of SEQ ID NO: 94 to SEQ ID NO: 101, particularly a Vλ FR4 according to SEQ ID NO: 94 or 101.
51. The pharmaceutical composition or the kit of item 50, wherein said CD3-BD comprises
- (i) a VH domain comprising the amino acid sequence of SEQ ID NO: 134 or 182, and
 - (ii) a VL domain comprising the amino acid sequence of SEQ ID NO: 138.
52. The pharmaceutical composition or the kit of any one of the preceding items, wherein the tumor cell associated antigen (TAA) is selected from the group consisting of CD138, CD79b, TPBG (5T4), HER2, MSLN, MUC1, CA-125 (MUC16), PSMA, BCMA, CD19, EpCAM, CLEC12A (CLL1), CD20, CD22, CEA, CD33, EGFR, GPC3, CD123, CD38, CD33, CD276, CDH3 (cadherin 3), FGFR1, SSTR2, CD133, EPHA2, HLA-A2, IL13RA2, ROR1, CEACAM6, CD135, GD-2, GA733, CD135 (FLT3), CSPG4 and TAG-72, preferably, wherein the TAA is selected from the group consisting of CD138, CD79b, CD123, HER2, MSLN, PSMA, BCMA, CD19, CD20, CEA, CD38, CD33, CLEC12a and ROR1,

in particular wherein the TAA is selected from the group consisting of HER2, MSLN and ROR1.

53. The pharmaceutical composition or the kit of any one of the items 1 to 52, wherein said MA2 comprises one TAA-BD.
54. The pharmaceutical composition or the kit of item 53, wherein said TAA-BD binds to said TAA with a monovalent dissociation constant (K_D) of less than 50 nM, particularly less than 20 nM, particularly less than 10 nM, particularly less than 5 nM, particularly of 0.01 to 2 nM, particularly of 0.02 to 1 nM, particularly of 0.03 to 0.5 nM as measured by SPR, particularly wherein said TAA-BD is an scFv.
55. The pharmaceutical composition or the kit of item 53 or 54, wherein said TAA-BD is a mesothelin binding domain (MSLN-BD), which specifically binds to mesothelin (MSLN).
56. The pharmaceutical composition or the kit of item 55, wherein said MSLN-BD comprises
- (i) the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 139, 140 and 141, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 143, 144 and 145, respectively; and
 - (ii) VH3 or VH4 domain framework sequences FR1 to FR4; preferably VH3 domain framework sequences FR1 to FR4; and
 - (iii) a VL domain comprising a VL framework comprising framework regions FR1, FR2 and FR3, which are selected from V κ subtypes, particularly from the V κ 1 and V κ 3 subtypes, particularly are of the V κ 1 subtype, and a framework FR4, which is selected from a V κ FR4 and a V λ FR4, particularly is a V λ FR4 comprising an amino acid sequence having at least 70, 80, 90 percent identity, particularly at least 90 percent identity, to any of SEQ ID NO: 94 to SEQ ID NO: 101, more particularly a V λ FR4 selected from any of SEQ ID NO: 94 to SEQ ID NO: 101, particularly a V λ FR4 according to SEQ ID NO: 94 or 101.
57. The pharmaceutical composition or the kit of item 55 or 56, wherein said MSLN-BD comprises
- a) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 139, 140 and 141, respectively,

- b) LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 143, 144 and 145, respectively,
 - c) a VH sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 142, and
 - d) a VL sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 146.
58. The pharmaceutical composition or the kit of any one of items 55 to 57, wherein said MSLN-BD:
- a. binds to human MSLN with a monovalent dissociation constant (K_D) of less than 10 nM, particularly of 0.01 to 5 nM, particularly of 0.02 to 1 nM, in particular as measured by SPR, particularly wherein said MSLN-BD is a scFv; and/or
 - b. is cross reactive with *Macaca fascicularis* (cynomolgus) MSLN, in particular binds to cynomolgus MSLN with a monovalent K_D of less than 15 nM, particularly of 0.01 to 10 nM, particularly of 0.02 to 5 nM as measured by SPR, particularly wherein said MSLN-BD is an scFv.
59. The pharmaceutical composition or the kit of item 53 or 54, wherein said TAA-BD is a HER2 binding domain (HER2-BD), which specifically binds to HER2 (HER2).
60. The pharmaceutical composition or the kit of item 55, wherein said HER2-BD comprises
- (i) the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 165, 166 and 167, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 170, 171 and 172, respectively; and
 - (ii) VH3 or VH4 domain framework sequences FR1 to FR4; preferably VH3 domain framework sequences FR1 to FR4; and
 - (iii) a VL domain comprising a VL framework comprising framework regions FR1, FR2 and FR3, which are selected from Vk subtypes, particularly from the Vk1 and Vk3 subtypes, particularly are of the Vk1 subtype, and a framework FR4, which is selected from a Vk FR4 and a Vλ FR4, particularly is a Vλ FR4 comprising an amino acid sequence having at least 70, 80, 90 percent identity, particularly at least 90 percent identity, to any of SEQ ID NO: 94 to SEQ ID NO: 101, more particularly a Vλ FR4 selected from any of SEQ ID NO: 94 to SEQ ID NO: 101, particularly a Vλ FR4 according to SEQ ID NO: 94 or 101.

61. The pharmaceutical composition or the kit of item 55 or 56, wherein said HER2-BD comprises
- a) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 165, 166 and 167, respectively,
 - b) LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 170, 171 and 172, respectively,
 - c) a VH sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 168 or 169, and
 - d) a VL sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 173 or 174.
62. The pharmaceutical composition or the kit of item 53 or 54, wherein said TAA-BD is a ROR1 binding domain (ROR1-BD), which specifically binds to ROR1.
63. The pharmaceutical composition or the kit of item 62, wherein said ROR1-BD comprises
- (i) the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 215, 216 and 217, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 218, 219 and 220, respectively; and
 - (ii) VH3 or VH4 domain framework sequences FR1 to FR4; preferably VH3 domain framework sequences FR1 to FR4; and
 - (iii) a VL domain comprising a VL framework comprising framework regions FR1, FR2 and FR3, which are selected from Vk subtypes, particularly from the Vk1 and Vk3 subtypes, particularly are of the Vk1 subtype, and a framework FR4, which is selected from a Vk FR4 and a Vλ FR4, particularly is a Vλ FR4 comprising an amino acid sequence having at least 70, 80, 90 percent identity, particularly at least 90 percent identity, to any of SEQ ID NO: 94 to SEQ ID NO: 101, more particularly a Vλ FR4 selected from any of SEQ ID NO: 94 to SEQ ID NO: 101, particularly a Vλ FR4 according to SEQ ID NO: 94 or 101,
64. The pharmaceutical composition or the kit of item 62 or 63, wherein said ROR1-BD comprises
- a) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 215, 216 and 217, respectively,

- b) LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 218, 219 and 220, respectively,
 - c) a VH sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 221 or 222, and
 - d) a VL sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 223.
65. The pharmaceutical composition or the kit of any one of the items 1 to 52, wherein the MA2 comprises two TAA-BDs.
66. The pharmaceutical composition or the kit of item 65, wherein the two TAA-BDs in MA2 bind the same antigen.
67. The pharmaceutical composition or the kit of item 65 or 66, wherein the TAA is selected from the group consisting of ROR1, HER2 and tumor cell associated antigens, whose extracellular part also occurs in soluble form in the serum of a patient, in particular wherein the TAA is selected from the group consisting of HER2, MSLN and ROR1, and/or wherein the TAA is selected from the group consisting of ROR1 and tumor cell associated antigens, which are also expressed on the surface of healthy cells, in amounts corresponding to 10 – 75 % of the particular TAA density on the surface of the cancer cells, as determined by antigen binding capacity measurements.
68. The pharmaceutical composition or the kit of any one of the items 65 to 67, wherein said TAA-BD binds to said TAA with a monovalent dissociation constant (K_D) in the range of 0.1 to 50 nM, particularly of 0.2 to 30 nM, particularly of 0.3 to 20 nM, particularly of 0.4 to 10 nM, as measured by SPR, particularly wherein said TAA-BD is an scFv.
69. The pharmaceutical composition or the kit of any one of the items 65 to 68, wherein said TAA-BD is a mesothelin binding domain (MSLN-BD), which specifically binds to mesothelin (MSLN), particularly human mesothelin.
70. The pharmaceutical composition or the kit of item 69, wherein said MSLN-BD binds to mesothelin (MSLN) with a monovalent dissociation constant (K_D) in the range of from 0.4 to 50 nM, preferably of from 0.4 to 40 nM, more preferably of

from 0.5 to 30 nM, even more preferably of from 0.5 to 20 nM, when measured by SPR, particularly wherein said MSLN-BD is an scFv.

71. The pharmaceutical composition or the kit of item 69 or 70, wherein said MSLN-BD is cross-reactive with *Macaca fascicularis* (cynomolgus) MSLN, in particular binds to Cynomolgus MSLN with a monovalent K_D in the range of 3 to 75 nM, particularly in the range of 3 to 60 nM, particularly of 4 to 50 nM, particularly of 5 to 40 nM, as measured by SPR, when measured by SPR, in particular wherein said MSLN-BD is an scFv.
72. The pharmaceutical composition or the kit of any one of the items 69 to 71, wherein said MSLN-BD comprises
- (i) the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 147, 148 (or 151) and 149, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 153, 154 and 155, respectively; or the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 157, 158 and 159, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 161, 162 and 163, respectively; or the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 197, 198 and 199, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 200, 201 and 202, respectively; and
 - (ii) VH3 or VH4 domain framework sequences FR1 to FR4; particularly VH3 domain framework sequences FR1 to FR4; and
 - (iii) a VL domain comprising a VL framework comprising framework regions FR1, FR2 and FR3, which are selected from V κ subtypes, particularly from the V κ 1 and V κ 3 subtypes, particularly are of the V κ 1 subtype, and a framework FR4, which is selected from a V κ FR4 and a V λ FR4, particularly is a V λ FR4 comprising an amino acid sequence having at least 70, 80, 90 percent identity, particularly at least 90 percent identity, to any of SEQ ID NO: 94 to SEQ ID NO: 101, more particularly a V λ FR4 selected from any of SEQ ID NO: 94 to SEQ ID NO: 101, particularly a V λ FR4 according to SEQ ID NO: 94 or 101.
73. The pharmaceutical composition or the kit of item 72, wherein said MSLN-BD comprises
- a.1) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 147, 148 (or 151) and 149, respectively,

- b.1) LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 153, 154 and 155, respectively,
- c.1) a VH sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 150, and
- d.1) a VL sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 156;
- or
- a.2) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 147, 148 (or 151) and 149, respectively,
- b.2) LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 153, 154 and 155, respectively,
- c.2) a VH sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 152, and
- d.2) a VL sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 156;
- or
- a.3) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 157, 158 and 159, respectively,
- b.3) LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 161, 162 and 163, respectively,
- c.3) a VH sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 160, and
- d.3) a VL sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 164.
- or
- a.4) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 157, 158 and 159, respectively,
- b.4) LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 161, 162 and 163, respectively,
- c.4) a VH sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 194 or 195, and
- d.4) a VL sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 196;
- or
- a.5) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 197, 198 and 199, respectively,

- b.5) LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 200, 201 and 202, respectively,
 - c.5) a VH sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 203 or 204, and
 - d.5) a VL sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 205.
74. The pharmaceutical composition or the kit of any one of the items 65 to 68, wherein said TAA-BDs are ROR1 binding domains (ROR1-BDs), which specifically bind to ROR1, particularly human ROR1.
75. The pharmaceutical composition or the kit of item 74, wherein said ROR1-BDs comprise
- (i) the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 206, 207 and 208, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 209, 210 and 211, respectively; and
 - (ii) VH3 or VH4 domain framework sequences FR1 to FR4; preferably VH3 domain framework sequences FR1 to FR4; and
 - (iii) a VL domain comprising a VL framework comprising framework regions FR1, FR2 and FR3, which are selected from Vk subtypes, particularly from the Vk1 and Vk3 subtypes, particularly are of the Vk1 subtype, and a framework FR4, which is selected from a Vk FR4 and a Vλ FR4, particularly is a Vλ FR4 comprising an amino acid sequence having at least 70, 80, 90 percent identity, particularly at least 90 percent identity, to any of SEQ ID NO: 94 to SEQ ID NO: 101, more particularly a Vλ FR4 selected from any of SEQ ID NO: 94 to SEQ ID NO: 101, particularly a Vλ FR4 according to SEQ ID NO: 94 or 101.
76. The pharmaceutical composition or the kit of item 74, wherein said ROR1-BDs comprise
- a.1) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 206, 207 and 208, respectively,
 - b.1) LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 209, 210 and 211, respectively,
 - c.1) a VH sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 212, and

- d.1) a VL sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 214;
or
 - a.2) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 206, 207 and 208, respectively,
 - b.2) LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 209, 210 and 211, respectively,
 - c.2) a VH sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 213, and
 - d.2) a VL sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 214.
77. The pharmaceutical composition or the kit of item 72, 73, 75 or 76, wherein said VH domain comprises a cysteine at position 51 (AHO numbering) and said VL domain comprises a cysteine at position 141 (AHO numbering).
78. The pharmaceutical composition or the kit of any one of the preceding items, wherein said multispecific antibody MA2 is in a format selected from the group consisting of: scDB; a bispecific T cell engager (BiTE; tandem di-scFv); tandem tri-scFv; Fab-(scFv); scFab-dsscFv; tribody (Fab-(scFv)₂); Fab₂; Fab-Fv₂; diabody; triabody; tetrabody; scDb-scFv; di-diabody; scFv-Fc-scFv fusion (ADAPTIR); DVD-Ig; IgG-scFv fusions, such as CODV-IgG, Morrison (IgG CH₃-scFv fusion (Morrison L) or IgG CL-scFv fusion (Morrison H)), bsAb (scFv linked to C-terminus of light chain), Bs1Ab (scFv linked to N-terminus of light chain), Bs2Ab (scFv linked to N-terminus of heavy chain), Bs3Ab (scFv linked to C-terminus of heavy chain), Ts1Ab (scFv linked to N-terminus of both heavy chain and light chain) and Ts2Ab (dsscFv linked to C-terminus of heavy chain); a DARTTM; a TRIDENTTM; a scDb, a tandem tri-scFv, a Fab-(scFv), a scFab-dsscFv, a Fab-(scFv)₂, a Fab₂, a Fab-Fv₂, a diabody or a scDb-scFv fused to the N- and/or the C-terminus of a heterodimerization domain other than heterodimeric Fc domains; a MATCH and DuoBodies.
79. The pharmaceutical composition or the kit of any one of the preceding items, wherein said multispecific antibody MA2 is in a format selected from the group consisting of: a Morrison L, a Morrison H, an scFv-Fc-scFv fusion, and a MATCH format, preferably a Morrison L and a MATCH format; particularly wherein said

MA2 is in a MATCH format; in particular where said MA2 is a scMATCH3, MATCH3 or a MATCH4.

80. The pharmaceutical composition or the kit of any one of the preceding items, wherein said multispecific antibody MA2 is a single-chain protein.
81. The pharmaceutical composition or the kit of item 80, wherein said single-chain protein comprises an amino acid sequence consisting of:

- (i) a first VL domain,
 - (ii) a first polypeptide linker,
 - (iii) a first VH domain,
 - (iv) a second polypeptide linker,
 - (v) a second VL domain,
 - (vi) a third polypeptide linker, and
 - (vii) a second VH domain,
- arranged one after another in the stated order,

wherein said first VL domain associates with said second VH domain to form a first binding domain, and said second VL domain associates with said first VH domain to form a second binding domain,

and wherein said single-chain protein further comprises

- (viii) a third binding domain, which is formed by a third VL domain and a third VH domain that are connected via a fourth polypeptide linker, where said third binding domain is fused C-terminally or N-terminally via a fifth polypeptide linker to said amino acid sequence,

wherein said three binding domains have the following specificities:

- a) the first binding domain either specifically binds to a TAA (TAA-BD), particularly to mesothelin (MSLN-BD), or specifically binds to hSA (hSA-BD);
- b) the second binding domain specifically binds to human CD3 (CD3-BD); and
- c) the third binding domain specifically binds to a TAA (TAA-BD), particularly to mesothelin (MSLN-BD).

82. The pharmaceutical composition or the kit of item 80 or 81, wherein said single-chain protein comprises an amino acid sequence having at least 90, 95, 96, 97, 98 or 99 percent identity to the amino acid sequence selected from SEQ ID NO: 175, more particularly comprises the amino acid sequence of SEQ ID NO: 175, especially consists of the amino acid sequence SEQ ID NO: 175.

83. The pharmaceutical composition or the kit of any one of the items 1 to 79, wherein said multispecific antibody MA2 is a hetero-dimeric protein in the MATCH3 or MATCH4 format comprising a first and a second single-chain protein, wherein said first single-chain protein comprises a first amino acid sequence consisting of (from the N- to the C-terminus):

- (ia) a first VL domain,
- (iia) a first polypeptide linker, and
- (iiia) a second VL domain, and

wherein said second single-chain protein comprises a second amino acid sequence consisting of (from the N- to the C-terminus):

- (ib) a first VH domain,
- (iib) a second polypeptide linker, and
- (iiib) a second VH domain, and

wherein said first VL domain associates with either said first or said second VH domain to form a first binding domain, and said second VL domain associates with the other of said VH domains to form a second binding domain,

and wherein at least one of said first and said second single-chain proteins further comprises

- (iv) a third binding domain, which is formed by a third VL domain and a third VH domain that are connected via a third polypeptide linker, where said third binding domain is fused via a fourth polypeptide linker to said first or said second amino acid sequence, and

wherein optionally, in the MATCH4 format, at least one of said first and said second single-chain proteins further comprises

- (v) a fourth binding domain, which is formed by a fourth VL domain and a fourth VH domain that are connected via a fifth polypeptide linker, where said fourth binding domain is fused via a sixth polypeptide linker to said first or said second amino acid sequence,

wherein said three (MATCH3), or optionally four (MATCH4), binding domains have the following specificities:

when three binding domains are present (MATCH3),

- a) one of the binding domains specifically binds to a TAA (TAA-BDs), particularly to mesothelin (MSLN-BD);
- b) another binding domain specifically binds to human CD3 (CD3-BD); and,
- c) the remaining binding domain either specifically binds to the same TAA (TAA-BDs), particularly to mesothelin (MSLN-BD), or to human serum albumin (hSA-BD);

or, when the optional fourth binding domain is present (MATCH4),

- a) two binding domains specifically bind to the same TAA (TAA-BDs), particularly to mesothelin (MSLN-BD);
- b) another binding domain specifically binds to human CD3 (CD3-BD); and,
- c) the remaining binding domain specifically binds to human serum albumin (hSA-BD).

84. The pharmaceutical composition or the kit of item 83, wherein the optional fourth binding domain is absent and wherein one of said first and second binding domains is a CD3-BD and the other one of said first and second binding domains is a TAA-BD.

85. The pharmaceutical composition or the kit of item 83, wherein the optional fourth binding domain is present and wherein the third binding domain is fused to either the first or the second amino acid sequence, and the fourth binding domain is fused to the other one of the said two amino acid sequences.

86. The pharmaceutical composition or the kit of item 83 or 85, wherein the optional fourth binding domain is present and wherein one of said first and second binding

domains is a CD3-BD and the other one of said first and second binding domains is a hSA-BD.

87. The pharmaceutical composition or the kit of any one of the items 83 to 86, wherein said hetero-dimeric protein does not comprise a cognate pair of a first and a second proteinaceous interaction domain, other than said first and second VL and VH domains, wherein said first proteinaceous interaction domain is comprised in said first single-chain protein and wherein said second proteinaceous interaction domain is comprised in said second single-chain protein.
88. The pharmaceutical composition or the kit of any one of the items 83 to 87, wherein said first single-chain protein and said second single-chain protein hetero-dimerize in a parallel orientation, *i. e.* said first VL domain associates with said first VH domain and said second VL domain associates with said second VH domain.
89. The pharmaceutical composition or the kit of any one of items 83 to 87, wherein said first single-chain protein and said second single-chain protein hetero-dimerize in an anti-parallel orientation, *i. e.* said first VL domain associates with said second VH domain and said second VL domain associates with said first VH domain.
90. The pharmaceutical composition or the kit of any one of items 83 to 89, wherein said first single-chain protein comprises an amino acid sequence having at least 90, 95, 96, 97, 98 or 99 percent identity to the amino acid sequence of SEQ ID NO: 176, more particularly comprises the amino acid sequence of SEQ ID NO: 176, especially consists of the amino acid sequence SEQ ID NO: 176 and said second single-chain protein comprises an amino acid sequence having at least 90, 95, 96, 97, 98 or 99 percent identity to the amino acid sequence of SEQ ID NO: 177, more particularly comprises the amino acid sequence of SEQ ID NO: 177, especially consists of the amino acid sequence SEQ ID NO: 177; or said first single-chain protein comprises an amino acid sequence having at least 90, 95, 96, 97, 98 or 99 percent identity to the amino acid sequence of SEQ ID NO: 178, more particularly comprises the amino acid sequence of SEQ ID NO: 178, especially consists of the amino acid sequence SEQ ID NO: 178 and said second single-chain protein comprises an amino acid sequence having at least 90, 95, 96, 97, 98 or 99 percent identity to the amino acid sequence of SEQ

ID NO: 179, more particularly comprises the amino acid sequence of SEQ ID NO: 179, especially consists of the amino acid sequence SEQ ID NO: 179; or said first single-chain protein comprises an amino acid sequence having at least 90, 95, 96, 97, 98 or 99 percent identity to the amino acid sequence of SEQ ID NO: 224, more particularly comprises the amino acid sequence of SEQ ID NO: 224, especially consists of the amino acid sequence SEQ ID NO: 224 and said second single-chain protein comprises an amino acid sequence having at least 90, 95, 96, 97, 98 or 99 percent identity to the amino acid sequence of SEQ ID NO: 225, more particularly comprises the amino acid sequence of SEQ ID NO: 225, especially consists of the amino acid sequence SEQ ID NO: 225; or said first single-chain protein comprises an amino acid sequence having at least 90, 95, 96, 97, 98 or 99 percent identity to the amino acid sequence of SEQ ID NO: 226, more particularly comprises the amino acid sequence of SEQ ID NO: 226, especially consists of the amino acid sequence SEQ ID NO: 226 and said second single-chain protein comprises an amino acid sequence having at least 90, 95, 96, 97, 98 or 99 percent identity to the amino acid sequence of SEQ ID NO: 227, more particularly comprises the amino acid sequence of SEQ ID NO: 227, especially consists of the amino acid sequence SEQ ID NO: 227; or said first single-chain protein comprises an amino acid sequence having at least 90, 95, 96, 97, 98 or 99 percent identity to the amino acid sequence of SEQ ID NO: 228, more particularly comprises the amino acid sequence of SEQ ID NO: 228, especially consists of the amino acid sequence SEQ ID NO: 228 and said second single-chain protein comprises an amino acid sequence having at least 90, 95, 96, 97, 98 or 99 percent identity to the amino acid sequence of SEQ ID NO: 229, more particularly comprises the amino acid sequence of SEQ ID NO: 229, especially consists of the amino acid sequence SEQ ID NO: 229; or said first single-chain protein comprises an amino acid sequence having at least 90, 95, 96, 97, 98 or 99 percent identity to the amino acid sequence of SEQ ID NO: 230, more particularly comprises the amino acid sequence of SEQ ID NO: 230, especially consists of the amino acid sequence SEQ ID NO: 230 and said second single-chain protein comprises an amino acid sequence having at least 90, 95, 96, 97, 98 or 99 percent identity to the amino acid sequence of SEQ ID NO: 231, more particularly comprises the amino acid sequence of SEQ ID NO: 231, especially consists of the amino acid sequence SEQ ID NO: 231; or said first single-chain protein comprises an amino acid sequence having at least 90, 95, 96, 97, 98 or 99 percent identity to the amino acid sequence of SEQ ID

NO: 232, more particularly comprises the amino acid sequence of SEQ ID NO: 232, especially consists of the amino acid sequence SEQ ID NO: 232 and said second single-chain protein comprises an amino acid sequence having at least 90, 95, 96, 97, 98 or 99 percent identity to the amino acid sequence of SEQ ID NO: 233, more particularly comprises the amino acid sequence of SEQ ID NO: 233, especially consists of the amino acid sequence SEQ ID NO: 233; or said first single-chain protein comprises an amino acid sequence having at least 90, 95, 96, 97, 98 or 99 percent identity to the amino acid sequence of SEQ ID NO: 234, more particularly comprises the amino acid sequence of SEQ ID NO: 234, especially consists of the amino acid sequence SEQ ID NO: 234 and said second single-chain protein comprises an amino acid sequence having at least 90, 95, 96, 97, 98 or 99 percent identity to the amino acid sequence of SEQ ID NO: 235, more particularly comprises the amino acid sequence of SEQ ID NO: 235, especially consists of the amino acid sequence SEQ ID NO: 235.

91. The pharmaceutical composition or the kit of any one of the preceding items, wherein at least one of said antibody variable domains of MA1 and MA2 comprises CDR regions derived from a parental rabbit antibody.
92. The pharmaceutical composition or the kit of any one of the preceding items, wherein the TAA-BD and the CD3-BD or at least one of the two TAA-BDs and the CD3-BD are capable of binding to their respective antigens simultaneously, particularly wherein the TAA-BD and the CD3-BD or the two TAA-BDs and the CD3-BD are capable of binding to their respective antigens simultaneously.
93. The pharmaceutical composition or the kit of any one of items 1 to 92 for use as a medicament.
94. The pharmaceutical composition or the kit of any one of items 1 to 92 for use in the treatment of a disease, particularly a human disease, more particularly a human disease selected from cancer.
95. The pharmaceutical composition or the kit of any one of items 1 to 92 for use in the treatment of a disease according to item 94, wherein said disease is a proliferative disease, particularly a cancer, particularly a cancer selected from

melanoma, mesothelioma, pancreatic cancer, stomach cancer, breast cancer, ovarian cancer and lung cancer.

96. A method for the treatment of a disease, particularly a human disease, more particularly a human disease selected from cancers, comprising the step of administering the pharmaceutical composition or the kit of any one of items 1 to 92.
97. The method of item 96, wherein said disease is a proliferative disease, particularly a cancer, particularly a cancer selected from melanoma, mesothelioma, pancreatic cancer, stomach cancer, breast cancer, ovarian cancer and lung cancer.
98. A method for treating a patient suffering from a disease, comprising the step of administering a first multispecific antibody (MA1) comprising one binding domain, which specifically binds to CD137 (CD137-BD), and one binding domain, which specifically binds to PDL1 (PDL1-BD), and a second multispecific antibody (MA2) comprising at least one binding domain, which specifically binds to a tumor cell associated antigen (TAA-BD), and one binding domain, which specifically binds to CD3 (CD3-BD), wherein said multispecific antibodies MA1 and MA2 are as defined in any of the items 1 to 94.
99. The method of item 98, wherein said disease is a proliferative disease, particularly a cancer, particularly a cancer selected from melanoma, mesothelioma, pancreatic cancer, stomach cancer, breast cancer, ovarian cancer and lung cancer.
100. A multispecific antibody MA1 comprising one binding domain, which specifically binds to CD137 (CD137-BD), and one binding domain, which specifically binds to PDL1 (PDL1-BD) for use in the treatment of a subject suffering from a disease, wherein said multispecific antibody MA1 is administered to said subject in combination with a multispecific antibody MA2 comprising at least one binding domain, which specifically binds to a tumor cell associated antigen (TAA-BD), and one binding domain, which specifically binds to CD3 (CD3-BD), wherein said multispecific antibodies MA1 and MA2 are as defined herein.

101. A multispecific antibody MA2 comprising one binding domain, which specifically binds to a tumor cell associated antigen (TAA-BD), and one binding domain, which specifically binds to CD3 (CD3-BD) for use in the treatment of a subject suffering from a disease, wherein said multispecific antibody MA2 is administered to said subject in combination with a multispecific antibody MA1 comprising at least one binding domain, which specifically binds to CD137 (CD137-BD), and one binding domain, which specifically binds to PDL1 (PDL1-BD), wherein said multispecific antibodies MA1 and MA2 are as defined herein.
102. The multispecific antibody MA1 for use according to item 100, or the multispecific antibody MA2 for use according to item 101, wherein said disease is a proliferative disease, particularly a cancer, particularly a cancer selected from melanoma, mesothelioma, pancreatic cancer, stomach cancer, breast cancer, ovarian cancer and lung cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

[0046] **FIG. 1** shows the target cell dependent activation of T cell co-stimulatory receptors by the multispecific antibodies applied in the present invention. Cross-linking of CD137 with a bivalent monoclonal antibody triggers systemic co-stimulation of T cells that is further boosted by FcγR binding-mediated cross-linking (**A**). The stable bi-/trispecific monovalent molecules used in the present invention cannot cross-link (or, by extension, agonize) co-stimulatory receptors on T cells in the absence of the cell-type being targeted for depletion (**B**). The stable bi-/trispecific monovalent molecules used in the present invention cross-link (or, by extension, agonize) costimulatory receptors on T cells in the presence of the cell-type being targeted for depletion (**C**). Concomitant binding to PDL1 and CD137 triggers selective activation of tumor-reactive T cells and simultaneously blocks PD-1 signaling (**D**).

[0047] **FIG. 2** shows the concentration-dependent activation of NF-κB signaling in Jurkat reporter cells (filled symbols) and inhibition of PDL1 activity in NFAT reporter cells (open symbols) of: PRO1124 with a PDL1 binding affinity (K_D) greater (worse) than that of CD137 (4-1BB) K_D (**A**), PRO885 with a PDL1 K_D less (better) than that of CD137 (4-1BB) K_D (**B**), and NM21-1480 (PRO1480) with a PDL1 K_D considerably

less (better) than that of CD137 (4-1BB) K_D (**C**). The grey arrow and the grey dashed line indicate the concentration at which maximal PDL1 antagonism is reached. The corresponding level of CD137 (4-1BB) agonism at that concentration and the breadth of concentrations, where maximal activity of both PDL1 blockade and CD137 (4-1BB) stimulation is observed, are important for optimal dose finding, as indicated by the shaded grey box in (**C**). By altering the K_D of the PDL1-BD to PDL1 to levels significantly lower than the K_D of the CD137-BD to CD137 (4-1BB), the EC₅₀ and IC₅₀ values for the respective functional activities become more closely matched and the plateau of CD137 (4-1BB) stimulation becomes broader. NM21-1480 (PRO1480) has exquisitely optimized PDL1 and CD137 (4-1BB) binding domains to allow activity of both PDL1 blockade and CD137 (4-1BB) activation at the same optimal dose and to extend the concentration range of maximal CD137 (4-1BB) signaling.

[0048] **FIG. 3** shows the cytotoxic activity and effect on CD8⁺ T cell activation of PRO2000 and PRO1872 in the presence of human serum albumin. (A) Specific killing of high MSLN expressing cancer cells (H226 cells). On cancer cells expressing high levels of mesothelin, the target cell killing potency observed for PRO2000 is 75-fold better than for PRO1872. (B) Specific killing of low MSLN expressing cancer cells (MeT-5A cells). On cells derived from healthy mesothelial tissue (MeT-5A; ATCC CRL-9444) expressing low mesothelin levels the monovalent mesothelin binding protein PRO1872 shows the best killing potency. (C) CD8⁺ T cell activation in presence of H226 cells, and (D) CD8⁺ T cell activation in presence of MeT-5A cells. Similar data were observed for CD8⁺ T cell activation. PBMCs from donor #1 were used. Target cells and CD8⁺ T cells were analyzed by flow cytometry 40 h after the beginning of their incubation with the respective molecules, and data were fitted using sigmoidal 4PL fit (GraphPad Prism).

[0049] **FIG. 4** shows the cytotoxic activity and effect on CD8⁺ T cell activation of PRO2000 and PRO1872 in absence or presence of sMSLN. (A to C) Cytotoxic activity of PRO2000 and PRO1872 on H226 target cells. Specific killing of H226 cells in absence of sMSLN (A), in presence of 50 ng/ml sMSLN (B), or in presence of 500 ng/ml sMSLN (C). PRO2000 killing potency is less affected by increasing concentrations of sMSLN as compared to PRO1872 (D to F) Similar data are observed for CD8⁺ T cell activation in the corresponding conditions. CD8⁺ T cell activation in presence of H226 cells without sMSLN (D), in presence of 50 ng/ml

sMLSN (E), or in presence of 500 ng/ml sMLSN (F). PBMCs from donor #2 were used. Target cells and CD8⁺ T cells were analyzed by flow cytometry 40 h after the beginning of their incubation with the respective molecules, and data were fitted using sigmoidal 4PL fit (GraphPad Prism).

[0050] **FIG. 5** shows MSLN-expressing NSCLC tumor cells xenograft experiment with molecule PRO2000 (biMSLN.CD3) revealing tumor growth inhibition for PRO2000 treatment relative to control conditions. (A) Longitudinal analysis of tumor growth in the presence or absence of treatment. The lines depict the median. Animals were subcutaneously co-implanted with 1×10^7 H292 MSLN-expressing NSCLC tumor cells and 1×10^7 PBMCs, and treatment was administered intravenously starting on day 5 and repeated every 5 days until the end of the experiment. (B) Day 40 data displayed as a scatter plot. Each point corresponds to one animal, and the data are displayed with the mean and standard deviation. After a two-way repeated measures ANOVA, the Tukey's multiple comparisons test was performed, and the significance of each data set is depicted relative to palivizumab control (Ctrl, lower line), or no treatment (upper line). ns = not significant; *, $p < 0.05$; **, $p < 0.01$, ***, $p < 0.001$. The spark line in gray indicates 0 on the y-axis.

