

00/075348) and Chi Lob 7 /4, a chimeric IgG1 antibody (US 2009/0074711). Furthermore, an antagonistic CD40 antibody has been disclosed, lucatumumab, a human IgG1 antibody (WO 02/028481).

5 CD137 (4-1BB) is also a member of the TNFR family. CD137 is a co-stimulatory molecule on CD8⁺ and CD4⁺ T cells, regulatory T cells (Tregs), Natural Killer T cells (NK(T) cells), B cells and neutrophils. On T cells, CD137 is not constitutively expressed, but induced upon T-cell receptor (TCR) activation (for example, on tumor infiltrating lymphocytes (TILs) (Gros et al., J. Clin Invest 2014;124(5):2246-59)). Stimulation via its natural ligand 4-1BBL or agonist antibodies leads to
10 signaling using TRAF-2 and TRAF-1 as adaptors. Early signaling by CD137 involves K-63 poly-ubiquitination reactions that ultimately result in activation of the nuclear factor (NF)-κB and mitogen-activated protein (MAP)-kinase pathways. Signaling leads to increased T cell co-stimulation, proliferation, cytokine production, maturation and prolonged CD8⁺ T-cell survival. Agonistic antibodies against CD137 have been shown to promote anti-tumor control by T cells in various pre-
15 clinical models (Murillo et al., Clin Cancer Res 2008;14(21):6895-906). Antibodies stimulating CD137 can induce survival and proliferation of T cells, thereby enhancing the anti-tumor immune response. Antibodies stimulating CD137 have been disclosed in the prior art, and include urelumab, a human IgG4 antibody (AU 2004279877) and utomilumab, a human IgG2 antibody (Fisher et al., 2012, Cancer Immunol. Immunother. 61: 1721-1733).

20 Westwood JA, et al., Leukemia Research 38 (2014), 948-954 discloses "Combination anti-CD137 and anti-CD40 antibody therapy in murine myc-driven hematological cancers". WO 2018/011421 provides binding agents, such as bispecific antibodies, binding human CD40 and binding human CD137.

25 However, despite these advances in the art there is a considerable need for improved therapies targeting CD40 and CD137.

Summary

30 In one aspect, the present disclosure provides a use of a binding agent in the manufacture of a medicament for reducing or preventing progression of a tumor or treating cancer in a subject, wherein the binding agent is to be administered to said subject in a suitable amount, and wherein the binding agent comprises a first binding region binding to human CD40, such as human CD40 comprising the sequence set forth in SEQ ID NO: 36, and a second binding region binding to human CD137, such as human CD137 comprising the sequence set forth in SEQ ID NO: 38.

35 In another aspect, the present disclosure provides a composition comprising a binding agent comprising a first binding region binding to human CD40 and a second binding region binding to human CD137,

wherein the amount of binding agent in the composition is between 3-200 mg or 20×10^{-9} - 1350×10^{-9} mol. In yet another aspect, the present disclosure provides a use of the composition as described herein in the manufacture of a medicament for reducing or preventing progression of a tumor or treating cancer in a subject.

5

In a first example, the present disclosure provides a binding agent for use in a method for reducing or preventing progression of a tumor or treating cancer in a subject, said method comprising administering to said subject the binding agent in a suitable amount, wherein the binding agent comprises a first binding region binding to human CD40, such as human CD40 comprising the sequence set forth in SEQ ID NO: 36, and a second binding region binding to human CD137, such as human CD137 comprising the sequence set forth in SEQ ID NO: 38.

10

In one example of the first example, the suitable amount of the binding agent is a therapeutically effective and safe amount. For example, the suitable amount of the binding agent is about 0.04-2.5

mg/kg body weight or about 3-200 mg in total; and/or about 0.25×10^{-9} - 16.9×10^{-9} mol/kg body weight or about 20×10^{-9} - 1350×10^{-9} mol in total.

