

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

In one aspect, there is provided use of a pharmaceutical composition comprising (a) an antibody, or antigen-binding portion thereof, that specifically binds to CD40, and (b) an immunotherapeutic agent that inhibits PD-1 function 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 immunotherapeutic agent that inhibits PD-1 function is an anti-PD-1 antibody or anti-PD-L1 antibody. In another 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 an immunotherapeutic agent that inhibits PD-1 function selected from the group consisting of an anti-PD-1 antibody and an anti-PD-L1 antibody. In another aspect, there is provided a pharmaceutical composition comprising (a) an antibody, or antigen-binding portion thereof, that specifically binds to CD40, and (b) an immunotherapeutic agent that inhibits PD-1 function, 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 immunotherapeutic agent that inhibits PD-1 function is an anti-PD-1 antibody or anti-PD-L1 antibody. In one example, there is provided 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.

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.

5 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 one example, 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.

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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.

25 In one example, the antibody or antigen-binding portion thereof that specifically binds to CD40 is as discussed above.

In one example, the further immunotherapeutic agent with efficacy in the treatment of cancer is as discussed above.

In one example, 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
5 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
10 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
15 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
20 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.

5 In one example, the further immunotherapeutic agent with efficacy in the treatment of cancer is as discussed above.

In one 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
10 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
15 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
20 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.

25 In one example, the antibody or antigen-binding portion thereof that specifically binds to CD40 is as discussed above.

In one example, the further immunotherapeutic agent with efficacy in the treatment of cancer is as discussed above.

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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
35 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.

5 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
10 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.

15 In one example, the further immunotherapeutic agent with efficacy in the treatment of cancer is as discussed above.

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)
20 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
5 light chain variable region of SEQ ID NO: 7 and the heavy chain variable region of SEQ ID NO: 8.

10 In one example, the antibody or antigen-binding portion thereof that specifically binds to CD40 is as discussed above.

In one example, the further immunotherapeutic agent with efficacy in the treatment of cancer is as discussed above.

15 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).

20 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.

25 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.

30 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.

CLAIMS

1. Use of a pharmaceutical composition comprising (a) an antibody, or antigen-binding portion thereof, that specifically binds to CD40, and (b) an immunotherapeutic agent that inhibits PD-1 function 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 immunotherapeutic agent that inhibits PD-1 function is an anti-PD-1 antibody or anti-PD-L1 antibody.

2. The use according to Claim 1, wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 comprises the following CDRs

V _L CDR1: CTGSSSNIGAGYNVY	[SEQ ID NO:1];
V _L CDR2: GNINRPS	[SEQ ID NO:2];
V _L CDR3: CAAWDKSISGLV	[SEQ ID NO:3];
V _H CDR1: GFTFSTYGMH	[SEQ ID NO:4];
V _H CDR2: GKGLEWLSYISGGSSYIFYADSVRGR	[SEQ ID NO:5]; and
V _H CDR3: CARILRGGSGMDL	[SEQ ID NO:6].

3. The use according to Claim 2, wherein the immunotherapeutic agent that inhibits PD-1 function is an anti-PD-1 antibody which blocks the interaction between PD1 and PD-L1.

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

5. The use 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 desmoplastic 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 use to any one of the preceding claims, wherein the solid tumour is a melanoma.

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

10. The use 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 the heavy chain variable region of SEQ ID NO: 8.

11. The use 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 the heavy chain constant region of SEQ ID NO: 12.

12. The use 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 the heavy chain of SEQ ID NO: 8 plus SEQ ID NO:12.

13. The use 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, Pidilizumab, and AMP-224.

14. 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 an immunotherapeutic agent that inhibits PD-1 function selected from the group consisting of an anti-PD-1 antibody and an anti-PD-L1 antibody.

15. The use according to Claim 14, wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 comprises the following CDRs:

V _L CDR1: CTGSSSNIGAGYNVY	[SEQ ID NO:1];
V _L CDR2: GNINRPS	[SEQ ID NO:2];
V _L CDR3: CAAWDKSIISGLV	[SEQ ID NO:3];
V _H CDR1: GFTFSTYGMH	[SEQ ID NO:4];
V _H CDR2: GKGLEWLSYISGGSSYIFYADSVRGR	[SEQ ID NO:5]; and
V _H CDR3: CARILRGGSGMDL	[SEQ ID NO:6].

16. The use according to Claim 15, wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 is to be used in combination with an anti-PD-1 antibody which blocks the interaction between PD1 and PD-L1.

17. The use 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 use according to Claim 15 or 16, wherein the immunotherapeutic agent that inhibits PD-1 function is as defined in Claim 13.

19. A pharmaceutical composition comprising (a) an antibody, or antigen-binding portion thereof, that specifically binds to CD40, and (b) an immunotherapeutic agent that inhibits PD-1 function,

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 immunotherapeutic agent that inhibits PD-1 function is an anti-PD-1 antibody or anti-PD-L1 antibody.

20. The pharmaceutical composition according to Claim 19, wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 comprises the following CDRs:

V _L CDR1: CTGSSSNIGAGYNVY	[SEQ ID NO:1];
V _L CDR2: GNINRPS	[SEQ ID NO:2];
V _L CDR3: CAAWDKSIISGLV	[SEQ ID NO:3];
V _H CDR1: GFTFSTYGMH	[SEQ ID NO:4];
V _H CDR2: GKGLEWLSYISGGSSYIFYADSVRGR	[SEQ ID NO:5]; and
V _H CDR3: CARILRGGSGMDL	[SEQ ID NO:6].

21. The pharmaceutical composition according to Claim 20, comprising an anti-PD-1 antibody which blocks the interaction between PD1 and PD-L1.

22. The pharmaceutical composition 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 pharmaceutical composition according to Claim 21 or 22, wherein the further immunotherapeutic agent that inhibits PD-1 function is as defined in Claim 13.

24. The use according to any one of Claims 1 to 18, wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 and the immunotherapeutic agent that inhibits PD-1 function are to be administered simultaneously or wherein the immunotherapeutic agent that inhibits PD-1 function 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.

25. The use according to any one of Claims 1 to 18 and 24, wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 is to be administered locally to the tumour site.

26. The use according to any one of Claims 1 to 18 and 24 to 25, 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.

27. The use according to any one of Claims 1 to 18 and 24 to 26, wherein the immunotherapeutic agent that inhibits PD-1 function is formulated as a composition suitable for systemic administration with at least one pharmaceutically acceptable diluent or carrier.

28. The use according to any one of Claims 1 to 18 and 24 to 27, wherein the antibody or antigen-binding portion thereof that specifically binds to CD40 is to be administered on multiple separate occasions and the immunotherapeutic agent that inhibits PD-1 function is to be administered such that exposure of the subject to the immunotherapeutic agent that inhibits PD-1 function is continuous for the duration of the use.

29. The use according to any one of Claims 1 to 18 and 24 to 28, wherein the subject is a human.