[0051] **FIG. 6** shows MSLN-expressing NSCLC tumor cells xenograft experiment with molecules PRO1872 (MSLN.CD3) and PRO1601 (PDL1.CD137) alone as well as with a combination of PRO1601 + PRO1872 (MSLN.CD3), revealing significantly enhanced tumor growth inhibition for the combination treatment relative to the PRO1872 and PRO1601 single treatments. (A) Longitudinal analysis of tumor growth in the presence or absence of treatment. The lines depict the median. Animals were subcutaneously co-implanted with 1×10^7 H292 MSLN-expressing NSCLC tumor cells and 1×10^7 PBMCs, and treatment was administered intravenously starting on day 5 and repeated every 5 days until the end of the experiment. (B) Enlarged representation of the 0 to 28 days section of PRO1601 single treatment revealing significant tumor growth inhibition for PRO1601 alone relative to control conditions. After a two-way repeated measures ANOVA, the Tukey's multiple comparisons test was performed. The significances of the tumor growth inhibition of the PRO1601 + PRO1872 combination relative to PRO1601 alone and PRO1601 alone relative to palivizumab control, respectively, are depicted (*, $p < 0.001$). The spark line in gray indicates 0 on the y-axis.

[0052] **FIG. 7** shows MSLN-expressing HPAC tumor cells xenograft experiment with molecules PRO2746 (MSLN.CD3) and PRO1601 (PDL1.CD137) alone as well as with a combination of PRO1601 + PRO2746 (MSLN.CD3), revealing significantly enhanced tumor growth inhibition for the combination treatment relative to the PRO2746 and PRO1601 single treatments. (A) Longitudinal analysis of tumor growth in the presence or absence of treatment. The lines depict the median. (B) Day 40 data displayed as a scatter plot. Each point corresponds to one animal, and the data are displayed with the mean and standard deviation. (C) and (D) displays the longitudinal trends for the individual animals in each group. Tumor growth regression was uniformly observed across animals for the combination of PRO2746 at 0.2 mg/kg and PRO1601 at 1 mg/kg, compared to either treatment alone.

[0053] **FIG. 8** shows a longitudinal analysis of an *in vitro*, ROR1-expressing cell line real time live cell imaging experiment to determine the ability of PRO1601 (4-1BBxPDL-1xhSA) and PRO2668 (ROR1xCD3xhSA) to effectively lyse cells in combination relative to individual molecules alone and no treatment controls. The number of dying cells in green were divided by the number of remaining target cells in red. A downward slope in the curve indicates cell growth.

DETAILED DESCRIPTION OF THE INVENTION

[0054] Known TAA/CD3 bsAbs-based immunotherapies typically suffer from dose-limiting toxicities and limited *in vivo* efficacy. There is thus a need in the medical field for improved TAA/CD3 bsAbs-based immunotherapies, which have higher efficacy but at the same time a similar or even lower toxicological profile than the currently available approaches.

[0055] The present invention provides pharmaceutical compositions or a kit comprising a first multispecific antibody, which comprise one CD137-agonizing binding domain and one PDL1-antagonizing binding domain but no immunoglobulin Fc region, and a second multispecific antibody, which specifically binds to a TAA and CD3. These multispecific antibody combinations exhibit a significantly greater efficacy in TAA-(re)directed target cell killing and tumor growth inhibition than the individual multispecific antibody components alone.

[0056] Albeit the multispecific CD137/PDL1 binding antibodies in the pharmaceutical compositions or the kit of the present invention are monovalent for CD137, they are able to cluster and to agonize CD137, however strictly in the presence of PDL1-positive cells, thus avoiding systemic activation of CD137. The monovalent CD137 binding and Fc-less structure of the multispecific antibody ensures that agonism of CD137 on effector cells can only arise when the antibody concomitantly binds to PDL1 on the surface of target cells. At the same time the toxicological profiles of the pharmaceutical compositions or the kit of the present invention are not worse than for the respective anti-TAAxCD3 multispecific antibody components alone that are comprised therein. Accordingly, the application of the pharmaceutical compositions or the kit of the present invention provides a significant risk-to-benefit gain when compared to the single application of the individual anti-TAAxCD3 multispecific antibodies.

[0057] When these multispecific CD137/PDL1 binding antibodies are combined with anti-TAAxCD3 multispecific antibodies comprising two TAA-BDs having medium to low binding affinity for the same TAA target, this approach in particular allows TAA-(re)directed target cell killing of tumor cell expressing non-clean TAAs, i.e. TAAs that are also expressed at significantly high amounts in healthy cells, such as Mesothelin (MSLN), EGFR, EpCAM and HER2. The application of these specific variants of the pharmaceutical compositions or the kits of the present invention provide a significant risk-to-benefit gain also for TAA-(re)directed target cell killing of tumor cell expressing non-clean TAAs when compared to single anti-TAAxCD3 antibody therapies.

[0058] Furthermore, the optional addition of a half-life-extending anti-hSA domain not only enables convenient dosing but should also promote delivery of the molecule to tumor microenvironments.

[0059] The pharmaceutical compositions or the kits of the present invention thus provide distinct therapeutic advantages over conventional compositions and therapies.

[0060] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by those of ordinary skill in the art to which this invention pertains.

[0061] The terms “comprising” and “including” are used herein in their open-ended and non-limiting sense unless otherwise noted. With respect to such latter embodiments, the term “comprising” thus includes the narrower term “consisting of”.

[0062] The terms “a” and “an” and “the” and similar references in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. For example, the term “a cell” includes a plurality of cells, including mixtures thereof. Where the plural form is used for compounds, salts, and the like, this is taken to mean also a single compound, salt, or the like.

[0063] In one aspect, the present invention relates to a pharmaceutical composition comprising:

- 1) a first multispecific antibody (MA1) comprising
 - a) one binding domain, which specifically binds to CD137 (CD137-BD), and
 - b) one binding domain, which specifically binds to PDL1 (PDL1-BD),
- 2) a second multispecific antibody (MA2) comprising
 - a) at least one binding domain, which specifically bind(s) to a tumor cell associated antigen (TAA-BD),
 - b) one binding domain, which specifically binds to CD3 (CD3-BD),
- 3) a pharmaceutically acceptable carrier.

[0064] In another aspect, the present invention relates to a kit comprising:

- 1) a first multispecific antibody (MA1) comprising
 - a) one binding domain, which specifically binds to CD137 (CD137-BD), and
 - b) one binding domain, which specifically binds to PDL1 (PDL1-BD), and
- 2) a second multispecific antibody (MA2) comprising
 - a) at least one binding domain, which specifically binds to a tumor cell associated antigen (TAA-BD), and
 - b) one binding domain, which specifically binds to CD3 (CD3-BD).

[0065] In particular embodiments, said second multispecific antibody (MA2) comprises one or two TAA-BD(s).

[0066] In particular embodiments, said multispecific antibody MA1 does not comprise an immunoglobulin Fc region polypeptide.

[0067] In a particular aspect, the present invention relates to a pharmaceutical composition comprising:

- 1) a first multispecific antibody (MA1) comprising

- a) one binding domain, which specifically binds to CD137 (CD137-BD), and
- b) one binding domain, which specifically binds to PDL1 (PDL1-BD),
- 2) a second multispecific antibody (MA2) comprising
 - a) one or two binding domain(s), which specifically bind(s) to a tumor cell associated antigen (TAA-BD),
 - b) one binding domain, which specifically binds to CD3 (CD3-BD),
- 3) a pharmaceutically acceptable carrier,

wherein said MA1 does not comprise an immunoglobulin Fc region polypeptide.

[0068] In another particular aspect, the present invention relates to a kit comprising:

- 1) a first multispecific antibody (MA1) comprising
 - a) one binding domain, which specifically binds to CD137 (CD137-BD), and
 - b) one binding domain, which specifically binds to PDL1 (PDL1-BD), and
- 2) a second multispecific antibody (MA2) comprising
 - a) one or two binding domain(s), which specifically bind(s) to a tumor cell associated antigen (TAA-BD), and
 - b) one binding domain, which specifically binds to CD3 (CD3-BD),

wherein said MA1 does not comprise an immunoglobulin Fc region polypeptide.

[0069] The term “antibody” and the like, as used herein, includes whole antibodies or single chains thereof; and any antigen-binding fragment (*i. e.*, “antigen-binding portion”) or single chains thereof; and molecules comprising antibody CDRs, VH regions or VL regions (including without limitation multispecific antibodies). A naturally occurring “whole antibody” is a glycoprotein comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as VH) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as VL) and a light chain constant region. The light chain constant region is comprised of one domain, CL. The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FRs). Each VH and VL is composed of three CDRs and four FRs arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant

regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (*e. g.*, effector cells) and the first component (C1q) of the classical complement system.

[0070] The term “immunoglobulin Fc region”, as used herein, refers to the CH2 and CH3 domains of the heavy chain constant regions.

[0071] The terms “binding domain”, “antigen-binding fragment thereof”, “antigen-binding portion” of an antibody, and the like, as used herein, refer to one or more fragments of an intact antibody that retain the ability to specifically bind to a given antigen (*e. g.*, PDL1, CD137, TAA, CD3, hSA). Antigen-binding functions of an antibody can be performed by fragments of an intact antibody. In some embodiments, a binding domain of a multispecific antibody applied in the pharmaceutical composition or the kit of the present invention is selected from the group consisting of a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; a F(ab)₂ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; an Fd fragment consisting of the VH and CH1 domains; an Fv fragment consisting of the VL and VH domains of a single arm of an antibody; a single domain antibody (dAb) fragment (Ward et al., 1989 Nature 341:544-546), which consists of a VH domain; an isolated complementarity determining region (CDR), a dsFv, a scAb, STAB, and binding domains based on alternative scaffolds including but limited to ankyrin-based domains, fynomers, avimers, anticalins, fibronectins, and binding sites being built into constant regions of antibodies (*e. g.* f-star technology (F-star’s Modular Antibody Technology™)). Suitably, the binding domain of an antibody applied in the present invention is a single-chain Fv fragment (scFv) or a single antibody variable domain. In a preferred embodiment, the binding domain of an antibody applied in the present invention is a single-chain Fv fragment (scFv). In particular embodiments, the two variable domains of an antigen-binding fragment, as in an Fv or an scFv fragment, are stabilized by an interdomain disulfide bond, in particular said VH domain comprises a single cysteine residue in position 51 (AHO numbering) and said VL domain comprises a single cysteine residue in position 141 (AHO numbering).

[0072] The term “Complementarity Determining Regions” (“CDRs”) refers to amino acid sequences with boundaries determined using any of a number of well-known schemes, including those described by Kabat et al. (1991), “Sequences of Proteins

of Immunological Interest,” 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD (“Kabat” numbering scheme); Al-Lazikani et al., (1997) JMB 273, 927-948 (“Chothia” numbering scheme); ImMunoGenTics (IMGT) numbering (Lefranc, M.-P., The Immunologist, 7, 132-136 (1999); Lefranc, M.-P. et al., Dev. Comp. Immunol., 27, 55-77 (2003)) (“IMGT” numbering scheme); and the numbering scheme described in Honegger & Plückthun, J. Mol. Biol. 309 (2001) 657-670 (“AHO” numbering). For example, for classic formats, under Kabat, the CDR amino acid residues in the heavy chain variable domain (VH) are numbered 31-35 (HCDR1), 50-65 (HCDR2), and 95-102 (HCDR3); and the CDR amino acid residues in the light chain variable domain (VL) are numbered 24-34 (LCDR1), 50-56 (LCDR2), and 89-97 (LCDR3). Under Chothia the CDR amino acids in the VH are numbered 26-32 (HCDR1), 52-56 (HCDR2), and 95-102 (HCDR3); and the amino acid residues in VL are numbered 24-34 (LCDR1), 50-56 (LCDR2), and 89-97 (LCDR3). By combining the CDR definitions of both Kabat and Chothia, the CDRs consist of amino acid residues 26-35 (HCDR1), 50-65 (HCDR2), and 95-102 (HCDR3) in human VH and amino acid residues 24-34 (LCDR1), 50-56 (LCDR2), and 89-97 (LCDR3) in human VL. Under IMGT the CDR amino acid residues in the VH are numbered approximately 26-35 (HCDR1), 51-57 (HCDR2) and 93-102 (HCDR3), and the CDR amino acid residues in the VL are numbered approximately 27-32 (LCDR1), 50-52 (LCDR2), and 89-97 (LCDR3) (numbering according to “Kabat”). Under IMGT, the CDRs of an antibody can be determined using the program IMGT/DomainGap Align. [0073] In the context of the present invention, the numbering system suggested by Honegger & Plückthun (“AHO”) is used (Honegger & Plückthun, J. Mol. Biol. 309 (2001) 657-670), unless specifically mentioned otherwise. In particular, the following residues are defined as CDRs according to AHO numbering scheme: LCDR1 (also referred to as CDR-L1): L24-L42; LCDR2 (also referred to as CDR-L2): L58-L72; LCDR3 (also referred to as CDR-L3): L107-L138; HCDR1 (also referred to as CDR-H1): H27-H42; HCDR2 (also referred to as CDR-H2): H57-H76; HCDR3 (also referred to as CDR-H3): H108-H138. For the sake of clarity, the numbering system according to Honegger & Plückthun takes the length diversity into account that is found in naturally occurring antibodies, both in the different VH and VL subfamilies and, in particular, in the CDRs, and provides for gaps in the sequences. Thus, in a

given antibody variable domain usually not all positions 1 to 149 will be occupied by an amino acid residue.

[0074] The term “binding specificity” as used herein refers to the ability of an individual antibody to react with one antigenic determinant and not with a different antigenic determinant. As use herein, the term “specifically binds to” or is “specific for” refers to measurable and reproducible interactions such as binding between a target and an antibody, which is determinative of the presence of the target in the presence of a heterogeneous population of molecules including biological molecules. For example, an antibody that specifically binds to a target (which can be an epitope) is an antibody that binds this target with greater affinity, avidity, more readily, and/or with greater duration than it binds to other targets. In its most general form (and when no defined reference is mentioned), “specific binding” is referring to the ability of the antibody to discriminate between the target of interest and an unrelated molecule, as determined, for example, in accordance with a specificity assay methods known in the art. Such methods comprise, but are not limited to Western blots, ELISA, RIA, ECL, IRMA, SPR (Surface plasmon resonance) tests and peptide scans. For example, a standard ELISA assay can be carried out. The scoring may be carried out by standard color development (e. g. secondary antibody with horseradish peroxidase and tetramethyl benzidine with hydrogen peroxide). The reaction in certain wells is scored by the optical density, for example, at 450 nm. Typical background (= negative reaction) may be about 0.1 OD; typical positive reaction may be about 1 OD. This means the ratio between a positive and a negative score can be 10-fold or higher. In a further example, an SPR assay can be carried out, wherein at least 10-fold, particularly at least 100-fold difference between a background and signal indicates on specific binding. Typically, determination of binding specificity is performed by using not a single reference molecule, but a set of about three to five unrelated molecules, such as milk powder, transferrin or the like.

[0075] Suitably, the antibodies applied in the pharmaceutical compositions or the kit of the invention are isolated antibodies. The term “isolated antibody”, as used herein, refers to an antibody that is substantially free of other antibodies having different antigenic specificities (e. g., an isolated antibody that specifically binds PDL1 and CD137 is substantially free of antibodies that specifically bind antigens other than PDL1 and CD137, an isolated antibody that specifically binds PDL1, CD137 and hSA

is substantially free of antibodies that specifically bind antigens other than PDL1, CD137 and hSA, and an isolated antibody that specifically binds MSLN, CD3 and hSA is substantially free of antibodies that specifically bind antigens other than MSLN, CD3 and hSA). Moreover, an isolated antibody may be substantially free of other cellular material and/or chemicals.

[0076] Suitably, the antibodies applied in the pharmaceutical compositions or the kit of the invention are monoclonal antibodies. The term “monoclonal antibody” or “monoclonal antibody composition” as used herein refers to antibodies that are substantially identical to amino acid sequence or are derived from the same genetic source. A monoclonal antibody composition displays a binding specificity and affinity for a particular epitope, or binding specificities and affinities for specific epitopes.

[0077] Antibodies applied in the pharmaceutical compositions or the kit of the invention include, but are not limited to, chimeric, human and humanized antibodies.

[0078] The term “chimeric antibody” (or antigen-binding fragment thereof) is an antibody molecule (or antigen-binding fragment thereof) in which (a) the constant region, or a portion thereof, is altered, replaced or exchanged so that the antigen-binding site (variable region) is linked to a constant region of a different or altered class, effector function and/or species, or an entirely different molecule which confers new properties to the chimeric antibody, *e. g.*, an enzyme, toxin, hormone, growth factor, drug, etc.; or (b) the variable region, or a portion thereof, is altered, replaced or exchanged with a variable region having a different or altered antigen specificity. For example, a mouse antibody can be modified by replacing its constant region with the constant region from a human immunoglobulin. Due to the replacement with a human constant region, the chimeric antibody can retain its specificity in recognizing the antigen while having reduced antigenicity in human as compared to the original mouse antibody.

[0079] The term “human antibody” (or antigen-binding fragment thereof), as used herein, is intended to include antibodies (and antigen-binding fragments thereof) having variable regions in which both the framework and CDR regions are derived from sequences of human origin. Furthermore, if the antibody contains a constant region, the constant region also is derived from such human sequences, *e. g.*, human germline sequences, or mutated versions of human germline sequences. The human antibodies and antigen-binding fragments thereof of the invention may

include amino acid residues not encoded by human sequences (*e. g.*, mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*). This definition of a human antibody specifically excludes a humanized antibody comprising non-human antigen-binding residues. Human antibodies can be produced using various techniques known in the art, including phage-display libraries (Hoogenboom and Winter, *J. Mol. Biol.*, 227:381 (1991); Marks et al, *J. Mol. Biol.*, 222:581 (1991)). Also available for the preparation of human monoclonal antibodies are methods described in Cole et al, *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, p. 77 (1985); Boemer et al, *J. Immunol.*, 147(1):86-95 (1991). See also van Dijk and van de Winkel, *Curr. Opin. Pharmacol.*, 5: 368-74 (2001). Human antibodies can be prepared by administering the antigen to a transgenic animal that has been modified to produce such antibodies in response to antigenic challenge, but whose endogenous loci have been disabled, *e. g.*, immunized xenomice (see, *e. g.*, U.S. Pat. Nos. 6,075,181 and 6,150,584 regarding XENOMOUSE™ technology). See also, for example, Li et al, *Proc. Natl. Acad. Sci. USA*, 103:3557- 3562 (2006) regarding human antibodies generated via a human B-cell hybridoma technology.

[0080] A “humanized” antibody (or antigen-binding fragment thereof), as used herein, is an antibody (or antigen-binding fragment thereof) that retains the reactivity of a non-human antibody while being less immunogenic in humans. This can be achieved, for instance, by retaining the non-human CDR regions and replacing the remaining parts of the antibody with their human counterparts (*i. e.*, the constant region as well as the framework portions of the variable region). Additional framework region modifications may be made within the human framework sequences as well as within the CDR sequences derived from the germline of another mammalian species. The humanized antibodies MA1 and MA2 applied in the pharmaceutical composition or the kit of the invention may include amino acid residues not encoded by human sequences (*e. g.*, mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*, or a conservative substitution to promote stability or manufacturing). See, *e. g.*, Morrison et al., *Proc. Natl. Acad. Sci. USA*, 81:6851-6855, 1984; Morrison and Oi, *Adv. Immunol.*, 44:65-92, 1988; Verhoeyen et al., *Science*, 239: 1534-1536, 1988; Padlan, *Molec. Immun.*, 28:489-498, 1991; and Padlan, *Molec. Immun.*, 31: 169-217, 1994. Other examples

of human engineering technology include but are not limited to the Xoma technology disclosed in U.S. Pat. No. 5,766,886.

[0081] The term “recombinant humanized antibody” as used herein, includes all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies isolated from a host cell transformed to express the humanized antibody, *e. g.*, from a transfectoma, and antibodies prepared, expressed, created or isolated by any other means that involve splicing of all or a portion of a human immunoglobulin gene, sequences to other DNA sequences.

[0082] Preferably, the antibodies applied in the pharmaceutical compositions or the kit of the invention are humanized. More preferably, the antibodies applied in the pharmaceutical compositions or the kit of the invention are humanized and comprises rabbit derived CDRs.

[0083] The term “multispecific antibody” as used herein, refers to an antibody that binds to two or more different epitopes on at least two or more different targets (*e. g.*, CD137 and PDL1). The term “multispecific antibody” includes bispecific, trispecific, tetraspecific, pentaspecific and hexaspecific. The term “bispecific antibody” as used herein, refers to an antibody that binds to at least two different epitopes on two different targets (*e. g.*, CD137 and PDL1). The term “trispecific antibody” as used herein, refers to an antibody that binds to at least three different epitopes on three different targets (*e. g.*, CD137, PDL1 and hSA).

[0084] The term “epitope” means a protein determinant capable of specific binding to an antibody. Epitopes usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually have specific three-dimensional structural characteristics, as well as specific charge characteristics. “Conformational” and “linear” epitopes are distinguished in that the binding to the former but not the latter is lost in the presence of denaturing solvents.

[0085] The term “conformational epitope” as used herein refers to amino acid residues of an antigen that come together on the surface when the polypeptide chain folds to form the native protein.

[0086] The term “linear epitope” refers to an epitope, wherein all points of interaction between the protein and the interacting molecule (such as an antibody) occurring linearly along the primary amino acid sequence of the protein (continuous).

[0087] The term “distal epitope” refers to an epitope which is comprised in the region of the extracellular part of a cell-bound antigen that is distant from the cell surface.

[0088] The term “proximal epitope” refers to an epitope which is comprised in the region of the extracellular part of a cell-bound antigen that is close to the cell surface.

[0089] The term “recognize” as used herein refers to an antibody antigen-binding fragment thereof that finds and interacts (*e. g.*, binds) with its conformational epitope.

[0090] The term “avidity” as used herein refers to an informative measure of the overall stability or strength of the antibody-antigen complex. It is controlled by three major factors: antibody epitope affinity; the valency of both the antigen and antibody; and the structural arrangement of the interacting parts. Ultimately these factors define the specificity of the antibody, that is, the likelihood that the particular antibody is binding to a precise antigen epitope.

[0091] Suitably, the CD137-BD of MA1 is characterized by one or more of the following parameters:

- a. binds to human CD137 with a monovalent dissociation constant (K_D) of less than 50nM, particularly with a monovalent K_D of 0.005 to 50 nM, more particularly of 0.01 to 30 nM, more particularly of 0.01 to 10 nM, more particularly of 0.1 to 5 nM, as measured by surface plasmon resonance (SPR), particularly wherein said CD137-BD is an scFv;
- b. binds to human CD137 with a K_{off} rate of 10^{-2} s^{-1} or less, more particularly of 10^{-2} s^{-1} to 10^{-6} s^{-1} more particularly of $5 \times 10^{-3} \text{ s}^{-1}$ to 10^{-5} s^{-1} , more particularly of 10^{-3} s^{-1} to $5 \times 10^{-4} \text{ s}^{-1}$, as measured by SPR;
- c. binds to human CD137 with a K_{on} rate of at least $10^4 \text{ M}^{-1}\text{s}^{-1}$ or greater, more particularly of $10^4 \text{ M}^{-1}\text{s}^{-1}$ to $10^7 \text{ M}^{-1}\text{s}^{-1}$, more particularly of $10^5 \text{ M}^{-1}\text{s}^{-1}$ to $5 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$, as measured by SPR;
- d. does not cross-compete with urelumab and utomilumab;
- e. is cross-reactive with *Macaca fascicularis* (cynomolgus) CD137, in particular binds to cynomolgus CD137 with a monovalent K_D of less than 50 nM, particularly with a monovalent K_D of 0.005 to 50 nM, more particularly of 0.01 to 30 nM, more particularly of 0.01 to 10 nM, more particularly of 0.1 to 5 nM, as measured by SPR, particularly wherein said CD137-BD is an scFv.

[0092] As used herein, the term “affinity” refers to the strength of interaction between antibody and antigen at single antigenic sites. Within each antigenic site,

the variable region of the antibody "arm" interacts through weak non-covalent forces with antigen at numerous sites; the more interactions, the stronger the affinity.

[0093] "Binding affinity" generally refers to the strength of the total sum of non-covalent interactions between a single binding site of a molecule (e. g., of an antibody) and its binding partner (e. g., an antigen or, more specifically, an epitope on an antigen). Unless indicated otherwise, as used herein, "binding affinity", "bind to", "binds to" or "binding to" refers to intrinsic binding affinity that reflects a 1:1 interaction between members of a binding pair (e. g., an antibody fragment and antigen). The affinity of a molecule X for its partner Y can generally be represented by the dissociation constant (K_D). Affinity can be measured by common methods known in the art, including those described herein. Low-affinity antibodies generally bind antigen slowly and tend to dissociate readily, whereas high-affinity antibodies generally bind antigen faster and tend to remain bound longer. A variety of methods of measuring binding affinity are known in the art, any of which can be used for purposes of the present invention. Specific illustrative and exemplary embodiments for measuring binding affinity, i. e. binding strength are described in the following.

[0094] The term " K_{assoc} ", " K_a " or " K_{on} ", as used herein, are intended to refer to the association rate of a particular antibody-antigen interaction, whereas the term " K_{dis} ", " K_d " or " K_{off} ", as used herein, is intended to refer to the dissociation rate of a particular antibody- antigen interaction. In one embodiment, the term " K_D ", as used herein, is intended to refer to the dissociation constant, which is obtained from the ratio of K_d to K_a (i. e. K_d/K_a) and is expressed as a molar concentration (M). The " K_D " or " K_D value" or "KD" or "KD value" according to this invention is in one embodiment measured by using surface-plasmon resonance assays. Affinity to CD137 was determined by surface plasmon resonance (SPR) measurements as described in EP 20164913.4 and EP 20177337.1. Affinity to PDL1 was measured by SPR as described in EP 20164913.4 and EP 20177337.1. Affinity to recombinant human mesothelin (human MSLN) and recombinant *Cynomolgus* MSLN (*Cynomolgus* MSLN) was determined by surface plasmon resonance (SPR) measurements as described in EP 20164913.4 and EP 20177337.1. Affinity to recombinant human CD3 was measured by SPR as described EP 20164913.4 and EP 20177337.1.

[0095] Suitably, the first multispecific antibody (MA1) is monovalent for CD137 and PDL1 specificity.

[0096] Suitably, the MA1 acts as a CD137 agonist in the presence of PDL1-positive cells. An “activator” or “activating antibody” or “agonist” or “agonist antibody” is one that enhances or initiates the innate activity of the antigen to which it binds usually triggered by binding of the antigen to its natural ligand, in particular signaling by the antigen. In the context of the present invention, the term “CD137 agonist” encompasses the MA1 used in the present invention that is capable to activate CD137 signaling upon clustering of CD137-antigen-binding fragments thereof, *e. g.*, wherein binding of at least two of said CD137-antigen-binding fragments allow for multimerization of the bound CD137 molecules and their activation. In some embodiments, agonist antibodies activate signaling without the presence of the natural ligand.

[0097] Suitable CD137-BDs for MA1 are binding domains provided in the present disclosure. The CD137-BDs used in the invention include, but are not limited to, the humanized CD137-binding domains whose sequences are listed in Table 1. Additional details regarding the generation and characterization of the MA1 and its binding domains, as described herein, are disclosed in the patent application WO 2019/072868, which is herewith incorporated by reference in its entirety.

[0098] The term “multivalent antibody” refers to a single binding molecule with more than one valency, where “valency” is described as the number of antigen-binding moieties that binds to epitopes on target molecules. As such, the single binding molecule can bind to more than one binding site on a target molecule and/or to more than one target molecule due to the presence of more than one copy of the corresponding antigen-binding moieties. Examples of multivalent antibodies include, but are not limited to bivalent antibodies, trivalent antibodies, tetravalent antibodies, pentavalent antibodies, and the like.

[0099] The term “monovalent antibody”, as used herein, refers to an antibody that binds to a single target molecule, and more specifically to a single epitope on a target molecule, such as CD137. Also, the term “binding domain” or “monovalent binding domain”, as used herein, refers to a binding domain that binds to a single epitope on a target molecule such as CD137.

[0100] The term “bivalent antibody” as used herein, refers to (i) a bispecific antibody comprising two different antigen-binding moieties that bind to two targets, (ii) an antibody comprising two different antigen-binding moieties that bind to two different

epitopes on two identical target molecules, such as CD137 target molecules, or (iii) an antibody comprising two identical antigen-binding moieties that bind to two identical target molecules, such as CD137 target molecules.

[0101] The inventors of the present invention have previously found that a multispecific antibody comprising (a) only one CD137 binding domain (CD137-BD) and (b) one PDL1 binding domain (PDL1-BD) is able to effectively activate CD137 signaling in a targeted manner. These multispecific antibodies are not capable of agonizing CD137 on T cells in the absence of another cell-type, which is recognized by PDL1 binding domain (Figure 1A). The effective activation of CD137 takes place only in the presence of PDL1-positive cells due to binding of anti-PDL1 domains of these multispecific antibodies to PDL1 molecules exposed on the surface of PDL1-positive cells (Figure 1B and 1C). This leads to increased density of the multispecific antibodies in a specific location, and thus increased density of CD137 binding domains. The CD137-BDs thus can effectively cluster and agonize CD137. This concomitant binding to PDL1 and CD137 triggers selective activation of tumor-reactive T cells and simultaneously blocks PD-1 signaling (Figure 1C). Due to high overexpression of PDL1 on tumor cells, CD137 signaling is activated only locally in the presence of said tumor cells, which leads to reduced systemic toxicity. These multispecific antibodies are thus expected to have several beneficial effects in comparison to current treatment options, such as (i) lower rate of immune-related adverse events, and (ii) lower rate of dose-limiting toxicities.

[0102] The inventors of the present invention have further found that a certain balancing of the affinities of the CD137-BD and PDL1-BD relative to each other, i.e. a significant higher affinity of the PDL1-BD to PDL1 relative to the affinity of the CD137-BD to CD137, is necessary to ensure that the effective concentration, at which the maximum inhibition of the PDL1/PD-1 interaction is achieved (IC_{100}), falls well within the concentration range, at which the maximum activation of CD137-driven NF- κ B signaling is achieved. Thereby, the concentration window of maximal activity is significantly extended (compare e.g. Figure 2C with Figure 2A), which is predicted to be beneficial for therapeutic applications and allows higher flexibility in dosing the multispecific antibody or a pharmaceutical composition comprising the multispecific antibody. If the affinities of the PDL1-BD and the CD137-BD to their respective binding-targets are similar or the affinity (K_D) of the PDL1-BD to PDL1 is

only marginally smaller (better) than the affinity (K_D) CD137-BD to CD137, the effective concentrations for achieving maximal PDL1-blockage and maximal CD137 mediated signaling are not overlapping (Figure 2A and 2B), which is believed to decrease the overall efficacy and the therapeutic applicability of such antibodies. Thus, in one embodiment, the multispecific antibody used in the present invention comprises at least one CD137-BD and at least one PDL1-BD, wherein said CD137-BD binds to human CD137 with a monovalent dissociation constant (K_D) of at least 5 times, preferably at least 10 times, e.g., at least 20, at least 30, at least 50, at least 100 times higher relative to a monovalent dissociation constant (K_D) of said PDL1-BD for binding to human PDL1, in particular, wherein said CD137-BD binds to human CD137 with a monovalent dissociation constant (K_D) that is 20 to 1000 times, preferably 30 to 800 times, in particular 50 - 500 times higher than the monovalent dissociation constant (K_D) of said PDL1-BD for binding to human PDL1, when measured by SPR.

[0103] Importantly, the multispecific antibody MA1 used in the present invention that is monovalent for CD137 specificity is not capable of inducing CD137 signaling systemically due to a lack of CD137 activation in the absence of clustering, which is caused by binding of PDL1-BD to its antigen.

[0104] In one embodiment, the multispecific antibody MA1 consists of one CD137-BD and one PDL1-BD.

[0105] The term "CD137" refers in particular to human CD137 with UniProt ID number Q07011, reproduced herein as SEQ ID NO: 89. Suitably, the CD137-BD of the present invention targets CD137, in particular human CD137 as shown in UniProt ID number Q07011, reproduced herein as SEQ ID NO: 89. Suitably, the multispecific antibody used in the invention comprises a CD137-BD that targets human and cynomolgus (*Macaca fascicularis*) CD137. Preferably, the multispecific antibody used in the invention comprises a CD137-BD that does not block CD137/CD137L interaction.

[0106] In one embodiment, the CD137-BD does not cross-compete for binding with urelumab. Thus, the CD137-BD binds to a different epitope than urelumab.

Urelumab, also referred to as BMS-663513, is a fully humanized IgG4 mAb from Bristol-Myers Squibb, and is described in WO 2004/010947, US 6,887,673 and US

7,214,493. In another embodiment, the CD137-BD used in the invention cross-competes for binding with urelumab.

[0107] In one embodiment, the CD137-BD does not cross-compete for binding with utomilumab. Thus, the CD137-BD binds to a different epitope than utomilumab. Utomilumab, also referred to as PF-05082566, is a fully human IgG2 mAb from Pfizer, and is described in WO 2012/032433 and US 8,821,867. In another embodiment, the CD137-BD used in the invention cross-competes for binding with utomilumab.

[0108] In a further embodiment, the CD137-BD does not cross-compete for binding neither with urelumab nor with utomilumab. Thus, the CD137-BD binds to a different epitope than urelumab and utomilumab.

[0109] The terms “compete” or “cross-compete” and related terms are used interchangeably herein to mean the ability of an antibody or other binding agent to interfere with the binding of other antibodies or binding agents to CD137 in a standard competitive binding assay.

