CLAIMS

1. A combination of
   (i) an immune checkpoint modulator and
   (ii) a T-cell redirecting multifunctional antibody, or an antigen binding fragment thereof, comprising:
      (a) a specificity against a T cell surface antigen;
      (b) a specificity against a cancer- and/or tumor-associated antigen; and
      (c) a binding site for human FcγRI, FcγRIIa and/or FcγRIII, wherein the antibody, or the antigen binding fragment thereof, binds with a higher affinity to human FcγRI, FcγRIIa and/or FcγRIII than to human FcγRIIb;

   for use in therapeutic treatment of a cancer disease.

2. The combination for use according to claim 1, wherein the antibody, or the antigen binding fragment thereof, is a monoclonal antibody.

3. The combination for use according to claim 1 or 2, wherein the T cell surface antigen is selected from the group consisting of CD2, CD3, CD4, CD5, CD6, CD8, CD28, CD40L and CD44.

4. The combination for use according to claim 3, wherein the T cell surface antigen is CD2 or CD3, preferably the T cell surface antigen is CD3.

5. The combination for use according to any of the preceding claims, wherein the cancer- and/or tumor-associated antigen is selected from the group consisting of EpCAM, HER2/neu, CEA, MAGE, proteoglycan, VEGF, EGFR, mTOR, PIK3CA, RAS, alpha(v)beta(3)-integrin, HLA, HLA-DR, ASC, carbonic anhydrase, CD1, CD2, CD4, CD6, CD7, CD8, CD11, CD13, CD14, CD19, CD20, CD21, CD22, CD23, CD24, CD30 CD33, CD37, CD38, CD40, CD41, CD47, CD52, CD138, c-erb-2, CALLA, MHCII, CD44v3, CD44v6, p97, GM1, GM2, GM3, GD1a, GD1b, GD2, GD3, GT1b, GT3, GQ1, NY-ESO-1, NFX2, SSX2, SSX4, Trp2, gp100, tyrosinase, MUC-1,

telomerase, survivin, p53, CA125, Wue antigen, Lewis Y antigen, HSP-27, HSP-70, HSP-72, HSP-90, Pgp, MCSP, EphA2 and cell surface targets GC182, GT468 or GT512.

6. The combination for use according to claim 5, wherein the cancer- and/or tumor-associated antigen is selected from the group consisting of EpCAM, HER2/neu, CEA, MAGE, VEGF, EGFR, mTOR, PIK3CA, RAS, GD2, CD19, CD20, CD30, CD33 and CD38, preferably the cancer- and/or tumor-associated antigen is selected from the group consisting of EpCAM, HER2/neu, CEA, GD2, CD19, CD20 and CD33, more preferably the cancer- and/or tumor-associated antigen is selected from the group consisting of EpCAM, HER2/neu, GD2 and CD20 and even more preferably the cancer- and/or tumor-associated antigen is EpCAM or GD2.

7. The combination for use according to claim 6, wherein the antibody, or the antigen binding fragment thereof, comprises a first specificity against CD3 and a second specificity against a cancer- and/or tumor-associated antigen selected from the group consisting of EpCAM, HER2/neu, CEA, GD2, CD19, CD20 and CD33.

8. The combination for use according to claim 7, wherein the antibody, or the antigen binding fragment thereof, comprises two specificities selected from anti-EpCAM x anti-CD3, anti-CD20 x anti-CD3, anti-HER2/neu x anti-CD3, anti-GD2 x anti-CD3 and anti -CD19 x anti-CD3.

9. The combination for use according to any of the preceding claims, wherein the antibody, or the antigen binding fragment thereof, comprises an Fc moiety.

10. The combination for use according to claim 9, wherein the antibody, or the antigen binding fragment thereof, comprises an Fc region.

11. The combination for use according to any of the preceding claims, wherein the binding site for human FcγRI, FcγRIIa and/or FcγRIII, in particular the Fc moiety, is mouse IgG2a/rat IgG2b.

12. The combination for use according to claim 11, wherein the antibody, or the antigen binding fragment thereof, comprises a mouse IgG2a/rat IgG2b Fc region.

13. The combination for use according to any of the preceding claims, wherein the antibody has an IgG-like format.

14. The combination for use according to any of the preceding claims, wherein the antibody, or the antigen binding fragment thereof, is a heterologous antibody or antigen binding fragment thereof.

15. The combination for use according to any of the preceding claims, wherein the antibody, or the antigen binding fragment thereof, comprises a heavy chain, which is derived from rat and/or mouse.

16. The combination for use according to claim 15, wherein the antibody, or the antigen binding fragment thereof, is a rat and/or mouse antibody, or antigen binding fragment thereof.