5 In one example of the first example, the binding agent is administered systemically, preferably intravenously.

10 In a second example, the present disclosure provides a composition comprising a binding agent comprising a first binding region binding to human CD40 and a second binding region binding to human CD137, wherein the amount of binding agent in the composition is between about 3-200 mg or about 20×10^{-9} - 1350×10^{-9} mol.

In a third example, the present disclosure provides a composition of the second example for use in a method for reducing or preventing progression of a tumor or treating cancer in a subject.

15 In a fourth example, the present disclosure provides a method for reducing or preventing progression of a tumor or treating cancer in a subject, said method comprising administering to said subject a binding agent in a suitable amount, wherein the binding agent comprises a first binding region binding to human CD40, such as human CD40 comprising the sequence set forth in SEQ ID NO: 36, and a second binding region binding to human CD137, such as human CD137 comprising the sequence set forth in SEQ ID
20 NO: 38.

25 In a fifth example, the present disclosure provides a method for reducing or preventing progression of a tumor or treating cancer in a subject, said method comprising administering to said subject a composition comprising binding agent in an amount between about 3-200 mg or about 20×10^{-9} - 1350×10^{-9} mol, wherein the binding agent comprises a first binding region binding to human CD40, such as human CD40 comprising the sequence set forth in SEQ ID NO: 36, and a second binding region binding to human CD137, such as human CD137 comprising the sequence set forth in SEQ ID NO: 38.

CLAIMS

1. Use of a binding agent in the manufacture of a medicament for reducing or preventing progression of a tumor or treating cancer in a subject, wherein the binding agent is to be administered to said subject in a suitable amount, and wherein the binding agent comprises a first binding region binding to human CD40, such as human CD40 comprising the sequence set forth in SEQ ID NO: 36, and a second binding region binding to human CD137, such as human CD137 comprising the sequence set forth in SEQ ID NO: 38.
2. The use of claim 1, wherein the suitable amount of the binding agent is a therapeutically effective and safe amount.
3. The use of any one of the preceding claims, wherein the suitable amount of the binding agent is 0.04-2.5 mg/kg body weight or 3-200 mg in total; and/or 0.25×10^{-9} - 16.9×10^{-9} mol/kg body weight or 20×10^{-9} - 1350×10^{-9} mol in total.
4. The use of any one of the preceding claims, wherein the binding agent is to be administered systemically, preferably intravenously.
5. The use of any one of the preceding claims, wherein
 - (I)
 - a) the first binding region comprises a heavy chain variable region (VH) comprising the CDR1, CDR2, and CDR3 sequences of SEQ ID NO: 7 or 9, and a light chain variable region (VL) comprising the CDR1, CDR2, and CDR3 sequences of SEQ ID NO: 8 or 10;
 - and
 - b) the second antigen-binding region comprises a heavy chain variable region (VH) comprising the CDR1, CDR2, and CDR3 sequences of SEQ ID NO: 17 or 19, and a light chain variable region (VL) comprising the CDR1, CDR2, and CDR3 sequences of SEQ ID NO: 18 or 20;
 - (II)
 - a) the first binding region comprises a heavy chain variable region (VH) comprising the CDR1, CDR2, and CDR3 sequences set forth in: SEQ ID NO: 1, 2, and 3, respectively, and a light chain variable region (VL) comprising the CDR1, CDR2, and CDR3 sequences set forth in: SEQ ID NO: 4, 5, and 6, respectively;
 - and

- b) the second antigen-binding region comprises a heavy chain variable region (VH) comprising the CDR1, CDR2, and CDR3 sequences set forth in: SEQ ID NO: 11, 12, and 13, respectively, and a light chain variable region (VL) comprising the CDR1, CDR2, and CDR3 sequences set forth in: SEQ ID NO: 14, 15, and 16, respectively;

5 (III)