[0110] The term “same epitope”, as used herein, refers to individual protein determinants on the same protein capable of specific binding to an antibody, where these individual protein determinants are identical, i.e. consist of identical chemically active surface groupings of molecules such as amino acids or sugar side chains having identical three-dimensional structural characteristics, as well as identical charge characteristics. The term “different epitope”, as used herein in connection with a specific protein target, refers to individual protein determinants on the same protein capable of specific binding to an antibody, where these individual protein determinants are not identical, i.e. consist of non-identical chemically active surface groupings of molecules such as amino acids or sugar side chains having different three-dimensional structural characteristics, as well as different charge characteristics. These different epitopes can be overlapping or non-overlapping.

[0111] Suitably, the CD137-BD of MA1 is further characterized by one or more of the following parameters:

- f. when being in scFv format, has a melting temperature (T_m), determined by differential scanning fluorimetry, of at least 50°C, preferably of at least 55°C, more preferably at least 60°C, in particular wherein said antibody or antigen binding fragment thereof is formulated in phosphate citrate buffer at pH 6.4, 150

- mM NaCl, in particular wherein said antibody is formulated in 50 mM phosphate citrate buffer with 150 mM NaCl at pH 6.4;
- g. when being in scFv format, has a loss in monomer content, after storage for at least two weeks, particularly for at least four weeks, at 4°C, of less than 7 %, e.g. less than 6 %, less than 5 %, less than 4 %, less than 3 %, less than 2 %, preferably less than 1 %, when said antibody is at a starting concentration of 10 mg/ml, and in particular wherein said antibody is formulated in 50 mM phosphate citrate buffer with 150 mM NaCl at pH 6.4;
 - h. when being in scFv format, has a loss in monomer content, after storage for at least two weeks, particularly for at least four weeks, at 40°C, of less than 5 %, e.g. less than 4 %, less than 3 %, less than 2 %, preferably less than 1 %, when said antibody is at a starting concentration of 10 mg/ml, and in particular wherein said antibody is formulated in 50 mM phosphate citrate buffer with 150 mM NaCl at pH 6.4.

[0112] DSF is described earlier (Egan, et al., *MAbs*, 9(1) (2017), 68-84; Niesen, et al., *Nature Protocols*, 2(9) (2007) 2212-2221). The midpoint of transition for the thermal unfolding of the scFv constructs is determined by Differential Scanning Fluorimetry using the fluorescence dye SYPRO® Orange (see Wong & Raleigh, *Protein Science* 25 (2016) 1834-1840). Samples in phosphate-citrate buffer at pH 6.4 are prepared at a final protein concentration of 50 µg/ml and containing a final concentration of 5x SYPRO® Orange in a total volume of 100 µl. Twenty-five microliters of prepared samples are added in triplicate to white-walled AB gene PCR plates. The assay is performed in a qPCR machine used as a thermal cycler, and the fluorescence emission is detected using the software's custom dye calibration routine. The PCR plate containing the test samples is subjected to a temperature ramp from 25°C to 96°C in increments of 1°C with 30 s pauses after each temperature increment. The total assay time is about 2 h. The T_m is calculated by the software GraphPad Prism using a mathematical second derivative method to calculate the inflection point of the curve. The reported T_m is an average of three measurements.

[0113] The loss in monomer content is as determined by area under the curve calculation of SE-HPLC chromatograms. SE-HPLC is a separation technique based on a solid stationary phase and a liquid mobile phase as outlined by the USP chapter 621. This method separates molecules based on their size and shape utilizing a

hydrophobic stationary phase and aqueous mobile phase. The separation of molecules is occurring between the void volume (V_0) and the total permeation volume (V_T) of a specific column. Measurements by SE-HPLC are performed on a Chromaster HPLC system (Hitachi High-Technologies Corporation) equipped with automated sample injection and a UV detector set to the detection wavelength of 280 nm. The equipment is controlled by the software EZChrom Elite (Agilent Technologies, Version 3.3.2 SP2) which also supports analysis of resulting chromatograms. Protein samples are cleared by centrifugation and kept at a temperature of 4-6°C in the autosampler prior to injection. For the analysis of scFv samples the column Shodex KW403-4F (Showa Denko Inc., #F6989202) is employed with a standardized buffered saline mobile phase (50 mM sodium-phosphate pH 6.5, 300 mM sodium chloride) at the recommended flow rate of 0.35 ml/min. The target sample load per injection was 5 µg. Samples are detected by an UV detector at a wavelength of 280 nm and the data recorded by a suitable software suite. The resulting chromatograms are analyzed in the range of V_0 to V_T thereby excluding matrix associated peaks with >10 min elution time.

[0114] The multispecific antibody MA1 used in the present invention comprises one PDL1 binding domain (PDL1-BD).

[0115] The term “PDL1” refers in particular to human PDL1 with UniProt ID number Q9NZQ7, reproduced herein as SEQ ID NO: 90. Suitably, the PDL1-BD used in the present invention targets PDL1, in particular human PDL1 as shown in UniProt ID number Q9NZQ7, reproduced herein as SEQ ID NO: 90. Suitably, the antibodies MA1 used in the present invention comprise a PDL1-BD that targets human and cynomolgus (*Macaca fascicularis*) PDL1, and preferably does not cross-react with *Mus musculus* PDL1. The PDL1-BD used in the present invention specifically binds to human PDL1 protein.

[0116] The PDL1-BD used in the present invention is a PDL1 inhibitor. The term “blocker” or “inhibitor” or “antagonist” refers to an antibody or binding domain thereof that inhibits or reduces a biological activity of the antigen it binds to. The PDL1-BD used in the present invention targets and decreases or inhibits the binding ability of PDL1 to its binding partners, thereby interfering with the PDL1 function. In particular, the PDL1-BD used in the present invention blocks the interaction of PDL1 with its receptor, specifically with PD-1. In particular, the PDL1-BD used in the present

invention blocks the interaction of PDL1 with its receptor or receptors, specifically with PD-1 and/or B7-1.

[0117] Suitable the PDL1-BDs of MA1 used in the invention are binding domains provided in the present disclosure. The PDL1-BDs used in the invention include, but are not limited to, the humanized PDL1-BDs whose sequences are listed in Table 2.

[0118] Suitably, the PDL1-BD used in the present invention is characterized by one or more of the following parameters:

- a. binds to human PDL1 with a monovalent dissociation constant (K_D) of less than 10 nM, particularly with a monovalent K_D of 0.05 pM to 10 nM, more particularly of 0.1 pM to 5 nM, more particularly of 0.2 pM to 1 nM, more particularly 0.5 pM to 500 pM, more particularly of 1 pM to 200 pM, more particularly of 1 pM to 100 pM, as measured by SPR;
- b. binds to human PDL1 with a K_{off} rate of $5 \times 10^{-3} \text{ s}^{-1}$ or less, more particularly of $5 \times 10^{-3} \text{ s}^{-1}$ to 10^{-7} s^{-1} , more particularly of 10^{-3} s^{-1} to $5 \times 10^{-6} \text{ s}^{-1}$, more particularly of 10^{-3} s^{-1} to 10^{-6} s^{-1} , as measured by SPR;
- c. binds to human PDL1 with a K_{on} rate of at least $10^4 \text{ M}^{-1}\text{s}^{-1}$ or greater, more particularly of $10^4 \text{ M}^{-1}\text{s}^{-1}$ to $10^8 \text{ M}^{-1}\text{s}^{-1}$, more particularly of $10^5 \text{ M}^{-1}\text{s}^{-1}$ to $5 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$, more particularly of $5 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$ to $10^7 \text{ M}^{-1}\text{s}^{-1}$, as measured by SPR;
- d. is cross-reactive with *Macaca fascicularis* (cynomolgus) PDL1;
- e. is non-cross reactive to *Mus musculus* PDL1.

[0119] Suitably, the PDL1-BD used in the present invention is further characterized by one or more of the following parameters:

- f. when being in scFv format, has a melting temperature (T_m), determined by differential scanning fluorimetry, of at least 55°C , e.g. at least 60°C , preferably at least 65°C , more preferably at least 70°C , in particular wherein said antibody or antigen-binding fragment thereof is formulated in phosphate citrate buffer at pH 6.4, 150 mM NaCl, in particular wherein said antibody is formulated in 50 mM phosphate citrate buffer with 150 mM NaCl at pH 6.4;
- g. when being in scFv format, has a loss in monomer content, after five consecutive freeze-thaw cycles, of less than 5 %, preferably less than 3 %, more preferably less than 1 %, when said antibody is at a starting concentration of 10 mg/ml, in particular wherein said antibody is formulated in 50 mM phosphate citrate buffer with 150 mM NaCl at pH 6.4; and/or
- h. when being in scFv format, has a loss in monomer content, after storage for at least two weeks, particularly for at least four weeks, at 4°C , of less than 15%,

e.g. less than 12 %, less than 10 %, less than 7 %, less than 5 %, less than 4 %, less than 3 %, less than 2 %, preferably less than 1 %, when said antibody is at a starting concentration of 10 mg/ml, and in particular wherein said antibody is formulated in 50 mM phosphate citrate buffer with 150 mM NaCl at pH 6.4.

[0120] Suitably, the multispecific antibodies MA1 do not comprise an immunoglobulin Fc region polypeptide. Thus, the multispecific antibodies MA1 used in the invention typically have a compact multi-domain and low molecular weight antibody architecture. The term "Fc region" herein is used to define a C-terminal region of an immunoglobulin heavy chain, including native-sequence Fc regions and variant Fc regions. Native-sequence Fc regions include human IgG1, IgG2 (IgG2A, IgG2B), IgG3 and IgG4. "Fc receptor" or "FcR" describes a receptor that binds to the Fc region of an antibody. Particularly, the FcR is a native sequence human FcR, which binds an IgG antibody (a gamma receptor) and includes receptors of the FcγRI, FcγRII, and FcγRIII subclasses, including allelic variants and alternatively spliced forms of these receptors, FcγRII receptors including FcγRIIA (an "activating receptor") and FcγRI IB (an "inhibiting receptor"), which have similar amino acid sequences that differ primarily in the cytoplasmic domains thereof. Activating receptor FcγRIIA contains an immunoreceptor tyrosine-based activation motif (ITAM) in its cytoplasmic domain. Inhibiting receptor FcγRIIB contains an immunoreceptor tyrosine-based inhibition motif (ITIM) in its cytoplasmic domain, (see M. Daeron, *Annu. Rev. Immunol.* 5:203-234 (1997). FcRs are reviewed in Ravetch and Kinet, *Annu. Rev. Immunol.* 9: 457-92 (1991); Capet et al, *Immunomethods* 4: 25-34 (1994); and de Haas et al, *J. Lab. Clin. Med.* 126: 330-41 (1995). Other FcRs, including those to be identified in the future, are encompassed by the term "FcR" herein. The term "Fc receptor" or "FcR" also includes the neonatal receptor, FcRn, which is responsible for the transfer of maternal IgGs to the fetus. Guyer et al., *J. Immunol.* 117: 587 (1976) and Kim et al., *J. Immunol.* 24: 249 (1994). Methods of measuring binding to FcRn are known (see, e. g., Ghetie and Ward, *Immunol. Today* 18: (12): 592-8 (1997); Ghetie et al., *Nature Biotechnology* 15 (7): 637-40 (1997); Hinton et al., *J. Biol. Chem. TJI* (8): 6213-6 (2004); WO 2004/92219 (Hinton et al). Binding to FcRn *in vivo* and serum half-life of human FcRn high-affinity binding polypeptides can be assayed, e. g., in transgenic mice or transfected human cell lines expressing human FcRn, or in primates to which the polypeptides having a variant Fc region are administered. WO 2004/42072 (Presta) describes antibody

variants which improved or diminished binding to FcRs. See also, *e. g.*, Shields et al., J. Biol. Chem. 9(2): 6591-6604 (2001).

[0121] In order to increase the number of specificities/functionalities at the same or lower molecular weight, it is advantageous to use antibodies comprising antibody fragments, such as Fv, scFv, Fab, Fab' and F(ab')₂ fragments and other antibody fragments. These smaller molecules retain the antigen-binding activity of the whole antibody and can also exhibit improved tissue penetration and pharmacokinetic properties in comparison to the whole immunoglobulin molecules. Whilst such fragments appear to exhibit a number of advantages over whole immunoglobulins, they also suffer from an increased rate of clearance from serum since they lack the Fc domain that imparts a long half-life *in vivo* (Medasan et al., 1997, J. Immunol. 158:2211-2217). Molecules with lower molecular weights penetrate more efficiently into target tissues (*e. g.* solid cancers) and thus hold the promise for improved efficacy at the same or lower dose.

[0122] The inventors have found that an addition of human serum albumin binding domain (hSA-BD) to the multispecific antibodies MA1 applied in the invention does not interfere with the ability of the other binding domains to bind to their respective targets. This finding is insofar surprising as it cannot *a priori* be expected that all three binding domains remain functional without sterically or otherwise inhibiting each other in a complex multi-target, multi-cell *in vivo* situation.

[0123] Suitably, the multispecific antibody MA1 applied in the pharmaceutical composition or the kit of the invention may comprise a further binding domain having a specificity to human serum albumin.

[0124] In one embodiment, the multispecific antibody MA1 comprises: (i) one CD137-BD; (ii) one PDL1-BD; and (iii) one hSA-BD.

[0125] The term "hSA" refers in particular to human serum albumin with UniProt ID number P02768. Human Serum Albumin (hSA) is a 66.4 kDa abundant protein in human serum (50 % of total protein) composed of 585 amino acids (Sugio, Protein Eng, Vol. 12, 1999, 439-446). Multifunctional hSA can transport a number of metabolites such as fatty acids, metal ions, bilirubin and some drugs (Fanali, Molecular Aspects of Medicine, Vol. 33, 2012, 209-290). hSA concentration in serum is around 3.5 - 5 g/dl. Albumin-binding antibodies and fragments thereof may be

used for example, for extending the *in vivo* serum half-life of drugs or proteins conjugated thereto.

[0126] In some embodiments, the hSA-BD is derived from a monoclonal antibody or antibody fragment.

[0127] Suitable hSA-BDs for the multispecific antibodies MA1 are binding domains provided in the present disclosure. The hSA-BDs of the multispecific antibodies MA1 include, but are not limited to, the humanized hSA-binding domains whose sequences are listed in Table 3. Additional sequences of suitable hSA-binding domains are listed in Table 7.

[0128] In particular, the hSA-BDs of the multispecific antibodies MA1 specifically bind to human serum albumin.

[0129] Another suitable hSA-BD for use in the multispecific antibody MA1 comprises or is derived from a binding domain selected from the group consisting of: (i) polypeptides that bind serum albumin (see, for example, Smith et al., 2001, Bioconjugate Chem. 12:750-756; EP 0 486 525; US 6,267,964; WO 2004/001064; WO 2002/076489; and WO 2001/45746); (ii) anti-serum albumin binding single variable domains described in Holt et al., Protein Engineering, Design & Selection, vol 21, 5, pp283-288, WO 2004/003019, WO 2008/096158, WO 2005/118642, WO 2006/0591056 and WO 2011/006915; (iii) anti-serum albumin antibodies described in WO 2009/040562, WO 2010/035012 and WO 2011/086091.

[0130] Suitably, the multispecific antibodies MA2 applied in the pharmaceutical compositions or the kit of the invention are monovalent for CD3 specificity.

[0131] Suitable CD3-BDs for use in the multispecific antibodies MA2 are binding domains provided in the present disclosure. The CD3-BDs of the invention include, but are not limited to, the humanized CD3-binding domains whose sequences are listed in Table 6.

[0132] Suitably, the multispecific antibodies MA2 applied in the pharmaceutical compositions or the kit of the invention comprise at least one TAA-BD. The MA2, which have two or more TAA-BDs, can have specificity for the same TAA or for two different TAAs.

[0133] The term "tumor-associated antigen (TAA)" refers to an antigen that is expressed on the surface of a tumor cell. In particular embodiments, a TAA is an antigen that is preferentially expressed on a tumor cell when compared to non-tumor

cells, particularly wherein expression of the TAA on a tumor cell is at least more than 5-fold, at least more than 10-fold, at least more than 20-fold, at least more than 50-fold, or at least more than 100-fold higher than on non-tumor cells from the same organism or patient. In particular, the TAA is taken from the group of: ADRB3, AFP, ALK, BCMA, beta human chorionic gonadotropin, CA-125 (MUC16), CAIX, CD123, CD133, CD135, CD135 (FLT3), CD138, CD171, CD19, CD20, CD22, CD24, CD276, CD33, CD38, CD44v6, CD79b, CD97, CDH3 (cadherin 3), CEA, CEACAM6, CLDN6, CLEC12A (CLL1), CSPG4, CYP1B1, EGFR, EGFRvIII, EPCAM, EPHA2, Ephrin B2, ERBBs (e. g. ERBB2), FAP, FGFR1, folate receptor alpha, folate receptor beta, Fos-related antigen, GA733, GD2, GD3, GFRalpha4, globoH, GPC3, GPR20, GPRC5D, HAVCR1, Her2/neu (HER2), HLA-A2, HMWMAA, HPV E6 or E7, human telomerase reverse transcriptase, IL-11Ra, IL-13Ra2, intestinal carboxyl esterase, KIT, Legumain, LewisY, LMP2, Ly6k, MAD-CT-1, MAD-CT-2, ML-IAP, MN-CA IX, MSLN, MUC1, mut hsp 70-2, NA-17, NCAM, neutrophil elastase, NY-BR-1, NY-ESO-1, o-acetyl-GD2, OR51E2, PANX3, PDGFR-beta, PLAC1, Polysialic acid, PSCA, PSMA, RAGE1, ROR1, sLe, sperm protein 17, SSEA-4, SSTR2, sTn antigen, sTn-O-Glycopeptides, TAG72, TARP, TEM1/CD248, TEM7R, thyroglobulin, Tn antigen, Tn-O-Glycopeptides, TPBG (5T4), TRP-2, TSHR, UPK2 and VEGFR2.

[0134] In particular embodiments, the TAA is selected from the group consisting of CD138, CD79b, TPBG (5T4), HER2, MSLN, MUC1, CA-125 (MUC16), PSMA, BCMA, CD19, EpCAM, CLEC12A (CLL1), CD20, CD22, CEA, CD33, EGFR, GPC3, CD123, CD38, CD33, CD276, CDH3 (cadherin 3), FGFR1, SSTR2, CD133, EPHA2, HLA-A2, IL13RA2, ROR1, CEACAM6, CD135, GD-2, GA733, CD135 (FLT3), CSPG4 and TAG-72, in particular selected from the group consisting of CD138, CD79b, CD123, HER2, MSLN, PSMA, BCMA, CD19, CD20, CEA, CD38, CD33, CLEC12a, and ROR1. In a special embodiment, the TAA is selected from the group consisting of HER2, MSLN and ROR1.

[0135] In one embodiment, the multispecific antibodies MA2 applied in the pharmaceutical compositions or the kit comprises one TAA-BD, i.e. is monovalent for TAA specificity.

[0136] In particular embodiments, the multispecific antibodies MA2 applied in the pharmaceutical compositions or the kit comprises one TAA-BD that binds to clean

TAA, i.e. TAAs that are almost exclusively expressed on cancer cells, such as oncofetal tumor antigens, such as ROR1.

[0137] In the context of the present invention, the term “clean TAA” refers to TAAs which are not expressed on the surface of healthy cells or which are expressed on the surface of healthy cells in amounts corresponding to less than 10 %, particularly less than 5 %, particularly less than 1 %, particularly less than 0.5 %, of the respective TAA density on the surface of the cancer cells.

[0138] In other particular embodiments, the multispecific antibodies MA2 applied in the pharmaceutical compositions or the kit comprises one TAA-BD that binds to non-clean TAAs, i.e. TAAs that are also expressed in significant amounts on the surface of healthy cells, such as Mesothelin (MSLN), EGFR, EpCAM and HER2.

[0139] In the context of the present invention, the term “clean TAA” refers to TAAs which are expressed on the surface of healthy cells in amounts corresponding to 10 – 90 %, particularly 10 - 80 %, particularly 10 – 75 %, of the respective TAA density on the surface of the cancer cells.

[0140] In these embodiment, said single TAA-BD binds to said TAA with a monovalent dissociation constant (K_D) of less than 50 nM, particularly less than 20 nM, particularly less than 10 nM, particularly less than 5 nM, particularly of 0.01 to 2 nM, particularly of 0.02 to 1 nM, particularly of 0.03 to 0.5 nM as measured by SPR, particularly wherein said TAA-BD is an scFv.

[0141] Specific examples of MA2 comprising one TAA-BD and one CD3-BD are PRO1872 (MSLN_{lowKD}×CD3xhSA), PRO2510 (ROR1×CD3xhSA), PRO2668 (ROR1×CD3xhSA), PRO1766 (HER2×CD3xhSA) and PRO1767 (HER2×CD3xhSA), whose sequences are listed in Table 11.

[0142] In another embodiment, the multispecific antibodies MA2 applied in the pharmaceutical compositions or the kit comprise two or three TAA-BDs, particularly two TAA-BDs, which have specificity for the same TAA.

[0143] In yet another embodiment, the multispecific antibodies MA2 applied in the pharmaceutical compositions or the kit comprise two, three or four TAA-BDs, particularly two TAA-BDs, which have specificity for two different TAAs.

[0144] In these embodiments, the TAA-BDs, independently of each other, bind clean and non-clean TAAs.

[0145] In particular embodiments, the multispecific antibodies MA2 applied in the pharmaceutical compositions or the kit comprise two TAA-BDs, which have specificity for the same TAA, and wherein the TAA is selected from non-clean TAAs.

[0146] In particular embodiments, the multispecific antibodies MA2 applied in the pharmaceutical compositions or the kit comprise two TAA-BDs, which have specificity for the same TAA, and wherein the TAA is selected from tumor cell associated antigens, whose extracellular part also occurs in soluble form in the serum of a patient.

[0147] In the context of the present invention, the term “occurs in soluble form in the serum of a patient” means that the concentration of the particular protein of interest, i.e. the extracellular part of the TAA, in the serum is at least 1 ng/ml.

[0148] The two TAA-BDs of the multispecific antibodies MA2, which have specificity for the same TAA, either bind the same or different epitopes on the extracellular part of said TAA target molecules. Preferably, the two TAA-BDs of the multispecific antibodies MA2, which have specificity for the same TAA, bind the same epitopes on the TAA target molecules.

[0149] In these embodiments, the two TAA-BDs of the multispecific antibodies MA2, which have specificity for the same TAA, bind to said TAA with a monovalent dissociation constant (K_D) in the range of 0.1 to 50 nM, particularly of 0.2 to 30 nM, particularly of 0.3 to 20 nM, particularly of 0.4 to 10 nM, as measured by SPR, particularly wherein said TAA-BD is an scFv.

[0150] These multispecific antibodies MA2, which comprise two low-affinity TAA-BDs, allows to more safely address non-clean TAAs, such as Mesothelin (MSLN), EGFR, EpCAM and HER2, due to avidity effects, which cause a significant increase in the potency of these multispecific antibodies MA2 towards high TAA expressing cells over healthy low TAA expressing cells. Furthermore, the binding of these multispecific antibodies MA2 to TAAs, whose extracellular part is shed into the serum of cancer patients (soluble TAA), which typically causes a significant reduction of the effective concentration of TAA binding drugs, is not much affected by the presence of significant amounts of such soluble TAAs. Examples of such TAAs are MSLN, PSMA and MUC1.

[0151] In a specific embodiment, the two TAA-BDs of the multispecific antibodies MA2 are MSLN-BDs which specifically bind to mesothelin (MSLN), particularly

human mesothelin. The two MSLN-BDs bind to any region of the extracellular part of MSLN, e.g. to Region I, Region II and/or Region III of MSLN. Preferably, the two MSLN-BDs of the multispecific antibodies MA2 of this specific embodiment bind to Region I and/or Region II, in particular to Region I of MSLN. Region I is the part of MSLN that is most distal from the cell surface, where MSLN is attached to.

[0152] The two MSLN-BDs of the multispecific antibodies MA2 of this specific embodiment either bind the same or different epitopes on the MSLN target molecules. Preferably, the two MSLN-BDs bind the same epitopes on the MSLN target molecules.

[0153] Suitable MSLN-BDs for use in the multispecific antibodies MA2 are binding domains provided in the present disclosure. The MSLN-BDs applied in the invention include, but are not limited to, the humanized MSLN-binding domains whose sequences are listed in Table 8.

[0154] Suitably, the multispecific antibody MA2 applied in the pharmaceutical composition or the kit of the invention may comprise a further binding domain having specificity to human serum albumin.

[0155] Suitable hSA-BDs for the multispecific antibodies MA2 are binding domains provided in the present disclosure, as defined above. The hSA-BDs of the multispecific antibodies MA2 include, but are not limited to, the humanized hSA-binding domains whose sequences are listed in Table 3 and Table 7.

[0156] Specific examples of MA2 comprising two low affinity MSLN-BDs and one CD3-BD (e.g. biMSLN_{high} K_D × CD3 × hSA) are PRO2000, RPO2100, PRO2562, PRO2566, PRO2567, PRO2660, PRO2741 and PRO2746 whose sequences are listed in Table 11. Further details regarding their manufacturing and functional properties are disclosed in the unpublished patent application PCT/EP2021/064427, which is herewith incorporated by reference.

[0157] The inventors of the present invention have previously found that the tri-specific molecules (biMSLN_{high} K_D × CD3 × hSA) PRO2000, PRO2562, PRO2565, PRO2566 and PRO2567 are capable of killing target cells, which have an approximately 7-fold higher MSLN expression level than healthy MeT-5A cells (ATCC CRL-9444), as determined by flow cytometry, with high efficiency and with an EC₅₀ that is at least 25-fold lower than the EC₅₀ for killing said MeT-5A cells, as determined in a T-cell driven cytotoxicity assay against said target cells and said

MeT-5A cells. Thus, although PRO2000, PRO2562, PRO2566 and PRO2567 exhibit a very high killing potency for high MSLN expressing target cells, their killing potency towards healthy cells is much lower, indicating a potentially large therapeutic window for treatments using PRO2000, PRO2562, PRO2566 and PRO2567. In contrast thereto, the potencies of a tri-specific reference molecule PRO1872 (MSLN_{low}KDxCD3xhSA), which comprises one MSLN-BD having a more than 5-fold better binding affinity (K_D) than the MSLN-BDs of PRO2000, PRO2562, PRO2566 and PRO2567, for killing said high MSLN expressing target cells and said healthy Met-5A cells do not differ significantly. This finding indicates that the therapeutic window for the use of the multispecific antibodies of the present invention in the treatment of cancer patients is significantly increased. In addition, the inventors of the present invention have surprisingly found that the EC_{50} values of the tri-specific molecules PRO2000, PRO2562, PRO2566 and PRO2567 (biMSLN_{high} KDxCD3xhSA) for killing target cells, which have an approximately 7-fold higher MSLN expression level than said healthy MeT-5A cells, as determined by flow cytometry, do not increase by more than 6-fold in the presence of 50 ng/ml soluble mesothelin (sMSLN), and by not more than 40-fold in the presence of 500 ng/ml soluble mesothelin (sMSLN), as determined in a T-cell driven cytotoxicity assay against said target cells. On the other hand, the EC_{50} value of the tri-specific reference molecule PRO1872 (MSLN_{low} KDxCD3xhSA) for killing said target cells increased by almost 8-fold in the presence of 50 ng/ml sMSLN and by more than 75-fold in the presence of 500 ng/ml sMSLN. Thus, the high killing potency of the tri-specific molecules PRO2000, PRO2562, PRO2566 and PRO2567 for high MSLN expressing target cells is only marginally affected by high concentrations of sMSLN.

[0158] In specific embodiments, the TAA-BD or the TAA-BDs of the multispecific antibodies MA2 specifically bind to ROR1.

[0159] The term "ROR1" refers in particular to *human* ROR1 with UniProt ID number Q01973. Suitably, the ROR1-BD of the present invention targets human ROR1, in particular the extracellular domain (ECD) of ROR1. In particular embodiments the ROR1-BD binds to the Ig-like and/or the frizzled domain of ROR1. In other particular embodiments the ROR1-BD does not block the binding of Wnt5 α to ROR1.

[0160] Suitably, the ROR1-BDs, when being in scFv format, are characterized by one or more of the following parameters:

- a. bind to the extracellular domain of human ROR1 with a monovalent dissociation constant (K_D) of 1 pM to 2 nM, particularly with a K_D of 2 pM to 1 nM, particularly of 5 to 500 pM, as measured by surface plasmon resonance (SPR);
- b. bind to human ROR1-expressing MDA-MB-231 cells with an EC_{50} of 5 pM to 10 nM, particularly with an EC_{50} of 10 pM to 5 nM, particularly with an EC_{50} of 20 pM to 4 nM, particularly with an EC_{50} of 30 pM to 3 nM.

[0161] Suitably, the ROR1-BDs, when being in scFv format, are further characterized by one or more of the following parameters:

- c. have a melting temperature (T_m), determined by differential scanning fluorimetry (DSF), of at least 58°C, particularly of at least 59°C, particularly of at least 60°C, particularly of at least 61°C, in particular wherein said scFvs are formulated in 50 mM phosphate citrate buffer with 150 mM NaCl at pH 6.4;
- d. have a loss in monomer content, after storage for at least four weeks at 4°C of less than 3 %, particularly less than 2 %, particularly less than 1 %, when said scFvs are at a starting concentration of 10 mg/ml, and in particular wherein said scFvs are formulated in 50 mM phosphate citrate buffer with 150 mM NaCl at pH 6.4; and/or
- e. have a loss in monomer content, after storage for at least four weeks at 40°C of less than 10 %, when said scFvs are at a starting concentration of 10 mg/ml, and in particular wherein said scFvs are formulated in 50 mM phosphate citrate buffer with 150 mM NaCl at pH 6.4; and/or
- f. have a loss in protein content, after storage for at least four weeks at 4°C or 40°C of less than 1 %, when said scFvs are at a starting concentration of 10 mg/ml, and in particular wherein said scFvs are formulated in 50 mM phosphate citrate buffer with 150 mM NaCl at pH 6.4.

[0162] Suitably, the ROR1-BDs applied in the multispecific antibodies MA2 include, but are not limited to, the humanized ROR1-BDs whose sequences are listed in Table 10.

[0163] In one particular embodiment, the multispecific antibody MA2 applied in the pharmaceutical composition or the kit of the invention does not comprise an immunoglobulin Fc region polypeptide.

[0164] In another particular embodiment, the multispecific antibody MA2 applied in the pharmaceutical composition or the kit of the invention does comprise an immunoglobulin Fc region polypeptide.

[0165] Other variable domains used in the invention include amino acid sequences that have been mutated, yet have at least 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identity in the CDR regions with the CDR regions depicted in the sequences described in Tables 1 to 3 and 6 to 10. Other variable domains used the invention include mutant amino acid sequences wherein no more than 1, 2, 3, 4 or 5 amino acids have been mutated in the CDR regions when compared with the CDR regions depicted in the sequence described in Tables 1 to 3 and 6 to 10.

[0166] Suitably, the VH domains of the binding domains used in the invention belong to a VH3 or VH4 family. In one embodiment, a binding domain used in the invention comprises a VH domain belonging to the VH3 family. In the context of the present invention, the term "belonging to VHx family (or VLx family)" means that the framework sequences FR1 to FR3 show the highest degree of homology to said VHx family (or VLx, respectively). Examples of VH and VL families are given in Knappik et al., J. Mol. Biol. 296 (2000) 57-86, or in WO 2019/057787. A specific example of a VH domain belonging to VH3 family is represented by SEQ ID NO: 91, and a specific example of a VH domain belonging to VH4 family is represented by SEQ ID NO: 92. In particular, framework regions FR1 to FR3 taken from SEQ ID NO: 91 belong to VH3 family (Table 4, regions marked in non-bold). Suitably, a VH belonging to VH3 family, as used herein, is a VH comprising FR1 to FR3 having at least 85 %, particularly at least 90 %, more particularly at least 95 % sequence identity to FR1 to FR3 of SEQ ID NO: 91. Alternative examples of VH3 and VH4 sequences, and examples of other VHx sequences, may be found in Knappik et al., J. Mol. Biol. 296 (2000) 57-86 or in WO 2019/057787. Suitably, the PDL1-BD, the CD137-BD, the hSA-BD, the CD3-BD, the MSLN-BD and the HER2-BD comprised in MA1 and MA2 that are applied in the pharmaceutical composition or the kit of the invention comprise: Vk frameworks FR1, FR2 and FR3, particularly Vk1 or Vk3 frameworks, particularly Vk1 frameworks FR1 to 3, and a framework FR4, which is selected from a Vk FR4, and a Vλ FR4, particularly a Vλ FR4. Suitable Vk1 frameworks FR1 to FR3 as well as exemplary Vλ FR4 are set forth in SEQ ID NO: 93 (Table 4, FR regions are marked in non-bold). Alternative examples of Vk1 sequences, and

examples of Vk2, Vk3 or Vk4 sequences, may be found in Knappik et al., J. Mol. Biol. 296 (2000) 57-86. Suitable Vk1 frameworks FR1 to 3 comprise the amino acid sequences having at least 70, 80, 90 percent identity to amino acid sequences corresponding to FR1 to FR3 and taken from SEQ ID NO: 93 (Table 4, FR regions are marked in non-bold). Suitable Vλ FR4 are as set forth in SEQ ID NO: 94 to SEQ ID NO: 100 and in SEQ ID NO: 101 comprising a single cysteine residue, particularly in a case where a second single cysteine is present in the corresponding VH chain, particularly in position 51 (AHO numbering) of VH, for the formation of an inter-domain disulfide bond. In one embodiment, the VL domains used in the present invention comprises Vλ FR4 comprising the amino acid sequence having at least 70, 80, 90 percent identity to an amino acid sequence selected from any of SEQ ID NO: 94 to SEQ ID NO: 101, particularly to SEQ ID NO: 94 or 101.

