The natural ligand of CD40, designated CD154 or CD40L, is mainly expressed on mature T lymphocytes. CD40L-mediated signalling triggers several biological events, including immune cell activation, proliferation, and production of cytokines and chemokines. Thus, stimulation via the CD40 receptor enhances cellular and immune functions. Its role in cell-mediated immune responses is well known. For example, the activation of dendritic cells via CD40 stimulation, induces activation of effector T cells. Treatment with CD40 agonists may thus provide the means to redirect the immune response and expand effector T cells directed to tumour

Antitumour effects have been reported for some anti-CD40 antibodies, with several mechanisms having been identified. An indirect effect is observed for CD40 negative tumors, involving the activation of antigen presenting cells, in particular increased activity by tumor specific cytotoxic T lymphocytes and natural killer cells (NK cells). Both indirect and direct antitumor mechanisms are observed for CD40 positive tumours, wherein the CD40 antibody binding to tumour cells induces cell apoptosis. These mechanisms for anti-tumour activity may be complemented by antibody mediated cellular cytotoxicity (ADCC). However, administration of anti-CD40 antibodies has also been associated with adverse side effects, such as cytokine release syndrome.

Accordingly there remains a need for improved cancer therapies, in particular anti-CD40 antibodies suitable for use in treating solid tumours and combination therapies thereof.

Summary

A first aspect of the invention provides a combination therapy for use in treating a solid tumour in a subject comprising (a) an antibody, or antigen-binding portion thereof, that specifically binds to CD40, and (b) a further immunotherapeutic agent with efficacy in the treatment of cancer, which agent is not an anti-CD40 antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 competes for binding to human CD40 with an antibody which comprises the light chain variable region of SEQ ID NO: 7 and the heavy chain variable region of SEQ ID NO: 8, and wherein the further immunotherapeutic agent specifically binds to an immune checkpoint molecule other than CD40.

In one example, the solid tumour is selected from the groups consisting of an adenoma, a blastoma, a carcinoma, a desmoid tumour, a desmopolastic small round cell tumour, an endocrine tumour, a germ cell tumour, a lymphoma, a sarcoma, a Wilms tumour, a lung tumour, a colon tumour, a lymph tumour, a breast tumour and a melanoma. For example, the solid tumour may be a melanoma, such as a metastatic melanoma.

In one example, the antibody or antigen-binding portion thereof that specifically binds to CD40 comprises or consists of an intact antibody.

In an alternative example, the antibody or antigen-binding portion thereof that specifically binds to CD40 comprises or consists of an antigen-binding fragment selected from the group consisting of: an Fv fragment (such as a single chain Fv fragment, or a disulphide-bonded Fv fragment), and a Fab-like fragment (such as a Fab fragment; a Fab' fragment or a $F(ab)_2$ fragment).

In one example, the antibody or antigen-binding portion thereof is human or humanised.

In one example, the antibody or antigen-binding portion thereof that specifically binds to CD40 comprises at least one CDR selected from SEQ ID NOs 1, 2, 3, 4, 5 and 6, or a 'core' CDR sequence thereof (see Example 1 below for sequence details).

Thus, the antibody or antigen-binding portion thereof that specifically binds to CD40 comprises the CDR sequences of SEQ ID NOs: 1, 2 and 3 and/or SEQ ID NOs: 4, 5 and 6, or a 'core' CDR sequence thereof.

For example, the antibody or antigen-binding portion thereof that specifically binds to CD40 comprises the light chain variable region of SEQ ID NO: 7 and/or the heavy chain variable region of SEQ ID NO: 8.

In one example, the antibody or antigen-binding portion thereof that specifically binds to CD40 comprises the light chain constant region of SEQ ID NO: 11 and/or the heavy chain constant region of SEQ ID NO: 12.

