CLAIMS

1. A combination product 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, wherein the T cell surface antigen is CD3;

(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, wherein the immune checkpoint modulator inhibits CTLA-4.

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

3. The combination product for use according to claim 1 or 2, wherein the immune checkpoint modulator and the T-cell redirecting multifunctional antibody, or the antigen binding fragment thereof, are directed to distinct targets.

4. The combination product for use according to any one of claims 1 to 3, wherein the T-cell redirecting multifunctional antibody, or the antigen binding fragment thereof, induces increased expression of an immune checkpoint molecule.

5. The combination product for use according to any one of claims 1 to 4, wherein the combination mediates sustained T-cell activation as compared to the T-cell activation induced by (i) the immune checkpoint modulator alone, or (ii) the T-cell redirecting multifunctional antibody, or the antigen binding fragment thereof, alone.

6. The combination product for use according to any one of claims 1 to 5, wherein the cancer- and/or tumor-associated antigen is not PD-L1.

7. The combination product for use according to any one of claims 1 to 6, wherein the cancer- and/or tumor-associated antigen is not an immune checkpoint molecule and/or a ligand thereof.

8. The combination product for use according to any one of claims 1 to 7, 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.

9. The combination product for use according to claim 8, 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.

10. The combination product for use according to claim 9, 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.

11. The combination product for use according to any one of claims 1 to 10, wherein the antibody, or the antigen binding fragment thereof, does not comprise a specificity against CD19.

12. The combination product for use according to any one of claims 1 to 11, wherein the antibody, or the antigen binding fragment thereof, does not comprise a specificity against CEA.

13. The combination product for use according to any one of claims 10 to 12, 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.

14. The combination product for use according to any one of claims 1 to 13, wherein the antibody, or the antigen binding fragment thereof, comprises an Fc moiety.

15. The combination product for use according to claim 14, wherein the antibody, or the antigen binding fragment thereof, comprises an Fc region.

16. The combination product for use according to any one of claims 1 to 15, wherein the binding site for human FcγRI, FcγRIIa and/or FcγRIII, in particular the Fc moiety, is mouse IgG2a/rat IgG2b.

17. The combination product for use according to claim 16, wherein the antibody, or the antigen binding fragment thereof, comprises a mouse IgG2a/rat IgG2b Fc region.

18. The combination product for use according to any one of claims 1 to 17, wherein the antibody has an IgG-like format.

19. The combination product for use according to any one of claims 1 to 18, wherein the antibody, or the antigen binding fragment thereof, is a heterologous antibody or antigen binding fragment thereof.

20. The combination product for use according to any one of claims 1 to 19, wherein the antibody, or the antigen binding fragment thereof, comprises a heavy chain, which is derived from rat and/or mouse.

21. The combination product for use according to claim 20, wherein the antibody, or the antigen binding fragment thereof, is a rat and/or mouse antibody, or antigen binding fragment thereof.

22. The combination product for use according to claim 21, wherein the antibody, or the antigen binding fragment thereof, is a rat/mouse antibody, or antigen binding fragment thereof.

23. The combination product for use according to claim 22, wherein the antibody, or the antigen binding fragment thereof, is a mouse IgG2a/rat IgG2b antibody, or antigen binding fragment thereof.

24. The combination product for use according to any one of claims 1 to 23, wherein the antibody, or the antigen binding fragment thereof, is a trifunctional antibody, in particular a trifunctional, bispecific antibody.

25. The combination product for use according to claim 24, 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.

26. The combination product for use according to any one of claims 1 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 product 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 product for use according to claim 26 or 27, wherein the antibody is catumaxomab and/or ektomab and the immune checkpoint modulator is an inhibitor of CTLA-4.

29. The combination product for use according to any one of claims 1 to 28, wherein the immune checkpoint modulator and the T-cell redirecting multifunctional antibody are administered at about the same time.

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

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

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

33. The combination product for use according to claim 32, wherein the immune checkpoint modulator is administered at least 6 hours, preferably at least 12 hours, more preferably at least 18 hours, even more preferably at least 24 hours, still more preferably at least 36 hours and most preferably at least 48 hours after the T-cell redirecting multifunctional antibody, or the antigen-binding fragment thereof.

34. The combination product for use according to claim 32 or 33, wherein the immune checkpoint modulator is administered no more than 96 hours, preferably no more than 84 hours, more preferably no more than 72 hours and most preferably no more than 60 hours after the T-cell redirecting multifunctional antibody, or the antigen-binding fragment thereof.

35. The combination product for use according to any one of claims 32 to 34, wherein (i) the first administration of the immune checkpoint modulator is applied 12 – 96 hours, preferably 24 – 84 hours, more preferably 36 – 72 hours, and most preferably 48 – 60 hours after the first administration of the T-cell redirecting multifunctional antibody, or the antigen-binding fragment thereof; and/or (ii) the final administration of the immune checkpoint modulator is applied 12 – 96 hours, preferably 24 – 84 hours, more preferably 36 – 72 hours, and most preferably 48 – 60 hours after the final administration of the T-cell redirecting multifunctional antibody, or the antigen-binding fragment thereof.