17. The combination for use according to claim 16, wherein the antibody, or the antigen binding fragment thereof, is a rat/mouse antibody, or antigen binding fragment thereof.

18. The combination for use according to claim 17, wherein the antibody, or the antigen binding fragment thereof, is a mouse IgG2a/rat IgG2b antibody, or antigen binding fragment thereof.

19. The combination for use according to any of the preceding claims, wherein the antibody, or the antigen binding fragment thereof, is a trifunctional antibody, in particular a trifunctional, bispecific antibody.

20. The combination for use according to claim 19, wherein the antibody, or the antigen binding fragment thereof, is selected from the group consisting of catumaxomab,

lymphomun, ertumaxomab, ektomab, preferably the antibody is catumaxomab and/or ektomab.

21. The combination for use according to any of the preceding claims, wherein the immune checkpoint modulator is an activator or an inhibitor of one or more immune checkpoint point molecule(s) selected from CD27, CD28, CD40, CD122, CD137, OX40, GITR, ICOS, A2AR, B7-H3, B7-H4, BTLA, CD40, CTLA-4, IDO, KIR, LAG3, PD-1, PD-L1, PD-L2, TIM-3, VISTA, CEACAM1, GARP, PS, CSF1R, CD94/NKG2A, TDO, GITR, TNFR and/or FasR/DcR3; or an activator or an inhibitor of one or more ligands thereof.

22. The combination for use according to any of the preceding claims, wherein the immune checkpoint modulator is an activator of a stimulatory or co-stimulatory checkpoint molecule or an inhibitor of an inhibitory checkpoint molecule or a combination thereof.

23. The combination for use according to claim 21 or 22, wherein the immune checkpoint modulator is an inhibitor of an inhibitory checkpoint molecule, preferably an inhibitor of A2AR, B7-H3, B7-H4, BTLA, CD40, CTLA-4, IDO, KIR, LAG3, PD-1, PD-L1, PD-L2, TIM-3, VISTA, CEACAM1, GARP, PS, CSF1R, CD94/NKG2A, TDO, TNFR and/or DcR3 or of a ligand thereof.

24. The combination for use according to claim 21 or 22, wherein the immune checkpoint modulator is an activator of a stimulatory or costimulatory checkpoint molecule, preferably an activator of CD27, CD28, CD40, CD122, CD137, OX40, GITR and/or ICOS or of a ligand thereof.

25. The combination for use according to any of claims 21 to 23, wherein the immune checkpoint modulator is an inhibitor of CTLA-4, PD-1, PD-L1 and/or PD-L2; more preferably the immune checkpoint modulator is an inhibitor of CTLA-4 and/or PD-1.

26. The combination for use according to any of claims 21 to 25, wherein more than one immune checkpoint modulator is used, in particular at least 2, 3, 4, 5, 6, 7, 8, 9 or 10

distinct immune checkpoint modulators are used, preferably 2, 3, 4 or 5 distinct immune checkpoint modulators are used, more preferably 2, 3 or 4 distinct immune checkpoint modulators are used, even more preferably 2 or 3 distinct immune checkpoint modulators are used and most preferably 2 distinct immune checkpoint modulators are used.

27. The combination for use according to claim 26, wherein at least (α) an inhibitor of CTLA-4 and (β) an inhibitor of PD-1, PD-L1 and/or PD-L2 are used, preferably at least (α) an inhibitor of CTLA-4 and (β) an inhibitor of PD-1 are used.

28. The combination for use according to any of claims 21 to 25, wherein the antibody is catumaxomab and/or ektomab and the immune checkpoint modulator is an inhibitor of CTLA-4.

29. The combination for use according to any of the preceding claims, wherein the immune checkpoint modulator and the T-cell redirecting multifunctional antibody are administered at about the same time.

30. The combination for use according to any of claims 1 to 28, wherein the immune checkpoint modulator and the T-cell redirecting multifunctional antibody are administered consecutively.

31. The combination for use according to claim 30, wherein the immune checkpoint modulator is administered before the T-cell redirecting multifunctional antibody.

32. The combination for use according to claim 30, wherein the immune checkpoint modulator is administered after the T-cell redirecting multifunctional antibody.

33. The combination for use according to any of the preceding claims, wherein the immune checkpoint modulator and the T-cell redirecting multifunctional antibody are administered via the same route of administration.

34. The combination for use according to any of claims 1 to 32, wherein the immune checkpoint modulator and the T-cell redirecting multifunctional antibody are administered via distinct routes of administration.

35. The combination for use according to any of the preceding claims, wherein the immune checkpoint modulator and the T-cell redirecting multifunctional antibody are provided in distinct compositions.