Thus, the antibody or antigen-binding portion thereof that specifically binds to CD40 comprises or consists of the light chain of SEQ ID NO: 7 plus SEQ ID NO:11, and/or the heavy chain of SEQ ID NO: 8 plus SEQ ID NO:12.

The combination therapies as disclosed herein additionally comprise a further immunotherapeutic agent, effective in the treatment of cancer, that specifically binds to an immune checkpoint molecule other than CD40. It will be appreciated that the therapeutic benefit of the further immunotherapeutic agent may be mediated by attenuating the function of an inhibitory immune checkpoint molecule and/or by activating the function of a stimulatory immune checkpoint molecule.

In another example, the further immunotherapeutic agent is selected from the groups consisting of:

(a) an immunotherapeutic agent that binds PD-1;
(b) an immunotherapeutic agent that binds CTLA-4;
(c) an immunotherapeutic agent that binds OX40; and
(d) an immunotherapeutic agent that binds CD137.

Thus, the further immunotherapeutic agent may be a PD1 inhibitor, such as an anti-PD1 antibody, or antigen-binding fragment thereof capable of inhibiting PD1 function (for example, Nivolumab, Pembrolizumab, Lambrolizumab, Pidilzumab and AMP-224). Alternatively, the PD1 inhibitor may comprise or consist of an anti-PD-L1 antibody, or antigen-binding fragment thereof capable of inhibiting PD1 function (for example, MEDI-4736 and MPDL3280A).

In another example, the further immunotherapeutic agent is a CTLA-4 inhibitor, such as an anti-CTLA-4 antibody or antigen-binding portion thereof.

In a further example, the further immunotherapeutic agent activates OX40, such as an agonistic anti-OX40 antibody or antigen-binding portion thereof.

In a still further example, the further immunotherapeutic agent activates CD137, such as an agonistic anti-CD137 antibody or antigen-binding portion thereof

It will be appreciated by persons skilled in the art that the presence of the two active agents (as detailed above) may provide a synergistic benefit in the treatment of a solid tumour in a subject. By "synergistic" we include that the therapeutic effect of the two agents in combination (*e.g.* as determined by reference to the rate of growth or the size of the tumour) is greater than the additive therapeutic effect of the two agents administered

on their own. Such synergism can be identified by testing the active agents, alone and in combination, in a relevant cell line model of the solid tumour.

Optionally, the combination therapy further comprises a third immunotherapeutic agent with efficacy in the treatment of cancer.

For example, the combination therapy may comprise (a) an antibody, or antigen-binding portion thereof, that specifically binds to CD40, (b) an antibody, or antigen-binding portion thereof, that specifically binds to PD1 or PD-L1, and (c) an antibody, or antigen-binding portion thereof, that specifically binds to CTLA-4.

In a second aspect, there is provided an antibody, or antigen-binding portion thereof, that specifically binds to CD40 for use in the treatment of a solid tumour, wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 competes for binding to human CD40 with an antibody which comprises the light chain variable region of SEQ ID NO: 7 and the heavy chain variable region of SEQ ID NO: 8, and wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 is for use in combination with a further immunotherapeutic agent with efficacy in the treatment of cancer, which agent specifically binds to an immune checkpoint molecule other than CD40.

In one example, there is provided an antibody, or antigen-binding portion thereof, that specifically binds to CD40 for use in a method of treating a solid tumour, wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 competes for binding to human CD40 with an antibody which comprises the light chain variable region of SEQ ID NO: 7 and the heavy chain variable region of SEQ ID NO: 8, and wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 is for use in combination with a further immunotherapeutic agent with efficacy in the treatment of cancer, which agent is not an anti-CD40 antibody or antigen-binding fragment thereof.

In one example, the antibody or antigen-binding portion thereof that specifically binds to CD40 is as discussed above in relation to the first aspect of the invention.

In one example, the further immunotherapeutic agent with efficacy in the treatment of cancer is as discussed above in relation to the first aspect of the invention.