- a) the first binding region comprises a heavy chain variable region (VH) comprising an amino acid sequence having at least 90%, at least 95%, at least 97%, at least 99%, or 100% sequence identity to SEQ ID NO: 7 or 9 and a light chain variable region (VL) region and comprising an amino acid sequence having at least 90%, at least 95%, at
10 least 97%, at least 99%, or 100% sequence identity to SEQ ID NO: 8 or 10;

- b) the second binding region comprises a heavy chain variable region (VH) comprising an amino acid sequence having at least 90%, at least 95%, at least 97%, at least 99%, or 25 100% sequence identity to SEQ ID NO: 17 or 19 and a light chain variable region (VL) region comprising an amino acid sequence having at least 90%, at least 95%, at least
15 97%, at least 99%, or 100% sequence identity to SEQ ID NO: 18 or 20;

(IV)

- a) the first binding region comprises a heavy chain variable region (VH) comprising the amino acid sequence set forth in SEQ ID NO: 7 or 9 and a light chain variable region (VL) region comprising the amino acid sequence set forth in SEQ ID NO: 8 or 10;

20 and

- b) the second binding region comprises a heavy chain variable region (VH) comprising the amino acid sequence set forth in SEQ ID NO: 17 or 19 and a light chain variable region (VL) region comprising the amino acid sequence set forth in SEQ ID NO: 18 or 20;

and/or

25 (V)

- a) the first binding region comprises a heavy chain variable region (VH) comprising the amino acid sequence set forth in SEQ ID NO: 9 and a light chain variable region (VL) region comprising the amino acid sequence set forth in SEQ ID NO: 10;

and

- b) the second binding region comprises a heavy chain variable region (VH) comprising the amino acid sequence set forth in SEQ ID NO: 19 and a light chain variable region (VL) region comprising the amino acid sequence set forth in SEQ ID NO: 20.
30

6. The use of any one of the preceding claims, wherein:

- 35 (i) the binding agent is a multispecific antibody, such as a bispecific antibody; and/or
(ii) the binding agent is in the format of a full-length antibody or an antibody fragment.

7. The use of claim 5 or 6, wherein each variable region comprises three complementarity determining regions (CDR1, CDR2, and CDR3) and four framework regions (FR1, FR2, FR3, and FR4), wherein optionally said complementarity determining regions and said framework regions are arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4.

8. The use of any one of claims 5-7, wherein:

(I) the binding agent comprises

- i) a polypeptide comprising, consisting of or consisting essentially of, said first heavy chain variable region (VH) and a first heavy chain constant region (CH), and
- ii) a polypeptide comprising, consisting of or consisting essentially of, said second heavy chain variable region (VH) and a second heavy chain constant region (CH);

(II) the binding agent comprises

- i) a polypeptide comprising said first light chain variable region (VL) and further comprising a first light chain constant region (CL), and
- ii) a polypeptide comprising said second light chain variable region (VL) and further comprising a second light chain constant region (CL);

and/or

(III) the binding agent is an antibody comprising a first binding arm and a second binding arm, wherein

the first binding arm comprises

- i) a polypeptide comprising said first heavy chain variable region (VH) and a first heavy chain constant region (CH), and
- ii) a polypeptide comprising said first light chain variable region (VL) and a first light chain constant region (CL);

and the second binding arm comprises

- iii) a polypeptide comprising said second heavy chain variable region (VH) and a second heavy chain constant region (CH), and
- iv) a polypeptide comprising said second light chain variable region (VL) and a second light chain constant region (CL).

9. The use of any one of the preceding claims, wherein the binding agent comprises

(I)

- i) a first heavy chain and light chain comprising said antigen-binding region capable of binding to CD40, and
- ii) a second heavy chain and light chain comprising said antigen-binding region capable of binding CD137;

and/or

(II)

- i) a first heavy chain and light chain comprising said antigen-binding region capable of binding to CD40, the first heavy chain comprising a first heavy chain constant region and the first light chain comprising a first light chain constant region; and
- ii) a second heavy chain and light chain comprising said antigen-binding region capable of binding CD137, the second heavy chain comprising a second heavy chain constant region and the second light chain comprising a second light chain constant region.