36. The combination product for use according to any one of claims 1 to 35, wherein the immune checkpoint modulator and the T-cell redirecting multifunctional antibody are administered via the same route of administration.

37. The combination product for use according to any of claims 1 to 35, wherein the immune checkpoint modulator and the T-cell redirecting multifunctional antibody are administered via distinct routes of administration.

38. The combination product for use according to any one of claims 1 to 37, wherein the immune checkpoint modulator and the T-cell redirecting multifunctional antibody are provided in distinct compositions.

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

40. The combination product for use according to any one of claims 1 to 39, wherein the combination is for use in therapeutic treatment of a cancer disease in a human subject.

41. The combination product for use according to claim 40, 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.

42. The combination product for use according to any one of claims 1 to 41, wherein the T-cell redirecting multifunctional antibody, or the antigen binding fragment thereof, is administered at a single dose in a range of 0.1 to 5000 μg, preferably at a single dose in a range of 1 to 1000 μg, more preferably at a single dose in a range of 2 μg to 750 μg, even more preferably at a single dose in a range of 3 μg to 700 μg, still more preferably at a single dose in a range of 5 μg to 600 μg, and most preferably at a single dose in a range of 10 μg – 500 μg.

43. The combination product for use according to any one of claims 1 to 42, wherein the T-cell redirecting multifunctional antibody, or the antigen binding fragment thereof, is administered at a single dose of no more than 1mg, preferably no more than 0.9 mg, more preferably no more than 0.8 mg, even more preferably no more than 0.75 mg and most preferably no more than 0.5 mg.

44. The combination product for use according to any one of claims 1 to 43, wherein the T-cell redirecting multifunctional antibody, or the antigen binding fragment thereof, is administered according to an escalating dosage regimen.

45. The combination product for use according to any one of claims 1 to 44, further comprising
(iii) a glucocorticoid.

46. The combination product for use according to claim 45, wherein the glucocorticoid is selected from the group consisting of prednisone, prednisolone, methylprednisolone,

triamcinolone, betamethasone, dexamethasone, cortisone acetate, prednylidene, deflazacort, cloprednole, fluocortolone and budenoside, most preferably the glucocorticoid is dexamethasone.

47. The combination product for use according to claim 45 or 46, wherein the glucocorticoid is administered before the administration of the T-cell redirecting multifunctional antibody, or the antigen binding fragment thereof, and/or before the administration of the immune checkpoint modulator.

48. The combination product for use according to claim 47, wherein the glucocorticoid is administered no longer than six hours, preferably no longer than five hours, more preferably no longer than four hours, even more preferably no longer than three hours, still more preferably no longer than two hours and most preferably no longer than one hour before the administration of the T-cell redirecting multifunctional antibody, or the antigen binding fragment thereof, and/or no longer than six hours, preferably no longer than five hours, more preferably no longer than four hours, even more preferably no longer than three hours, still more preferably no longer than two hours and most preferably no longer than one hour before the administration of the immune checkpoint modulator.

49. The combination product for use according to any one of claims 45 to 48, wherein the glucocorticoid is administered at about the same time as the T-cell redirecting multifunctional antibody, or the antigen binding fragment thereof, and/or the glucocorticoid is administered at about the same time the immune checkpoint modulator.

50. 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, wherein the T cell surface antigen is CD3;

(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, wherein the immune checkpoint modulator inhibits CTLA-4.

51. The kit for use according to claim 50, wherein the immune checkpoint modulator and/or the T-cell redirecting multifunctional antibody, or the antigen-binding fragment thereof, are as defined in any one of claims 2 to 25 and/or 26 to 28, respectively.

52. The kit for use according to claim 50 or 51, wherein the immune checkpoint modulator and/or the T-cell redirecting multifunctional antibody, or the antigen-binding fragment thereof, are provided in the same composition or in distinct compositions.

53. The kit for use according to any one of claims 50 to 52, wherein the T-cell redirecting multifunctional antibody, or the antigen-binding fragment thereof, is provided in single doses, wherein each single dose does not exceed 1mg, preferably each single dose does not exceed 0.9 mg, more preferably each single dose does not exceed 0.8 mg, even more preferably each single dose does not exceed 0.75 mg and most preferably each single dose does not exceed 0.5 mg.

54. The kit for use according to any one of claims 50 to 53, further comprising
(iii) a glucocorticoid.

55. The kit for use according to claim 54, wherein the glucocorticoid is selected from the group consisting of prednisone, prednisolone, methylprednisolone, triamcinolone, betamethasone, dexamethasone, cortisone acetate, prednylidene, deflazacort, cloprednole, fluocortolone and budenoside, most preferably the glucocorticoid is dexamethasone.

