

The activity of conventional DR5 targeting molecules as described above is dependent on Fc Receptor (FcR) mediated hyperclustering, and is influenced by the immune infiltration and activation status in the tumor (Li and Ravetch, PNAS 2012; Wilson, Cancer Cell 2011; WO 2011/098520). The Fc/FcR interactions can be impaired
5 by physiological human IgG levels. Thus, the activity of conventional DR5 targeting molecules is often limited to a few infiltrating cells (Moessner, Blood 2010). By using a bispecific antibody targeting both DR5 and FAP, the percentage of sensitive tumor cells can be significantly increased by hypercrosslinking via FAP and the risk of an intrinsic resistance to DR5 agonists is decreased. The novel DR5 binding moieties are only active
10 after crosslinking with FAP, which could result in an improved safety and toxicology profile compared to the DR5 binders Drozitumab and Tigatuzumab. The DR5 agonists that have been tested so far were safe in the clinic; however, these clinical programs have been impeded by a low efficacy of the DR5 targeting molecules.

It remains a problem in the art to find ways of effective therapies for targeting
15 cancer using DR5 agonist antibodies.

SUMMARY

Broadly, the present disclosure relates to bispecific antibodies combining a Death Receptor 5 (DR5) targeting antigen binding site with a second antigen binding site that
20 targets Fibroblast Activation Protein (FAP) and their use in combination with a further chemotherapeutic agent. The bispecific antibodies employed in accordance with the present disclosure enable the death receptors become cross linked and induce apoptosis of the targeted tumor cell. The advantage over conventional death receptor targeting antibodies is the specificity of induction of apoptosis only at the site where FAP is
25 expressed as well as the higher potency of these bispecific antibodies due to the induction of DR5 hyperclustering.

Accordingly, in one aspect, the present disclosure provides a bispecific antibody that binds to Death Receptor 5 (DR5) and Fibroblast Activation Protein (FAP) comprising at least one antigen binding site specific for DR5 and at least one antigen binding site specific for FAP for use
30 as a combination therapy in a method of treating cancer, wherein the bispecific antibody is used in combination with a chemotherapeutic agent selected

from Irinotecan, Doxorubicin, Oxaliplatin, 5-FU, a MDM2 inhibitor, a Bcl-2 inhibitor, Abraxane, Paclitaxel, Gemcitabine, Bortezomib, Cyclopamine, a PARP inhibitor, Ifosfamide or an anti-VEGF antibody.

Preferably, the chemotherapeutic agent is selected from Irinotecan, Doxorubicin,

- 5 Oxaliplatin, Ifosfamide or an anti-VEGF antibody. In one embodiment, the bispecific antibody is used in combination with Irinotecan. In one such embodiment the cancer to be treated is colorectal cancer. In one embodiment, the bispecific antibody is used in combination with an anti-VEGF antibody. In one such embodiment the cancer to be treated is colorectal cancer. In one embodiment, the bispecific antibody is used in
10 combination with doxorubicin. In one such embodiment the cancer to be treated is a sarcoma. In one embodiment, the bispecific antibody is used in combination with doxorubicin Ifosfamide . In one such embodiment the cancer to be treated is a sarcoma.

- In one embodiment, the bispecific antibody is used in combination with Gemcitabine and
15 Abraxane. In one such embodiment the cancer to be treated is pancreatic cancer.

In one embodiment the MDM2 inhibitor is RG7388.

In one embodiment the Bcl-2 inhibitor is ABT199.

In one embodiment the PARP inhibitor is PJ34.

- 20 In one embodiment the PARP inhibitor is Olaparip.

- In one embodiment the present disclosure provides a bispecific antibody that binds to Death Receptor 5 (DR5) and Fibroblast Activation Protein (FAP) comprising at least one antigen binding site specific for DR5 and at least one antigen binding site specific for
25 FAP for use as a combination therapy in a method of treating cancer, wherein the cancer is colorectal cancer, sarcoma, head and neck cancer, squamous cell carcinoma, breast cancer, pancreatic cancer, gastric cancer, non-small-cell lung carcinoma, small-cell lung cancer and mesothelioma.

In one embodiment the cancer is colorectal cancer.

- 30 In one embodiment the sarcoma is chondrosarcoma, leiomyosarcoma, gastrointestinal stromal tumours, fibrosarcoma, osteosarcoma, liposarcoma or malignant fibrous histiocyoma.

In one embodiment the present disclosure provides a bispecific antibody that binds to Death Receptor 5 (DR5) and Fibroblast Activation Protein (FAP) comprising at least one antigen binding site specific for DR5 and at least one antigen binding site specific for FAP for use as a combination therapy in a method of treating cancer, wherein the
5 bispecific antibody and the chemotherapeutic agent are administered together, optionally as a combined formulation.