10. The use of claim 8 or 9, wherein:

(1) each of the first and second heavy chain constant regions (CH) comprises one or more of a constant heavy chain 1 (CH1) region, a hinge region, a constant heavy chain 2 (CH2) region and a constant heavy chain 3 (CH3) region, preferably at least a hinge region, a CH2 region and a CH3 region;

(2) each of the first and second heavy chain constant regions (CHs) comprises a CH3 region and wherein the two CH3 regions comprise asymmetrical mutations;

(3) in said first heavy chain constant region (CH) at least one of the amino acids in a position corresponding to a position selected from the group consisting of T366, L368, K370, D399, F405, Y407, and K409 in a human IgG1 heavy chain according to EU numbering has been substituted, and in said second heavy chain constant region (CH) at least one of the amino acids in a position corresponding to a position selected from the group consisting of T366, L368, K370, D399, F405, Y407, and K409 in a human IgG1 heavy chain according to EU numbering has been substituted, and wherein said first and said second heavy chains are not substituted in the same positions;

and/or

(4) (i) the amino acid in the position corresponding to F405 in a human IgG1 heavy chain according to EU numbering is L in said first heavy chain constant region (CH), and the amino acid in the position corresponding to K409 in a human IgG1 heavy chain according to EU numbering is R in said second heavy chain constant region (CH), or (ii) the amino acid in the position corresponding to K409 in a human IgG1 heavy chain according to EU numbering is R in said first heavy chain, and the amino acid in the position corresponding to F405 in a human IgG1 heavy chain according to EU numbering is L in said second heavy chain.

11. The use of any of the preceding claims, wherein said binding agent induces Fc-mediated effector function to a lesser extent compared to another antibody comprising the same first and second antigen binding regions and two heavy chain constant regions (CHs) comprising human IgG1 hinge, CH2 and CH3 regions, wherein optionally said first and second heavy chain constant

regions (CHs) are modified so that the antibody induces Fc-mediated effector function to a lesser extent compared to an antibody which is identical except for comprising non-modified first and second heavy chain constant regions (CHs), wherein optionally each of said non-modified first and second heavy chain constant regions (CHs) comprises the amino acid sequence set forth in SEQ ID NO: 21 or 29, wherein optionally said Fc-mediated effector function is measured by binding to Fcγ receptors, binding to C1q, or induction of Fe-mediated crosslinking of Fcγ receptors, wherein optionally said Fc-mediated effector function is measured by binding to C1q, wherein optionally said first and second heavy chain constant regions have been modified so that binding of C1q to said antibody is reduced compared to a wild-type antibody, preferably reduced by at least 70%, at least 80%, at least 90%, at least 95%, at least 97%, or 100%, wherein C1q binding is preferably determined by ELISA.

12. The use of any one of claims 8-11, wherein in at least one of said first and second heavy chain constant regions (CH), one or more amino acids in the positions corresponding to positions L234, L235, D265, N297, and P331 in a human IgG1 heavy chain according to EU numbering, are not L, L, D, N, and P, respectively.

13. The use of claim 12, wherein:

(a) the positions corresponding to positions L234 and L235 in a human IgG1 heavy chain according to EU numbering are F and E, respectively, in said first and second heavy chains; and/or

(b) the positions corresponding to positions L234, L235, and D265 in a human IgG1 heavy chain according to EU numbering are F, E, and A, respectively, in said first and second heavy chain constant regions (HCs); and/or

(c) the positions corresponding to positions L234 and L235 in a human IgG1 heavy chain according to EU numbering of both the first and second heavy chain constant regions are F and E, respectively, and wherein (i) the position corresponding to F405 in a human IgG1 heavy chain according to EU numbering of the first heavy chain constant region is L, and the position corresponding to K409 in a human IgG1 heavy chain according to EU numbering of the second heavy chain is R, or (ii) the position corresponding to K409 in a human IgG1 heavy chain according to EU numbering of the first heavy chain constant region is R, and the position corresponding to F405 in a human IgG1 heavy chain according to EU numbering of the second heavy chain is L; and/or