36. The combination for use according to any of claims 1 to 29 and 33, wherein the immune checkpoint modulator and the T-cell redirecting multifunctional antibody are provided in the same composition.

37. The combination for use according to any of the preceding claims, wherein the combination is for use in therapeutic treatment of a cancer disease in a human subject.

38. The combination for use according to any of the preceding claims, wherein the cancer disease is selected from lung cancer, gastric cancer, ovarian cancer, breast cancer, melanoma, prostate cancer, head and neck squamous cell carcinoma, Hodgkin's lymphoma, non-Hodgkin's lymphomas, bladder tumor, plasmocytoma, and/or sarcoma.

39. A kit comprising

(i) an immune checkpoint modulator and

(ii) a T-cell redirecting multifunctional antibody, or an antigen binding fragment thereof, comprising:

(a) a specificity against a T cell surface antigen;

(b) a specificity against a cancer- and/or tumor-associated antigen; and

(c) a binding site for human FcγRI, FcγRIIa and/or FcγRIII, wherein the antibody, or the antigen binding fragment thereof, binds with a higher affinity to human FcγRI, FcγRIIa and/or FcγRIII than to human FcγRIIb;

for use in therapeutic treatment of a cancer disease, in particular in a human subject.

40. The kit for use according to claim 39, wherein the immune checkpoint modulator and the antibody, or antigen-binding fragment thereof, are as defined in any of claims 2 to 28 and 35 to 36.

41. The kit for use according to claim 39 or 40, wherein the kit further comprises a package insert or label with directions to treat cancer by using a combination of the immune checkpoint modulator and the antibody, or antigen-binding fragment thereof.

42. A composition comprising
    (i) an immune checkpoint modulator and
    (ii) a T-cell redirecting multifunctional antibody, or an antigen binding fragment thereof, comprising:
        (a) a specificity against a T cell surface antigen;
        (b) a specificity against a cancer- and/or tumor-associated antigen; and
        (c) a binding site for human FcγRI, FcγRIIa and/or FcγRIII, wherein the antibody, or the antigen binding fragment thereof, binds with a higher affinity to human FcγRI, FcγRIIa and/or FcγRIII than to human FcγRIIb.

43. The composition according to claim 42, wherein the immune checkpoint modulator and/or the antibody, or antigen-binding fragment thereof, are as defined in any of claims 2 to 28 and 35 to 36.

44. The composition according to claim 42 or 43, wherein the composition comprises a pharmaceutically acceptable carrier.

45. The composition according to any of claims 42 to 44 for use in medicine.

46. The composition for use according to claim 45 for use in the therapeutic treatment of a cancer disease, in particular in a human subject.

47. A method for therapeutically treating cancer or initiating, enhancing or prolonging an anti-tumor-response in a subject in need thereof comprising administering to the subject

(i) an immune checkpoint modulator and

(ii) a T-cell redirecting multifunctional antibody, or an antigen binding fragment thereof, comprising:

(a) a specificity against a T cell surface antigen;

(b) a specificity against a cancer- and/or tumor-associated antigen; and

(c) a binding site for human FcγRI, FcγRIIa and/or FcγRIII, wherein the antibody, or the antigen binding fragment thereof, binds with a higher affinity to human FcγRI, FcγRIIa and/or FcγRIII than to human FcγRIIb.

48. The method according to claim 47, wherein the immune checkpoint modulator and/or the antibody, or antigen-binding fragment thereof, are as defined in any of claims 2 to 28 and 35 to 36.

49. The method of claim 47 or 48, wherein the subject is a human subject diagnosed with cancer.

50. A combination therapy for therapeutically treating cancer, wherein the combination therapy comprises administration of

(i) an immune checkpoint modulator and

(ii) a T-cell redirecting multifunctional antibody, or an antigen binding fragment thereof, comprising:

(a) a specificity against a T cell surface antigen;

(b) a specificity against a cancer- and/or tumor-associated antigen; and

(c) a binding site for human FcγRI, FcγRIIa and/or FcγRIII, wherein the antibody, or the antigen binding fragment thereof, binds with a higher affinity to human FcγRI, FcγRIIa and/or FcγRIII than to human FcγRIIb.

51. The combination therapy according to claim 50, wherein the immune checkpoint modulator and/or the antibody, or antigen-binding fragment thereof, are as defined in any of claims 2 to 28 and 35 to 36.

52. The combination therapy according to claim 50 or 51, wherein the immune checkpoint modulator and the T-cell redirecting multifunctional antibody, or an antigen binding fragment thereof, are administered to a human subject.