[0167] The binding domains used in the invention comprise a VH domain listed in Tables 1 to 3 and 6 to 10. Suitably, a binding domain used in the invention comprises a VH amino acid sequence listed in one of Tables 1 to 3 and 6 to 10, wherein no more than 20 amino acids in a framework sequence (for example, a sequence which is not a CDR) have been mutated (wherein a mutation is, as various non-limiting examples, an addition, substitution or deletion). Suitably, a binding domain used in the present invention comprises a VH amino acid sequence listed in one of Tables 1 to 3 and 6 to 10, wherein no more than 15 amino acids, particularly no more than 10 amino acids, particularly no more than 5 amino acids in a framework sequence (for example, a sequence which is not a CDR) have been mutated (wherein a mutation is, as various non-limiting examples, an addition, substitution or deletion). Other binding domains used in the invention include amino acids that have been mutated, yet have at least 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identity in the VH regions with the VH regions depicted in the corresponding sequences described in one of Tables 1 to 3 and 6 to 10, including VH domains comprising at least positions 5 to 140 (AHO numbering), particularly at least positions 3 to 145 of one of the sequences shown in Tables 1 to 3 and 6 to 10.

[0168] In particular, a binding domain used in the invention comprises a VL domain listed in one of Tables 1 to 3 and 6 to 10. Suitably, a binding domain used in the invention comprises a VL amino acid sequence listed in one of Tables 1 to 3 and 6 to 10, wherein no more than about 10 amino acids in a framework sequence (for

example, a sequence which is not a CDR) have been mutated (wherein a mutation is, as various non-limiting examples, an addition, substitution or deletion). Suitably, a binding domain used in the invention comprises a VL amino acid sequence listed in one of Tables 1 to 3 and 6 to 10, wherein no more than about 20 amino acids in a framework sequence (for example, a sequence which is not a CDR) have been mutated (wherein a mutation is, as various non-limiting examples, an addition, substitution or deletion). Other binding domains used in the invention include amino acids that have been mutated, yet have at least 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identity in the VL regions with a VL region depicted in the sequences described in Tables 1 to 3 and 6 to 10, including VL domains comprising at least positions 5 to 140 (AHO numbering), particularly at least positions 3 to 145 of one of the sequences shown in Tables 1 to 3 and 6 to 10.

[0169] In the context of the present invention, the term “binding domain used in the present invention” relates to a binding domain as such, *i. e.* independent of a multispecific context, and, in particular, to a binding domain comprised in a multispecific construct, *e. g.* one of the binding domains comprised in a bispecific, trispecific or tetraspecific construct.

[0170] Suitably, the binding domains of the multispecific antibodies MA1 and MA2 are selected from the group consisting of: a Fab, an Fv, an scFv, dsFv, a scAb, and STAB.

[0171] Suitably, the binding domains of the multispecific antibodies MA1 and MA2 are operably linked. The binding domains of the multispecific antibodies MA1 and MA2 are capable of binding to their respective antigens or receptors simultaneously. The term “simultaneously”, as used in this connection and in connection with the MA1, refers to the simultaneous binding of the CD137-BDs and the PDL1-BD. Similarly, the term “simultaneously”, as used in connection with the MA2, refers to the simultaneous binding of at least one of the TAA-BDs and the CD3-BD. In specific cases, *e.g.* in cases where the applied MA2 has two or more TAA-BDs that are specific for the same TAA and the target cells have a high density of said TAA on the cell surface, it might also be possible that three binding domains, *i. e.* two TAA-BDs and the CD3-BD, bind simultaneously.

[0172] The multispecific antibodies MA1 comprises one CD137-BD and one PDL1-BD, wherein said CD137-BDs, and said PDL1-BD are operably linked to each other.

[0173] The multispecific antibodies MA1 comprises at least one TAA-BD, and one CD3-BD, wherein said at least one TAA-BD, and said CD3-BD are operably linked to each other.

[0174] The term “operably linked”, as used herein, indicates that two molecules (e. g., polypeptides, domains, binding domains) are attached in a way that each molecule retains functional activity. Two molecules can be “operably linked” whether they are attached directly or indirectly (e. g., via a linker, via a moiety, via a linker to a moiety). The term “linker” refers to a peptide or other moiety that is optionally located between binding domains or antibody fragments used in the invention. A number of strategies may be used to covalently link molecules together. These include, but are not limited to, polypeptide linkages between N- and C-termini of proteins or protein domains, linkage via disulfide bonds, and linkage via chemical cross-linking reagents. In one aspect of this embodiment, the linker is a peptide bond, generated by recombinant techniques or peptide synthesis. Choosing a suitable linker for a specific case where two polypeptide chains are to be connected depends on various parameters, including but not limited to the nature of the two polypeptide chains (e. g., whether they naturally oligomerize), the distance between the N- and the C-termini to be connected if known, and/or the stability of the linker towards proteolysis and oxidation. Furthermore, the linker may contain amino acid residues that provide flexibility.

[0175] In the context of the present invention, the term “polypeptide linker” refers to a linker consisting of a chain of amino acid residues linked by peptide bonds that is connecting two domains, each being attached to one end of the linker. The polypeptide linker should have a length that is adequate to link two molecules in such a way that they assume the correct conformation relative to one another so that they retain the desired activity. In particular embodiments, the polypeptide linker has a continuous chain of between 2 and 30 amino acid residues (e. g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 amino acid residues). In addition, the amino acid residues selected for inclusion in the polypeptide linker should exhibit properties that do not interfere significantly with the activity of the polypeptide. Thus, the linker peptide on the whole should not exhibit a charge that would be inconsistent with the activity of the polypeptide, or interfere with internal folding, or form bonds or other interactions with amino acid

residues in one or more of the monomers that would seriously impede the binding of receptor monomer domains. In particular embodiments, the polypeptide linker is non-structured polypeptide. Useful linkers include glycine-serine, or GS linkers. By “Gly-Ser” or “GS” linkers is meant a polymer of glycines and serines in series (including, for example, (Gly-Ser)_n, (GSGGS)_n, (GGGGS)_n and (GGGS)_n, where n is an integer of at least one), glycine-alanine polymers, alanine-serine polymers, and other flexible linkers such as the tether for the shaker potassium channel, and a large variety of other flexible linkers, as will be appreciated by those in the art. Glycine-serine polymers are preferred since oligopeptides comprising these amino acids are relatively unstructured, and therefore may be able to serve as a neutral tether between components. Secondly, serine is hydrophilic and therefore able to solubilize what could be a globular glycine chain. Third, similar chains have been shown to be effective in joining subunits of recombinant proteins such as single-chain antibodies. [0176] Suitably, the multispecific antibody MA1 is in a format selected from any suitable multispecific format known in the art, *i.e.* any formats that are at least bispecific and do not comprise immunoglobulin Fc region(s), including, by way of non-limiting example, a single-chain diabody (scDb); a bispecific T cell engager (BiTE; tandem di-scFv); a tandem tri-scFv; Fab-(scFv); scFab-dsscFv; tribody (Fab-(scFv)₂; Fab₂; Fab-Fv₂; diabody; triabody; scDb-scFv; a scDb, a tandem tri-scFv, a Fab-(scFv), a scFab-dsscFv, a Fab-(scFv)₂, a Fab₂, a Fab-Fv₂, a diabody or a scDb-scFv fused to the N- and/or the C-terminus of a heterodimerization domain other than heterodimeric Fc domains; and a MATCH (described in WO 2016/0202457; Egan T., et al., MABS 9 (2017) 68-84) and DuoBodies. Particularly suitable for use herein is a scDb, a scDb-scFv, a scMATCH3 and a MATCH3, especially a scDb-scFv, a scMATCH3 and a MATCH3.

[0177] The term “diabodies” refers to antibody fragments with two antigen-binding sites, which fragments comprise a VH connected to VL in the same polypeptide chain (VH-VL). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain to create two antigen-binding sites. Diabodies may be bivalent or bispecific. Diabodies are described more fully in, for example, EP 404 097, WO 93/01161, Hudson et al., Nat. Med. 9:129-134 (2003), and Holliger et al.,

Proc. Natl. Acad. Sci. USA 90: 6444-6448 (1993). Triabodies and tetrabodies are also described in Hudson et al., Nat. Med. 9:129-134 (2003).

[0178] The bispecific scDb, in particular the bispecific monomeric scDb, particularly comprises two variable heavy chain domains (VH) or fragments thereof and two variable light chain domains (VL) or fragments thereof connected by linkers L1, L2 and L3 in the order VHA-L1-VLB-L2-VHB-L3-VLA, VHA-L1-VHB-L2-VLB-L3-VLA, VLA-L1-VLB-L2-VHB-L3-VHA, VLA-L1-VHB-L2-VLB-L3-VHA, VHB-L1-VLA-L2-VHA-L3-VLB, VHB-L1-VHA-L2-VLA-L3-VLB, VLB-L1-VLA-L2-VHA-L3-VHB or VLB-L1-VHA-L2-VLA-L3-VHB, wherein the VLA and VHA domains jointly form the antigen-binding site for the first antigen, and VLB and VHB jointly form the antigen-binding site for the second antigen.

[0179] The linker L1 particularly is a peptide of 2-10 amino acids, more particularly 3-7 amino acids, and most particularly 5 amino acids, and linker L3 particularly is a peptide of 1-10 amino acids, more particularly 2-7 amino acids, and most particularly 5 amino acids. In particular embodiments, the linker L1 and/or L3 comprises one or two units of four (4) glycine amino acid residues and one (1) serine amino acid residue (GGGGS)_n, wherein n=1 or 2, particularly n=1.

[0180] The middle linker L2 particularly is a peptide of 10-40 amino acids, more particularly 15-30 amino acids, and most particularly 20-25 amino acids. In particular embodiments, said linker L2 comprises two or more units of four (4) glycine amino acid residues and one (1) serine amino acid residue (GGGGS)_n, wherein n= 2, 3, 4, 5, 6, 7 or 8, particularly n=4 or 5.

[0181] In one embodiment, the multispecific antibody MA1 is a scDb-scFv. The term "scDb-scFv" refers to an antibody format, wherein a single-chain Fv (scFv) fragment is fused by a flexible Gly-Ser linker to a single-chain diabody (scDb). In one embodiment, said flexible Gly-Ser linker is a peptide of 2-40 amino acids, e. g., 2-35, 2-30, 2-25, 2-20, 2-15, 2-10 amino acids, particularly 10 amino acids. In particular embodiments, said linker comprises one or more units of four (4) glycine amino acid residues and one (1) serine amino acid residue (GGGGS)_n, wherein n=1, 2, 3, 4, 5, 6, 7 or 8, particularly n=2.

[0182] In another embodiment, the multispecific antibody MA1 is in a scMATCH3 or a MATCH3 format described in WO 2016/0202457; Egan T., et al., MABS 9 (2017) 68-84.

[0183] In one embodiment, the multispecific antibodies MA1 applied in the pharmaceutical compositions or the kit of the invention do not comprise CH1 and/or CL regions.

[0184] Specific but non-limiting examples of multispecific antibodies MA1 that can suitably be applied in the pharmaceutical compositions or the kit of the invention are the scDb-based antibodies PRO885, PRO951, PRO1123, PRO1124, PRO1125, PRO1126, PRO1134, and the scDb-scFv-based antibodies PRO963, PRO966, PRO1057, PRO1058, PRO1175, PRO1186, PRO1430, PRO1479, PRO1482, PRO1431, PRO1432, PRO1473, PRO1476, PRO1480, PRO1481, PRO1480diS, PRO1599, RPO1600, RPO1601, whose sequences are listed in Table 5. Particularly suitable as multispecific antibodies MA1 are PRO1480, PRO1481, PRO1480diS, and RPO1601.

[0185] These multispecific antibodies MA1, in particular PRO1480, PRO1481, PRO1480diS and PRO1601 exhibit very advantageous safety properties. For example, PRO1480, when tested in female cynomolgus monkeys, after single-dose administration of PRO1480 up to 20 mg/kg, there was:

- no elevation of liver enzymes (ALT/AST/GGT/CK), which are the key clinical pathology indicators of hepatotoxicity caused by urelumab;
- no neutropenia or thrombocytopenia, which has been observed upon application of urelumab in the clinic;
- no atypical liver weights when compared to avelumab;
- no significant expansion of systemic central and effector memory T cells (less than reported values for well tolerated utomilumab), confirming specific activity on 4-1BB exclusively in the TME;
- a prolonged serum half-life of 5 – 5.5 days, corresponding to approximately 2 weeks in humans.

[0186] Furthermore, in a second 4-week repeated dose toxicology study with PRO1480 in cynomolgus monkeys, there was:

- no treatment related findings in alterations of organ weights, macroscopic observations and microscopic histopathological evaluation of tissue sections;
- no signs of toxicity and in particular, no elevations of transaminases or liver inflammation, markers for hepatotoxicity;
- no test-article related effects in clinical chemistry, hematology and urinalysis;

- no release of the cytokines GM-CSF, Interleukin 18, IL1B, IFNg, IL-2, IL-4, IL-5 and GM-CSF following the pre-dose, the first dose and the fourth dose of PRO1480;
- only moderate induction of the cytokines IL-6, MCP-1 and IL-10 in some of low- and mid-dose animals following dosing of PRO1480, which is consistent with ADA response.

[0187] In particular, the intra-venous infusion of PRO1480 was generally well tolerated and not associated with any signs of toxicity in cynomolgus monkeys up to 140 mg/kg/dose. Such an excellent toxicological profile has not been seen for any corresponding anti-CD137xPDL1 antibody therapeutics of the prior art, due to the presence of the Fc domain.

[0188] Suitably, the multispecific antibodies MA2 are in a format selected from any suitable multispecific, *e. g.* at least bispecific, format known in the art, including, by way of non-limiting example, a tandem scDb (Tandab); a bispecific T cell engager (BiTE; tandem di-scFv); a tandem tri-scFv; Fab-(scFv); scFab-dsscFv; tribody (Fab-(scFv)₂); Fab₂; Fab-Fv₂; diabody; triabody; tetrabody; scDb-scFv; di-diabody; scFv-Fc-scFv fusion (ADAPTIR); DVD-Ig; IgG-scFv fusions, such as CODV-IgG, Morrison (IgG CH₃-scFv fusion (Morrison L) or IgG CL-scFv fusion (Morrison H)), bsAb (scFv linked to C-terminus of light chain), Bs1Ab (scFv linked to N-terminus of light chain), Bs2Ab (scFv linked to N-terminus of heavy chain), Bs3Ab (scFv linked to C-terminus of heavy chain), Ts1Ab (scFv linked to N-terminus of both heavy chain and light chain) and Ts2Ab (dsscFv linked to C-terminus of heavy chain); a DARTTM; a TRIDENTTM; a scDb, a tandem tri-scFv, a Fab-(scFv), a scFab-dsscFv, a Fab-(scFv)₂, a Fab₂, a Fab-Fv₂, a diabody or a scDb-scFv fused to the N- and/or the C-terminus of a heterodimerization domain other than heterodimeric Fc domains; a MATCH (described in WO 2016/0202457; Egan T. et al., MABS 9 (2017) 68-84) and DuoBodies (bispecific IgGs prepared by the Duobody technology) (MAbs. 2017 Feb/Mar;9(2):182-212. doi: 10.1080/19420862.2016.1268307).

[0189] In one embodiment, the multispecific antibody MA2 is in a MATCH format described in WO 2016/0202457; Egan T., et al., MABS 9 (2017) 68-84. In particular, the multispecific antibody MA2 is in a MATCH3 or a MATCH4 format.

[0190] In another embodiment, the multispecific antibodies MA2 are in an IgG-scFv fusion format selected from CODV-IgG, Morrison (IgG CH₃-scFv fusion (Morrison L)

or IgG CL-scFv fusion (Morrison H)), bsAb (scFv linked to C-terminus of light chain), Bs1Ab (scFv linked to N-terminus of light chain), Bs2Ab (scFv linked to N-terminus of heavy chain), Bs3Ab (scFv linked to C-terminus of heavy chain), Ts1Ab (scFv linked to N-terminus of both heavy chain and light chain), Ts2Ab (dsscFv linked to C-terminus of heavy chain), a DARTTM and a TRIDENTTM.

[0191] Specific but non-limiting examples of multispecific antibodies MA2 that can suitably be applied in the pharmaceutical compositions or the kit of the invention are the scMATCH3-based antibodies PRO1766, PRO1767, PRO1872, PRO2510, PRO2668 and the MATCH4-based antibodies PRO2000, PRO2100, PRO2562, PRO2566, PRO2567, PRO2590, PRO2660, PRO2670, PRO2741 and PRO2746 whose sequences are listed in Table 11.

[0192] Further antibodies that can suitably be applied as MA2 in the pharmaceutical compositions or the kit of the invention are antibodies described in the prior art that comprise one or two TAA-BDs and one CD3-BD, as defined herein. Non-limiting examples of antibodies described in the prior art that can suitably be applied as MA2 are:

- The bispecific monovalent anti-HER2 x CD3 antibodies based on the knob-into-whole technology disclosed in WO 2015/095418;
- The bispecific 1Fab-IgG-based anti-HER2 x CD3 antibodies having two low-affinity HER2 binding domains and one anti-CD3 ϵ binding domain disclosed in WO 2019/157308 (to Genentech), in particular BTRC-4017A;
- The bispecific monovalent anti-HER2 x CD3 antibody GBR-1302 from Glenmark;
- The bispecific anti-MSLN x CD3 antibodies MG1122-A, having two low-affinity MSLN binding domains and one anti-CD3 ϵ binding domain, and MG1122-B, having two low-affinity MSLN binding domains and one anti-CD3 ϵ binding domain, as disclosed in Yoon et al. (Biomolecules, 2020,10(3), 399);
- The (scFv)₂-Fc-(scFv)₂ fusion (ADAPTIR) bispecific anti-ROR1 x CD3 antibody APVO-425 from Aptevo;
- The anti-TAA x CD3 (ROR1 x CD3) DARTTM antibodies DART-1 to DART-33 and DART-A to DART-D disclosed in WO 2017/142928 (to Macrogenics).

[0193] The multispecific antibodies MA1 and MA2 that are applied in the pharmaceutical composition or the kit of the invention can be produced using any convenient antibody-manufacturing method known in the art (see, e. g., Fischer, N. &

Leger, O., Pathobiology 74 (2007) 3-14 with regard to the production of bispecific constructs; Hornig, N. & Färber-Schwarz, A., Methods Mol. Biol. 907 (2012) 713-727, and WO 99/57150 with regard to bispecific diabodies and tandem scFvs). Specific examples of suitable methods for the preparation of the bispecific construct further include, inter alia, the Genmab (see Labrijn et al., Proc. Natl. Acad. Sci. USA 110 (2013) 5145-5150) and Merus (see de Kruif et al., Biotechnol. Bioeng. 106 (2010) 741-750) technologies. Methods for production of bispecific antibodies comprising a functional antibody Fc part are also known in the art (see, e. g., Zhu et al., Cancer Lett. 86 (1994) 127-134); and Suresh et al., Methods Enzymol. 121 (1986) 210-228).

[0194] These methods typically involve the generation of monoclonal antibodies, for example by means of fusing myeloma cells with the spleen cells from a mouse that has been immunized with the desired antigen using the hybridoma technology (see, e. g., Yokoyama et al., Curr. Protoc. Immunol. Chapter 2, Unit 2.5, 2006) or by means of recombinant antibody engineering (repertoire cloning or phage display/yeast display) (see, e. g., Chames & Baty, FEMS Microbiol. Letters 189 (2000) 1-8), and the combination of the antigen-binding domains or fragments or parts thereof of two or more different monoclonal antibodies to give a bispecific or multispecific construct using known molecular cloning techniques.

[0195] The multispecific molecules MA1 and MA2 used in the invention can be prepared by conjugating the constituent binding specificities, using methods known in the art. For example, each binding specificity of the bispecific molecule can be generated separately and then conjugated to the other(s). When the binding specificities are proteins or peptides, a variety of coupling or cross-linking agents can be used for covalent conjugation. Examples of cross-linking agents include protein A, carbodiimide, N-succinimidyl-5-acetyl-thioacetate (SATA), 5,5'-dithiobis (2-nitrobenzoic acid) (DTNB), o-phenylenedimaleimide (oPDM), N-succinimidyl-3-(2-pyridyldithio)propionate (SPDP), and sulfosuccinimidyl 4-(N-maleimidomethyl)-cyclohexane-1-carboxylate (sulfo-SMCC) (see e. g., Karpovsky et al., 1984 J. Exp. Med. 160: 1686; Liu, M A et al., 1985 Proc. Natl. Acad. Sci. USA 82:8648). Other methods include those described in Paulus, 1985 Behring Ins. Mitt. No. 78, 118-132; Brennan et al., 1985 Science 229:81-83), and Glennie et al., 1987 J. Immunol. 139: 2367-2375). Conjugating agents are SATA and sulfo-SMCC, both available from Pierce Chemical Co. (Rockford, 111).

[0196] When the binding specificities are antibodies, they can be conjugated by sulfhydryl bonding of the C-terminus hinge regions of the two heavy chains. In a particular embodiment, the hinge region is modified to contain an odd number of sulfhydryl residues, for example one, prior to conjugation.

[0197] Alternatively, two or more binding specificities can be encoded in the same vector and expressed and assembled in the same host cell. This method is particularly useful where the bispecific molecule is a mAb x mAb, mAb x Fab, Fab x F (ab')₂ or ligand x Fab fusion protein. The multispecific antibody used in the invention can be a single chain multispecific antibody comprising at least two binding determinants. The multispecific antibody use in the invention can also comprise at least two of said single-chain molecules. Methods for preparing multispecific antibodies and molecules are described for example in U.S. Pat. No. 5,260,203; U.S. Pat. No. 5,455,030; U.S. Pat. No. 4,881,175; U.S. Pat. No. 5,132,405; U.S. Pat. No. 5,091,513; U.S. Pat. No. 5,476,786; U.S. Pat. No. 5,013,653; U.S. Pat. No. 5,258,498; and U.S. Pat. No. 5,482,858.

[0198] Binding of the multispecific antibodies to their specific targets can be confirmed by, for example, enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (REA), FACS analysis, bioassay (e. g., growth inhibition), or Western Blot assay. Each of these assays generally detects the presence of protein-antibody complexes of particular interest by employing a labeled reagent (e. g., an antibody) specific for the complex of interest.

[0199] Suitably, the pharmaceutical composition further comprises a pharmaceutically acceptable carrier.

[0200] "Pharmaceutically acceptable carrier" means a medium or diluent that does not interfere with the structure of the antibodies. Pharmaceutically acceptable carriers enhance or stabilize the composition, or facilitate preparation of the composition. Certain, of such carries enable pharmaceutical compositions to be formulated as, for example, tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspension and lozenges for the oral ingestion by a subject. Certain of such carriers enable pharmaceutical compositions to be formulated for injection, infusion or topical administration. For example, a pharmaceutically acceptable carrier can be a sterile aqueous solution.

[0201] Pharmaceutically acceptable carriers include but are not limited to solvents, buffer solutions, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible.

[0202] The pharmaceutical compositions of the present invention can be prepared in accordance with methods well known and routinely practiced in the art. See, *e. g.*, Remington: The Science and Practice of Pharmacy, Mack Publishing Co., 20th ed., 2000; and Sustained and Controlled Release Drug Delivery Systems, J. R. Robinson, ed., Marcel Dekker, Inc., New York, 1978. Pharmaceutical compositions are preferably manufactured under GMP conditions. Typically, a therapeutically effective dose or efficacious dose of the multispecific antibodies MA1 and MA2 is employed in the pharmaceutical compositions of the invention. The multispecific antibodies MA1 and MA2 are formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art. Dosage regimens are adjusted to provide the optimum desired response (*e. g.*, a therapeutic response). For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit contains a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier.

[0203] Actual dosage levels of the active ingredients in the pharmaceutical compositions or the kit can be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient. The selected dosage level depends upon a variety of pharmacokinetic factors including the activity of the particular compositions used in the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials

used in combination with the particular compositions employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors.

[0204] The pharmaceutical compositions or the kit of the invention can be administered by a variety of methods known in the art. In the case of administering the multispecific antibody components of the kits, administration may be done concomitantly or sequentially. In the case of a sequential administration, the multispecific antibody components may be administered based on individually adjusted administration schemes and regimens. The route and/or mode of administration vary depending upon the desired results. Administration can be intravenous, intramuscular, intraperitoneal, or subcutaneous, or administered proximal to the site of the target. The pharmaceutically acceptable carrier should be suitable for intravenous, intramuscular, subcutaneous, parenteral, spinal or epidermal administration (*e. g.*, by injection or infusion). Depending on the route of administration, the active compound, *i. e.*, the multispecific antibodies MA1 and MA2 applied in the pharmaceutical composition of the invention, may be coated in a material to protect the compound from the action of acids and other natural conditions that may inactivate the compound.

[0205] The pharmaceutical composition or the kit of the invention is usually administered on multiple occasions. Intervals between single dosages can be weekly, monthly or yearly. Intervals can also be irregular as indicated by measuring blood levels of the multispecific antibody in the patient. Alternatively, the pharmaceutical composition of the invention can be administered as a sustained release formulation, in which case less frequent administration is required. Dosage and frequency vary depending on the half-life of the antibodies MA1 and MA2 in the patient. In general, humanized antibodies show longer half-life than that of chimeric antibodies and nonhuman antibodies. The dosage and frequency of administration can vary depending on whether the treatment is prophylactic or therapeutic. In prophylactic applications, a relatively low dosage is administered at relatively infrequent intervals over a long period of time. Some patients continue to receive treatment for the rest of their lives. In therapeutic applications, a relatively high dosage at relatively short intervals is sometimes required until progression of the disease is reduced or terminated, and preferably until the patient shows partial or

complete amelioration of symptoms of disease. Thereafter, the patient can be administered a prophylactic regime.

[0206] In one aspect, the present invention relates to the pharmaceutical composition or the kit of the invention for use as a medicament. In a suitable embodiment, the present invention provides the pharmaceutical composition or the kit for use in treatment of a proliferative disease, in particular a cancer in a subject in need thereof.

[0207] In another aspect, the present invention provides the pharmaceutical composition for use in a manufacture of a medicament for treatment of a proliferative disease, in particular a cancer.

[0208] In another aspect, the present invention relates to the use of the pharmaceutical composition or the kit for treating a proliferative disease, in particular a cancer in a subject in need thereof.

[0209] In another aspect, the present invention relates to a method of treating a subject comprising administering to the subject a therapeutically effective amount of the pharmaceutical composition of the present invention. In a suitable embodiment, the present invention relates to a method of treating a proliferative disease, in particular a cancer in a subject comprising administering to the subject a therapeutically effective amount of the pharmaceutical composition of the present invention.

[0210] In yet another aspect, the present invention relates to a method for treating a subject suffering from a proliferative disease, particularly a cancer,, comprising the step of administering to said subject a first multispecific antibody (MA1) comprising one binding domain, which specifically binds to CD137 (CD137-BD), and one binding domain, which specifically binds to PDL1 (PDL1-BD), and a second multispecific antibody (MA2) comprising at least one binding domain, which specifically binds to a tumor cell associated antigen (TAA-BD), and one binding domain, which specifically binds to CD3 (CD3-BD), wherein said multispecific antibodies MA1 and MA2 are as defined herein.

[0211] In another aspect, the present invention relates to (i) a multispecific antibody MA1 comprising one binding domain, which specifically binds to CD137 (CD137-BD), and one binding domain, which specifically binds to PDL1 (PDL1-BD), for use in the treatment of a subject suffering from a proliferative disease, particularly a cancer,

wherein said multispecific antibody MA1 is administered to said subject in combination with a second multispecific antibody MA2 comprising at least one binding domain, which specifically binds to a tumor cell associated antigen (TAA-BD), and one binding domain, which specifically binds to CD3 (CD3-BD), or (ii) a multispecific antibody MA2 comprising one binding domain, which specifically binds to a tumor cell associated antigen (TAA-BD), and one binding domain, which specifically binds to CD3 (CD3-BD), for use in the treatment of a subject suffering from a proliferative disease, particularly a cancer, wherein said multispecific antibody MA2 is administered to said subject in combination with a second multispecific antibody MA1 comprising at least one binding domain, which specifically binds to CD137 (CD137-BD), and one binding domain, which specifically binds to PDL1 (PDL-BD); wherein said multispecific antibodies MA1 and MA2 are as defined herein.

[0212] The term “subject” includes human and non-human animals.

[0213] The term “animals” include all vertebrates, *e. g.*, non-human mammals and non-mammals, such as non-human primates, sheep, dog, cow, chickens, amphibians, and reptiles. Except when noted, the terms “patient” or “subject” are used herein interchangeably.

[0214] The terms “treatment”, “treating”, “treat”, “treated”, and the like, as used herein, refer to obtaining a desired pharmacologic and/or physiologic effect. The effect may be therapeutic in terms of a partial or complete cure for a disease and/or adverse effect attributable to the disease or delaying the disease progression.

“Treatment”, as used herein, covers any treatment of a disease in a mammal, *e. g.*, in a human, and includes: (a) inhibiting the disease, *i. e.*, arresting its development; and (b) relieving the disease, *i. e.*, causing regression of the disease.

[0215] The term “therapeutically effective amount” or “efficacious amount” refers to the amount of an agent that, when administered to a mammal or other subject for treating a disease, is sufficient to affect such treatment for the disease. The “therapeutically effective amount” will vary depending on the agent, the disease and its severity and the age, weight, etc., of the subject to be treated.

[0216] In one embodiment, the proliferative disease is a cancer. The term “cancer” refers to a disease characterized by the rapid and uncontrolled growth of aberrant cells. Cancer cells can spread locally or through the bloodstream and lymphatic

system to other parts of the body. The terms “tumor” and “cancer” are used interchangeably herein, *e. g.*, both terms encompass solid and liquid, *e. g.*, diffuse or circulating, tumors. As used herein, the term “cancer” or “tumor” includes premalignant, as well as malignant cancers and tumors. The term “cancer” is used herein to mean a broad spectrum of tumors, including all solid and hematological malignancies. Examples of such tumors include, but are not limited to: a benign or especially malignant tumor, solid tumors, mesothelioma, brain cancer, kidney cancer, liver cancer, adrenal gland cancer, bladder cancer, breast cancer, stomach cancer (*e. g.*, gastric tumors), esophageal cancer, ovarian cancer, cervical cancer, colon cancer, rectum cancer, prostate cancer, pancreatic cancer, lung cancer (*e. g.* non-small cell lung cancer and small cell lung cancer), vaginal cancer, thyroid cancer, melanoma (*e. g.*, unresectable or metastatic melanoma), renal cell carcinoma, sarcoma, glioblastoma, multiple myeloma or gastrointestinal cancer, especially colon carcinoma or colorectal adenoma, a tumor of the neck and head, endometrial cancer, Cowden syndrome, Lhermitte-Duclos disease, Bannayan-Zonana syndrome, prostate hyperplasia, a neoplasia, especially of epithelial character, preferably mammary carcinoma or squamous cell carcinoma, chronic lymphocytic leukemia, chronic myelogenous leukemia (*e. g.*, Philadelphia chromosome-positive chronic myelogenous leukemia), acute lymphoblastic leukemia (*e. g.*, Philadelphia chromosome-positive acute lymphoblastic leukemia), non-Hodgkin’s lymphoma, plasma cell myeloma, Hodgkin’s lymphoma, a leukemia, and any combination thereof. In a preferred embodiment, the cancer is a cancer selected from melanoma, mesothelioma, pancreatic cancer, stomach cancer, breast cancer, ovarian cancer and lung cancer.

[0217] The pharmaceutical composition or the kit of the present invention inhibits the growth of solid tumors, but also liquid tumors. In a further embodiment, the proliferative disease is a solid tumor. The term “solid tumor” especially means a mesothelioma, breast cancer, ovarian cancer, colon cancer, rectum cancer, prostate cancer, stomach cancer (especially gastric cancer), cervical cancer, lung cancer (*e. g.*, non-small cell lung cancer and small cell lung cancer), pancreatic cancer and a tumor of the head and neck. Further, depending on the tumor type and the particular combination used, a decrease of the tumor volume can be obtained. The pharmaceutical composition or the kit of the present invention is also suited to

prevent the metastatic spread of tumors and the growth or development of micro-metastases in a subject having a cancer.

Sequence listing (mutations designated according to AHO numbering scheme; the CDRs defined according to Numab CDR definition, unless specified otherwise)

Table 1. Examples of CD137 binding domains as used in the present invention (CDR residues shown in bold and italic letters).

