

[Citation List]

[Patent Literature]

[0006]

5 [PTL 1] WO2013/180200

[Non Patent Literature]

[0007]

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20 [Summary]

[Technical Problem]

[0008]

The present disclosure relates to anticancer agents comprising an anti-CD137 antigen-binding molecule, and combination therapies with another anticancer agent.

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[Solution to Problem]

[0008a]

In one aspect, the present disclosure relates to an anticancer agent comprising as an active ingredient an anti-CD137 antigen-binding molecule comprising any combination of HVR-H1, HVR-H2, HVR-H3, HVR-L1, HVR-L2, and HVR-L3 selected from (a) to (i) below:

30 (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 7, HVR-H2 comprising the amino acid sequence of SEQ ID NO: 8, HVR-H3 comprising the amino acid sequence of SEQ ID NO: 17, HVR-L1 comprising the amino acid sequence of SEQ ID NO: 21, HVR-L2 comprising the amino acid sequence of SEQ ID NO: 26, and HVR-L3 comprising the amino acid

35 sequence of SEQ ID NO: 27;

(i) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 7, HVR-H2 comprising the amino acid sequence of SEQ ID NO: 14, HVR-H3 comprising the amino acid sequence of SEQ ID NO: 19, HVR-L1 comprising the amino acid sequence of SEQ ID NO: 24, HVR-L2 comprising the amino acid sequence of SEQ ID NO: 26, and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 27.

[0008a]

In another aspect, the present application relates to an anticancer agent comprising an anti-CD137 antigen-binding molecule which comprises any combination of VH and VL selected from (a) to (i) below:

- 10 (a) a VH comprising the amino acid sequence of SEQ ID NO: 43, and a VL comprising the amino acid sequence of SEQ ID NO: 54;
- (b) a VH comprising the amino acid sequence of SEQ ID NO: 44, and a VL comprising the amino acid sequence of SEQ ID NO: 55;
- (c) a VH comprising the amino acid sequence of SEQ ID NO: 45, and a VL comprising the amino acid sequence of SEQ ID NO: 55;
- 15 (d) a VH comprising the amino acid sequence of SEQ ID NO: 46, and a VL comprising the amino acid sequence of SEQ ID NO: 54;
- (e) a VH comprising the amino acid sequence of SEQ ID NO: 48, and a VL comprising the amino acid sequence of SEQ ID NO: 56;
- 20 (f) a VH comprising the amino acid sequence of SEQ ID NO: 49, and a VL comprising the amino acid sequence of SEQ ID NO: 57;
- (g) a VH comprising the amino acid sequence of SEQ ID NO: 51, and a VL comprising the amino acid sequence of SEQ ID NO: 59;
- (h) a VH comprising the amino acid sequence of SEQ ID NO: 51, and a VL comprising the amino acid sequence of SEQ ID NO: 60;
- 25 (i) a VH comprising the amino acid sequence of SEQ ID NO: 50, and a VL comprising the amino acid sequence of SEQ ID NO: 59.

[0008c]

In another aspect, the present disclosure relates to an anticancer agent comprising an anti-CD137 antigen-binding molecule which comprises any combination of VH, VL, CH and CL selected from (i) to (xxxviii) below:

- 30 (i) VH comprising the amino acid sequence of SEQ ID NO: 43, CH comprising the amino acid sequence of SEQ ID NO: 64, VL comprising the amino acid sequence of SEQ ID NO: 54, and CL comprising the amino acid sequence of SEQ ID NO: 63

- [illegible]

- [illegible]

(xxxviii) VH comprising the amino acid sequence of SEQ ID NO: 51, CH comprising the amino acid sequence of SEQ ID NO: 85, VL comprising the amino acid sequence of SEQ ID NO: 60, and CL comprising the amino acid sequence of SEQ ID NO: 63.