56. The kit for use according to any one of claims 50 to 55, wherein the kit further comprises a package insert or label with directions to treat cancer by using a combination of (i) the immune checkpoint modulator and (ii) the antibody, or antigen-binding fragment thereof, and, optionally, (iii) the glucocorticoid.

57. The kit for use according to claim 56, wherein the directions include administration regimens as defined in any one of claims 29 –37, 40 –44, and 47 –49.

58. 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, wherein the T cell surface antigen is CD3;

(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,

wherein the immune checkpoint modulator inhibits CTLA-4.

59. The composition according to claim 58, wherein the immune checkpoint modulator and/or the T-cell redirecting multifunctional antibody, or the antigen-binding fragment thereof, are as defined in any one of claims 2 to 25 and/or 26 to 28, respectively.

60. The composition according to claim 58 or 59, further comprising

(iii) a glucocorticoid.

61. The composition according to claim 60, wherein the glucocorticoid is selected from the group consisting of prednisone, prednisolone, methylprednisolone, triamcinolone, betamethasone, dexamethasone, cortisone acetate, prednylidene, deflazacort, cloprednole, fluocortolone and budenoside, most preferably the glucocorticoid is dexamethasone.

62. The composition according to any one of claims 58 to 61, wherein the composition comprises a pharmaceutically acceptable carrier.

63. The composition according to any one of claims 58 to 62 for use in medicine.

64. The composition for use according to claim 63 for use in the therapeutic treatment of a cancer disease, in particular in a human subject.

65. A medicament for therapeutically treating cancer or initiating, enhancing or prolonging an anti-tumor-response in a subject in need thereof, 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, wherein the T cell surface antigen is CD3;

(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,

wherein the immune checkpoint modulator inhibits CTLA-4.

66. The medicament according to claim 65, wherein the immune checkpoint modulator and/or the T-cell redirecting multifunctional antibody, or the antigen-binding fragment thereof, are as defined in any of claims 2 to 25 and 26 to 28, respectively.

67. The medicament according to claim 65 or 66, wherein the immune checkpoint modulator and/or the T-cell redirecting multifunctional antibody, or the antigen-binding fragment thereof, are provided in the same composition or in distinct compositions.

68. The medicament according to any one of claims 65 to 67, wherein

(iii) a glucocorticoid is further administered to the subject.

69. The medicament according to claim 68, wherein the glucocorticoid is selected from the group consisting of prednisone, prednisolone, methylprednisolone, triamcinolone, betamethasone, dexamethasone, cortisone acetate, prednylidene, deflazacort, cloprednole, fluocortolone and budenoside, most preferably the glucocorticoid is dexamethasone.

70. The medicament according to any one of claims 65 to 69, wherein the subject is a human subject diagnosed with cancer.

71. The medicament according to any one of claims 65 to 70, wherein (i) the immune checkpoint modulator, and/or (ii) the T-cell redirecting multifunctional antibody, or the antigen binding fragment thereof, and/or, optionally, (iii) the glucocorticoid is/are administered as defined in any one of claims 29 –37, 40 –44, and 47 –49.

72. A medicament of prolonging T-cell activation in a subject, comprising 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, wherein the T cell surface antigen is CD3;

(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,

wherein the immune checkpoint modulator inhibits CTLA-4.

73. A medicament for therapeutically treating cancer, wherein

(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, wherein the T cell surface antigen is CD3;

(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

are administered in combination, and wherein the immune checkpoint modulator inhibits CTLA-4.

74. The medicament according to claim 73, wherein the immune checkpoint modulator and/or the T-cell redirecting multifunctional antibody, or the antigen-binding fragment thereof, are as defined in any one of claims 2 to 25 and/or 26 to 28, respectively.

75. The medicament according to claim 73 or 74, wherein the immune checkpoint modulator and/or the T-cell redirecting multifunctional antibody, or the antigen-binding fragment thereof, are provided in the same composition or in distinct compositions.

76. The medicament according to any one of claims 73 to 75, wherein

(iii) a glucocorticoid is further administered to the subject.

77. The medicament according to claim 76, wherein the glucocorticoid is selected from the group consisting of prednisone, prednisolone, methylprednisolone, triamcinolone, betamethasone, dexamethasone, cortisone acetate, prednylidene, deflazacort,

cloprednole, fluocortolone and budenoside, most preferably the glucocorticoid is dexamethasone.

78. The medicament according to any one of claims 73 to 77, wherein the immune checkpoint modulator and the T-cell redirecting multifunctional antibody, or an antigen binding fragment thereof, are administered to a human subject.

79. The medicament according to any one of claims 73 to 78, wherein (i) the immune checkpoint modulator, and/or (ii) the T-cell redirecting multifunctional antibody, or the antigen binding fragment thereof, and/or, optionally, (iii) the glucocorticoid is/are administered as defined in any one of claims 29 –37, 40 –44, and 47 –49.

80. A combination method for use in therapeutic treatment of a cancer disease, comprising combining

(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, wherein the T cell surface antigen is CD3;

(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;

wherein the immune checkpoint modulator inhibits CTLA-4.