SEQ ID NUMBER	Ab region	Sequence
38-02-A04		
SEQ ID NO: 1	HCDR1 (H27-H42; AHO numbering)	GF ~~S~~ FSNSYWIC
SEQ ID NO: 2	HCDR2 (H57-H76; AHO numbering)	CTFVGSSDSTYYANWAKG
SEQ ID NO: 3	HCDR3 (H108-H138; AHO numbering)	RHPSDAVYGYANNL
SEQ ID NO: 4	VH (VH4) (38-02-A04 sc01)	QVQLQESGPGLVKPSSETLSLTCKVSG ~~S~~ FSNSY WIC WIRQPPGKGLEWIG CTFV GSSDSTYYANWAKGR VTISVDSSKNQFSLKLSSTAAADTA VYYCA RHPSDAVY GYAN LWGQGLVTVSS
SEQ ID NO: 5	VH (VH4) (38-02-A04 sc05 IF) Mutations VH: I44V; F89V; Y105F.	QVQLQESGPGLVKPSSETLSLTCKVSG ~~S~~ FSNSY WIC WVRQPPGKGLEWIG CTF VGSSDSTYYANWAKGR VTISVDSSKNQVSLKLSSTAAADTA VYFCAR HPSDAV YGYAN LWGQGLVTVSS
SEQ ID NO: 6	VH (VH4) (38-02-A04 sc06 Full) Mutations VH: V25A; I44V; V82K; F89V; Y105F.	QVQLQESGPGLVKPSSETLSLTCKASG ~~S~~ FSNSY WIC WVRQPPGKGLEWIG CTF VGSSDSTYYANWAKGR VTISKDSSKNQVSLKLSSTAAADTA VYFCAR HPSDAV YGYAN LWGQGLVTVSS
SEQ ID NO: 7	VH (VH3) (38-02-A04 sc13)	EVQLVESGGGLVQPGGSLRLSCAASG ~~S~~ FSNSY WIC WVRQAPGKCLEWIG CTF VGSSDSTYYANWAKGR FTISRDNKNTVYLQMNSLR AEDTA VYYCA RHPSDA VYGYAN LWGQGLVTVSS

	Mutations VH: G51C (AHo numbering)	
SEQ ID NO: 8	LCDRI (L24-L42; AHo numbering) (Kabat definition)	QASQSINNVL A
SEQ ID NO: 9	LCDR2 (L58-L72; AHo numbering) (Kabat definition)	RASTLAS
SEQ ID NO: 10	LCDR3 (L107-L138; AHo numbering) (Kabat definition)	QSSYGNYGD
SEQ ID NO: 11	VL (Vk1-sk17) (38-02-A04 sc01)	DIQMTQSPSSLSASVGDRVTITCQASQSINNVLAWYQQKPGKAPKLLIYRASTL ASGVPSRFSGSGGTDFTLTISLQPEDFATYYCQSSYGNYGDFGTGKVTVLG
SEQ ID NO: 12	VL (Vk1-sk17) (38-02-A04 sc05 IF) Mutations VL: A51P	DIQMTQSPSSLSASVGDRVTITCQASQSINNVLAWYQQKPGKPPKLLIYRASTL ASGVPSRFSGSGGTDFTLTISLQPEDFATYYCQSSYGNYGDFGTGKVTVLG
SEQ ID NO: 13	VL (Vk1-sk17) (38-02-A04 sc06 Full) Mutations VL: I2L; A51P	DLQMTQSPSSLSASVGDRVTITCQASQSINNVLAWYQQKPGKPPKLLIYRASTL ASGVPSRFSGSGGTDFTLTISLQPEDFATYYCQSSYGNYGDFGTGKVTVLG
SEQ ID NO: 14	VL (Vk1-sk17) (38-02-A04 sc13) Mutations VL: T141C (AHo numbering)	DIQMTQSPSSLSASVGDRVTITCQASQSINNVLAWYQQKPGKAPKLLIYRASTL ASGVPSRFSGSGGTDFTLTISLQPEDFATYYCQSSYGNYGDFGCGTKVTVLG
SEQ ID NO: 15	scFv (VL-linker-VH) (38-02-A04 sc01)	DIQMTQSPSSLSASVGDRVTITCQASQSINNVLAWYQQKPGKAPKLLIYRASTL ASGVPSRFSGSGGTDFTLTISLQPEDFATYYCQSSYGNYGDFGTGKVTVLG GGGSGGGGGGGGGGGGGGQVQLQESGPGLVKPSETLSLTCKVSGFSFSNSY

		<i>WICWIRQPPGKGLEWIGCTFV/GSSDSTYYANWAKGRVTISVDSSKNQFSLKLSS</i> <i>VTAADTAVYYCARHPSDAVYGYANNLWGQGTLLVTVSS</i>
SEQ ID NO: 16	scFv (VL-linker-VH) (38-02-A04 sc05 IF)	<i>DIQMTQSPSSLSASVGDRVTITCQASQINNVLAWYQQKPKPPKLLIYR4STL</i> <i>ASGVPSRFSGSGGTDFTLTISLQPEDFATYYCQSSYGNYGDFGTGKVTVLG</i> <i>GGGSGGGSGGGSGGGSQVQLQESGPGLVKPSSETLSLTCKVSGFSFSNSY</i> <i>WICWVRQPPGKGLEWIGCTFV/GSSDSTYYANWAKGRVTISVDSSKNQVSLKLS</i> <i>SVTAADTAVYFCARHPSDAVYGYANNLWGQGTLLVTVSS</i>
SEQ ID NO: 17	scFv (VL-linker-VH)(38-02-A04 sc06 Full)	<i>DLQMTQSPSSLSASVGDRVTITCQASQINNVLAWYQQKPKPPKLLIYR4STL</i> <i>ASGVPSRFSGSGGTDFTLTISLQPEDFATYYCQSSYGNYGDFGTGKVTVLG</i> <i>GGGSGGGSGGGSGGGSQVQLQESGPGLVKPSSETLSLTCKASGFSFSNSY</i> <i>WICWVRQPPGKGLEWIGCTFV/GSSDSTYYANWAKGRVTISKDSKNQVSLKLS</i> <i>SVTAADTAVYFCARHPSDAVYGYANNLWGQGTLLVTVSS</i>
SEQ ID NO: 18	scFv (VL-linker-VH) (38-02-A04 sc13)	<i>DIQMTQSPSSLSASVGDRVTITCQASQINNVLAWYQQKPKAPKLLIYR4STL</i> <i>ASGVPSRFSGSGGTDFTLTISLQPEDFATYYCQSSYGNYGDFGCGTKVTVLG</i> <i>GGGSGGGSGGGSGGGSQVQLVESGGGLVQPGGSLRLSCAASGFSFSNS</i> <i>YWICWVRQAPGKCLEWIGCTFV/GSSDSTYYANWAKGRFTISRDNSKNTVYVYQ</i> <i>MNSLRAEDTAVYYCARHPSDAVYGYANNLWGQGTLLVTVSS</i>
38-27-C05 sc01		
SEQ ID NO: 19	HCDR1 (H27-H42; AHO numbering)	GFSFNNDYDMC
SEQ ID NO: 20	HCDR2 (H57-H76; AHO numbering)	CIDTGDGSTYYASWAKG
SEQ ID NO: 21	HCDR3 (H108-H138; AHO numbering)	REAASSSGYGMGYFDL
SEQ ID NO: 22	VH (VH4)	<i>QVQLQESGPGLVKPSSETLSLTCKVSGFSFNNDYDMC</i> <i>WIRQPPGKGLEWIGCID</i> <i>TGDSSTYYASWAKGRVTISVDSSKNQFSLKLSVTAADTAVYYCAR4A4SSSG</i> <i>YGMGYFDLWGQGTLLVTVSS</i>
SEQ ID NO: 23	LCDR1 (L24-L42; AHO numbering) (Kabat definition)	QSSQSVYDNNWLA
SEQ ID NO: 24	LCDR2	RASNLAS

	(L58-L72; AHo numbering) (Kabat definition)	
SEQ ID NO: 25	LCDR3 (L107-L138; AHo numbering) (Kabat definition)	QGTYLSSNWWYWA
SEQ ID NO: 26	VL (Vk1-sk17)	DIQMTQSPSSLSASVGDRVTITC <i>QSSQSVYDNNWLA</i> WYQQKPGKAPKLLIYRA SNLASGVPSRFGSGSGTDFTLTISSLQPEDFATYYC <i>QGTYLSSNWWYWA</i> AFGTGT KVTVLG
SEQ ID NO: 27	scFv (VL-linker-VH)	DIQMTQSPSSLSASVGDRVTITC <i>QSSQSVYDNNWLA</i> WYQQKPGKAPKLLIYRA SNLASGVPSRFGSGSGTDFTLTISSLQPEDFATYYC <i>QGTYLSSNWWYWA</i> AFGTGT KVTVLGGGGGGGGGGGGGGGQVQLQESGPGLVKPSSETLSLTCKVSG <i>FSFNNDYDMC</i> WIRQPPGKGLEWIGCIDT <i>GDGSTYYASWAKGRVTISVDSSKNQ</i> FSLKLSVTAADTA VYYC <i>AREAASSSGYGMGYFDLW</i> GQGTLVTVSS
38-27-A11		
SEQ ID NO: 28	HCDR1 (H27-H42; AHo numbering)	GFSSSANYPC
SEQ ID NO: 29	HCDR2 (H57-H76; AHo numbering)	CIYGGSSDITYDANWTK
SEQ ID NO: 30	HCDR3 (H108-H138; AHo numbering)	RSAWYSGWGGDL
SEQ ID NO: 31	VH (VH3) (38-27-A11 sc02)	EVQLVESGGGLVQPGGSLRLSCAAS <i>GFSSANYYPCWVRQAPGKGLEWIGCIY</i> <i>GGSSDITYDANWTK</i> GRFTISRDN SKNTVY LQMNSLRAEDTAVYYC <i>RS4WYS</i> <i>WGDDL</i> WGQGLVTVSS
SEQ ID NO: 32	VH (VH3) (38-27-A11 sc03)	EVQLVESGGGLVQPGGSLRLSCAAS <i>GFSSANYYPCWVRQAPGKGLEWIGCIY</i> <i>GGSSDITYDANWTK</i> GRFTISRDN SKNTVY LQMNSLRAEDTAVYYC <i>RS4WYS</i> <i>WGDDL</i> WGQGLVTVSS
SEQ ID NO: 33	VH (VH3) (38-27-A11 sc07) (G51C)	EVQLVESGGGLVQPGGSLRLSCAAS <i>GFSSANYYPCWVRQAPGKCLEWIGCIY</i> <i>GGSSDITYDANWTK</i> GRFTISRDN SKNTVY LQMNSLRAEDTAVYYC <i>RS4WYS</i> <i>WGDDL</i> WGQGLVTVSS
SEQ ID NO: 34	LCDR1	QASQISNRLA

	(L24-L42; AHo numbering) (Kabat definition)	
SEQ ID NO: 35	LCDR2 (L58-L72; AHo numbering) (Kabat definition)	SASTLAS
SEQ ID NO: 36	LCDR3 (L107-L138; AHo numbering) (Kabat definition)	QSTYYGNDGNA
SEQ ID NO: 37	VL (Vk1-sk17) (38-27-A11 sc02)	DIQMTQSPSSLSASVGDRVTITCQASQISINRLAWYQQKPGKAPKLLIYSASTLA SGVPSRFSGSGGTDFLTITSSLPEDFATYYCQSTYYGNDGNAFGTGKVTVL G
SEQ ID NO: 38	VL (Vk1-sk17) (38-27-A11 sc03)	DFQLTQSPSSLSASVGDRVTITCQASQISINRLAWYQQKPGKPPKLLIYSASTLA SGVPSRFSGSGGTDFLTITSSLPEDFATYYCQSTYYGNDGNAFGTGKVTVL G
SEQ ID NO: 39	VL (Vk1-sk17) (38-27-A11 sc07) (T141C)	DIQMTQSPSSLSASVGDRVTITCQASQISINRLAWYQQKPGKAPKLLIYSASTLA SGVPSRFSGSGGTDFLTITSSLPEDFATYYCQSTYYGNDGNAFGTGKVTVL G
SEQ ID NO: 40	scFv (VL-linker-VH) (38-27-A11 sc02) (PRO1359)	DIQMTQSPSSLSASVGDRVTITCQASQISINRLAWYQQKPGKAPKLLIYSASTLA SGVPSRFSGSGGTDFLTITSSLPEDFATYYCQSTYYGNDGNAFGTGKVTVL GGGGSGGGSGGGGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFSFSA NYYPWCWVRQAPGKGLEWIGCIYGGSSDITYDANWTKGRFTISRDNKNTVYLQ MNSLRAEDTAVYYCARSAWYSGWGDDLWGQGLVTVSS
SEQ ID NO: 41	scFv (VL-linker-VH) (38-27-A11 sc03) (PRO1360)	DFQLTQSPSSLSASVGDRVTITCQASQISINRLAWYQQKPGKPPKLLIYSASTLA SGVPSRFSGSGGTDFLTITSSLPEDFATYYCQSTYYGNDGNAFGTGKVTVL GGGGSGGGSGGGGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFSFSA NYYPWCWVRQAPGKGLEWIGCIYGGSSDITYDANWTKGRFTISRDNKNTVYLQ MNSLRAEDTAVYFCARSAWYSGWGDDLWGPGTLVTVSS
SEQ ID NO: 42	scFv (VL-linker-VH) (38-27-A11 sc07) (VL-T141C; VH-G51C)	DIQMTQSPSSLSASVGDRVTITCQASQISINRLAWYQQKPGKAPKLLIYSASTLA SGVPSRFSGSGGTDFLTITSSLPEDFATYYCQSTYYGNDGNAFGTGKVTVL GGGGSGGGSGGGGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFSFSA

	(PRO1704)	NYPCWVRQAPGKCLEWIGCIYGGSSDITYDANWTKGRFTISRDNKNTVYLQ MNSLRAEDTAVYYCARSAWYSGWGGDLWGQGTLLVTVSS
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Table 2. Examples of PDL1 binding domains as used in the present invention (CDR residues shown in bold and italic letters).

SEQ ID NUMBER	Ab region	Sequence
37-20-B03		
SEQ ID NO: 43	HCDR1 (H27-H42; AHo numbering)	GFNSDYYWY
SEQ ID NO: 44	HCDR2 (H57-H76; AHo numbering)	SIYGGSSGNTQYASWAQG
SEQ ID NO: 45	HCDR3 (H108-H138; AHo numbering)	RGYVDYGGATDL
SEQ ID NO: 46	VH (VH4) (37-20-B03 sc01)	QVQLQESGPGLVKPSETLSLTCKVSGFSFNSDYWYIWRQPPGKGLEWIGSIYGGSGNTQYASWAQGRVTISVDSSKNQFSLKLSVTAADTAVYYCARGYVDYGGATDLWGQGTLLVTVSS
SEQ ID NO: 47	VH (VH1) (37-20-B03 sc02)	QVQLVQSGAEVKKPGASVKVCKASGFSFNSDYWYIWRQAPGQGLEWMGSIYGGSSGNTQYASWAQGRVTMTTRDTSISTAYMELSSLRSED TAVYYCARGYVDYGGATDLWGQGTLLVTVSS
SEQ ID NO: 48	VH (VH3) (37-20-B03 sc09.1) Mutations: G56A; Y105F	EVQLVESGGGLVQPGGSLRLSCAASGFSFNSDYWYIWRQAPGKGLEWIASIYGGSSGNTQYASWAQGRFTISRDNKNTVYLQMNSLRAEDTAVYFCARGYVDYGGATDLWGQGTLLVTVSS
SEQ ID NO: 49	LCDR1 (L24-L42; AHo numbering) (Kabat definition)	QASQSIGTYLA
SEQ ID NO: 50	LCDR2 (L58-L72; AHo numbering) (Kabat definition)	RAFILAS
SEQ ID NO: 51	LCDR3 (L107-L138; AHo numbering)	QSNFYSDSTTIGPNA

SEQ ID NO: 52	(Kabat definition)	
	VL (Vk1-sk17) (37-20-B03 sc01) (37-20-B03 sc02)	DIQMTQSPSSLSASVGDRVTITC <i>QASQSIGTYLAWYQQKPGKAPKLLIYRAFI</i> <i>LAGVPSRFS</i> SGSGTDFTLTISSLQPEDFATYYC <i>QSNFYSDSTTIGPNA</i> FGTGKV TVLG
SEQ ID NO: 53	VL (Vk1-sk17) (37-20-B03 sc09.1) Mutations: S9A; A51P	DIQMTQSPASLSASVGDRVTITC <i>QASQSIGTYLAWYQQKPGKPPKLLIYRAFI</i> <i>LAGVPSRFS</i> SGSGTDFTLTISSLQPEDFATYYC <i>QSNFYSDSTTIGPNA</i> FGTGKV TVLG
SEQ ID NO: 54	scFv (VL-linker-VH) (37-20-B03 sc01) (PRO997)	DIQMTQSPSSLSASVGDRVTITC <i>QASQSIGTYLAWYQQKPGKAPKLLIYRAFI</i> <i>LAGVPSRFS</i> SGSGTDFTLTISSLQPEDFATYYC <i>QSNFYSDSTTIGPNA</i> FGTGKV TVLGGGGSGGGSGGGSGGGVQLQESGPGLVKPSSETLSLTCCKVSGFS <i>FNSDYW</i> YIWIRPPGKGLEWIGSIYGGSSGNTQYASW <i>AQGRVTISVDSSKNQFS</i> LKLSSVTAADTA VYYC <i>ARGVVDYGGATDLWGQGT</i> LVTVSS
SEQ ID NO: 55	scFv (VL-linker-VH) (37-20-B03 sc02) (PRO1013)	DIQMTQSPSSLSASVGDRVTITC <i>QASQSIGTYLAWYQQKPGKAPKLLIYRAFI</i> <i>LAGVPSRFS</i> SGSGTDFTLTISSLQPEDFATYYC <i>QSNFYSDSTTIGPNA</i> FGTGKV TVLGGGGSGGGSGGGSGGGVQLVQSGAEVKKPGASVKVSKASGF <i>SFNSDYW</i> YIYWVRQAPGQGLEWMGSIYGGSSGNTQYASW <i>AQGRVTMTTRDTSIS</i> TAYMELSSLRSEDTAVYYC <i>ARGVVDYGGATDLWGQGT</i> LVTVSS
SEQ ID NO: 56	scFv (VL-linker-VH) (37-20-B03 sc09.1)	DIQMTQSPASLSASVGDRVTITC <i>QASQSIGTYLAWYQQKPGKPPKLLIYRAFI</i> <i>LAGVPSRFS</i> SGSGTDFTLTISSLQPEDFATYYC <i>QSNFYSDSTTIGPNA</i> FGTGK VTVLGGGGSGGGSGGGSGGGVQLVESGGGLVQPGGSLRLSCAASGF <i>SFNSDYW</i> YIYWVRQAPGKGLEWIASIYGGSSGNTQYASW <i>AQGRFTISRDNSKN</i> TVYLMNSLR AEDTA VYFCARGYVDYGGATDLWGQGTLVTVSS
33-03-G02		
SEQ ID NO: 57	HCDR1 (H27-H42; AHo numbering)	GFSFSSGYDMC
SEQ ID NO: 58	HCDR2 (H57-H76; AHo numbering)	CVVAGSV DITYYASWAKG
SEQ ID NO: 59	HCDR3 (H108-H138; AHo numbering)	RKDAYSDAFNL

SEQ ID NO: 60	VH (VH4) (33-03-G02 sc01)	QVQLQESGPGLVKPSSETLSLTCKVSGFSFSSGYDMCWVRQPPGKGLEWIGCVV AGSVDTITYY4SWAKGRVVTISVDSSKNQSLKSSVTAADTAVYYCARKDAYSD AFNLWGQGTLVTVSS
SEQ ID NO: 61	VH (VH4) (33-03-G02 sc03 Full) (Mutations: V2S; V25A; I44V; G56A; V82K; F89V; Y105F)	QVQLQESGPGLVKPSSETLSLTCKASGFSFSSGYDMCWVRQPPGKGLEWIGCVV AGSVDTITYY4SWAKGRVVTISKDSSKNQSLKSSVTAADTAVYYFCARKDAYSD AFNLWGQGTLVTVSS
SEQ ID NO: 62	VH (VH4) (33-03-G02 sc18) Mutations VH: V25A; I44; G56A; V82K; F89V (AHO numbering)	QVQLQESGPGLVKPSSETLSLTCKASGFSFSSGYDMCWVRQPPGKGLEWIGCVV AGSVDTITYY4SWAKGRVVTISKDSSKNQSLKSSVTAADTAVYYCARKDAYSD AFNLWGQGTLVTVSS
SEQ ID NO: 63	LCDR1 (L24-L42; AHO numbering) (Kabat definition)	QASQSINDYLA
SEQ ID NO: 64	LCDR2 (L58-L72; AHO numbering) (Kabat definition)	KASTLAS
SEQ ID NO: 65	LCDR3 (L107-L138; AHO numbering) (Kabat definition)	QQGYIITDIDNV
SEQ ID NO: 66	VL (Vk1-sk17) (33-03-G02 sc01) (33-03-G02 sc18)	DIQMTQSPSSLSASVGDRVTITCQASQSINDYLAWYQQKPGKAPKLLIYKASTL ASGVPSRFSGSGSGTDFTLTISSLPEDFATYYCQQGYIITDIDNVFGTGKVTVL LG
SEQ ID NO: 67	VL (Vk1-sk17) (33-03-G02 sc03 Full) (Mutations VL: I2F; M4L; A51P)	DFQLTQSPSSLSASVGDRVTITCQASQSINDYLAWYQQKPGKSPKLLIYKASTLA SGVPSRFSGSGSGTDFTLTISSLPEDFATYYCQQGYIITDIDNVFGTGKVTVL G

SEQ ID NO: 68	scFv (VL-linker-VH) (33-03-G02 sc01) (PRO830)	DIQMTQSPSSLSASVGDRVTITTC QASQ SINDYLAWYQQKPGKAPKLLIY KASTL ASG VPSTRFSGSGGTDFLTITSLQPEDFATYYC QQGYIITDIDN VFGTGTKVTV LGGGGSGGGSGGGSGGGGSQLQESGPGLVKPSSETLSLTCKV SGFSFS GYDMC WIRQPPGKGLEWIGCVV AGSV DITYYASWAKGR VTISVDSSKNQVSLK LSSVTAADTA VYYC ARKDA YSDAFNLWGQGTLVTVSS
SEQ ID NO: 69	scFv (VL-linker-VH) (33-03-G02 sc03 Full)	DFQLTQSPSSLSASVGDRVTITTC QASQ SINDYLAWYQQKPGKSPKLLIY KASTLA SGV PSRFSGSGGTDFLTITSLQPEDFATYYC QQGYIITDIDN VFGTGTKVTVL GGGGSGGGSGGGSGGGGSQLQESGPGLVKPSSETLSLTCK ASGFSFSSG YDMC WVRQPPGKGLEWIA CVV AGSV DITYYASWAKGR VTISKDSSKNQVSLK SSVTAADTA VYYC ARKDA YSDAFNLWGQGTLVTVSS
SEQ ID NO: 70	scFv (VL-linker-VH) (33-03-G02 sc18)	DIQMTQSPSSLSASVGDRVTITTC QASQ SINDYLAWYQQKPGKAPKLLIY KASTL ASG VPSTRFSGSGGTDFLTITSLQPEDFATYYC QQGYIITDIDN VFGTGTKVTV LGGGGSGGGSGGGSGGGGSQLQESGPGLVKPSSETLSLTCK ASGFSFS GYDMC WVRQPPGKGLEWIA CVV AGSV DITYYASWAKGR VTISKDSSKNQVSLK LSSVTAADTA VYYC ARKDA YSDAFNLWGQGTLVTVSS

Table 3. Examples of human serum albumin binding domains as used in the present invention (CDR residues shown in bold and italic letters).

SEQ ID NUMBER	Ab region	Sequence
19-01-H04 sc03		
SEQ ID NO: 71	HCDR1 (H27-H42; AHo numbering)	GFSLSSNAMG
SEQ ID NO: 72	HCDR2 (H57-H76; AHo numbering)	IISVGGFTYYASWAKG
SEQ ID NO: 73	HCDR3 (H108-H138; AHo numbering)	RDRHGGDSSGAFYL
SEQ ID NO: 74	VH	EVQLVESGGGLVQPGGSLRLSCAAS GFSLSS NAMGWVRQAPGKGLLEYIG IISV GGFTYYASWAKGR FTISRDNSKNTVYLMNSLR AEDTATYFC ARDRHHGGDSS GAFY LWGQGTLVTVSS
SEQ ID NO: 75	LCDR1	QSSSEVYSNNQLS

	(L24-L42; AHo numbering) (Kabat definition)	
SEQ ID NO: 76	LCDR2 (L58-L72; AHo numbering) (Kabat definition)	DASDLAS
SEQ ID NO: 77	LCDR3 (L107-L138; AHo numbering) (Kabat definition)	AGGFSSSSDTA
SEQ ID NO: 78	VL	DIQMTQSPSSLSASVGDRVTITCQSSSEVYSNNQLSWYQQKPGQPPKLLIYDAS DLASGVPSRFSGSGGTDFTLTISLQPEDFATYYCAGGFSSSSDTAFGGGTKLT VLG
SEQ ID NO: 79	scFv (VL-linker-VH)	DIQMTQSPSSLSASVGDRVTITCQSSSEVYSNNQLSWYQQKPGQPPKLLIYDAS DLASGVPSRFSGSGGTDFTLTISLQPEDFATYYCAGGFSSSSDTAFGGGTKLT VLGGGGSGGGGGGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFSL SSN ~~AM~~ GWVRQAPGKGLYIGIISVGGFTYYASWAKGRFTISRDN SKNTVY LQM NSLRAEDTATYFCARDRHGGDSSGAFYLVWGQGLVTVSS
23-13-A01 sc03		
SEQ ID NO: 80	HCDR1 (H27-H42; AHo numbering)	GFSSSYWIC
SEQ ID NO: 81	HCDR2 (H57-H76; AHo numbering)	CVFTGDGTTYASWAKG
SEQ ID NO: 82	HCDR3 (H108-H138; AHo numbering)	RPVSVYYYGMDL
SEQ ID NO: 83	VH	EVQLVESGGGLVQPGGSLRLSCAASGFSFSSSYWICWVRQAPGKGLEWVGCV FTGDGTTYASWAKGRFTISRDN SKNTVY LQMNSLRAEDTATYFCARPISVYY YGM DLWGQGLVTVSS
SEQ ID NO: 84	LCDR1 (L24-L42; AHo numbering) (Kabat definition)	QASQIISRSA
SEQ ID NO: 85	LCDR2 (L58-L72; AHo numbering)	QASKLAS

SEQ ID NO: 86	(Kabat definition) LCDR3 (L107-L138; AHo numbering)	QCTYIDSNFGA
SEQ ID NO: 87	(Kabat definition) VL	DVVMQTSPSSLASVGDRTTITC <i>QASQI</i> SSRSAWYQQKPGQPPKLLIY <i>QASKLA</i> SGVPSRFSGSGGTDFLTITSSLPEDFATYYC <i>QCTYID</i> SNFGAFGGGTCLTVLG
SEQ ID NO: 88	scFv (VL-linker-VH)	DVVMQTSPSSLASVGDRTTITC <i>QASQI</i> SSRSAWYQQKPGQPPKLLIY <i>QASKLA</i> SGVPSRFSGSGGTDFLTITSSLPEDFATYYC <i>QCTYID</i> SNFGAFGGGTCLTVLG GGGSGGGGGGGGGGGGGGGVQLVESGGGLVQPGGSLRLSCAAS <i>GFSSSY</i> <i>WICW</i> VRQAPGKGLEWVGCV <i>FTGDGTTYASWAKGR</i> FTISRDNKNTVYVLM NSLRAEDTATYFCAR <i>RPVSV</i> YYYGMDLWGQGTLVTVSS

Table 4. Other sequences related to the present invention.

SEQ ID NUMBER	Ab region	Sequence
SEQ ID NO: 89	Human CD137	MGNSCYNIVATLLLVLNFERTRSLQDPCSNCPAGTFCDNRRNQICSPCPPNSFSS AGGQRTCDICRQCKGVFRTRKECSSTSAECDCTPGFHCLGAGCSMCEQDCK QQQLTKKGCKDCCFGTFNDQKRIGICRPWTNCSLDGKSVLVNGTKERDVVCG PSPADLSPGASSVTPPAPAREPGHSPQISFFLALTSTALLFLFFLTLRFSVVKRG RKLLYIFKQPFMRPVQTTQEEDGCSRFPEEEGGCEL
SEQ ID NO: 90	Human PDL1	MRIFAVFIFMTYWHLNFAFTVTPKDLVYVEYGSNMTIECKFPVEKQLDLAAL IVYWEMEDKNIIQFVHGEEDLKVQHSSYRQARLLKDQLSLGNAALQITDVKL QDAGVYRCMISYGGADYKRITVKVNAPYNKINQRILVVDPVTSHELTCCQAE YPKAEVIWTSSDHQVLSGKTTTNSKREEKLFNVSTLRINTTTNEIFYCTFRRL DPEENHTAELVIPPLAHPNERTHLVILGAILLCLGVALTIFIRLRKGRMMDV KKGIGQDTNSKKQSDTHLEET
SEQ ID NO: 91	VH3	EVQLVESGGGLVQPGGSLRLSCAAS <i>GFSSAN</i> YYPGWVRQAPGKGLEWIGCIY <i>GGSDITYDANWTKGR</i> FTISRDNKNTVYVLMNSLRAEDTAVYYCAR <i>RS4WYS</i> <i>GWGGDL</i> WGQGTLVTVSS

SEQ ID NO: 92	VH4	QVQLQESGPGLVKPSSETLSLTCKVSGFSFSNSYWCWIRQPPGKGLEWIGCTFV GSSDSTYYANWAKGRVTISVDSSKNQFSKLSSVTAADTAVYYCARHPSPDAVY GYANNLWGQGTLLVTVSS
SEQ ID NO: 93	Vkappa1	DIQMTQSPSSLSASVGDRVTITTCQASQSIINNVLAWYQQKPGKAPKLLIYR4STL ASGVPSRFSGSGGTDFTLTISSLQPEDFATYYCQSSYGNYGDFGTGTVTLG
SEQ ID NO: 94	Vλ germline-based FR4 (Sk17)	FGTGTGTVTLG
SEQ ID NO: 95	Vλ germline-based FR4 (Sk12)	FGGGTKLTVLG
SEQ ID NO: 96	Vλ germline-based FR4	FGGGTQLIILG
SEQ ID NO: 97	Vλ germline-based FR4	FGEGTELTVLG
SEQ ID NO: 98	Vλ germline-based FR4	FGSGTKVTVLG
SEQ ID NO: 99	Vλ germline-based FR4	FGGGTQLTVLG
SEQ ID NO: 100	Vλ germline-based FR4	FGGGTQLTALG
SEQ ID NO: 101	Vλ germline-based FR4 G141C	FGCGTKVTVLG
SEQ ID NO: 102	Linker	GGGGSGGGSGGGSGGGGS
SEQ ID NO: 103	Linker	GGGS
SEQ ID NO: 104	Linker	GGGGSGGGGS

Table 5. Examples of multispecific antibodies (MAI) as used in the present invention (Linkers are shown in bold).