[0008d]

5 In another aspect, the present application relates to use of the anticancer agent as disclosed herein in the manufacture of a medicament for treating a cancer in a patient, wherein the cancer is (i) a solid cancer infiltrated with one or more cells selected from a B cell, a dendritic cell, a natural killer cell, a macrophage, and a CD8+ T cell, and/or (ii) a solid cancer infiltrated with a regulatory T (Treg) cell or CD4+ T cell.

10 [0009]

 In order to provide anti-CD137 antigen-binding molecules which have immunocyte-activating effect, cytotoxic activity, or antitumor activity and meanwhile have reduced effect on non-tumor tissues such as normal tissues and have less side effects, and provide methods of using the same, the present disclosure provides anticancer agents comprising as an active
15 ingredient an anti-CD137 antigen-binding molecule characterized in that their binding activity to CD137 varies depending on various compounds (e.g. small molecule compounds) in target tissues (e.g. tumor tissues). The present disclosure also provides combination therapies using such an anticancer agent comprising an anti-CD137 antigen-binding molecule and another agent.

[CLAIMS]

1. An anticancer agent comprising as an active ingredient an anti-CD137 antigen-binding molecule comprising any combination of HVR-H1, HVR-H2, HVR-H3, HVR-L1, HVR-L2, and HVR-L3 selected from (a) to (i) below:

- (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 7, HVR-H2 comprising the amino acid sequence of SEQ ID NO: 8, HVR-H3 comprising the amino acid sequence of SEQ ID NO: 17, HVR-L1 comprising the amino acid sequence of SEQ ID NO: 21, HVR-L2 comprising the amino acid sequence of SEQ ID NO: 26, and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 27;
- (b) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 7, HVR-H2 comprising the amino acid sequence of SEQ ID NO: 9, HVR-H3 comprising the amino acid sequence of SEQ ID NO: 17, HVR-L1 comprising the amino acid sequence of SEQ ID NO: 22, HVR-L2 comprising the amino acid sequence of SEQ ID NO: 26, and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 27;
- (c) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 7, HVR-H2 comprising the amino acid sequence of SEQ ID NO: 10, HVR-H3 comprising the amino acid sequence of SEQ ID NO: 17, HVR-L1 comprising the amino acid sequence of SEQ ID NO: 22, HVR-L2 comprising the amino acid sequence of SEQ ID NO: 26, and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 27;
- (d) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 7, HVR-H2 comprising the amino acid sequence of SEQ ID NO: 11, HVR-H3 comprising the amino acid sequence of SEQ ID NO: 18, HVR-L1 comprising the amino acid sequence of SEQ ID NO: 21, HVR-L2 comprising the amino acid sequence of SEQ ID NO: 26, and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 27;
- (e) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 7, HVR-H2 comprising the amino acid sequence of SEQ ID NO: 12, HVR-H3 comprising the amino acid sequence of SEQ ID NO: 18, HVR-L1 comprising the amino acid sequence of SEQ ID NO: 21, HVR-L2 comprising the amino acid sequence of SEQ ID NO: 26, and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 28;
- (f) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 7, HVR-H2 comprising the amino acid sequence of SEQ ID NO: 13, HVR-H3 comprising the amino acid sequence of SEQ ID NO: 18, HVR-L1 comprising the amino acid sequence of SEQ ID NO: 21, HVR-L2 comprising the amino acid sequence of SEQ ID NO: 26, and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 29;

- (g) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 7, HVR-H2 comprising the amino acid sequence of SEQ ID NO: 15, HVR-H3 comprising the amino acid sequence of SEQ ID NO: 20, HVR-L1 comprising the amino acid sequence of SEQ ID NO: 24, HVR-L2 comprising the amino acid sequence of SEQ ID NO: 26, and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 27;
- (h) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 7, HVR-H2 comprising the amino acid sequence of SEQ ID NO: 15, HVR-H3 comprising the amino acid sequence of SEQ ID NO: 20, HVR-L1 comprising the amino acid sequence of SEQ ID NO: 25, HVR-L2 comprising the amino acid sequence of SEQ ID NO: 26, and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 27;
- (i) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 7, HVR-H2 comprising the amino acid sequence of SEQ ID NO: 14, HVR-H3 comprising the amino acid sequence of SEQ ID NO: 19, HVR-L1 comprising the amino acid sequence of SEQ ID NO: 24, HVR-L2 comprising the amino acid sequence of SEQ ID NO: 26, and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 27.