In a third aspect, there is provided use of an antibody, or antigen-binding portion thereof, that specifically binds to CD40 in the preparation of a medicament for treating a solid tumour in a subject, wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 competes for binding to human CD40 with an antibody which comprises the light chain variable region of SEQ ID NO: 7 and the heavy chain variable region of SEQ ID NO: 8. and wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 is to be used in combination with a further immunotherapeutic agent with efficacy in the treatment of cancer, which agent specifically binds to an immune checkpoint molecule other than CD40.

In one example, there is provided the use of an antibody, or antigen-binding portion thereof, that specifically binds to CD40 in the preparation of a medicament for treating a solid tumour, wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 competes for binding to human CD40 with an antibody which comprises the light chain variable region of SEQ ID NO: 7 and the heavy chain variable region of SEQ ID NO: 8, and wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 is for use in combination with a further immunotherapeutic agent with efficacy in the treatment of cancer, which agent is not an anti-CD40 antibody or antigen-binding fragment thereof.

In one example, the antibody or antigen-binding portion thereof that specifically binds to CD40 is as discussed above in relation to the first aspect of the invention.

In one example, the further immunotherapeutic agent with efficacy in the treatment of cancer is as discussed above in relation to the first aspect of the invention.

In a fourth aspect, there is provided a pharmaceutical composition comprising (a) an antibody, or antigen-binding portion thereof, that specifically binds to CD40, and (b) a further immunotherapeutic agent with efficacy in the treatment of cancer, which agent is not an anti-CD40 antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 competes for binding to human CD40 with an antibody which comprises the light chain variable region of SEQ ID NO: 7 and the heavy chain variable region of SEQ ID NO: 8, and wherein the further immunotherapeutic agent specifically binds to an immune checkpoint molecule other than CD40.

In another example, there is provided a pharmaceutical composition comprising (a) an antibody, or antigen-binding portion thereof, that specifically binds to CD40, and (b) a further immunotherapeutic agent with efficacy in the treatment of cancer, which agent is not an anti-CD40 antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 competes for binding to human CD40 with an antibody which comprises the light chain variable region of SEQ ID NO: 7 and the heavy chain variable region of SEQ ID NO: 8.

In one example, the antibody or antigen-binding portion thereof that specifically binds to CD40 is as discussed above in relation to the first aspect of the invention.

In one example, the further immunotherapeutic agent with efficacy in the treatment of cancer is as discussed above in relation to the first aspect of the invention.

In a fifth aspect, there is provided a kit for treating a solid tumour comprising (a) an antibody, or antigen-binding portion thereof, that specifically binds to CD40, and (b) a further immunotherapeutic agent with efficacy in the treatment of cancer, which agent is not an anti-CD40 antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 competes for binding to human CD40 with an antibody which comprises the light chain variable region of SEQ ID NO: 7 and the heavy

chain variable region of SEQ ID NO: 8, and wherein the further immunotherapeutic agent specifically binds to an immune checkpoint molecule other than CD40.

In one example, there is provided a kit for treating a solid tumour comprising (a) an antibody, or antigen-binding portion thereof, that specifically binds to CD40, and (b) a further immunotherapeutic agent with efficacy in the treatment of cancer, which agent is not an anti-CD40 antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 competes for binding to human CD40 with an antibody which comprises the light chain variable region of SEQ ID NO: 7 and the heavy chain variable region of SEQ ID NO: 8.

In one example, the antibody or antigen-binding portion thereof that specifically binds to CD40 is as discussed above in relation to the first aspect of the invention.

In one example, the further immunotherapeutic agent with efficacy in the treatment of cancer is as discussed above in relation to the first aspect of the invention.