SEQ ID NUMBER	Ab Format	Sequence
PRO885 (38-02-A04 sc01 scDb-i/33-03-G02 sc01 scDb-o)		
SEQ ID NO: 105	scDb	DIQMTQSPSSLSASVGDRVTITTCQASQSIINDYLAWYQQKPGKAPKLLIYKASTLAS GVPSRFSGSGGTDFTLTISSLQPEDFATYYCQQGYITDIDNVFGTGTGTVTLGGG GGSQVQLQESGPGLVKPSSETLSLTCKVSGFSFSNSYWCWIRQPPGKGLEWIGCTF VGSSDSTYYANWAKGRVTISVDSSKNQFSKLSSVTAADTAVYYCARHPSPDAVY GYANNLWGQGTLLVTVSSGGGGSGGGSGGGSGGGSGGGSGGGSGGGSGGGSGGG DRVITTCQASQSIINNVLAWYQQKPGKAPKLLIYR4STLASGVPSRFSGSGGTDFTL LTISSLQPEDFATYYCQSSYGNYGDFGTGTVTLGGGGSGGGSGGGSGGGSGGGSGGG

			PSETLSLTKVSGFSFGYDMCWIRQPPGKGLEWIGCVVAGSVDITYYASWAKG RVTISVDSSKNQFSLKLSVTAADTA VYYCARKDAYSDAFNLWGQGLVTVSS
PRO951 (38-27-C05 sc02 scDb-i/33-03-G02 sc01 scDb-o)			
SEQ ID NO: 106	scDb		DIQMTQSPSSLSASVGDRVTITCQASQINDYLAWYQQKPGKAPKLLIYKASTLAS GVPSRFGSGSGTDFTLTISLQPEDFATYYCQGYITIDNVEFGTKVTVLGGG GGSEVQLVESGGGLVQPGGSLRLSCAASGFSFNNDYDMCWVRQAPGKLEWIG CIDTGDGSTYYASWAKGRFTISRDNKNTVYLQMNLSRAEDTA VYYCAREAAAS SGYGMGYFDLWGQGLVTVSSGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG ASVGDRVTITCQSSQSVYDNNWLAWYQQKPGKAPKLLIYRASNLASGVPSRFG SGSGTDFTLTISLQPEDFATYYCQGYITIDNVEFGTKVTVLGGGGGGGGGGGG QLQESGPGLVKPSSETLSLTKVSGFSFGYDMCWIRQPPGKLEWIGCVVAGSV DITYYASWAKGRVTISVDSSKNQFSLKLSVTAADTA VYYCARKDAYSDAFNLW GQGLVTVSS
PRO1123 (38-02-A04 sc05 IF scDb-i/33-03-G02 sc01 scDb-o)			
SEQ ID NO: 107	scDb		DIQMTQSPSSLSASVGDRVTITCQASQINDYLAWYQQKPGKAPKLLIYKASTLAS GVPSRFGSGSGTDFTLTISLQPEDFATYYCQGYITIDNVEFGTKVTVLGGG GGSQVQLQESGPGLVKPSSETLSLTKVSGFSFNNDYDMCWVRQPPGKLEWIGCT FVGSSDSTYYANWAKGRVTISVDSSKNQVSLKLSVTAADTA VYFCARHPSDAV YGYANLWGGGLVTVSSGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG GDRVTITCQASQINNVLA WYQQKPGKPPKLLIYRASNLASGVPSRFGSGSGTDF TLTISLQPEDFATYYCQSSYGNYGDFGTGTVTVLGGGGGGGGGGGGGGGGGGGG KPSETLSLTKVSGFSFGYDMCWIRQPPGKLEWIGCVVAGSVDITYYASWAK GRVTISVDSSKNQFSLKLSVTAADTA VYYCARKDAYSDAFNLWGQGLVTVSS
PRO1124 (38-02-A04 sc06 Full scDb-i/33-03-G02 sc01 scDb-o)			
SEQ ID NO: 108	scDb		DIQMTQSPSSLSASVGDRVTITCQASQINDYLAWYQQKPGKAPKLLIYKASTLAS GVPSRFGSGSGTDFTLTISLQPEDFATYYCQGYITIDNVEFGTKVTVLGGG GGSQVQLQESGPGLVKPSSETLSLTKVSGFSFNNDYDMCWVRQPPGKLEWIGCT FVGSSDSTYYANWAKGRVTISVDSSKNQVSLKLSVTAADTA VYFCARHPSDAV YGYANLWGGGLVTVSSGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG GDRVTITCQASQINNVLA WYQQKPGKPPKLLIYRASNLASGVPSRFGSGSGTDF TLTISLQPEDFATYYCQSSYGNYGDFGTGTVTVLGGGGGGGGGGGGGGGGGGGG

[illegible]

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PRO1057 (38-02-A04 sc01 scDb-i/33-03-G02 sc01 scDb-o/23-12-A01-sc03, skl17sh4)	scDb-scFv SEQ ID NO: 114 DIQMTQSPSSLSASVGDRVTITCQASQINDYLAWYQQKPGKAPKLLIYKASTLAS GVPSRFGSGSGTDFLTITSSLQPEDFATYYCQQGYIITDIDNVFGTGKVTVLGGG GGSQVQLQESGPGLVKPSSETLSLTKVSGFSFSNSYWICWIRPPGKGLEWIGCTF VGSSTYYANWAKGRVTISVDSKKNQFSLKSSVTAADTAVYCARHPSDAVY GYANNLWGQGLVTVSSGGGGGGGGGGGGGGGGGGGGSIQMTQSPSSLSASV DRVTITCQASQINNVLAWYQQKPGKAPKLLIYRASTLASGVPSRFGSGSGTDF LTITSLQPEDFATYYCQSSYGNYGDFGTGKVTVLGGGGGGSQVQLQESGPGLVK PSETLSLTKVSGFSFGSYDMCWIRQPPGKGLEWIGCVVAGSVDIYYASWAKG RVTISVDSKKNQFSLKSSVTAADTAVYCARKDAYSDAFNLWGQGLVTVSSG GGGGGGGGSVMTQSPSSLSASVGDRVTITCQASQIHSRSAYQQKPGQP PKLLIYQASKLASGVPSRFGSGSGTDFLTITSSLQPEDFATYYCQCTYIDSNF GAFGGGT KLTVLGGGGGGGGGGGGGGGGGGGGSEVQLVESGGGLVQPGGSLR LSCAASGFSFSSYWICWVRQAPGKLEWVGCVFTGDGTTYASWAKGRFTISRD NSKNTVYLQMNSLR AEDTATYFCARPVS VYYYGMDLWGQGLVTVSS
PRO1058 (38-27-C05 sc01 scDb-i/33-03-G02 sc01 scDb-o/23-13-A01-sc03, skl17sh4)	scDb-scFv SEQ ID NO: 115 DIQMTQSPSSLSASVGDRVTITCQASQINDYLAWYQQKPGKAPKLLIYKASTLAS GVPSRFGSGSGTDFLTITSSLQPEDFATYYCQQGYIITDIDNVFGTGKVTVLGGG GGSQVQLQESGPGLVKPSSETLSLTKVSGFSFNNDYDMCWIRQPPGKGLEWIGCI DTGDGSTYYASWAKGRVTISVDSKKNQFSLKSSVTAADTAVYCARAAASSG YGMGYFDLWGQGLVTVSSGGGGGGGGGGGGGGGGGGGGSIQMTQSPSSLSAS VGDRVTITCQSSQSVYDNNVLAWYQQKPGKAPKLLIYRASNLASGVPSRFGSG SGTDFLTITSSLQPEDFATYYCQGTYSNWWYAFGTGKVTVLGGGGGGSQVQL QESGPGLVKPSSETLSLTKVSGFSFGSYDMCWIRQPPGKGLEWIGCVVAGSV DIT YYASWAKGRVTISVDSKKNQFSLKSSVTAADTAVYCARKDAYSDAFNLWGQ GLTVTVSSGGGGGGGGGGGGGGGGGGGGSVMTQSPSSLSASVGDRVTITCQASQI HSRSAYQQKPGQP PKLLIYQASKLASGVPSRFGSGSGTDFLTITSSLQPEDFATYYCQCTYIDS NFGAFGGG TKLTVLGGGGGGGGGGGGGGGGGGGGSEVQLVESGGGLVQPGGGS LRLSCAASGFSFSSYWICWVRQAPGKLEWVGCVFTGDGTTYASWAKGRFTI SRD NSKNTVYLQMNSLR AEDTATYFCARPVS VYYYGMDLWGQGLVTVSS
PRO1175 (37-20-B03-sc01-o/38-02-A04 sc01-i/19-01-H04sc03 scFv)	

[illegible]

[illegible]

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		FTISRDNKNTVYLQMNSLRAEDTAVYCARHPSDAVGYANNLWGQGLTVTV SSGGGGSGGSIQMTQSPSSLASVGDRTVITCQSSSEVYNNQLSWYQQKPG QPPKLLIYDASDLASGVPSRFSGSGTDFTLTISSLQPEDFATYYCAGGFSST AFGGGTLTVLGGGGSGGSGGSGGSEVQLVESGGGLVQPGGSLRL SCAASGFSLSNMGWVRQAPGKGLYIGIISVGGFTYYASWAKGRFTISRDNK NTVYLQMNSLRAEDTATYFCARDRHGGDSSGAFYLVGGQGLTVTVSS
PRO1480 (38-27-A11 sc02 scDb-i/37-20-B03 sc09.1 scDb-o/19-01-H04 sc03 scFv)		
SEQ ID NO: 125	scDb-scFv	DIQMTQSPASLSASVGDRTVITCQASQSIGTYLAWYQQKPGKPKLLIYRAFI LGVPSRFSGSGTDFTLTISSLQPEDFATYYCQSNFYSDSTTIGPNAFGTKVTVL GGGGSEVQLVESGGGLVQPGGSLRLSCAASGFSFSAHYPCWVRQAPGKGL WIGCIYGGSDITYDANWTKGRFTISRDNKNTVYLQMNSLRAEDTAVYCAR AWYSGWGGDLWGQGLTVTVSSGGGGSGGSGGSGGSIQMTQSPSSL ASVGDRTVITCQASQISNRLAWYQQKPGKPKLLIYASATLASGVPSRFSGSG TDFTLTISSLQPEDFATYYCQSTYYGNDGNAGFTGTVTVLGGGGSEVQLV ESGGGLVQPGGSLRLSCAASGFSFSDYWIYVVRQAPGKGLWIASIYGGSGNTQ YASWAQGRFTISRDNKNTVYLQMNSLRAEDTAVYFCARGYVDYGGATDLWG QGTLTVTVSSGGGGSGGSIQMTQSPSSLASVGDRTVITCQSSSEVYNNQLSW YQQKPGKPKLLIYDASDLASGVPSRFSGSGTDFTLTISSLQPEDFATYYCAGG FSSTDTAFGGGTLTVLGGGGSGGSGGSGGSEVQLVESGGGLVQPGGSLRL SCAASGFSLSNMGWVRQAPGKGLYIGIISVGGFTYYASWAKGRFTISR DNKNTVYLQMNSLRAEDTATYFCARDRHGGDSSGAFYLVGGQGLTVTVSS
PRO1481 (38-27-A11 sc03 scDb-i/37-20-B03 sc09.1 scDb-o/19-01-H04 sc03 scFv)		
SEQ ID NO: 126	scDb-scFv	DIQMTQSPASLSASVGDRTVITCQASQSIGTYLAWYQQKPGKPKLLIYRAFI LGVPSRFSGSGTDFTLTISSLQPEDFATYYCQSNFYSDSTTIGPNAFGTKVTVL GGGGSEVQLVESGGGLVQPGGSLRLSCAASGFSFSAHYPCWVRQAPGKGL WIGCIYGGSDITYDANWTKGRFTISRDNKNTVYLQMNSLRAEDTAVYCAR AWYSGWGGDLWGQGLTVTVSSGGGGSGGSGGSGGSIQMTQSPSSL ASVGDRTVITCQASQISNRLAWYQQKPGKPKLLIYASATLASGVPSRFSGSG TDFTLTISSLQPEDFATYYCQSTYYGNDGNAGFTGTVTVLGGGGSEVQLV ESGGGLVQPGGSLRLSCAASGFSFSDYWIYVVRQAPGKGLWIASIYGGSGNTQ YASWAQGRFTISRDNKNTVYLQMNSLRAEDTAVYFCARGYVDYGGATDLWG QGTLTVTVSSGGGGSGGSIQMTQSPSSLASVGDRTVITCQSSSEVYNNQLSWY

		QKPGQPPKLLIYDASDLASGVPSRFSGSGTDFTLTISLQPEDFATYYCAGGFS SSSDTAFGGGTKLTVLGGGGSGGGSGGGSGGGSEVQLVESGGGLVQPG GSLRLSCAASGFSLSNNAAGWVRQAPGKGLYIGIISVGGFTYYASWAKGRFTISR DNSKNTVYLMNSLR AEDTATYFCARDRHGGDSSGAFYLVGQGTLLTVSS
PRO1480diS (38-27-A11 sc07 scDb-i/37-20-B03 sc09.1 scDb-o/19-01-H04 sc03 scFv)	scDb-scFv	DIQMTQSPASLSASVGDRTITCQASQSIGTYLAWYQQKPKPKLLIYRAFILAS GVPSRFSGSGTDFTLTISLQPEDFATYYCQSNFYSDSTTIGPNAFGTGKVTVL GGGGSEVQLVESGGGLVQPGGSLRLSCAASGFSFSAHYPCWVRQAPGKCLE WIGCIYGGSDITYDANWTKGRFTISRDNKNTVYLMNSLR AEDTAVYYCARS AWYSGWGGDLWGQGTLLTVSSGGGGSGGGSGGGSGGGSIQMTQSPSSLS ASVGDRTITCQASQISNRLAWYQQKPKAPKLLIYASLTASGVPSRFSGSG TDFTLTISLQPEDFATYYCQSTYYGNDGNAGCGTKVTVLGGGGSEVQLVES GGGLVQPGGSLRLSCAASGFSFSDYWIYWRQAPGKGLWIASIYGGSGNTQ YASWAKGRFTISRDNKNTVYLMNSLR AEDTAVYFCARGYVDYGGATDLWG QGTLLTVSSGGGGSGGGSIQMTQSPSSLSASVGDRTITCQSSSEVYNNQLSW YQQKPGQPPKLLIYDASDLASGVPSRFSGSGTDFTLTISLQPEDFATYYCAGG FSSSDTAFGGGTKLTVLGGGGSGGGSGGGSGGGSEVQLVESGGGLVQPG GSLRLSCAASGFSLSNNAAGWVRQAPGKGLYIGIISVGGFTYYASWAKGRFTI SRDNKNTVYLMNSLR AEDTATYFCARDRHGGDSSGAFYLVGQGTLLTVSS
PRO1599 (38-02-A04 sc13 scDb-i/37-20-B03 sc01 scDb-o/23-13-A01 sc02 scFv)	scDb-scFv	MTQSPSSLSASVGDRTITCQASQSIGTYLAWYQQKPKAPKLLIYRAFILASGVP SRFSGSGTDFTLTISLQPEDFATYYCQSNFYSDSTTIGPNAFGTGKVTVLGGG GGSEVQLVESGGGLVQPGGSLRLSCAASGFSFSAHYPCWVRQAPGKCLEWIGCT FVGSSTYYANWAKGRFTISRDNKNTVYLMNSLR AEDTAVYYCARHPSDAV YGYANLWGQGTLLTVSSGGGGSGGGSGGGSGGGSIQMTQSPSSLSASV DRVTITCQASQISNRLAWYQQKPKAPKLLIYASLTASGVPSRFSGSGTDFT LTISLQPEDFATYYCQSSYGNVDFGCGTKVTVLGGGGSGVQLQESGPGLVKP SETLSLCKVSGFSFSDYWIYWRQAPGKGLWIASIYGGSGNTQYASWAKGR VTISVDSKNTQFSLKSSVTAADTAVYYCARGYVDYGGATDLWGQGTLLTVSSG GGSGGGGVMTQSPSSLSASVGDRTITCQASQISNRLAWYQQKPKAPKLLI YQASKLASGVPSRFSGSGTDFTLTISLQPEDFATYYCQTYIDSNFGAFGGGT KLTVLGGGGSGGGSGGGSGGGSGGGSEVQLVESGGGLVQPGGSLRLSCAASGFS

		FSSSYWICWVRQAPGKGLEWVGCVFTGDGTTYASWAKGRFTISRDNKNTVYL QMNSLRAEDTATYFCARPVSVYYGMDLWGQGTLVTVSSLESRGPV
PRO1600 (38-02-A04 sc13 scDb-i/37-20-B03 sc09.1 scDb-o/23-13-A01 sc02 scFv)		
SEQ ID NO: 129	scDb-scFv	dIQMTQSPSSLASVGDRTITCQASQSIGTYLAWYQQKPGKAPKLLIYRAFILASG VPSRFSGSGTDFTLTISLQPEDFATYQCQSNFYSDSTIGPNAFGTKVTVLG GGGSEVQLVESGGGLVQPGGSLRLSCAASGFSFSNSYWCWVRQAPGKCLEWI GCTFVGSSDSTYYANWAKGRFTISRDNKNTVYLQMNSLRAEDTAVYCARHPS DAVYGYANNLWGQGTLVTVSSGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG SVGDRVTITCQASQINNVLAWYQQKPGKAPKLLIYRASTLASGVPSRFSGSGGT DFTLTISLQPEDFATYQCQSSYGNYGDFGCGTKVTVLGGGGGQVQLQESGPG VKPSETLSLTCKVSGFSFNSDYWIYWRPPGKGLEWIGSIYGGSSGNTQYASWA QGRVTISVDSSKNQFSLKSSVTAADTAVYCARGYVDYGGATDLWGQGTLV VSSGGGGGGGGVMTQSPSSLASVGDRTITCQASQIISRSAYQQKPGQPP KLLIYQASKLASGVPSRFSGSGTDFTLTISLQPEDFATYQCQTYIDSNFGAFG GGTKLVLGSGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG GFSFSSSYWICWVRQAPGKGLEWVGCVFTGDGTTYASWAKGRFTISRDNKNT VYLQMNSLRAEDTATYFCARPVSVYYGMDLWGQGTLVTVSS
PRO1601 (38-27-A11 sc02 scDb-i/37-20-B03 sc09.1 scDb-o/23-13-A01 sc02 scFv)		
SEQ ID NO: 130	scDb-scFv	DIQMTQSPASLSASVGDRTITCQASQSIGTYLAWYQQKPGKPPKLLIYRAFILAS GVPSRFSGSGTDFTLTISLQPEDFATYQCQSNFYSDSTIGPNAFGTKVTVL GGGGSEVQLVESGGGLVQPGGSLRLSCAASGFSFSANYPCWVRQAPGKGLE WIGCIYGGSSDITYDANWTKGRFTISRDNKNTVYLQMNSLRAEDTAVYCAR AWYSGWGGDLWGQGTLVTVSSGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG SVGDRVTITCQASQISNRLAWYQQKPGKAPKLLIYSASTLASGVPSRFSGSGGT DFTLTISLQPEDFATYQCQSTYYGNDGNAGTKVTVLGGGGGSEVQLVESGG GLVQPGGSLRLSCAASGFSFNSDYWIYWRQAPGKGLEWIASIYGGSSGNTQYAS WAQGRFTISRDNKNTVYLQMNSLRAEDTAVYFCARGYVDYGGATDLWGQGT VTVSSGGGGGGGGVMTQSPSSLASVGDRTITCQASQIISRSAYQQKPG QPPKLLIYQASKLASGVPSRFSGSGTDFTLTISLQPEDFATYQCQTYIDSNFG AFGGGTKLVLGSGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG AASGFSFSSSYWICWVRQAPGKGLEWVGCVFTGDGTTYASWAKGRFTISRDN KNTVYLQMNSLRAEDTATYFCARPVSVYYGMDLWGQGTLVTVSS

Table 6. Examples of CD3 binding domains as used in the present invention (CDR residues shown in bold and italic letters).

SEQ ID NUMBER:	Ab region	Sequence
28-21-D09 sc04		
SEQ ID NO: 131	HCDR1 (H27-H42; AHo numbering)	GFSLSSYDMS
SEQ ID NO: 132	HCDR2 (H57-H76; AHo numbering)	ASYASGPTY ~~Y~~ ASWAKG
SEQ ID NO: 133	HCDR3 (H108-H138; AHo numbering)	RGGWGTGTS ~~HSNI~~
SEQ ID NO: 134	VH 28-21-D09 sc04	EVQLVESGGGLVQPGGSLRLSCAAS GFSLSSYDMS WVRQAPGKGLAWIGAS YASGPTY ~~Y~~ ASWAKGRFTISRDNKNTVYLQMNLSRAEDTATYFCAR GGW ~~TGT~~ SHSN WGQGTLVTVSS
SEQ ID NO: 182	VH 28-21-D09 sc04 (L12R, L144Q)	EVQLVESGGGRVQPGGSLRLSCAASGFSLSSYDMSWVRQAPGKGLAWIGAS YASGPTY ~~Y~~ ASWAKGRFTISRDNKNTVYLQMNLSRAEDTATYFCARGGWTG TSHSNIWGGGTQVTVSS
SEQ ID NO: 135	LCDR1 (L24-L42; AHo numbering) (Kabat definition)	QSSQSVFSNNYLA
SEQ ID NO: 136	LCDR2 (L58-L72; AHo numbering) (Kabat definition)	SASTLAS
SEQ ID NO: 137	LCDR3 (L107-L138; AHo numbering) (Kabat definition)	LGSYACSSADCYV
SEQ ID NO: 138	VL (28-21-D09 sc04)	DIQMTQSPSSLSASVGDRVTITC QSSQSV FSNNYLAWFQQKPGQSPKRLIY SAS TLAS GVPSRFSGSGGTDFLTITSSLPEDFATY YCLGSYACSS ADCY ~~V~~ FGTGT KVTVLG

Table 7. Examples of further human serum albumin binding domains as used in the present invention (CDR residues shown in bold and italic letters).

italic letters).

19-04-A10			
SEQ ID NO: 183	HCDR1 (H27-H42; AHo numbering)		GFSLSSYAMN
SEQ ID NO: 184	HCDR2 (H57-H76; AHo numbering)		HINAGDIAYYATWAKG
SEQ ID NO: 185	HCDR3 (H108-H138; AHo numbering)		RGAGGFSTGPFKL
SEQ ID NO: 186	LCDR1 (L24-L42; AHo numbering) (Kabat definition)		QASEINSRLA
SEQ ID NO: 187	LCDR2 (L58-L72; AHo numbering) (Kabat definition)		DASDLTS
SEQ ID NO: 188	LCDR3 (L107-L138; AHo numbering) (Kabat definition)		QGYGGSSTTT
SEQ ID NO: 189	VH 19-04-A10-sc02_(L12R, V103T, L144Q)		EVQLVESGGGRVQPGGSLRLSCAASGFSLSYAMNWVRQAPGKLEWIGHI NAGDIAYYATWAKGRFTISRDNKNTVYLQMNSLRAEDTATYFCARGAGGF STGPFKLWGQGTQVTVSS
SEQ ID NO: 190	VH 19-04-A10-sc06_(G51C) (PRO2317)		EVQLVESGGGLVQPGGSLRLSCAASGFSLSYAMNWVRQAPGKLEWIGHI NAGDIAYYATWAKGRFTISRDNKNTVYLQMNSLRAEDTAVYFCARGAGGF STGPFKLWGQGTQVTVSS
SEQ ID NO: 191	VH 19-04-A10-sc06 (L12R, G51C, V103T, L144Q)		EVQLVESGGGRVQPGGSLRLSCAASGFSLSYAMNWVRQAPGKLEWIGHI NAGDIAYYATWAKGRFTISRDNKNTVYLQMNSLRAEDTATYFCARGAGGF STGPFKLWGQGTQVTVSS
SEQ ID NO: 192	VL19-04-A10-sc06 (G141C) (PRO2317)		AFELTQSPSSLSASVGDRTITCOASEINSRLAWYQQKPGQPPKLLIYDASDL TSGVPSRFSGSGGTDFTLTISSLQPEDFATYYCQGYGGSSTTTFGCGTKLTVL G

SEQ ID NO: 193	VL19-04-A10-sc06 (G141T)	AFELTQSPSSLSASVGDRVTITCQASESINSRLAWYQQKPGQPPKLLIYDASDL TSGVPSRFSGSGGTDFTLTISSLQPEDFATYYCQYGGSTTTFTGTGKLTVL G
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Table 8. Examples of MSLN binding domains of the present invention (CDR residues shown in bold and italic letters).

SEQ ID NUMBER:	Description	Sequence
54-22-H03-sc01 (high affinity)		
SEQ ID NO: 139	HCDR1 (H27-H42; AHo numbering)	GISVSNDDYMC
SEQ ID NO: 140	HCDR2 (H57-H76; AHo numbering)	CISTYIGNTHYASWAKG
SEQ ID NO: 141	HCDR3 (H108-H138; AHo numbering)	KNAGYPGYRYAIDL
SEQ ID NO: 142	VH (PRO1795)	EVQLVESGGGLVQPGGSLRLSCAASGISVSNDDYMCWVRQAPGKGLE WIGCISTYIGNTHYASWAKGRFTISRDNSKNTVYLMNSLRAEDTAVY YCAKNAGYPGYRYAIDLWGQGTLVTVSS
SEQ ID NO: 143	LCDR1 (L24-L42; AHo numbering) (Kabat definition)	QASEIGNYLA
SEQ ID NO: 144	LCDR2 (L58-L72; AHo numbering) (Kabat definition)	SASTLAS
SEQ ID NO: 145	LCDR3 (L107-L138; AHo numbering) (Kabat definition)	QSTDYGDYSYI
SEQ ID NO: 146	VL (PRO1795)	DIQMTQSPSSLSASVGDRVTITCQASESIGNNYLAWYQQKPGKAPKLLIY SASTLASGVPSRFSGSGGTDFTLTISSLQPEDFATYYCQSTDYGDYSYIF GTGKVTVLG
54-01-G02 (low affinity)		

SEQ ID NO: 147	HCDR1 (H27-H42; AHo numbering)	GFSLSYAMG	
SEQ ID NO: 148	HCDR2 (H57-H76; AHo numbering)	YISTINNTYYASWAKG	
SEQ ID NO: 149	HCDR3 (H108-H138; AHo numbering)	REIRSGWVDYGFISI	
SEQ ID NO: 150	VH 54-01-G02-sc01 (PRO1783)	QVQLVESGGGLVQPGGSLRLSCAASGFSLSYAMGWVVRQAPGKGLEW IGYISTINNTYYASWAKGRFTISRDN SKNTVYLQMNSLRAEDTAVYYC AREIRSGWVDYGFISIWGGTLVTVSS	
SEQ ID NO: 151	HCDR2 54-01-G02_N62A (H57-H76; AHo numbering)	YISTANTYYASWAKG	
SEQ ID NO: 152	VH 54-01-G02-sc03; mutation: N62A (PRO2197)	QVQLVESGGGLVQPGGSLRLSCAASGFSLSYAMGWVVRQAPGKGLEW IGYISTANTYYASWAKGRFTISRDN SKNTVYLQMNSLRAEDTAVYYC AREIRSGWVDYGFISIWGGTLVTVSS	
SEQ ID NO: 153	LCDR1 (L24-L42; AHo numbering) (Kabat definition)	QASQNIYSNLA	
SEQ ID NO: 154	LCDR2 (L58-L72; AHo numbering) (Kabat definition)	DASDLAS	
SEQ ID NO: 155	LCDR3 (L107-L138; AHo numbering) (Kabat definition)	QQVRSSDDIDNP	
SEQ ID NO: 156	VL 54-01-G02-sc01 (PRO1783 and PRO2197)	DIQMTQSPSSLSASVGDRTITTCQASQNIYSNLAWYQQKPGKAPKLLIY DASDLASGVPSRFSGSGGTDFTLTISSLQPEDFATYYCQQVRSSDDIDN PFGTGTKVTVLG	
54-32-A07 (low affinity)			
SEQ ID NO: 157	HCDR1 (H27-H42; AHo numbering)	GFSLSYAMG	
SEQ ID NO: 158	HCDR2	YISKIGTTYASWAKG	

SEQ ID NO: 159	(H57-H76; AHo numbering) HCDR3 (H108-H138; AHo numbering)	RGSSGGYLDDGFD
SEQ ID NO: 160	VH 54-32-A07-sc02 (PRO1925)	QSQLVESGGGLVQPGGSLRLSCAVSGFSLSSYAMGWVRQAPGKCLEYI GYISKIGTTYYASWAKGRFTISKDNSKNTVYLMNSLRAEDTAVYFCA RGSSGGYLDDGFD
SEQ ID NO: 194	VH 54-32-A07-sc09 (G51C) (PRO2309)	QSQLVESGGGLVQPGGSLRLSCAVSGFSLSSYAMGWVRQAPGKCLEYI GYISKIGTTYYASWAKGRFTISKDNSKNTVYLMNSLRAEDTAVYFCA RGSSGGYLDDGFD
SEQ ID NO: 195	VH 54-32-A07-sc09 (L12R, G51C, V103T, L144Q)	QSQLVESGGGLVQPGGSLRLSCAVSGFSLSSYAMGWVRQAPGKCLEYI GYISKIGTTYYASWAKGRFTISKDNSKNTVYLMNSLRAEDTAVYFCA RGSSGGYLDDGFD
SEQ ID NO: 161	LCDRI (L24-L42; AHo numbering) (Kabat definition)	QASQISNYLA
SEQ ID NO: 162	LCDR2 (L58-L72; AHo numbering) (Kabat definition)	DASDLAS
SEQ ID NO: 163	LCDR3 (L107-L138; AHo numbering) (Kabat definition)	QQVYDSNNVENV
SEQ ID NO: 164	VL 54-32-A07-sc02 (PRO1925)	ALQMTQSPSSLSASVGDRTITTCQASQISNYLA WYQQKPKPKFLIY DASDLAS GVSSRFSGSGGTDFLTISLQPEDFATYYCQQVYDSNNVE NVFGTGKVTVLG
SEQ ID NO: 196	VL 54-32-A07-sc09 (S14R, T22K, T87R, T141C) (PRO2309)	ALQMTQSPSSLSARVGDRTITTCQASQISNYLA WYQQKPKPKFLIY DASDLAS GVSPSRFSGSGGTDFLTISLQPEDFATYYCQQVYDSNNVE NVFGTGKVTVLG
54-21-H03-sc01 (PRO1922)		
SEQ ID NO: 197	HCDRI (H27-H42; AHo numbering)	GFSTTYYMC

SEQ ID NO: 198	HCDR2 (H57-H76; AHo numbering)	CTNTASSVRITYATWAKG
SEQ ID NO: 199	HCDR3 (H108-H138; AHo numbering)	RDMGFADYALNL
SEQ ID NO: 200	LCDR1 (L24-L42; AHo numbering) (Kabat definition)	QASESIYSSLA
SEQ ID NO: 201	LCDR2 (L58-L72; AHo numbering) (Kabat definition)	LASTLAS
SEQ ID NO: 202	LCDR3 (L107-L138; AHo numbering) (Kabat definition)	QSTDYTTSTHRNS
SEQ ID NO: 203	VH 54-21-H03-sc01 (PRO1922)	EVQLVESGGGLVQPGGSLRLSCAASGFSFTTYYMCWVRQAPGKGLE WIGCTNTASSVRITYATWAKGRFTISRDNKNTVYLMNSLRAEDTAV YYCARDMGFADYALNLWGQGLVTVSS
SEQ ID NO: 204	VH 54-21-H03-sc01 (L12R, V103T, L144Q)	EVQLVESGGGRVQPGGSLRLSCAASGFSFTTYYMCWVRQAPGKGLE WIGCTNTASSVRITYATWAKGRFTISRDNKNTVYLMNSLRAEDTAT YYCARDMGFADYALNLWGQGTQVTVSS
SEQ ID NO: 205	VL 54-21-H03-sc01 (PRO1922)	DIQMTQSPSSLSASVGDRVTITCQASESIYSSLAAYQQKPGKAPKLLIYL ASTLASGVPSRFSFGSGGTDFTLTISLQPEDFATYYCQSTDYTTSTHRNS FGTGTKVTVLG

Table 9. Examples of HER2 binding domains as used in the present invention (CDR residues shown in bold and italic letters).

SEQ ID NUMBER:	Ab region	Sequence
HER2-Trastuzumab		
SEQ ID NO: 165	HCDR1 Trastuzumab (H27-H42; AHo numbering)	GFNIKDTYIH

SEQ ID NO: 166	HCDR2 Trastuzumab (H57-H76; AHo numbering)	RIYPTNGYTRYADSVKG
SEQ ID NO: 167	HCDR3 Trastuzumab (H108-H138; AHo numbering)	RWGGDGFYAMDY
SEQ ID NO: 168	VH Trastuzumab HER2-Trastuzumab scFv (PRO1705)	EVQLVESGGGLVQPGGSLRLSCAASG FN IKD TYIH WVRQAPGK G LEWV VARI YPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGG DGFYAMDYWGQGT LVTVSS
SEQ ID NO: 169	VH Trastuzumab (G51C) Her2-Trastuzumab-diS scFv (PRO1706)	EVQLVESGGGLVQPGGSLRLSCAASG FN IKD TYIH WVRQAPGK C LEWV VARI YPTNGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGG DGFYAMDYWGQGT LVTVSS
SEQ ID NO: 170	LCDR1 Trastuzumab (L24-L42; AHo numbering) (Kabat definition)	RASQDVNTAVA
SEQ ID NO: 171	LCDR2 Trastuzumab (L58-L72; AHo numbering) (Kabat definition)	SASFLYS
SEQ ID NO: 172	LCDR3 Trastuzumab (L107-L138; AHo numbering) (Kabat definition)	QQHYTTPPT
SEQ ID NO: 173	VL Trastuzumab (λ -capped) HER2-Trastuzumab scFv (PRO1705)	DIQMTQSPSSLSASVGDRV/TITCRASQDVNTAVAWYQQKPGKAPKLLIYSAS FLYSGVPSRFSRSGTDFLT TISSLQPEDFATYYC QQHYTTPPT FGGGTKLT VLG
SEQ ID NO: 174	VL Trastuzumab (G141C) (λ -capped) Her2-Trastuzumab-diS scFv (PRO1706)	DIQMTQSPSSLSASVGDRV/TITCRASQDVNTAVAWYQQKPGKAPKLLIYSAS FLYSGVPSRFSRSGTDFLT TISSLQPEDFATYYC QQHYTTPPT FGGGTKLT VLG

Table 10. Examples of ROR1 binding domains as used in the present invention (CDR residues shown in bold and italic letters).

SEQ ID NUMBER	Ab region	Sequence
55-38-D07		
SEQ ID NO: 206	HCDR1	GFDLSSYAVS

SEQ ID NO: 207	(H27-H42; AHo numbering) HCDR2 (H57-H76; AHo numbering)	<i>IIYPRANTYYASWAKG</i>
SEQ ID NO: 208	(H108-H138; AHo numbering) HCDR3 (H108-H138; AHo numbering)	<i>RDRYDSGAYLYTTYFNL</i>
SEQ ID NO: 209	(L24-L42; AHo numbering) LCDR1 (L24-L42; AHo numbering)	<i>RASENIYSGLA</i>
SEQ ID NO: 210	(L58-L72; AHo numbering) LCDR2 (L58-L72; AHo numbering)	<i>R4STLAS</i>
SEQ ID NO: 211	(L107-L138; AHo numbering) LCDR3 (L107-L138; AHo numbering)	<i>QGGYSSSSSTYIA</i>
SEQ ID NO: 212	VH (55-38-D07-sc06) mutation G51C (PRO2291)	QSQVVEGGGLVQPGSLRLSCAVSGFDLSSYA ¹ SWVRQAPGKCLEWIGIIYP RANTYYASWAKGRFTISKDNSKNTVY ¹ LQMNSLRAEDTAVYFCARDRYDSGAY LYTTYFNLWGQGT ¹ LVTVSS
SEQ ID NO: 213	VH (55-38-D07-sc06) mutation L12R, G51C, V103T, L144Q (PRO2291)	QSQVVEGGGRVQPGSLRLSCAVSGFDLSSYA ¹ SWVRQAPGKCLEWIGIIYP RANTYYASWAKGRFTISKDNSKNTVY ¹ LQMNSLRAEDTAVYFCARDRYDSGAY LYTTYFNLWGQGT ¹ QVTVSS
SEQ ID NO: 214	VL (55-38-D07-sc06) mutation T141C (PRO2291)	DVQMTQSPSSLSASVGDRT ¹ ITTCRASENIYSGLA ¹ AWYQQKPGKPPKLLIYR4STL ASGVSSRFSGSGGTDF ¹ LTISLQPEDFATY ¹ YCQGGYSSSSSTYIA ¹ FGCGTKVT VLG
55-39-G02		
SEQ ID NO: 215	(H27-H42; AHo numbering) HCDR1 (H27-H42; AHo numbering)	<i>GLSLSRNAMS</i>
SEQ ID NO: 216	(H57-H76; AHo numbering) HCDR2 (H57-H76; AHo numbering)	<i>IIITSGSTYYASWAKG</i>
SEQ ID NO: 217	(H108-H138; AHo numbering) HCDR3 (H108-H138; AHo numbering)	<i>RGIASSSLKSF</i>
SEQ ID NO: 218	LCDR1	<i>QASQNVWNNNYLS</i>

	(L24-L42; AHo numbering)	
SEQ ID NO: 219	LCDR2 (L58-L72; AHo numbering)	TASTLAS
SEQ ID NO: 220	LCDR3 (L107-L138; AHo numbering)	AGGFSGEIRA
SEQ ID NO: 221	VH (55-39-G02-sc05) mutation G51C (PRO2292)	QSQLVESGGGLVQPGGSLRLSCAVS GLSLSR NAMSWVRQAPGK CLEWIGIILT SGSTYYASWAKGRF TISKDNSKNTVYLQMNSLRAEDTAVYFCV RGIASSSLKSF WGQGTLVTVSS
SEQ ID NO: 222	VH (55-39-G02-sc05) mutations L12R, G51C, V103T, L144Q	QSQLVESGGGRVQPGGSLRLSCAVS GLSLSR NAMSWVRQAPGK CLEWIGIILT SGSTYYASWAKGRF TISKDNSKNTVYLQMNSLRAEDTAVYFCV RGIASSSLKSF WGQGTQVTVSS
SEQ ID NO: 223	VL (55-39-G02-sc05) mutation T141C (PRO2292)	AQQLTQSPSSLSASVGDRTVTITC QASQNVWNNYL SWFQQKPGKPKLLIV TA STLAS GVSSRFSGSGGTDFTLTISSLPEDFATY CAGGFSGEIRA FGCGTKVT VLG

Table 11. Examples of multispecific antibodies (MA2) as used in the present invention.