(d) the positions corresponding to positions L234, L235, and D265 in a human IgG1 heavy chain according to EU numbering of both the first and second heavy chain constant regions are F, E, and A, respectively, and wherein (i) the position corresponding to F405 in a human IgG1 heavy chain according to EU numbering of the first heavy chain constant region is L, and the position

corresponding to K409 in a human IgG1 heavy chain according to EU numbering of the second heavy chain constant region is R, or (ii) the position corresponding to K409 in a human IgG1 heavy chain according to EU numbering of the first heavy chain is R, and the position corresponding to F405 in a human IgG1 heavy chain according to EU numbering of the second heavy chain is L.

14. The use of any one of claims 8-13, wherein:

(A) the constant region of said first and/or second heavy chain comprises or consists essentially of or consists of an amino acid sequence selected from the group consisting of

- a) the sequence set forth in SEQ ID NO: 21 or 29 [IgG1-FC];
- b) a subsequence of the sequence in a), such as a subsequence, wherein 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 consecutive amino acids has/have been deleted, starting from the N-terminus or C-terminus of the sequence defined in a); and
- c) a sequence having at most 10 substitutions, such as at most 9 substitutions, at most 8, at most 7, at most 6, at most 5, at most 4, at most 3, at most 2 substitutions or at most 1 substitution, compared to the amino acid sequence defined in a) or b);

or

(B) the constant region of said first or second heavy chain, such as the second heavy chain, comprises or consists essentially of or consists of an amino acid sequence selected from the group consisting of

- a) the sequence set forth in SEQ ID NO: 22 or 30 [IgG1-F405L];
- b) a subsequence of the sequence in a), such as a subsequence, wherein 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 consecutive amino acids has/have been deleted, starting from the N-terminus or C-terminus of the sequence defined in a); and
- c) a sequence having at most 9 substitutions, such as at most 8, at most 7, at most 6, at most 5, at most 4, at most 3, at most 2 substitutions or at most 1 substitution, compared to the amino acid sequence defined in a) or b);

or

(C) the constant region of said first or second heavy chain, such as the first heavy chain comprises or consists essentially of or consists of an amino acid sequence selected from the group consisting of

- a) the sequence set forth in SEQ ID NO: 23 or 31 [IgG1-F409R];
- b) a subsequence of the sequence in a), such as a subsequence, wherein 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 consecutive amino acids has/have been deleted, starting from the N-terminus or C-terminus of the sequence defined in a); and

c) a sequence having at most 10 substitutions, such as at most 9 substitutions, at most 8, at most 7, at most 6, at most 5, at most 4 substitutions, at most 3, at most 2 substitutions or at most 1 substitution, compared to the amino acid sequence defined in a) or b);

or

(D) the constant region of said first and/or second heavy chain comprises or consists essentially of or consists of an amino acid sequence selected from the group consisting of

a) the sequence set forth in SEQ ID NO: 24 or 32 [IgG1-Fc_FEA];

b) a subsequence of the sequence in a), such as a subsequence, wherein 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 consecutive amino acids has/have been deleted, starting from the N-terminus or C-terminus of the sequence defined in a); and

c) a sequence having at most 7 substitutions, such as at most 6 substitutions, at most 5, at most 4, at most 3, at most 2 substitutions or at most 1 substitution, compared to the amino acid sequence defined in a) or b);

and/or

(E) the constant region of said first and/or second heavy chain, such as the second heavy chain, comprises or consists essentially of or consists of an amino acid sequence selected from the group consisting of

a) the sequence set forth in SEQ ID NO: 25 or 33[IgG1-Fc_FEAL];