In one example, there is provided a method for treating a solid tumour in a subject, the method comprising administering to the subject a therapeutically effect amount of (a) administering to the subject a therapeutically effect amount of an antibody, or antigen-binding portion thereof, that specifically binds to CD40, and (b) administering to

the subject a therapeutically effect amount of a further immunotherapeutic agent with efficacy in the treatment of cancer, which agent is not an anti-CD40 antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 competes for binding to human CD40 with an antibody which comprises the light chain variable region of SEQ ID NO: 7 and the heavy chain variable region of SEQ ID NO: 8.

In one example, the antibody or antigen-binding portion thereof that specifically binds to CD40 is as discussed above in relation to the first aspect of the invention.

In one example, the further immunotherapeutic agent with efficacy in the treatment of cancer is as discussed above in relation to the first aspect of the invention.

In a further example, steps (a) and (b) are carried out simultaneously or wherein step (b) is carried out between 24 hours and two weeks after step (a), between 24 hours and one week after step (a), between 24 and 72 hours after step (a), or between 24 and 48 hours after step (a).

In one example, step (a) comprises local administration of the antibody to the tumour site.

In one example, at least 30% of the amount of antibody administered in step (a) is retained at the tumour site at four hours after administration, preferably wherein at least 40% of the said amount is retained at the tumour site at four hours after administration.

In one example, the additional therapeutic agent of step (b) is formulated as a composition suitable for systemic administration with at least one pharmaceutically acceptable diluent or carrier.

In one example, step (a) is conducted on multiple separate occasions and step (b) is conducted such that exposure of the subject to the additional therapeutic agent is continuous for the duration of the method.

In one example, the subject is a human.

The inventors have also surprisingly shown that certain anti-CD40 antibodies are retained at the site of a solid tumour after administration to a subject. Thus, only a small proportion of the antibody escapes from the tumour site into the vascular or lymphatic circulation of the subject.

This results in a highly effective treatment, as well as reduced side-effects, enabling a lower dose of antibody to be used. These advantages are particularly apparent when such an antibody is locally administered to a tumour site in a subject, but may also be apparent when the antibody is systemically administered.

However, it will be appreciated by persons skilled in that art that the anti-CD40 antibody may also be administered to the subject systemically, *e.g.* intravenous or sub-cutaneous.

The inventors have also surprisingly shown that combining administration of an anti-CD40 antibody which is retained at the tumour site with the systemic administration to a subject of an additional therapeutic agent results in an improvement in the treatment effect, relative to the administration of the anti-CD40 antibody alone.

The disclosure therefore provides a method for treating a solid tumour in a subject, the method comprising (a) administering to the subject a therapeutically effective amount of an antibody that specifically binds to CD40 and that is retained at the tumour site following administration, and optionally (b) systemically administering to the subject a therapeutically effective amount of an additional therapeutic agent. Steps (a) and (b) may be carried out simultaneously. Alternatively steps (a) and (b) may be carried our sequentially provided step (a) precedes step (b). In step (a), the anti-CD40 antibody is preferably administered locally to the tumour.

The disclosure also provides a kit for treating a solid tumour in a subject, the kit comprising (a) a therapeutically effective amount of an antibody that specifically binds to CD40 and that is retained at the tumour site following administration and optionally (b) a therapeutically effective amount of an additional therapeutic agent that is suitable for systemic administration to a subject. The antibody that specifically binds to CD40 is preferably provided in a form suitable for local administration to a tumour.

CLAIMS

1. A combination therapy for use in the treatment of a solid tumour in a subject comprising (a) an antibody, or antigen-binding portion thereof, that specifically binds to CD40, and (b) a further immunotherapeutic agent with efficacy in the treatment of cancer, which agent is not an anti-CD40 antibody or antigen-binding fragment thereof,

wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 competes for binding to human CD40 with an antibody which comprises the light chain variable region of SEQ ID NO: 7 and the heavy chain variable region of SEQ ID NO: 8,

and wherein the further immunotherapeutic agent specifically binds to an immune checkpoint molecule other than CD40.