SEQ ID NUMBER	Ab Format	Sequence
PRO1872 (MSLN x CD3 x hSA) (54-22-H03-sc01 scFv/28-21-D09-sc04 scDb-i/23-13-A01-sc02 diS scDb-o)		
SEQ ID NO: 175	scDb-scFv	DVVMTQSPSSLSASVGDRTVTITC QASQI SSRSAWYQQKPGQPKLLIYQASKLASGVP SRFSGSGGTDFTLTISSLPEDFATY YCQCT YIDSNFGAFGCGTKLTVLGGGGSEVQ LVESGGGLVQPGGSLRLSCAA SGFSL SSYDMWVRQAPGKGLAWIGASYASGPTYYA SWAKGRFTISRDNKNTVYLQMNSLRAEDTATYFCARGGWGTGTSNHWGQGTLV VSSGGGGSGGGGGGGGGSDIQMTQSPSSLSASVGDRTVTITCQSSQSVFSNNYL AWFQQKPGQPKRLIY SASTLAS GVPSRFSGSGGTDFTLTISSLPEDFATY YCLGSY ACSSADCYVFGTGKVTVLGGGGSEVQLVESGGGLVQPGGSLRLSCAA SGFSFSSSY WICWVRQAPGKCLEWVGCVFTGDGTTYASWAKGRFTISRDNKNTVYLQMNSLR AEDTATYFCARPVSVYYGYGMDLWGQGTLVTVSSGGGGGGGGSDIQMTQSPSSLSAS

			VGDRVTTITCQASESIGNYLAWYQQKPGKAPKLLIYASATLASGVPSRFSGSGSGTDFTL TISSLQPEDFATYYCQSTDYGDSYIFGTGKVTVLGGGGSGGGSGGGGGGGSE VQLVESGGGLVQPGGSLRLSCAASGISVNDYIMCWVRQAPGKLEWIGCISTYIGN THYASWAKGRFTISRDNKNTVYLQMNSLRAEDTAVYYCAKNAGYPGYRYAIDLW GQGTLVTVSS
PRO2000 (<i>biMSLN_{low affinity}</i> x CD3 x hSA) (54-01-G02-sc01_ (G ₄ S) ₂ 28-21-D09-sc04_ (G ₃ S) ₂ 23-13-A01-sc02 diS VH/54-01-G02-sc01 (G ₄ S) ₂ 23-13-A01-sc02 diS (G ₂ S) ₂ 28-21-D09-sc04 VL)			
SEQ ID NO: 176	MATCH4 (CHAIN_1)		DIQMTQSPSSLSASVGDRVTITCQASQNIYSNLAWYQQKPKGAPKLLIYDASDLASGV PSRFSGSGGTDFTLTISSLQPEDFATYYCQVRRSSDIDNPFGTGKVTVLGGGGSG GGGGGGGGGGGQVQLVESGGGLVQPGGSLRLSCAASGFSLSYAMGWVRQAPG KLEWIGYISTINNTYYASWAKGRFTISRDNKNTVYLQMNSLRAEDTAVYYCAREIR SGWVDYGFSIWGQGTLLVTVSSGGGGGGGGSEVQLVESGGGLVQPGGSLRLSCAAS GFSLSYDMSWVRQAPGKGLAWIGASYASGPTYASWAKGRFTISRDNKNTVYLQ MNSLRAEDTATYFCARGGTGTSHSNWQGTLLVTVSSGGGGGGSEVQLVESGGG LVQPGGSLRLSCAASGFSFSSYWICWVRQAPGKCLEWVGCFTGDTTTYASWAK GRFTISRDNKNTVYLQMNSLRAEDTATYFCARPVSYYGMDLWGQGTLLVTVSS
SEQ ID NO: 177	MATCH4 (CHAIN_2)		DIQMTQSPSSLSASVGDRVTITCQASQNIYSNLAWYQQKPKGAPKLLIYDASDLASGV PSRFSGSGGTDFTLTISSLQPEDFATYYCQVRRSSDIDNPFGTGKVTVLGGGGSG GGGGGGGGGGGQVQLVESGGGLVQPGGSLRLSCAASGFSLSYAMGWVRQAPG KLEWIGYISTINNTYYASWAKGRFTISRDNKNTVYLQMNSLRAEDTAVYYCAREIR SGWVDYGFSIWGQGTLLVTVSSGGGGGGGGSDVMTQSPSSLSASVGDRVTITCQAS QIISRSWYQQKPGQPPLIYQASKLASGVPSRFSGSGGTDFTLTISSLQPEDFATY YCQCTYIDSNFGAFGCGTKLTVLGGGGGGDIQMTQSPSSLSASVGDRVTITCQSSQSV FSNNYLAWFQQKPGQSPKRLIYASATLASGVPSRFSGSGGTDFTLTISSLQPEDFATY YCLGSYACSSADCYVFGTGKVTVLG
PRO2100 (<i>biMSLN_{low affinity}</i> x CD3 x hSA) (54-01-G02-sc03_ (G ₄ S) ₂ 28-21-D09-sc04_ (G ₃ S) ₂ 23-13-A01-sc02 diS VH/54-01-G02-sc03 (G ₄ S) ₂ 23-13-A01-sc02 diS (G ₂ S) ₂ 28-21-D09-sc04 VL)			
SEQ ID NO: 178	MATCH4 (CHAIN_1)		DIQMTQSPSSLSASVGDRVTITCQASQNIYSNLAWYQQKPKGAPKLLIYDASDLASGV PSRFSGSGGTDFTLTISSLQPEDFATYYCQVRRSSDIDNPFGTGKVTVLGGGGSG GGGGGGGGGGGQVQLVESGGGLVQPGGSLRLSCAASGFSLSYAMGWVRQAPG KLEWIGYISTINNTYYASWAKGRFTISRDNKNTVYLQMNSLRAEDTAVYYCAREIR SGWVDYGFSIWGQGTLLVTVSSGGGGGGGGSEVQLVESGGGLVQPGGSLRLSCAAS

SEQ ID NO: 179	MATCH4 (CHAIN_2)	GFSLSYDMSWVRQAPGKGLAWIGASYASGPTYTASWAKGRFTISRDNKNTVYLQ MNSLRAEDATATYFCARGGWGTGTHSNIWGGQTLTVSSGGSGGGSEVQLVESGGG LVQPGGSLRLSCAASGFSFSSSYWICWVRQAPGKCLEWVGCFTGDTTYASWAK GRFTISRDNKNTVYLQMNSLRAEDATATYFCARPVSYYGMDLWGQGTLVTVSS DIQMTQSPSSLSASVGDRTVITTCQASESIYSSNLAWYQQKPGKAPKLLIYDASDLASGV PSRFSGSGTDFTLTISLQPEDFATYYCQVRSDDIDNPFGTGKVTVLGGGGSG GGGGGGGGGGVQLVESGGGLVQPGGSLRLSCAASGFSLSYAMGWVRQAPG KGLEWIGYISTIANITYASWAKGRFTISRDNKNTVYLQMNSLRAEDATAVYYCAREIR SGWVDYGFSIWGGQTLTVSSGGGGGGGGSDVMTQSPSSLSASVGDRTVITTCQAS QIISRSWYQQKPGQPPKLLIYQASKLASGVPSRFSGSGTDFTLTISLQPEDFATY YCQCTYIDSNFAGCGTKLTVLGGGGGGDIQMTQSPSSLSASVGDRTVITTCQSSQSV FSNNYLAWFQQKPGQSPKRLIYASLTASGVPSRFSGSGTDFTLTISLQPEDFATY YCLGSYACSSADCYVFGTGKVTVLG
PRO2741 (MATCH4)		
SEQ ID NO: 224	CHAIN_1PRO2741	DIQMTQSPSSLSASVGDRTVITTCQASESIYSSNLAWYQQKPGKAPKLLIYLASTLASGVP SRFSGSGTDFTLTISLQPEDFATYYCQSTDYTTSTHRNSFGTGKVTVLGGGGSG GGGGGGGGGGVQLVESGGGRVQPGGSLRLSCAASGFSSTTYMCMWVRQAP GKLEWIGCTNTASSVITYATWAKGRFTISRDNKNTVYLQMNSLRAEDATATYC ARMDGFADYALNLWGQGTQVTVSSGGGGGGGGSEVQLVESGGGRVQPGGSLRLS CAASGFSLSYDMSWVRQAPGKGLAWIGASYASGPTYTASWAKGRFTISRDNKNT VYLQMNSLRAEDATATYFCARGGWGTGTHSNIWGGQGTQVTVSSGGGGGGGGSGGE VQLVESGGGRVQPGGSLRLSCAASGFSLSYAMNWRQAPGKCLEWIGHINAGDIAY YATWAKGRFTISRDNKNTVYLQMNSLRAEDATATYFCARGAGGFSTGPFKLWGQGT QVTVSS
SEQ ID NO: 225	CHAIN_2PRO2741	DIQMTQSPSSLSASVGDRTVITTCQASESIYSSNLAWYQQKPGKAPKLLIYLASTLASGVP SRFSGSGTDFTLTISLQPEDFATYYCQSTDYTTSTHRNSFGTGKVTVLGGGGSG GGGGGGGGGGVQLVESGGGRVQPGGSLRLSCAASGFSSTTYMCMWVRQAP GKLEWIGCTNTASSVITYATWAKGRFTISRDNKNTVYLQMNSLRAEDATATYC ARMDGFADYALNLWGQGTQVTVSSGGGGGGGGSAFELTQSPSSLSASVGDRTVITTC

		QASEINSRLAWYQQKPGQPPKLLIYDASDLTSGVPSRFSGSGTDFTLTISLQPEDF ATYYCQGYGGSSTTTFGCGTKLTVLGGSGGSDIQTQSPSSLSASVGDRVTITCQSS QSVFSNNYLAWFQQKPGQSPKRLIYSASTLASGVPSRFSGSGTDFTLTISLQPEDFA TYYCLGSYACSSADCYVFGTGKVTVLG
PRO2746 (MATCH4)		
SEQ ID NO: 226	CHAIN_1 ^{PRO2746}	AFELTQSPSSLSASVGDRVTITCQASEINSRLAWYQQKPGQPPKLLIYDASDLTSGVPS RFSGSGTDFTLTISLQPEDFATYYCQGYGGSSTTTFGTKLTVLGGSGGSGGGG SGGGSGGGGSEVQLVESGGGRVQPGGSLRLSCAASGFSLSYAMNWRQAPGKGL EWIGHINAGDIAYYATWAKGRFTISRDNSKNTVYLMNSLRAEDTATYFCARGAGGF STGPEKLWGQGTQVTVSSGGGGGGGSEVQLVESGGGRVQPGGSLRLSCAASGFSL SSYDMSWVRQAPGKGLAWIGASYAGPTYYASWAKGRFTISRDNSKNTVYLMNSL RAEDTATYFCARGGWTGTSNSNIWQGTQVTVSSGGGGGGGSGGSGGSQLVESGG GRVQPGGSLRLSCAVSGFSLSSYAMGWVRQAPGKCLEYIGYISKIGTTYASWAKGR FTISKDNSKNTVYLMNSLRAEDTATYFCARGSSGGYLDDGFDPWGQGTQVTVSS
SEQ ID NO: 227	CHAIN_2 ^{PRO2746}	ALQMTQSPSSLSARVGDRVTIKCQASQISINYLAWYQQKPGKPKFLIYDASDLASGV PSRFSGSGGRDFTLTISLQPEDFATYYCQGYGGSSTTTFGCGTKVTVLGGGGGS GGGGSGGGGSGGSQLVESGGGRVQPGGSLRLSCAVSGFSLSSYAMGWVRQAP GKCLEYIGYISKIGTTYASWAKGRFTISKDNSKNTVYLMNSLRAEDTATYFCARGS SSGYLDDGFDPWGQGTQVTVSSGGGGGGGSGGSGGSQLVESGGGRVQPGGSLRLSCA ASQISINYLAWYQQKPGKPKFLIYDASDLASGVPSRFSGSGGRDFTLTISLQPEDFA TYYCQQVYDSNNVENVFGCGTKVTVLGGGGGGDIQMTQSPSSLSASVGDRVTITCQ SSQSVFSNNYLAWFQQKPGQSPKRLIYSASTLASGVPSRFSGSGGTDFTLTISLQPED FATYYCLGSYACSSADCYVFGTGKVTVLG
PRO2562 (MATCH4)		
SEQ ID NO: 228	CHAIN_1 ^{PRO2562}	ALQMTQSPSSLSARVGDRVTIKCQASQISINYLAWYQQKPGKPKFLIYDASDLASGV PSRFSGSGGRDFTLTISLQPEDFATYYCQGYGGSSTTTFGCGTKVTVLGGGGGS GGGGSGGGGSGGSQLVESGGGLVQPGGSLRLSCAVSGFSLSSYAMGWVRQAP

		GKCLEYIGYISKIGTTYASWAKGRFTISKDNKNTVYLQMNSLRAEDTAVYFCARGSSGGYLDGDFDPWGQGTLVTVSSGGGGGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFSLSYDMWVRQAPGKGLAWIGASYASGPTYTAAWAKGRFTISRDNKNTVYLQMNSLRAEDTATYFCARGGWTGTSNHWGQGTLVTVSSGGGGGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFSLSYAMNWRQAPGKCLEWIGHINAGDIAYATWAKGRFTISRDNKNTVYLQMNSLRAEDTAVYFCARGAGGFSTGPFKLWGQGTLVTVSS
SEQ ID NO: 229	CHAIN_2 ^{PRO2562}	ALQMTQSPSSLSARVGDRTITKCAQSQSISNYLAWYQQKPKPKFLIYDASDLASGVPSRFSGSGGRDFTLTISLQPEDFATYQCQVYDSNNVENVFEGCTKVTVLGGGGSGGGGGGGGGGSSQLVESGGGLVQPGGSLRLSCAASGFSLSYAMGWVRQAPGKCLEYIGYISKIGTTYASWAKGRFTISKDNKNTVYLQMNSLRAEDTAVYFCARGSSGGYLDGDFDPWGQGTLVTVSSGGGGGGGGSAFELTQSPSSLSASVGDRVTITCQASEINSRLAWYQQKPGQPKLLIYDASDLTSGVPSRFSGSGGSDIQTQSPSSLSASVGDRVTIYYCQYGGSTTTFGCGTKLVLGGGGGGGGSDIQTQSPSSLSASVGDRVTITCQSSQSVFSNNYLAWFQQKPGQSPKRLIYASATLASGVPSRFSGSGGTDFLTISLQPEDFATYCYCLGSYACSSADCYVFGTGTKVTVLG
PRO2566 (MATCH4)		
SEQ ID NO: 230	CHAIN_1 ^{PRO2566}	AFELTQSPSSLSASVGDRVTITCQASEINSRLAWYQQKPGQPKLLIYDASDLTSGVPSRFSGSGGTDFLTISLQPEDFATYQCQYGGSTTTFGTGKLVLGGGGGGGGSGGGGGGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFSLSYAMNWRQAPGKGLWIGHINAGDIAYATWAKGRFTISRDNKNTVYLQMNSLRAEDTAVYFCARGAGGFSTGPFKLWGQGTLVTVSSGGGGGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFSLSYDMWVRQAPGKGLAWIGASYASGPTYTAAWAKGRFTISRDNKNTVYLQMNSLRAEDTATYFCARGGWTGTSNHWGQGTLVTVSSGGGGGGGGGSGGSSQLVESGGLVQPGGSLRLSCAASGFSLSYAMGWVRQAPGKCLEYIGYISKIGTTYASWAKGRFTISKDNKNTVYLQMNSLRAEDTAVYFCARGSSGGYLDGDFDPWGQGTLVTVSS

SEQ ID NO: 231	CHAIN_2 ^{PRO2566}	ALQMTQSPSSLSARVGDRVTIKCQASQISNLYAWYQQKPGKPKFLIYDASDLASGV PSRFSGSGGRDFTLTISLQPEDFATYYCQVYDSNNVENVFGCGTKVTVLGGGGGS GGGGGGGGGSSQSQLVESGGGLVQPGGSLRLSCAVSGFSLSSYAMGWVRQAP GKCLEYIGYISKIGTTYASWAKGRFTISKDNSKNTVYLQMNSLRAEDTAVYFCARGS SSGYLDDGFDPPWGGTLVTVSSGGGGGGGSSALQMTQSPSSLSARVGDRVTIKCQ ASQISNLYAWYQQKPGKPKFLIYDASDLASGVPSRFSGSGGRDFTLTISLQPEDFA TYCQVYDSNNVENVFGCGTKVTVLGGGGGGGSGGSDIQMTQSPSSLSASVGD RVTITCQSSQSVFSNNYLAWFQQKPGQSPKRLIYASATLASGVPSRFSGSGGTDFTLTI SSLQPEDFATYYCLGSYACSSADCYVFGTGKVTVLG
PRO2567 (MATCH4)		
SEQ ID NO: 232	CHAIN_1 ^{PRO2567}	AFELTQSPSSLSARVGDRVTITCQASESINSRLAWYQQKPGQPPKLLIYDASDLTSGVPS RFSGSGGTDFTLTISLQPEDFATYYCQYGGSTTTFTGTGKLTVLGGGGGGGG SGGGGGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFSLSSYAMNWVRQAPGKGL EWIGHINAGDIAYYATWAKGRFTISRDNSKNTVYLQMNSLRAEDTAVYFCARGAGGF STGPFKLWGGTLVTVSSGGGGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFSL SSYDMSWVRQAPGKGLAWIGASYASGPTYASWAKGRFTISRDNSKNTVYLQMNSL RAEDTATYFCARGGWGTGSHSNWGGTLVTVSSGGGGGGGSGGSQLVESGG GLVQPGGSLRLSCAVSGFSLSSYAMGWVRQAPGKCLEYIGYISKIGTTYASWAKGR FTISKDNSKNTVYLQMNSLRAEDTAVYFCARGSSGGYLDGFDPPWGGTLVTVSS
SEQ ID NO: 233	CHAIN_2 ^{PRO2567}	ALQMTQSPSSLSARVGDRVTIKCQASQISNLYAWYQQKPGKPKFLIYDASDLASGV PSRFSGSGGRDFTLTISLQPEDFATYYCQVYDSNNVENVFGCGTKVTVLGGGGGS GGGGGGGGGSSQSQLVESGGGLVQPGGSLRLSCAVSGFSLSSYAMGWVRQAP GKCLEYIGYISKIGTTYASWAKGRFTISKDNSKNTVYLQMNSLRAEDTAVYFCARGS SSGYLDDGFDPPWGGTLVTVSSGGGGGGGSSALQMTQSPSSLSARVGDRVTIKCQ ASQISNLYAWYQQKPGKPKFLIYDASDLASGVPSRFSGSGGRDFTLTISLQPEDFA TYCQVYDSNNVENVFGCGTKVTVLGGGGGGGSDIQMTQSPSSLSASVGDRTITCQ

		SNNQLSWYQQKPGQPPKLLIYDASDLASGVPSRFSGSGSGTDFTLTISLQPEDFATYYCAGGFSSSDTAFGGGKLTVLGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFSLSYDMSWVRQAPGKGLAWIGASYASGPTYASWAKGRFTISRDNKNTVYLQMNSLR AEDTATYFCARGGWGTGTSNHWGQGTLLTVSSGGGGGGGSIQMTQSPSSLSASV GDRVTTICRASQDVNTAVAWYQQKPGKAPKLLIYASFLYSGVPSRFSRSGTDFTL TISLQPEDFATYYCQHHYTPPTFGCGTKLTVLGGGGGGGGSGGGGGGGSEV QLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKCLEWVARIYPTNGYTR YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWWGGDGFYAMDYWGQGT LVTVSS
PRO1767 (HER2 x CD3₄₅ x hSA)	(28-21-D09-sc04-diS-scDb-o/19-01-H04-sc03-scDb-i/Her2-diS scFv)	
SEQ ID NO: 181	scDb-scFv	DIQMTQSPSSLSASVGDRTITTCQSSQSVFSNNYLAWFQKPGQSPKRLIYASSTLASG VPSRFSGSGTDFTLTISLQPEDFATYYCLGSYACSSADCYVFGCGTKVTVLGGGG GSEVQLVESGGGLVQPGGSLRLSCAASGFSLSNNAWGVRQAPGKGLYIGIISVGGF TYASWAKGRFTISRDNKNTVYLQMNSLRAEDTATYFCARDRHGGDSSGAFYLVG QGTLTVSSGGGGGGGGGGGGSIQMTQSPSSLSASVGDRTITTCQSSSEVY SNNQLSWYQQKPGQPPKLLIYDASDLASGVPSRFSGSGSGTDFTLTISLQPEDFATYY CAGGFSSSDTAFGGGKLTVLGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFSLS SYDMSWVRQAPGKGLAWIGASYASGPTYASWAKGRFTISRDNKNTVYLQMNSLR AEDTATYFCARGGWGTGTSNHWGQGTLLTVSSGGGGGGGGSIQMTQSPSSLSASV GDRVTTICRASQDVNTAVAWYQQKPGKAPKLLIYASFLYSGVPSRFSRSGTDFTL TISLQPEDFATYYCQHHYTPPTFGCGTKLTVLGGGGGGGGSGGGGGGGSEV QLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKCLEWVARIYPTNGYTR YADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWWGGDGFYAMDYWGQGT LVTVSS
PRO2510 (ROR1 x CD3 x hSA)		
SEQ ID NO: 236	scMATCH3	AFELTQSPSSLSASVGDRTITTCQASEINSRLAWYQQKPGQPPKLLIYDASDLTSGVPS RFSGSGSGTDFTLTISLQPEDFATYYCQYGGSTTFGCGTKLTVLGGGGGGSEVQL VESGGGLVQPGGSLRLSCAASGFSLSYDMSWVRQAPGKGLAWIGASYASGPTYAS WAKGRFTISRDNKNTVYLQMNSLRAEDTATYFCARGGWGTGTSNHWGQGTLLTV SGGGGGGGGGGGGGGGGGGSIQMTQSPSSLSASVGDRTITTCQSSQSVFSNNYLA WFQKPGQSPKRLIYASSTLASGVPSRFSGSGSGTDFTLTISLQPEDFATYYCLGSYA CSSADCYVFGTGTKTVTVLGGGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFSLSYA

		MNWRQAPGKCLEWIGHINAGDIAYYATWAKGRFTISRDN SKNTVYLQMNSLRAED TAVYFCARGAGGFSTGPKLWGQGTLVTVSSGGGGSGGSAQQLTQSPSSLSASVG DRVTTTCQASQNVWNNNYSWFQKPGPKLLIVTASTLASGVSSRFSGSGGTDF LTISSLQPEDFATYYCAGGFSGEIRAFGCGTKVTVLGGGGSGGGSGGGGGGS QSQLVESGGGLVQPGGSLRLSCAVSGLSLSRNAMSWVRQAPGKCLEWIGHILTSYSTY YASWAKGRFTISKDN SKNTVYLQMNSLRAEDTAVYFCVRGIASSLSKSFVGQGT VSS
PRO2668 (RORI x CD3 x hSA)		
SEQ ID NO: 237	scMATCH3	AFELTQSPSSLSASVGDRVTTTCQASEINSRLAWYQQKPGQPPKLLIYDASDLTSGVPS RFSGSGGTDFTLTISSLQPEDFATYYCQYGGSTTTFGCGTKLVLGGGGSEVQL VESGGGRVQPGGSLRLSCAASGFSLSYDMSWVRQAPGKGLAWIGASYASGPTYAYAS WAKGRFTISRDN SKNTVYLQMNSLRAEDTATYFCARGGWGTGSHSNIWGQGTQVTV SSGGGGSGGGSGGGGGDIQMTQSPSSLSASVGDRVTTTCQSSQSVFSNNYLA WFQKPGQSPKRLIYASATLASGVPSRFSGSGGTDFTLTISSLQPEDFATYYCLGSYA CSSADCYVFGTGTKVTVLGGGGSEVQLVESGGGRVQPGGSLRLSCAASGFSLSYA MNWRQAPGKCLEWIGHINAGDIAYYATWAKGRFTISRDN SKNTVYLQMNSLRAED TATYFCARGAGGFSTGPKLWGQGTQVTVSSGGGGSGGSAQQLTQSPSSLSASVG DRVTTTCQASQNVWNNNYSWFQKPGPKLLIVTASTLASGVSSRFSGSGGTDF LTISSLQPEDFATYYCAGGFSGEIRAFGCGTKVTVLGGGGSGGGSGGGGGGS QSQLVESGGGRVQPGGSLRLSCAVSGLSLSRNAMSWVRQAPGKCLEWIGHILTSYSTY YASWAKGRFTISKDN SKNTVYLQMNSLRAEDTATYFCVRGIASSLSKSFVGQGTQV VSS
PRO2590 (biRORI x CD3 x hSA)		
SEQ ID NO: 238	MATCH4 (chain_1)	DVQMTQSPSSLSASVGDRVTTTCRASENIYSLAWYQQKPGKPKLLIYRASTLASGV SSRFSGSGGTDFTLTISSLQPEDFATYYCQGGYSSSTYIAFGCGTKVTVLGGGGGS GGGGSGGGSGGGSSQSVVESGGGLVQPGGSLRLSCAVSGEDLSYAVSWVRQAP GKCLEWIGHIYPRANTYYASWAKGRFTISKDN SKNTVYLQMNSLRAEDTAVYFCARD RYDSGAYLYTTYFNLWGQGTLVTVSSGGGGSGGSAFELTQSPSSLSASVGDRVTT CQASEINSRLAWYQQKPGQPPKLLIYDASDLTSGVPSRFSGSGGTDFTLTISSLQPED FATYYCQYGGSTTTFGCGTKLVLGGGGSGGDIQMTQSPSSLSASVGDRVTTTCQS SQSVFSNNYLAWFQKPGQSPKRLIYASATLASGVPSRFSGSGGTDFTLTISSLQPEDF ATYYCLGSYACSSADCYVFGTGTKVTVLG

SEQ ID NO: 239	MATCH4 (chain_2)	DVQMTQSPSSLSASVGDRTVITCRASENIYSLAWYQQKPGKPKLLIYRASTLASGV SSRFSGSGSGTDFTLTISSLQPEDFATYYCQGGYSSSSTYIAFGCGTKVTVLGGGGGS GGGSGGGSGGGSSQSVVESGGGLVQPGGSLRLSCAVSGFDLSSYAVSWVRQAP GKCLEWIGHYPRANTYYASWAKGRFTISKDNSKNTVYLQMNSLRAEDTAVYFCARD RYDSGAYLYTTYFNLWGQGTQVTVSSGGGGSGGGSEVQLVESGGGLVQPGGSLRL SCAASGFSLSYDMSWVRQAPGKGLAWIGASYASGPTYASWAKGRFTISRDNKNT VYLQMNSLRAEDTATYFCARGGWGTSHSNWVGQGTQVTVSSGGGGSGGGSGGE VQLVESGGGLVQPGGSLRLSCAASGFSLSYAMNWVRQAPGKCLEWIGHINAGDIAY YATWAKGRFTISRDNKNTVYLQMNSLRAEDTAVYFCARGAGGFSTGPFKLWGQGT LVTVSS
PRO2670 (biRORI x CD3 x hSA)		
SEQ ID NO: 240	MATCH4 (chain_1)	DVQMTQSPSSLSASVGDRTVITCRASENIYSLAWYQQKPGKPKLLIYRASTLASGV SSRFSGSGSGTDFTLTISSLQPEDFATYYCQGGYSSSSTYIAFGCGTKVTVLGGGGGS GGGSGGGSGGGSSQSVVESGGGRVQPGGSLRLSCAVSGFDLSSYAVSWVRQAP GKCLEWIGHYPRANTYYASWAKGRFTISKDNSKNTVYLQMNSLRAEDTATYFCARD RYDSGAYLYTTYFNLWGQGTQVTVSSGGGGSGGGSAFELTQSPSSLSASVGDRTV TCQASESINSLAWYQQKPGQPKLLIYDASDLTSGVPSRFSGSGGTDFTLTISLQPE DFATYYCQYGGSTTTFGCGTKLTVLGGSGGSDIQMTQSPSSLSASVGDRTVITCQ SSQSVFSNNYLAWFQKPGQSPKRLIYSASTLASGVPSRFSGSGGTDFTLTISLQPED FATYYCLGSYACSSADCYVFGTGKTVTLG
SEQ ID NO: 241	MATCH4 (chain_2)	DVQMTQSPSSLSASVGDRTVITCRASENIYSLAWYQQKPGKPKLLIYRASTLASGV SSRFSGSGSGTDFTLTISSLQPEDFATYYCQGGYSSSSTYIAFGCGTKVTVLGGGGGS GGGSGGGSGGGSSQSVVESGGGRVQPGGSLRLSCAVSGFDLSSYAVSWVRQAP GKCLEWIGHYPRANTYYASWAKGRFTISKDNSKNTVYLQMNSLRAEDTATYFCARD RYDSGAYLYTTYFNLWGQGTQVTVSSGGGGSGGGSEVQLVESGGGRVQPGGSLRL SCAASGFSLSYDMSWVRQAPGKGLAWIGASYASGPTYASWAKGRFTISRDNKNT VYLQMNSLRAEDTATYFCARGGWGTSHSNWVGQGTQVTVSSGGGGSGGGSGGE VQLVESGGGRVQPGGSLRLSCAASGFSLSYAMNWVRQAPGKCLEWIGHINAGDIAY YATWAKGRFTISRDNKNTVYLQMNSLRAEDTATYFCARGAGGFSTGPFKLWGQGT QVTVSS

[0218] Throughout the text of this application, should there be a discrepancy between the text of the specification (e. g., Tables 1 to 11) and the sequence listing, the text of the specification shall prevail.

5 [0219] It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable sub-combination. All combinations of the
10 embodiments pertaining to the invention are specifically embraced by the present invention and are disclosed herein just as if each and every combination was individually and explicitly disclosed. In addition, all sub-combinations of the various embodiments and elements thereof are also specifically embraced by the present invention and are disclosed herein just as if each and every such sub-combination
15 was individually and explicitly disclosed herein.

[0220] The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the
20 scope of the appended claims.

[0221] To the extent possible under the respective patent law, all patents, applications, publications, test methods, literature, and other materials cited herein are hereby incorporated by reference.

[0222] The following Examples illustrates the invention described above, but is not,
25 however, intended to limit the scope of the invention in any way. Other test models known as such to the person skilled in the pertinent art can also determine the beneficial effects of the claimed invention.

Examples

Example 1: Assessment of the CD137 agonistic effect of anti-PDL1xCD137 molecules (MA1) by using a cell-based assay of transgenic NF-kB Jurkat reporter cell line expressing CD137:

The ability of the bispecific scDb-based antibodies PRO885, PRO951, PRO1123, PRO1124, PRO1125, PRO1126, PRO1134, and the trispecific scDb-scFv-based antibodies PRO963, PRO966, PRO1057, PRO1058, PRO1175, PRO1186, PRO1430, PRO1479, PRO1482, PRO1431, PRO1432, PRO1473, PRO1476, PRO1480, PRO1481, PRO1480diS, PRO1599, RPO1600, RPO1601, to activate CD137 signaling in Jurkat cells was assessed by using a cell-based assay of transgenic NF-kB Jurkat reporter cell line expressing CD137. The measurements were performed in the presence of PDL1 expressing CHO (clone A2) and HCC827 cells and, as a negative control, in the presence of CHO WT cells without PDL1 expression.

The measurements demonstrated that the bispecific scDb-based antibodies as well as trispecific scDb-scFv-based antibodies activated CD137 signaling more efficient in the presence of PDL1 expressing CHO cells than urelumab. In the absence of PDL1, neither of these antibodies could activate CD137 in reporter cells while urelumab showed activation of CD137 signaling independently of PDL1. The same results could be obtained when the assessment was repeated in the presence of cells expressing lower amounts of PDL1.