b) a subsequence of the sequence in a), such as a subsequence, wherein 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 consecutive amino acids has/have been deleted, starting from the N-terminus or C-terminus of the sequence defined in a); and

c) a sequence having at most 6 substitutions, such as at most 5 substitutions, at most 4 substitutions, at most 3, at most 2 substitutions or at most 1 substitution, compared to the amino acid sequence defined in a) or b);

and/or

(F) the constant region of said first and/or second heavy chain, such as the first heavy chain, comprises or consists essentially of or consists of an amino acid sequence selected from the group consisting of

a) the sequence set forth in SEQ ID NO: 26 or 34 [IgG1-Fc_FEAR];

b) a subsequence of the sequence in a), such as a subsequence, wherein 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 consecutive amino acids has/have been deleted, starting from the N-terminus or C-terminus of the sequence defined in a); and

c) a sequence having at most 6 substitutions, such as at most 5 substitutions, at most 4, at most 3, at most 2 substitutions or at most 1 substitution, compared to the amino acid sequence defined in a) or b).

15. The use of any one of the preceding claims, wherein:

(i) said binding agent comprises a kappa (κ) light chain constant region;
(ii) said binding agent comprises a lambda (λ) light chain constant region;
(iii) said first light chain constant region is a kappa (κ) light chain constant region or a lambda (λ) light chain constant region;
5 (iv) said second light chain constant region is a lambda (λ) light chain constant region or a kappa (κ) light chain constant region; and/or
(v) said first light chain constant region is a kappa (κ) light chain constant region and said second light chain constant region is a lambda (λ) light chain constant region or said first light chain constant region is a lambda (λ) light chain constant region and said second light chain constant
10 region is a kappa (κ) light chain constant region.

16. The use of claim 15, wherein

(A) the kappa (κ) light chain comprises an amino acid sequence selected from the group consisting of

- 15 a) the sequence set forth in SEQ ID NO: 27,
b) a subsequence of the sequence in a), such as a subsequence, wherein 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 consecutive amino acids has/have been deleted, starting from the N-terminus or C-terminus of the sequence defined in a); and
c) a sequence having at most 10 substitutions, such as at most 9 substitutions, at most 8, at
20 most 7, at most 6, at most 5, at most 4 substitutions, at most 3, at most 2 substitutions or at most 1 substitution, compared to the amino acid sequence defined in a) or b);

and/or

(B) the lambda (λ) light chain comprises an amino acid sequence selected from the group consisting of

- 25 a) the sequence set forth in SEQ ID NO: 28,
b) a subsequence of the sequence in a), such as a subsequence, wherein 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 consecutive amino acids has/have been deleted, starting from the N-terminus or C-terminus of the sequence defined in a); and
c) a sequence having at most 10 substitutions, such as at most 9 substitutions, at most 8, at
30 most 7, at most 6, at most 5, at most 4 substitutions, at most 3, at most 2 substitutions or at most 1 substitution, compared to the amino acid sequence defined in a) or b).

17. The use of any one of the preceding claims, wherein:

(1) the binding agent is of an isotype selected from the group consisting of IgG1, IgG2, IgG3,
35 and IgG4;

(2) the binding agent is a full-length IgG1 antibody;

(3) the binding agent is an antibody of the IgG1m(f) allotype; and/or

(4) the subject is a human subject.