2. An anticancer agent comprising an anti-CD137 antigen-binding molecule which comprises any combination of VH and VL selected from (a) to (i) below:

- (a) a VH comprising the amino acid sequence of SEQ ID NO: 43, and a VL comprising the amino acid sequence of SEQ ID NO: 54;
- (b) a VH comprising the amino acid sequence of SEQ ID NO: 44, and a VL comprising the amino acid sequence of SEQ ID NO: 55;
- (c) a VH comprising the amino acid sequence of SEQ ID NO: 45, and a VL comprising the amino acid sequence of SEQ ID NO: 55;
- (d) a VH comprising the amino acid sequence of SEQ ID NO: 46, and a VL comprising the amino acid sequence of SEQ ID NO: 54;
- (e) a VH comprising the amino acid sequence of SEQ ID NO: 48, and a VL comprising the amino acid sequence of SEQ ID NO: 56;
- (f) a VH comprising the amino acid sequence of SEQ ID NO: 49, and a VL comprising the amino acid sequence of SEQ ID NO: 57;
- (g) a VH comprising the amino acid sequence of SEQ ID NO: 51, and a VL comprising the amino acid sequence of SEQ ID NO: 59;
- (h) a VH comprising the amino acid sequence of SEQ ID NO: 51, and a VL comprising the amino acid sequence of SEQ ID NO: 60;
- (i) a VH comprising the amino acid sequence of SEQ ID NO: 50, and a VL comprising the amino acid sequence of SEQ ID NO: 59.

3. The anticancer agent of claim 1 or 2, wherein the anti-CD137 antigen-binding molecule is a human antibody, humanized antibody, or chimeric antibody, or an antigen-binding fragment of any of them.

4. The anticancer agent of any one of claims 1 to 3, wherein the anti-CD137 antigen-binding molecule comprises an altered Fc region, and the altered Fc region comprises any one combination of amino acid alterations selected from the following according to EU numbering:

L235W/G236N/H268D/Q295L/K326T/A330K/P343R/D413K;

K214R/L235W/G236N/H268D/Q295L/K326T/A330K/P343R/D413K;

L234Y/P238D/T250V/V264I/T307P/A330K/P343R/D413K;

L234Y/P238D/V264I/A330K/P343R/D413K;

L234Y/G237D/P238D/T250V/T307P/A330K/P343R/D413K;

L234Y/G237D/P238D/A330K/P343R/D413K;

L235W/G236N/H268D/Q295L/K326T/A330K/Q311R/P343R;

L234Y/P238D/T250V/V264I/T307P/A330K/Q311R/P343R;

L234Y/P238D/V264I/A330K/Q311R/P343R;

L234Y/G237D/P238D/T250V/T307P/A330K/Q311R/P343R;

L234Y/G237D/P238D/A330K/Q311R/P343R;

L235W/G236N/H268D/Q295L/K326T/A330K/P343R;

K214R/L235W/G236N/H268D/Q295L/K326T/A330K/P343R;

L235W/G236N/H268D/Q295L/K326T/A330K/D413K;

K214R/G236N/H268D/A330K/P343R;

K214R/L235W/G236N/H268D/A330K/P343R;

K214R/G236N/H268D/A330K/D413K;

K214R/G236N/H268D/A330K/P343R/D413K;

K214R/L235W/G236N/H268D/A330K/P343R/D413K;

K214R/G236N/H268D/A330K/Q311R;

K214R/L235W/G236N/H268D/A330K/Q311R;

K214R/G236N/H268D/A330K/Q311R/P343R;

K214R/L235W/G236N/H268D/A330K/Q311R/P343R;

K214R/G236N/H268D/A330K/Q311R/D413K;

K214R/L235W/G236N/H268D/A330K/Q311R/D413K; and

K214R/L235W/G236N/H268D/Q295L/K326T/A330K/Q311R.