2. The combination therapy according to Claim 1,

wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 comprises light chain CDR sequences of SEQ ID NOs: 1, 2 and 3 and heavy chain CDR sequences of SEQ ID NOs: 4, 5 and 6,

and wherein the further immunotherapeutic agent is selected from the groups consisting of:

(a) an immunotherapeutic agent that binds PD-1;
(b) an immunotherapeutic agent that binds CTLA-4;
(c) an immunotherapeutic agent that binds OX40; and
(d) an immunotherapeutic agent that binds CD137.

3. The combination therapy according to Claim 2,

wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 comprises light chain CDR sequences of SEQ ID NOs: 1, 2 and 3 and heavy chain CDR sequences of SEQ ID NOs: 4, 5 and 6,

and wherein the further immunotherapeutic agent is an anti-PD-1 antibody which blocks the interaction between PD1 and PD-L1.

4. The combination therapy according to one of the preceding claims, wherein the combination therapy provides a synergistic benefit in the treatment of a solid tumour in a subject.

5. The combination therapy according to one of the preceding claims, wherein the solid tumour is selected from the groups consisting of an adenoma, a blastoma, a carcinoma, a desmoid tumour, a desmopolastic small round cell tumour, an endocrine tumour, a germ cell tumour, a lymphoma, a sarcoma, a Wilms tumour, a lung tumour, a colon tumour, a lymph tumour, a breast tumour and a melanoma.

6. The combination therapy to any one of the preceding claims, wherein the solid tumour is a melanoma.

7. The combination therapy according to any one of the preceding claims, wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 comprises or consists of an intact antibody.

8. The combination therapy according to any one of Claims 1 to 6, wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 comprises or consists of an antigen-binding fragment selected from the group consisting of: an Fv fragment and a Fab-like fragment.

9. The combination therapy according to any one of the preceding claims, wherein the antibody or antigen-binding portion thereof is human or humanised.

10. The combination therapy according to any one of the preceding claims, wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 comprises the light chain variable region of SEQ ID NO: 7 and/or the heavy chain variable region of SEQ ID NO: 8.

11. The combination therapy according to any one of the preceding claims, wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 comprises the light chain constant region of SEQ ID NO: 11 and/or the heavy chain constant region of SEQ ID NO: 12.

12. The combination therapy according to any one of the preceding claims, wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 comprises or consists of the light chain of SEQ ID NO: 7 plus SEQ ID NO:11, and/or the heavy chain of SEQ ID NO: 8 plus SEQ ID NO:12.

13. The combination therapy according to any one of Claims 3 to 12, wherein the anti-PD-1 antibody is selected from the group consisting of Nivolumab, Pembrolizumab, Lambrolizumab, Pidilzumab, and AMP-224.

14. An antibody, or antigen-binding portion thereof, that specifically binds to CD40 for use in the treatment of a solid tumour,

wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 competes for binding to human CD40 with an antibody which comprises the light chain variable region of SEQ ID NO: 7 and the heavy chain variable region of SEQ ID NO: 8,

and wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 is for use in combination with a further immunotherapeutic agent with efficacy in the treatment of cancer, which agent specifically binds to an immune checkpoint molecule other than CD40.

15. The antibody, or antigen-binding portion thereof, according to Claim 14, wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 comprises light chain CDR sequences of SEQ ID NOs: 1, 2 and 3 and heavy chain CDR sequences of SEQ ID NOs: 4, 5 and 6,

and wherein the further immunotherapeutic agent is selected from the groups consisting of:

(a) an immunotherapeutic agent that binds PD-1;
(b) an immunotherapeutic agent that binds CTLA-4;
(c) an immunotherapeutic agent that binds OX40; and
(d) an immunotherapeutic agent that binds CD137.