18. The use of any one of the preceding claims, wherein the tumor or cancer is a solid tumor,
wherein optionally the tumor or cancer is selected from the group consisting of melanoma,
5 ovarian cancer, lung cancer (*e.g.*, non-small cell lung cancer (NSCLC)), colorectal cancer, head
and neck cancer, gastric cancer, breast cancer, renal cancer, urothelial cancer, bladder cancer,
esophageal cancer, pancreatic cancer, hepatic cancer, thymoma and thymic carcinoma, brain
cancer, glioma, adrenocortical carcinoma, thyroid cancer, other skin cancers, sarcoma, multiple
10 myeloma, leukemia, lymphoma, myelodysplastic syndromes, ovarian cancer, endometrial
cancer, prostate cancer, penile cancer, cervical cancer, Hodgkin's lymphoma, non-Hodgkin's
lymphoma, Merkel cell carcinoma and mesothelioma,
wherein optionally the tumor or cancer is selected from the group consisting of lung cancer (*e.g.*,
non-small cell lung cancer (NSCLC)), melanoma, colorectal cancer, urothelial cancer (cancer
of the bladder, ureter, urethra, or renal pelvis), endometrial cancer (EC), breast cancer (*e.g.*,
15 triple negative breast cancer (TNBC)), squamous cell carcinoma of the head and neck (SCCHN)
(*e.g.*, cancer of the oral cavity, pharynx or larynx) and cervical cancer,
wherein optionally the tumor or cancer is selected from the group consisting of lung cancer,
melanoma, and colorectal cancer.

19. The use of claim 18, wherein:
(A) the cancer is a non-small cell lung cancer (NSCLC), such as a squamous or non-squamous
NSCLC wherein optionally the NSCLC does not have an epidermal growth factor (EGFR)-
sensitizing mutation and/or anaplastic lymphoma (ALK) translocation / ROS1 rearrangement,
and/or
25 the subject has received up to four prior systemic treatment regimens for advanced/metastatic
disease and has experienced disease progression on or after last prior systemic treatment, such
as disease progression determined by radiography, wherein optionally the subject has received
platinum-based chemotherapy, or the subject is not eligible for platinum-based therapy and has
alternative chemotherapy, *e.g.*, a treatment with gemcitabine-containing regimen, and/or
30 the subject has received prior treatment with checkpoint inhibitor(s), such as agent(s) targeting
PD-1/PD-L, such as a PD-1/PD-L1 inhibitor, and/or
the subject has experienced disease progression on or after last prior systemic treatment, such
as disease progression determined by radiography;
(B) the cancer is cutaneous, acral, or mucosal melanoma, wherein optionally the subject has
35 received up to four prior systemic treatments for advanced/metastatic disease and has
experienced disease progression on or after last prior systemic treatment, such as disease
progression determined by radiography, and/or

the subject has received prior treatment with checkpoint inhibitor(s), such as agent(s) targeting PD-1/PD-L, such as a PD-1/PD-L1 inhibitor;

or

(C) the cancer is colorectal cancer, wherein the subject has received up to four prior systemic treatments for advanced/metastatic disease and has experienced disease progression on or after last prior systemic treatment, such as disease progression determined by radiography, and/or the subject has received 5-FU-based therapy, and/or the subject has not received treatment with an ICP inhibitor.

20. The use of any one of the preceding claims, wherein:

(a) the binding agent is to be administered in at least one treatment cycle, each treatment cycle being three weeks (21 days);

(b) one dose is to be administered every third week (1Q3W);

(c) one dose is to be administered on day 1 of each treatment cycle; and/or

(d) each dose is infused over a minimum of 30 minutes, such as over a minimum of 60 minutes, a minimum of 90 minutes, a minimum of 120 minutes or a minimum of 240 minutes.

21. A composition comprising a binding agent comprising a first binding region binding to human CD40 and a second binding region binding to human CD137, wherein the amount of binding agent in the composition is between 3-200 mg or 20×10^{-9} - 1350×10^{-9} mol.

22. The composition of claim 21, wherein:

(i) the composition comprises about 40 mg of said binding agent;

(ii) the binding agent is as defined in any one of claims 1-21.

(iii) the composition is for systemic administration;

(iv) the composition is for injection or infusion, such as intravenous injection or infusion;

(v) the binding agent is in aqueous solution, such in 0.9% NaCl (saline), at a volume of 50-500 ml, such as 100-250 ml; and/or

(vi) the composition is a dosage unit form.

23. Use of the composition of claim 21 or 22 in the manufacture of a medicament for reducing or preventing progression of a tumor or treating cancer in a subject.