In one embodiment the bispecific antibody and the chemotherapeutic agent are administered by alternation.

10 In one embodiment the chemotherapeutic agent is administered before the bispecific antibody.

In one embodiment the chemotherapeutic agent is administered after the bispecific antibody.

15 In one embodiment the combination is administered at intervals from about one week to three weeks.

In some embodiments, the present disclosure employs a bispecific antibody in which the antigen binding site specific for DR5 comprises:

- (a) a heavy chain CDR1 of SEQ ID NO.:1;
- 20 (b) a heavy chain CDR2 of SEQ ID NO.:2;
- (c) a heavy chain CDR3 of SEQ ID NO.:3;
- (d) a light chain CDR1 of SEQ ID NO.:4;
- (e) a light chain CDR2 of SEQ ID NO.:5; and
- (f) a light chain CDR3 of SEQ ID NO.:6.

25 In some embodiments, the present disclosure employs a bispecific antibody in which the antigen binding site specific for FAP comprises

- (a) a heavy chain CDR1 of SEQ ID NO.:9;
- (b) a heavy chain CDR2 of SEQ ID NO.:10;
- 30 (c) a heavy chain CDR3 of SEQ ID NO.:11;
- (d) a light chain CDR1 of SEQ ID NO.:12;
- (e) a light chain CDR2 of SEQ ID NO.:13; and

(f) a light chain CDR3 of SEQ ID NO.:14.

In one embodiment, the bispecific antibody comprises at least one antigen binding site specific for DR5 comprising a variable heavy chain and a variable light chain
5 comprising an amino acid sequence of : SEQ ID NO.:7 and SEQ ID NO.:8.

In some embodiments, the present disclosure, the bispecific antibody comprises the antigen binding site specific for FAP comprises a variable heavy chain and a variable light chain comprising an amino acid sequence selected from the group of SEQ ID
10 NO.:15 and SEQ ID NO.:16.

In some embodiments, the present disclosure, the bispecific antibody comprises the antigen binding site specific for DR5 comprises: (a) a heavy chain CDR1 of SEQ ID NO.:1; (b) a heavy chain CDR2 of SEQ ID NO.:2; (c) a heavy chain CDR3 of SEQ ID NO.:3; (d) a light chain CDR1 of SEQ ID NO.:4; (e) a light chain CDR2 of SEQ ID
15 NO.:5; (f) a light chain CDR3 of SEQ ID NO.:6 and the antigen binding site specific for FAP comprises: (a) a heavy chain CDR1 of SEQ ID NO.:9; (b) a heavy chain CDR2 of SEQ ID NO.:10; (c) a heavy chain CDR3 of SEQ ID NO.:11; (d) a light chain CDR1 of SEQ ID NO.:12; (e) a light chain CDR2 of SEQ ID NO.:13; (f) a light chain CDR3 of SEQ ID NO.:14.

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In one embodiment, the bispecific antibody comprises at least one antigen binding site specific for DR5 comprising a variable heavy chain comprising an amino acid sequence of SEQ ID NO.:7 and a variable light chain comprising an amino acid sequence of SEQ ID NO.:8; and at least one antigen binding site specific for FAP comprising a
25 heavy chain variable region comprising an amino acid sequence of SEQ ID NO.:15 and a light chain variable region comprising an amino acid sequence of SEQ ID NO.:16.

In some embodiments, the present disclosure, the bispecific antibody comprises the bispecific antibody comprises amino acid sequences of SEQ ID NO: 18, 19
30 and 20 or the bispecific antibody comprises amino acid sequences SEQ ID NO: 17, 19 and 20.

In the present disclosure, advantageously said bispecific antibody is human or humanized.

In one embodiment said bispecific antibody comprises an Fc domain, which comprises one or more amino acid substitution that reduces binding to Fc receptors and/or effector function. In one embodiment said one or more amino acid substitution is at one or more positions selected from the group of L234, L235, and P329. In one embodiment each
5 subunit of the Fc domain comprises three amino acid substitutions that abolish binding to an activating or inhibitory Fc receptor and/or effector function wherein said amino acid substitutions are L234A, L235A and P329G.

In a further aspect, the present disclosure provides a pharmaceutical composition
10 comprising a bispecific antibody as described herein and a chemotherapeutic agent selected from Irinotecan, Doxorubicin, Oxaliplatin, 5-FU, a MDM2 inhibitor, a Bcl-2 inhibitor, Abraxane, Paclitaxel, Gemcitabine, Bortezomib, Cyclopamine, a PARP inhibitor, Ifosfamide or an anti-VEGF antibody. In one embodiment, the pharmaceutical composition comprises a bispecific antibody as described herein, Gemcitabine and
15 Paclitaxel or Abraxane.