16. The antibody or antigen-binding portion thereof according to Claim 15,

wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 comprises light chain CDR sequences of SEQ ID NOs: 1, 2 and 3 and heavy chain CDR sequences of SEQ ID NOs: 4, 5 and 6,

and wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 is for use in combination with a further immunotherapeutic agent with efficacy in the treatment

of cancer, which agent is an anti-PD-1 antibody which blocks the interaction between PD1 and PD-L1.

17. The antibody or antigen-binding portion thereof according to Claim 14, wherein the antibody or antigen-binding portion thereof is as defined in any one of Claims 7 to 12.

18. The antibody or antigen-binding portion thereof according to Claim 16 or 17, wherein the further immunotherapeutic agent with efficacy in the treatment of cancer is as defined in Claim 13.

19. Use of an antibody, or antigen-binding portion thereof, that specifically binds to CD40 in the preparation of a medicament for treating a solid tumour in a subject,

wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 competes for binding to human CD40 with an antibody which comprises the light chain variable region of SEQ ID NO: 7 and the heavy chain variable region of SEQ ID NO: 8.

and wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 is to be used in combination with a further immunotherapeutic agent with efficacy in the treatment of cancer, which agent specifically binds to an immune checkpoint molecule other than CD40.

20. The use according to Claim 19, wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 comprises light chain CDR sequences of SEQ ID NOs: 1, 2 and 3 and heavy chain CDR sequences of SEQ ID NOs: 4, 5 and 6,

and wherein the further immunotherapeutic agent is selected from the groups consisting of:

(a) an immunotherapeutic agent that binds PD-1;
(b) an immunotherapeutic agent that binds CTLA-4;
(c) an immunotherapeutic agent that binds OX40; and
(d) an immunotherapeutic agent that binds CD137.

21. The use according to Claim 20,

wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 comprises light chain CDR sequences of SEQ ID NOs: 1, 2 and 3 and heavy chain CDR sequences of SEQ ID NOs: 4, 5 and 6,

and wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 is to be used in combination with a further immunotherapeutic agent with efficacy in the treatment of cancer, which agent is an anti-PD-1 antibody which blocks the interaction between PD1 and PD-L1.

22. The use according to Claim 19, wherein the antibody or antigen-binding portion thereof is as defined in any one of Claims 7 to 12.

23. The use according to Claim 21 or 22, wherein the further immunotherapeutic agent with efficacy in the treatment of cancer is as defined in Claim 13.

24. A pharmaceutical composition comprising (a) an antibody, or antigen-binding portion thereof, that specifically binds to CD40, and (b) a further immunotherapeutic agent with efficacy in the treatment of cancer, which agent is not an anti-CD40 antibody or antigen-binding fragment thereof,

wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 competes for binding to human CD40 with an antibody which comprises the light chain variable region of SEQ ID NO: 7 and the heavy chain variable region of SEQ ID NO: 8,

and wherein the further immunotherapeutic agent specifically binds to an immune checkpoint molecule other than CD40.

25. A pharmaceutical composition according to Claim 24, wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 comprises light chain CDR sequences of SEQ ID NOs: 1, 2 and 3 and heavy chain CDR sequences of SEQ ID NOs: 4, 5 and 6,

and wherein the further immunotherapeutic agent is selected from the groups consisting of:

(a) an immunotherapeutic agent that binds PD-1;
(b) an immunotherapeutic agent that binds CTLA-4;
(c) an immunotherapeutic agent that binds OX40; and

(d) an immunotherapeutic agent that binds CD137.

26. A pharmaceutical composition according to Claim 25, comprising (a) an antibody, or antigen-binding portion thereof, that specifically binds to CD40 and comprises light chain CDR sequences of SEQ ID NOs: 1, 2 and 3 and heavy chain CDR sequences of SEQ ID NOs: 4, 5 and 6, and (b) a further immunotherapeutic agent with efficacy in the treatment of cancer, which agent is an anti-PD-1 antibody which blocks the interaction between PD1 and PD-L1.