[0223] Further information and details on the multispecific antibodies MA1 applied in the invention as well as on the binding domains comprised therein, such as:

- their general description,
- their manufacturing,
- their biophysical characterization, such as stability studies and the evaluation of the monomeric content, or

- their complete functional characterization, including the assessment of their anti-tumor efficacy in the human cell line-derived lung cancer xenograft model HCC827,

are disclosed in detail in the patent application WO 2019/072868, which are herewith
5 incorporated by reference in its entirety, in particular the above-mentioned additional information.

Example 2: Generation, pharmacodynamic characterization and functional characterization of exemplary anti-MSLN multispecific antibodies MA2:

10 [0224] The generation, pharmacodynamic characterization and functional characterization of the exemplary anti-MSLN multispecific antibodies PRO1872, PRO2000, PRO2100, PRO2562, PRO2566, PRO2567, PRO2660, PRO2741 and PRO2746 are disclosed in detail in the unpublished patent applications EP
15 20164913.4 (PRO1872) and PCT/EP2021/064427 (PRO2000, PRO2100, PRO2562, PRO2566, PRO2567, PRO2660, PRO2741 and PRO2746), which are herewith incorporated by reference. Besides, the cytotoxicity assay (T-cell driven target cell depletion) data disclosed in PCT/EP2021/064427 demonstrate that for example the bivalent anti-MSLN antibodies PRO2000 and PRO2100, which comprise two low
20 affinity MSLN-BDs and one CD3-BD (e.g. biMSLN_{high} K_DCD3xhSA), are capable of killing target cells in an antigen density-dependent manner by taking advantage of avidity effects, which the monovalent anti-MSLN antibody PRO1872 (MSLN_{low} K_DCD3xhSA) could not (Figure 3). Furthermore, the data demonstrates that the potency of for example PRO2000 and PRO2100 to initiate T-cell driven target cell
25 killing is not much affected, i.e. decreases only by 17-folds, in the presence of 500 ng/ml soluble MSLN (sMSLN) (Figure 4).

Example 3: Generation, biophysical characterization of exemplary anti-HER2 multispecific antibodies MA2:

[0225] The HER2-BD used in the exemplary anti-HER2 multispecific antibodies PRO1766 and PRO1767 are based on the VH and VL CDR sequences of the anti-HER2-BDs of trastuzumab, wherein FW4 of the VL sequence was replaced by the V λ germline-based FR4 of SEQ-ID NO: 95 (AHO numbering). Furthermore, to generate a scFv construct a linker sequence was introduced between said VH and VL domains. In addition, the glycine residues at positions 51 of the VH sequence and at position 141 in the V λ -FR4 of the VL sequence (AHO numbering) were replaced by cysteines to allow the formation of an internal disulfide bridge in the final scFv format. Finally, this trastuzumab-based HER2 scFv was combined with the scDB, comprising the CD3-BD (28-21-D09-sc04 or the disulfide stabilized variant 28-21-D09-sc04-diS) and the hSA-BD (19-01-H04-sc03), through a further linker to generate a scMATCH3 format. The sequences of the final anti-(HER2 x CD3diS x hSA) scMATCH3 molecules PRO1766 and PRO1767 are listed in Table 11.

[0226] The MATCH is a format invented by Numab that consists solely of variable domains connected by different linkers that allow for the specific pairing of matching domain pairs only (Egan TJ et al. Novel multi-specific heterodimeric antibody format allowing modular assembly of variable domain fragments. MAbs. 2016 Oct 27:0. [<http://dx.doi.org/10.1080/19420862.2016.1248012>]). This format is particularly well suited for the convenient screening of different combinations of antigen binding domains for optimal cooperativity. The MATCH, such as the scMATCH3 and MATCH4, can be expressed recombinantly from mammalian cells. For the purification, a conventional affinity chromatography step can be used.

[0227] Anti-(HER2 x CD3diS x hSA) scMATCH3 molecules PRO1766 and PRO1767 were produced from mammalian cells using standard protein production methods, as for example described in the unpublished patent application EP20164913.4.

[0228] PRO1766 and in particular PRO1767, when formulated at a concentration of 10 mg/ml in 50 mM phosphate-citrate buffer at pH 6.4 with 150 mM NaCl, exhibit a high midpoint of the unfolding transition (T_m) of above 55°C, as determined by DSF, and also showed excellent stability upon storage over four weeks at 4°C as well as at 25°C with virtually no loss in protein content as well as monomeric content.

Example 4: In vivo tumor growth inhibition with PRO2000**(biMSLN_{high} KDxCD3xhSA):****5 Introduction**

[0229] An *in vivo*, mesothelin-expressing cell line xenograft experiment was performed at Charles River Laboratories in order to determine the ability of PRO2000 (biMSLN_{high} KDxCD3xhSA) to effectively control tumor growth relative to control
10 animals.

Methods*Animals*

15 [0230] Female NCG mice from Charles River Laboratories were bred and housed under conditions suitable for humanized mouse work. Animals were used between 8-12 weeks of age.

Study design

20 [0231] Animals in treatment groups (n = 5-6 per group) were subcutaneously co-implanted with 1 x 10⁷ H292 NSCLC tumor cells and 1 x 10⁷ PBMCs in the flank. After 5 days, animals were dosed intravenously with molecules of interest, with additional doses every 5 days until the end of the experiment. During the experiment, animals were monitored at regular intervals for tumor growth using caliper measurements and
25 for weight loss. Animals were euthanized either when the mean tumor volume in the control group was 800 mm³ or at 40 days, whichever came first. Animals were monitored and euthanized according to animal health and welfare regulations at Charles River Laboratories.

30 Results

[0232] We assessed the efficacy of PRO2000 (biMSLN_{high} KDXCD3xhSA) in promoting tumor growth inhibition using a PBMC/H292 co-implantation model, as described in the methods. H292 cells express moderate levels of MSLN and are established from non-small cell lung carcinoma. Multiple dose levels of PRO2000 were administered intravenously, as shown in Figure 5. As comparisons, we used palivizumab (anti-RSV antibody) as a control IgG treatment, as well as tumor cells engrafted in the absence of PBMCs (no treatment). We observed that control conditions resulted in tumor outgrowth (light gray lines, Figure 5A). Treatment with the PRO2000 (biMSLN_{high} KDXCD3xhSA) molecule resulted in tumor growth inhibition at 1 and 5 mg/kg relative to controls (black lines and dark gray lines in Figure 5A, respectively). We examined the significance of the treatments using two-way ANOVA, followed by Tukey's multiple comparisons test; day 40 data are shown in Figure 5B, with each point representing an individual animal. The two higher doses (1 mg/kg and 5 mg/kg) resulted in significantly lower tumor volumes relative to palivizumab-treated animals (ctrl) and untreated animals. The lowest dose (0.2 mg/kg) appeared to be suboptimal, as these comparisons were not significant as compared to palivizumab-treated animals. There appeared to be no adverse effects on overall animal health, as animal weights were relatively stable throughout the experiment (data not shown). Taken together, these data indicate that the multispecific antibody PRO2000 (biMSLN_{high} KDXCD3xhSA) has tumor growth inhibition activity *in vivo* and is a suitable MA2 for the pharmaceutical compositions or the kit of the present invention.

Example 5: In vivo combination study: Comparing the effects of PRO1601 alone or in combination with a mesothelin-targeting molecule:

Experimental description

[0233] An *in vivo*, mesothelin-expressing cell line xenograft experiment was performed at Charles River Laboratories in order to determine the abilities of PRO1601 (anti-PDL1xCD137xhSA), PRO1872 (anti-MSLNxCD3xhSA) and a combination of PRO1601 with PRO1872 to effectively control tumor growth relative to control animals.

Methods

Animals

- 5 [0234] Female NCG mice from Charles River Laboratories were bred and housed under conditions suitable for humanized mouse work. Animals were used between 8-12 weeks of age.

Study design

- 10 [0235] Animals in treatment groups (n=7-8 per group) were subcutaneously co-implanted with 1×10^7 H292 NSCLC tumor cells and 1×10^7 PBMCs in the flank. After 5 days, animals were dosed intravenously with molecules of interest, with additional doses every 5 days until the end of the experiment. During the experiment, animals were monitored at regular intervals for tumor growth using caliper measurements and
15 for weight loss. Animals were euthanized either when the mean tumor volume in the control group was 1000 mm^3 or at 50 days, whichever came first. Animals were monitored and euthanized according to animal health and welfare regulations at Charles River Laboratories.

20 *Data analysis*

- [0236] Data analysis was performed using GraphPad Prism. Groups were compared using two-way ANOVA and the Tukey's multiple comparisons post-hoc test. A value of $p < 0.05$ was considered statistically significant. * indicates $p < 0.05$.

25 **Results and discussion**

- [0237] We assessed the efficacy of the 4-1BB (CD137) and PDL1 targeting molecule PRO1601, as well as the MSLN- and CD3-specific multispecific molecule PRO1872 in promoting tumor growth inhibition using a PBMC/H292 co-implantation model, as
30 described in the methods. H292 cells express moderate levels of MSLN and are established from non-small cell lung carcinoma. This cell line intermediate levels of

PDL1, making it a potential target for PRO1601 as well. PRO1601 (1 mg/kg) and PRO1872 (0.2 mg/kg or 1 mg/kg), as well as a combination of the two molecules were administered intravenously, as shown in Figure 6A. As comparison, we used palivizumab (anti-RSV antibody) as a control IgG treatment.

5

[0238] We observed that the control condition resulted in tumor outgrowth (medium gray line with triangles, Figure 6A). Treatment with the PRO1601 molecule resulted in significant tumor growth inhibition at multiple time points relative to palivizumab, as shown in Figure 6B (dark gray line with diamonds vs. medium gray line with triangles).

10 Treatment with the combination of PRO1601 + PRO1872 resulted in significant tumor growth inhibition relative to PRO1601 alone by the end of the experiment (black lines vs. dark gray lines with diamonds, Figure 6A). Treatment with 0.2 mg/kg of PRO1872 alone (light gray dashed line with circles) resulted in a significantly poorer tumor growth inhibition compared to PRO1601 + PRO1872 at day 28 (both doses, black lines, $p < 0.001$).

15

[0239] There appeared to be no adverse effects on overall animal health related to the treatments, as animal weights were relatively stable throughout the experiment (data not shown). Taken together, these data indicate the promise of combination therapy using PRO1601 and PRO1872 to inhibit tumor growth activity in vivo and is a promising conceptual candidate for cancer immunotherapy.

20

Example 6: *In vivo* tumor growth inhibition with combination of PRO2746 and PRO1601

25

Introduction

[0240] An *in vivo*, mesothelin-expressing cell line human xenograft experiment was performed at Charles River Laboratories in order to determine the ability of PRO1601 (4-1BBxPDL-1xhSA) and PRO2746 (biMSLNxCD3xhSA) to effectively control tumor growth in combination relative to individual molecules alone and control animals.

30

Methods

Animals

- 5 [0241] Female NCG mice from Charles River Laboratories were bred and housed under conditions suitable for humanized mouse work. Animals were used between 8-12 weeks of age.

Study design

- 10 [0242] Animals in treatment groups ($n = 8$ per group) were subcutaneously co-implanted with 1×10^7 HPAC tumor cells and 2.5×10^6 PBMCs in the flank. After 5 days, animals were dosed intravenously with molecules of interest, with additional doses every 5 days until the end of the experiment. During the experiment, animals were monitored at regular intervals for tumor growth using caliper measurements and
15 for weight loss. Animals were euthanized either when the mean tumor volume in the control group was 1500 mm^3 or at 40 days, whichever came first. Animals were monitored and euthanized according to animal health and welfare regulations at Charles River Laboratories.

20 Results

- [0243] We assessed the efficacy of the combination of PRO1601 (4-1BBxPDL-1xhSA) and PRO2746 (biMSLNxCD3xhSA) in promoting tumor growth inhibition using a PBMC/HPAC co-implantation model, as described in the methods. HPAC cells
25 express intermediate to high levels of MSLN and are established from pancreatic adenocarcinoma. Multiple dose levels of PRO2746 (biMSLNxCD3xhSA) were administered intravenously with or without PRO1601, as shown in Figure 7. We used palivizumab (anti-RSV antibody) as a negative control IgG treatment. We observed that the control condition resulted in tumor outgrowth over time (inverted triangle, dark gray line, Figure 7A). Tumor regression was observed when treating with PRO2746 at
30 1 mg/kg (gray circle), and tumor growth was less well controlled with decreasing doses

of PRO2746 (dashed lines). PRO1601 treatment alone at 1 mg/kg did not result in tumor growth inhibition and tumors grew similarly to the control condition. The combination of PRO2746 at the suboptimal dose of 0.2 mg/kg with PRO1601 at 1 mg/kg resulted in tumor regression (dark gray square, solid line) relative to PRO2746 alone at that dose (dark gray square, dashed line), and a significantly improved tumor growth inhibition was observed for the combination of PRO2746 at 0.04 mg/kg and PRO1601 at 1 mg/kg (triangle, solid line) compared to treatment alone (triangle, dashed line). The data at the end of the experiment are displayed on Figure 7B. Each individual point represents one animal. Figures 7C and 7D displays the longitudinal trends for the individual animals in each group. Tumor growth regression was uniformly observed across animals for the combination of PRO2746 at 0.2 mg/kg and PRO1601 at 1 mg/kg, compared to either treatment alone. There appeared to be no adverse effects on overall animal health, as animal weights were relatively stable throughout the experiment and did not decrease (data not shown).

[0244] Taken together, these data indicate that suboptimal doses of the multispecific antibody PRO2746 (biMSLNxCD3xhSA) in combination with PRO1601 has highly improved tumor growth inhibition activity *in vivo* compared to PRO2746 alone. It is believed that the initial engagement of T cells and tumor cells with PRO2746 likely results in T cells that can be engaged further through the action of PRO1601 and mediate more efficient tumor cell killing. These data indicate that this is a promising concept for cancer immunotherapy.

Example 7: In vitro cell lysis with combination of PRO2668 and PRO1601

Introduction

[0245] An *in vitro*, ROR1-expressing cell line real time live cell imaging experiment was performed to determine the ability of PRO1601 (4-1BBxPDL-1xhSA) and PRO2668 (ROR1xCD3xhSA) to effectively lyse cells in combination relative to individual molecules alone and no treatment controls.

Methods

Study design

[0246] The ROR1 expressing breast cancer cell line MDA-MB-231 was cocultured with healthy allogeneic T cells at an effector to target ratio of 5:1, in the presence of either 0.4 nM NM21-1480 or 0.4 nM of NM32-2668, or the combination thereof. Wells were imaged at regular intervals until the end of the experiment. The number of dying cells in green were divided by the number of remaining target cells in red. A downward slope in the curve indicates cell growth.

Results

[0247] As shown in Figure 8, the no construct control (light gray) demonstrated a lack of dying cells relative to remaining target cells, and a similar trend was observed for the addition of NM21-1480. The suboptimal concentration of 0.4 nM NM32-2668 was determined from previous experiments. Compared to 0.4 nM NM32-2668 alone (darkest gray) which resulted in more dying cells than control or 0.4 nM NM21-1480, the combination of NM23-2668 NM21-1480 resulted in the largest extent of dying cells relative to remaining target cells of all the conditions. These data indicate that the combination of a T cell engager together with the costimulatory molecule such as NM21-1480 result in improved cell lysis.

Example 8: Generation, pharmacodynamic characterization and functional characterization of exemplary anti-ROR1 multispecific antibodies MA2:

[0248] The Generation, pharmacodynamic characterization and functional characterization of the exemplary anti-ROR1 multispecific antibodies PRO2510 and PRO2590 are disclosed in detail in the unpublished patent applications EP21154786.4, which is herewith incorporated by reference.

CLAIMS

1. A pharmaceutical composition comprising:
 - 1) a first multispecific antibody (MA1) comprising
 - a) one binding domain, which specifically binds to CD137 (CD137-BD), and
 - b) one binding domain, which specifically binds to PDL1 (PDL1-BD),
 - 2) a second multispecific antibody (MA2) comprising
 - a) one or two binding domain(s), which specifically bind(s) to a tumor cell associated antigen (TAA-BD),
 - b) one binding domain, which specifically binds to CD3 (CD3-BD),
 - 3) a pharmaceutically acceptable carrier,wherein said MA1 does not comprise an immunoglobulin Fc region polypeptide.
2. A kit comprising:
 - 1) a first multispecific antibody (MA1) comprising
 - a) one binding domain, which specifically binds to CD137 (CD137-BD), and
 - b) one binding domain, which specifically binds to PDL1 (PDL1-BD), and
 - 2) a second multispecific antibody (MA2) comprising
 - a) one or two binding domain(s), which specifically bind(s) to a tumor cell associated antigen (TAA-BD),
 - b) one binding domain, which specifically binds to CD3 (CD3-BD),wherein said MA1 does not comprise an immunoglobulin Fc region polypeptide.
3. The pharmaceutical composition of claim 1, or the kit of claim 2, wherein said MA1 or both antibodies MA1 and MA2, further comprises one human serum albumin binding domain (hSA-BD).
4. The pharmaceutical composition or the kit of any one of the preceding claims, wherein said CD137-BD comprises
 - (a) a VH sequence of SEQ ID NO: 4 and a VL sequence of SEQ ID NO: 11;
 - (b) a VH sequence of SEQ ID NO: 5 and a VL sequence of SEQ ID NO: 12;
 - (c) a VH sequence of SEQ ID NO: 6 and a VL sequence of SEQ ID NO: 13;

- (d) a VH sequence of SEQ ID NO: 7 and a VL sequence of SEQ ID NO: 14;
 (e) a VH sequence of SEQ ID NO: 22 and a VL sequence of SEQ ID NO: 26;
 (f) a VH sequence of SEQ ID NO: 31 and a VL sequence of SEQ ID NO: 37;
 (g) a VH sequence of SEQ ID NO: 32 and a VL sequence of SEQ ID NO: 38; or
 5 (h) a VH sequence of SEQ ID NO: 33 and a VL sequence of SEQ ID NO: 39;
 and/or said PDL1-BD comprises
 (a) a VH sequence of SEQ ID NO: 46 and a VL sequence of SEQ ID NO: 52;
 (b) a VH sequence of SEQ ID NO: 47 and a VL sequence of SEQ ID NO: 52;
 (c) a VH sequence of SEQ ID NO: 48 and a VL sequence of SEQ ID NO: 53;
 10 (d) a VH sequence of SEQ ID NO: 60 and a VL sequence of SEQ ID NO: 66;
 (e) a VH sequence of SEQ ID NO: 61 and a VL sequence of SEQ ID NO: 67; or
 (f) a VH sequence of SEQ ID NO: 62 and a VL sequence of SEQ ID NO: 66;
 and said hSA-BD, if present, comprises
 (a) a VH sequence of SEQ ID NO: 74 and a VL sequence of SEQ ID NO: 78;
 15 (b) a VH sequence of SEQ ID NO: 83 and a VL sequence of SEQ ID NO: 87;
 in particular wherein said CD137-BD comprises
 (f) a VH sequence of SEQ ID NO: 31 and a VL sequence of SEQ ID NO: 37;
 (g) a VH sequence of SEQ ID NO: 32 and a VL sequence of SEQ ID NO: 38; or
 (h) a VH sequence of SEQ ID NO: 33 and a VL sequence of SEQ ID NO: 39;
 20 said PDL1-BD comprises
 (a) a VH sequence of SEQ ID NO: 46 and a VL sequence of SEQ ID NO: 52;
 (b) a VH sequence of SEQ ID NO: 47 and a VL sequence of SEQ ID NO: 52; or
 (c) a VH sequence of SEQ ID NO: 48 and a VL sequence of SEQ ID NO: 53;
 and said hSA-BD, if present, comprises
 25 (a) a VH sequence of SEQ ID NO: 74 and a VL sequence of SEQ ID NO: 78;
 (b) a VH sequence of SEQ ID NO: 83 and a VL sequence of SEQ ID NO: 87.
5. The pharmaceutical composition or the kit of any one of claims 1 to 4, wherein
 said MA1 is selected from the scDBs of SEQ ID NOs: 105, 106, 107, 108, 109,
 30 110, and 111 and from the scDb-scFvs of SEQ ID NOs: 112, 113, 114, 115, 116,
 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129 and 130,
 preferably wherein said MA1 is selected from the scDb-scFvs of SEQ ID NOs:
 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127,

128, 129 and 130, more preferably wherein said MA1 is selected from the scDb-scFvs of SEQ ID NO: 125, 126, 127 and 130, in particularly wherein said MA1 is selected from the scDb-scFvs of SEQ ID NO: 125, 127 and 130.

- 5 6. The pharmaceutical composition or the kit of any one of the preceding claims, wherein the tumor cell associated antigen (TAA) is selected from the group consisting of CD138, CD79b, TPBG (5T4), HER2, MSLN, MUC1, CA-125 (MUC16), PSMA, BCMA, CD19, EpCAM, CLEC12A (CLL1), CD20, CD22, CEA, CD33, EGFR, GPC3, CD123, CD38, CD33, CD276, CDH3 (cadherin 3), FGFR1,
 - 10 SSTR2, CD133, EPHA2, HLA-A2, IL13RA2, ROR1, CEACAM6, CD135, GD-2, GA733, CD135 (FLT3), CSPG4 and TAG-72,
 - preferably, wherein the TAA is selected from the group consisting of CD138, CD79b, CD123, HER2, MSLN, PSMA, BCMA, CD19, CD20, CEA, CD38, CD33, CLEC12a and ROR1,
 - 15 in particular wherein the TAA is selected from the group consisting of HER2, MSLN and ROR1.
7. The pharmaceutical composition or the kit of any one of the preceding claims, wherein said MA2 comprises one TAA-BD.
- 20 8. The pharmaceutical composition or the kit of claim 7, wherein the TAA-BD is a mesothelin binding domain (MSLN-BD), which specifically binds to mesothelin (MSLN), particularly a MSLN-BD comprising
 - (i) the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 139, 140 and
 - 25 141, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 143, 144 and 145, respectively; and
 - (ii) VH3 or VH4 domain framework sequences FR1 to FR4; preferably VH3 domain framework sequences FR1 to FR4; and
 - (iii) a VL domain comprising a VL framework comprising framework regions
 - 30 FR1, FR2 and FR3, which are selected from V_k subtypes, particularly from the V_k1 and V_k3 subtypes, particularly are of the V_k1 subtype, and a framework FR4, which is selected from a V_k FR4 and a V_λ FR4, particularly is a V_λ FR4 comprising an amino acid sequence having at least 70, 80, 90

- percent identity, particularly at least 90 percent identity, to any of SEQ ID NO: 94 to SEQ ID NO: 101, more particularly a V λ FR4 selected from any of SEQ ID NO: 94 to SEQ ID NO: 101, particularly a V λ FR4 according to SEQ ID NO: 94 or 101,
- 5 particularly a MSLN-BD comprising
- a) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 139, 140 and 141, respectively,
 - b) LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 143, 144 and 145, respectively,
 - 10 c) a VH sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 142, and
 - d) a VL sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 146;
- or
- 15 a HER2 binding domain (HER2-BD), which specifically binds to HER2 (HER2), particularly a HER2-BD comprising
- (i) the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 165, 166 and 167, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 170, 171 and 172, respectively; and
 - 20 (ii) VH3 or VH4 domain framework sequences FR1 to FR4; preferably VH3 domain framework sequences FR1 to FR4; and
 - (iii) a VL domain comprising a VL framework comprising framework regions FR1, FR2 and FR3, which are selected from Vk subtypes, particularly from the Vk1 and Vk3 subtypes, particularly are of the Vk1 subtype, and a framework FR4,
 - 25 which is selected from a Vk FR4 and a V λ FR4, particularly is a V λ FR4 comprising an amino acid sequence having at least 70, 80, 90 percent identity, particularly at least 90 percent identity, to any of SEQ ID NO: 94 to SEQ ID NO: 101, more particularly a V λ FR4 selected from any of SEQ ID NO: 94 to SEQ ID NO: 101, particularly a V λ FR4 according to SEQ ID NO: 94 or 101.
- 30 particularly a HER2-BD comprising
- a) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 165, 166 and 167, respectively,

- b) LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 170, 171 and 172, respectively,
 - c) a VH sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 168 or 169, and
 - 5 d) a VL sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 173 or 174;
- or
- a ROR1 binding domain (ROR1-BD), which specifically binds to ROR1, particularly a ROR1-BD comprising
- 10 (i) the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 215, 216 and 217, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 218, 219 and 220, respectively; and
 - (ii) VH3 or VH4 domain framework sequences FR1 to FR4; preferably VH3 domain framework sequences FR1 to FR4; and
 - 15 (iii) a VL domain comprising a VL framework comprising framework regions FR1, FR2 and FR3, which are selected from Vk subtypes, particularly from the Vk1 and Vk3 subtypes, particularly are of the Vk1 subtype, and a framework FR4, which is selected from a Vk FR4 and a Vλ FR4, particularly is a Vλ FR4 comprising an amino acid sequence having at least 70, 80, 90
 - 20 percent identity, particularly at least 90 percent identity, to any of SEQ ID NO: 94 to SEQ ID NO: 101, more particularly a Vλ FR4 selected from any of SEQ ID NO: 94 to SEQ ID NO: 101, particularly a Vλ FR4 according to SEQ ID NO: 94 or 101,
- particularly a ROR1-BD comprising
- 25 a) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 215, 216 and 217, respectively,
 - b) LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 218, 219 and 220, respectively,
 - c) a VH sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical
 - 30 to the amino acid sequence SEQ ID NO: 221 or 222, and
 - d) a VL sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 223.

9. The pharmaceutical composition or the kit of any one of claims 1 to 6, wherein the MA2 comprises two TAA-BDs, particularly two TAA-BDs, which bind to the same antigen.
- 5 10. The pharmaceutical composition or the kit of claim 9, wherein said TAA-BDs are mesothelin binding domains (MSLN-BDs), which specifically bind to mesothelin (MSLN), particularly MSLN-BDs comprising
- 10 (i) the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 147, 148 (or 151) and 149, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 153, 154 and 155, respectively; or the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 157, 158 and 159, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 161, 162 and 163, respectively; or the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 197, 198 and 199, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 200, 201 and 202, respectively; and
- 15 (ii) VH3 or VH4 domain framework sequences FR1 to FR4; particularly VH3 domain framework sequences FR1 to FR4; and
- (iii) a VL domain comprising a VL framework comprising framework regions FR1, FR2 and FR3, which are selected from V_k subtypes, particularly from the V_{k1} and V_{k3} subtypes, particularly are of the V_{k1} subtype, and a framework FR4, which is selected from a V_k FR4 and a V_λ FR4, particularly is a V_λ FR4 comprising an amino acid sequence having at least 70, 80, 90 percent identity, particularly at least 90 percent identity, to any of SEQ ID NO: 94 to SEQ ID NO: 101, more particularly a V_λ FR4 selected from any of SEQ ID NO: 94 to SEQ ID NO: 101, particularly a V_λ FR4 according to SEQ ID NO: 94 or 101;
- 20 particularly MSLN-BDs comprising
- a.1) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 147, 148 (or 151) and 149, respectively,
- 30 b.1) LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 153, 154 and 155, respectively,
- c.1) a VH sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 150, and

- d.1) a VL sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 156;
or
a.2) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 147, 148 (or 151) and 149, respectively,
5 b.2) LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 153, 154 and 155, respectively,
c.2) a VH sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 152, and
10 d.2) a VL sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 156;
or
a.3) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 157, 158 and 159, respectively,
15 b.3) LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 161, 162 and 163, respectively,
c.3) a VH sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 160, and
d.3) a VL sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent
20 identical to the amino acid sequence SEQ ID NO: 164;
or
a.4) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 157, 158 and 159, respectively,
b.4) LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 161, 162 and 163,
25 respectively,
c.4) a VH sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 194 or 195, and
d.4) a VL sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 196;
30 or
a.5) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 197, 198 and 199, respectively,

- b.5) LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 200, 201 and 202, respectively,
- c.5) a VH sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 203 or 204, and
- 5 d.5) a VL sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 205.
11. The pharmaceutical composition or the kit of claim 9, wherein said TAA-BDs are ROR1 binding domains (ROR1-BDs), which specifically bind to ROR1, particularly
- 10 ROR1-BDs comprising
- (i) the HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 206, 207 and 208, respectively, and the LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 209, 210 and 211, respectively; and
- (ii) VH3 or VH4 domain framework sequences FR1 to FR4; preferably VH3 domain framework sequences FR1 to FR4; and
- 15 (iii) a VL domain comprising a VL framework comprising framework regions FR1, FR2 and FR3, which are selected from Vk subtypes, particularly from the Vk1 and Vk3 subtypes, particularly are of the Vk1 subtype, and a framework FR4, which is selected from a Vk FR4 and a Vλ FR4, particularly
- 20 is a Vλ FR4 comprising an amino acid sequence having at least 70, 80, 90 percent identity, particularly at least 90 percent identity, to any of SEQ ID NO: 94 to SEQ ID NO: 101, more particularly a Vλ FR4 selected from any of SEQ ID NO: 94 to SEQ ID NO: 101, particularly a Vλ FR4 according to SEQ ID NO: 94 or 101,
- 25 particularly ROR1-BDs comprising
- a.1) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 206, 207 and 208, respectively,
- b.1) LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 209, 210 and 211, respectively,
- 30 c.1) a VH sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 212, and
- d.1) a VL sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 214;

or

a.2) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 206, 207 and 208, respectively,

b.2) LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 209, 210 and 211, respectively,

c.2) a VH sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 213, and

d.2) a VL sequence at least 90, 91, 92, 93, 94, 95, 96, 97, 98 or 99 percent identical to the amino acid sequence SEQ ID NO: 214.

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12. The pharmaceutical composition or the kit of any of the preceding claims, wherein said CD3-BD comprises

(i) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 131, 132 and 133, embedded in an antibody VH framework, particularly in a human antibody VH framework, particularly in a human VH3 framework, and

15

(ii) LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 135, 136 and 137, embedded in an antibody VH framework, particularly in a human antibody VL framework, wherein the VL framework comprises framework regions FR1, FR2 and FR3, which are selected from Vk subtypes, particularly from the Vk1 and Vk3 subtypes, particularly are of the Vk1 subtype, and a framework FR4, which is selected from a Vk FR4 and a Vλ FR4, particularly is a Vλ FR4 comprising an amino acid sequence having at least 70, 80, 90 percent identity, particularly at least 90 percent identity, to any of SEQ ID NO: 94 to SEQ ID NO: 101, more particularly a Vλ FR4 selected from any of SEQ ID NO: 94 to SEQ ID NO: 101, particularly a Vλ FR4 according to SEQ ID NO: 94 or 101;

20

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particularly wherein said CD3-BD comprises

(i) a VH domain comprising the amino acid sequence of SEQ ID NO: 134 or 182, and

(ii) a VL domain comprising the amino acid sequence of SEQ ID NO: 138.

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13. The pharmaceutical composition or the kit of any of the preceding claims, wherein said hSA-BD comprises

(i) a VH domain comprising the amino acid sequence of SEQ ID NO: 74, and

- a VL domain comprising the amino acid sequence of SEQ ID NO: 78; or
(ii) a VH domain comprising the amino acid sequence of SEQ ID NO: 83, and
a VL domain comprising the amino acid sequence of SEQ ID NO: 87; or
(iii) a VH domain comprising the amino acid sequence of SEQ ID NO: 190, and
5 a VL domain comprising the amino acid sequence of SEQ ID NO: 192; or
(iv) a VH domain comprising the amino acid sequence of SEQ ID NO: 191, and
a VL domain comprising the amino acid sequence of SEQ ID NO: 192; or
(v) a VH domain comprising the amino acid sequence of SEQ ID NO: 189, and
a VL domain comprising the amino acid sequence of SEQ ID NO: 193.
- 10 14. The pharmaceutical composition or the kit of any one of the preceding claims,
wherein said MA2 is selected from the group consisting of:
the scMATCH3-based antibodies of SEQ ID NOs: 175, 180, 181, 236 and 237;
and
15 the MATCH4-based heterodimeric antibodies of SEQ ID NOs: 176 and 177, 178
and 179, 224 and 225, 226 and 227, 228 and 229, 230 and 231, 232 and 233, 234
and 235, 238 and 239 and 240 and 241.
- 20 15. The pharmaceutical composition or the kit of any one of claims 1 to 14 for use in
the treatment of a disease, particularly a human disease, more particularly a
human disease selected from cancer, particularly a cancer selected from
mesothelioma, pancreatic cancer, gastric cancer, lung cancer, breast cancer and
ovarian cancer, an inflammatory and an autoimmune disease.
- 25 16. A method for the treatment of a disease, particularly a human disease, more
particularly a human disease selected from cancers, particularly a cancer selected
from mesothelioma, pancreatic cancer, gastric cancer, lung cancer, breast cancer
and ovarian cancer, comprising the step of administering the pharmaceutical
composition or the kit of any one of claim 1 to 14.
- 30 17. A method for treating a patient suffering from cancer, particularly a cancer selected
from melanoma, mesothelioma, pancreatic cancer, stomach cancer, breast
cancer, ovarian cancer and lung cancer, comprising the step of administering a

5 first multispecific antibody (MA1) comprising one binding domain, which specifically binds to CD137 (CD137-BD), and one binding domain, which specifically binds to PDL1 (PDL1-BD), and a second multispecific antibody (MA2) comprising at least one binding domain, which specifically binds to a tumor cell associated antigen (TAA-BD), and one binding domain, which specifically binds to CD3 (CD3-BD), to said patient, wherein said MA1 and MA2 are as defined in claims 1 to 14.