In one embodiment the MDM2 inhibitor is RG7388.

In one embodiment the Bcl-2 inhibitor is ABT199.

In one embodiment the PARP inhibitor is PJ34.

20 In one embodiment the PARP inhibitor is Olaparip.

The present disclosure also provides a pharmaceutical composition comprising a bispecific antibody as described herein and a chemotherapeutic agent selected from Irinotecan, Doxorubicin, Oxaliplatin, Ifosfamide or an anti-VEGF antibody.

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The present disclosure also provides a pharmaceutical composition comprising a bispecific antibody as described herein and Irinotecan.

The present disclosure also provides a pharmaceutical composition comprising a bispecific antibody as described herein, Paclitaxel and Gemcitabine or Abraxane.

In a further aspect, the present disclosure provides the use of a combination of a bispecific antibody that binds to Death Receptor 5 (DR5) and Fibroblast Activation Protein (FAP) as described herein and a chemotherapeutic agent in the manufacture of a medicament for the treatment of cancer, wherein the bispecific antibody is used in
5 combination with a chemotherapeutic agent selected from Irinotecan, Doxorubicin, Oxaliplatin, 5-FU, a MDM2 inhibitor, a Bcl-2 inhibitor ABT199, Abraxane, Paclitaxel, Gemcitabine, Bortezomib, Cyclophosphamide, a PARP inhibitor, Ifosfamide or an anti-VEGF antibody. The present disclosure also provides the use of a combination of a bispecific antibody that binds to Death Receptor 5 (DR5) and Fibroblast Activation Protein (FAP),
10 Paclitaxel and Abraxane in the manufacture of a medicament for the treatment of cancer.

The present disclosure also provides the use of a combination of a bispecific antibody that binds to Death Receptor 5 (DR5) and Fibroblast Activation Protein (FAP) and a chemotherapeutic agent in the manufacture of a medicament for the treatment of
15 cancer, wherein the bispecific antibody is used in combination with a chemotherapeutic agent selected from Irinotecan, Doxorubicin, Oxaliplatin, 5-FU, the MDM2 inhibitor RG7388, the Bcl-2 inhibitor ABT199, Abraxane, Paclitaxel, Gemcitabine, Bortezomib, Cyclophosphamide, the PARP inhibitor PJ34, Ifosfamide or an anti-VEGF antibody.

20 In a further aspect, the present disclosure provides a kit comprising:

(i) a first container comprising a composition which comprises a bispecific antibody as described herein; and

(ii) a second container comprising a composition comprising a chemotherapeutic agent selected from Irinotecan, Doxorubicin, Oxaliplatin, 5-FU, a MDM2 inhibitor, a
25 Bcl-2 inhibitor, Abraxane, Paclitaxel, Gemcitabine, Bortezomib, Cyclophosphamide, a PARP inhibitor, Ifosfamide or an anti-VEGF antibody.

The present disclosure also provides a kit comprising:

(i) a first container comprising a composition which comprises a bispecific
30 antibody as described herein; and

(ii) a second container comprising a composition comprising a chemotherapeutic agent selected from Irinotecan, Doxorubicin, Oxaliplatin, 5-FU, the MDM2 inhibitor

RG7388, the Bcl-2 inhibitor ABT199, Abraxane, Paclitaxel, Gemcitabine, Bortezomib, Cyclopamine, the PARP inhibitor PJ34, Ifosfamide or an anti-VEGF antibody.

The present disclosure also provides a kit comprising:

- 5 (i) a first container comprising a composition which comprises a bispecific antibody as described herein; and
- (ii) a second container comprising Abraxane, and
- (iii) a third container comprising Gemcitabine.

10 The present disclosure also provides a method for the treatment of a cancer comprising administering a therapeutic combination as a combined formulation or by alternation to a mammal, wherein the therapeutic combination comprises a therapeutically effective amount of a bispecific antibody that binds to Death Receptor 5 (DR5) and Fibroblast Activation Protein (FAP) comprising at least one antigen binding site specific

15 for DR5 and at least one antigen binding site specific for FAP and a therapeutically effective amount of a chemotherapeutic agent selected from Irinotecan, Doxorubicin, Oxaliplatin, 5-FU, a MDM2 inhibitor, a Bcl-2 inhibitor, Abraxane, Paclitaxel, Gemcitabine, Bortezomib, Cyclopamine, a PARP inhibitor, Ifosfamide or an anti-VEGF antibody.