27. A pharmaceutical composition according to Claim 24, wherein the antibody or antigen-binding portion thereof is as defined in any one of Claims 7 to 12.

28. A pharmaceutical composition according to Claim 26 or 27, wherein the further immunotherapeutic agent with efficacy in the treatment of cancer is as defined in Claim 13.

29. A kit for treating a solid tumour comprising (a) an antibody, or antigen-binding portion thereof, that specifically binds to CD40, and (b) a further immunotherapeutic agent with efficacy in the treatment of cancer, which agent is not an anti-CD40 antibody or antigen-binding fragment thereof,

wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 competes for binding to human CD40 with an antibody which comprises the light chain variable region of SEQ ID NO: 7 and the heavy chain variable region of SEQ ID NO: 8,

and wherein the further immunotherapeutic agent specifically binds to an immune checkpoint molecule other than CD40.

30. A kit according to Claim 29, wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 comprises light chain CDR sequences of SEQ ID NOs: 1, 2 and 3 and heavy chain CDR sequences of SEQ ID NOs: 4, 5 and 6,

and wherein the further immunotherapeutic agent is selected from the groups consisting of:

(a) an immunotherapeutic agent that binds PD-1;
(b) an immunotherapeutic agent that binds CTLA-4;
(c) an immunotherapeutic agent that binds OX40; and
(d) an immunotherapeutic agent that binds CD137.

31. A kit according to Claim 30, comprising (a) an antibody, or antigen-binding portion thereof, that specifically binds to CD40 and comprises light chain CDR sequences of SEQ ID NOs: 1, 2 and 3 and heavy chain CDR sequences of SEQ ID NOs: 4, 5 and 6 and (b) a further immunotherapeutic agent with efficacy in the treatment of cancer, which agent is an anti-PD-1 antibody which blocks the interaction between PD1 and PD-L1.

32. A kit according to Claim 29, wherein the antibody or antigen-binding portion thereof is as defined in any one of Claims 7 to 12.

33. A kit according to Claim 31 or 32, wherein the further immunotherapeutic agent with efficacy in the treatment of cancer is as defined in Claim 13.

34. The combination therapy according to any one of Claims 1 to 13, or the use according to any one of Claims 19 to 23, wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 and the further immunotherapeutic agent are to be administered simultaneously or wherein the further immunotherapeutic agent is to be administered between 24 hours and two weeks, between 24 hours and one week, between 24 and 72 hours, or between 24 and 48 hours after the antibody or antigen-binding portion thereof that specifically binds to CD40 is to be administered.

35. The combination therapy according to any one of Claims 1 to 13 and 34, or the use according to any one of Claims 19 to 23 and 34, wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 is to be administered locally to the tumour site.

36. The combination therapy according to any one of Claims 1 to 13 and 34 to 35, or the use according to any one of Claims 19 to 23 and 34 to 35, wherein at least 30% of the amount of the antibody or antigen-binding portion thereof that specifically binds to CD40 to be administered is to be retained at the tumour site at four hours after administration, preferably wherein at least 40% of the said amount is to be retained at the tumour site at four hours after administration.

37. The combination therapy according to any one of Claims 1 to 13 and 34 to 36, or the use according to any one of Claims 19 to 23 and 34 to 36, wherein the further immunotherapeutic agent is formulated as a composition suitable for systemic administration with at least one pharmaceutically acceptable diluent or carrier.

38. The combination therapy according to any one of Claims 1 to 13 and 34 to 37, or the use according to any one of Claims 19 to 23 and 34 to 37, wherein the antibody or antigen-

binding portion thereof that specifically binds to CD40 is to be administered on multiple separate occasions and the further immunotherapeutic agent is to be administered such that exposure of the subject to the further immunotherapeutic agent is continuous for the duration of the use.

39. The combination therapy according to any one of Claims 1 to 13 and 34 to 38, or the use according to any one of Claims 19 to 23 and 34 to 38, wherein the subject is a human.