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 The present disclosure also provides a method for the treatment of a cancer comprising administering a therapeutic combination as a combined formulation or by alternation to a mammal, wherein the therapeutic combination comprises a therapeutically effective amount of a bispecific antibody that binds to Death Receptor 5 (DR5) and Fibroblast Activation Protein (FAP)

25 comprising at least one antigen binding site specific for DR5 and at least one antigen binding site specific for FAP and a therapeutically effective amount of a chemotherapeutic agent selected from selected from Irinotecan, Doxorubicin, Oxaliplatin, 5-FU, the MDM2 inhibitor RG7388, the Bcl-2 inhibitor ABT199, Abraxane, Paclitaxel, Gemcitabine, Bortezomib, Cyclopamine, the PARP inhibitor PJ34, Ifosfamide or an anti-VEGF antibody.

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 The present disclosure also provides a method for the treatment of a cancer comprising administering a therapeutic combination as a combined formulation or

by alternation to a mammal, wherein the therapeutic combination comprises a therapeutically effective amount of a bispecific antibody that binds to Death Receptor 5 (DR5) and Fibroblast Activation Protein (FAP) comprising at least one antigen binding site specific for DR5 and at least one antigen binding site specific for FAP and a
5 therapeutically effective amount of Abraxane and a therapeutically effective amount of Gemcitabine.

In some embodiments, the cancer is colorectal cancer, sarcoma, head and neck cancers, squamous cell carcinomas, breast cancer, pancreatic cancer, gastric cancer, non-
10 small-cell lung carcinoma, small-cell lung cancer, desmoplastic melanoma and mesothelioma. In one embodiment, the cancer is colorectal cancer. In other embodiments, the sarcoma is chondrosarcoma, leiomyosarcoma, gastrointestinal stromal tumours, fibrosarcoma, osteosarcoma, liposarcoma or malignant fibrous histiocytoma.

In some embodiments, the bispecific antibody and the chemotherapeutic agent are
15 administered together, optionally as a combined formulation. Alternatively, the bispecific antibody and the chemotherapeutic agent may be administered by alternation, with either the chemotherapeutic agent administered before the bispecific antibody, or the chemotherapeutic agent administered after the bispecific antibody. The combination may be administered in accordance with clinical practice, for example being administered at
20 intervals from about one week to three weeks.

Embodiments of the present disclosure will now be described by way of example and not limitation with reference to the accompanying figures. However various further aspects and embodiments of the present disclosure will be apparent to those skilled in the art in view of the present disclosure.

25 “and/or” where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. For example “A and/or B” is to be taken as specific disclosure of each of (i) A, (ii) B and (iii) A and B, just as if each is set out individually herein.

Unless context dictates otherwise, the descriptions and definitions of the features
30 set out above are not limited to any particular aspect or embodiment of the disclosure and apply equally to all aspects and embodiments which are described.

37. A kit comprising:

a first container comprising a composition which comprises a bispecific antibody of claims 1 to 35;

a second container comprising a composition comprising a chemotherapeutic

5 agent selected from Irinotecan, Doxorubicin, Oxaliplatin, 5-FU, a MDM2 inhibitor, a Bcl-2 inhibitor, Abraxane, Paclitaxel, Gemcitabine, Bortezomib, Cyclopamine, a PARP inhibitor, Ifosfamide or an anti-VEGF antibody.

38. Use of a combination of a bispecific antibody that binds to Death Receptor 5

10 (DR5) and Fibroblast Activation Protein (FAP) of any one of claims 1 to 35 and a chemotherapeutic agent in the manufacture of a medicament for the treatment of cancer, wherein the bispecific antibody is used in combination with a chemotherapeutic agent selected from Irinotecan, Doxorubicin, Oxaliplatin, 5-FU, a MDM2 inhibitor, a Bcl-2 inhibitor, Abraxane, Paclitaxel, Gemcitabine, Bortezomib, Cyclopamine, a PARP
15 inhibitor, Ifosfamide or an anti-VEGF antibody.

39. The use of claim 38, wherein the medicament is for treatment of colorectal cancer, sarcoma, head and neck cancers, squamous cell carcinomas, **breast cancer**, pancreatic cancer, gastric cancer, non-small-cell lung carcinoma, small-cell lung cancer and
20 mesothelioma.

40. The use of claim 39, wherein the sarcoma is chondrosarcoma, leiomyosarcoma, gastrointestinal stromal tumours, fibrosarcoma, osteosarcoma, liposarcoma or malignant fibrous histiocytoma.

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