5. An anticancer agent comprising an anti-CD137 antigen-binding molecule which comprises any combination of VH, VL, CH and CL selected from (i) to (xxxviii) below:

- (i) VH comprising the amino acid sequence of SEQ ID NO: 43, CH comprising the amino acid sequence of SEQ ID NO: 64, VL comprising the amino acid sequence of SEQ ID NO: 54, and CL comprising the amino acid sequence of SEQ ID NO: 63;
- (ii) VH comprising the amino acid sequence of SEQ ID NO: 43, CH comprising the amino acid sequence of SEQ ID NO: 66, VL comprising the amino acid sequence of SEQ ID NO: 54, and CL comprising the amino acid sequence of SEQ ID NO: 63;
- (iii) VH comprising the amino acid sequence of SEQ ID NO: 43, CH comprising the amino acid sequence of SEQ ID NO: 67, VL comprising the amino acid sequence of SEQ ID NO: 54, and CL comprising the amino acid sequence of SEQ ID NO: 63;
- (iv) VH comprising the amino acid sequence of SEQ ID NO: 43, CH comprising the amino acid sequence of SEQ ID NO: 68, VL comprising the amino acid sequence of SEQ ID NO: 54, and CL comprising the amino acid sequence of SEQ ID NO: 63;
- (v) VH comprising the amino acid sequence of SEQ ID NO: 43, CH comprising the amino acid sequence of SEQ ID NO: 69, VL comprising the amino acid sequence of SEQ ID NO: 54, and CL comprising the amino acid sequence of SEQ ID NO: 63;
- (vi) VH comprising the amino acid sequence of SEQ ID NO: 43, CH comprising the amino acid sequence of SEQ ID NO: 70, VL comprising the amino acid sequence of SEQ ID NO: 54, and CL comprising the amino acid sequence of SEQ ID NO: 63;
- (vii) VH comprising the amino acid sequence of SEQ ID NO: 43, CH comprising the amino acid sequence of SEQ ID NO: 71, VL comprising the amino acid sequence of SEQ ID NO: 54, and CL comprising the amino acid sequence of SEQ ID NO: 63;
- (viii) VH comprising the amino acid sequence of SEQ ID NO: 43, CH comprising the amino acid sequence of SEQ ID NO: 73, VL comprising the amino acid sequence of SEQ ID NO: 54, and CL comprising the amino acid sequence of SEQ ID NO: 63;
- (ix) VH comprising the amino acid sequence of SEQ ID NO: 43, CH comprising the amino acid sequence of SEQ ID NO: 75, VL comprising the amino acid sequence of SEQ ID NO: 54, and CL comprising the amino acid sequence of SEQ ID NO: 63;
- (x) VH comprising the amino acid sequence of SEQ ID NO: 43, CH comprising the amino acid sequence of SEQ ID NO: 78, VL comprising the amino acid sequence of SEQ ID NO: 54, and CL comprising the amino acid sequence of SEQ ID NO: 63;
- (xi) VH comprising the amino acid sequence of SEQ ID NO: 43, CH comprising the amino acid sequence of SEQ ID NO: 80, VL comprising the amino acid sequence of SEQ ID NO: 54, and CL comprising the amino acid sequence of SEQ ID NO: 63;

- [illegible]

[illegible]

(xxxvi) VH comprising the amino acid sequence of SEQ ID NO: 51, CH comprising the amino acid sequence of SEQ ID NO: 83, VL comprising the amino acid sequence of SEQ ID NO: 60, and CL comprising the amino acid sequence of SEQ ID NO: 63;

(xxxvii) VH comprising the amino acid sequence of SEQ ID NO: 51, CH comprising the amino acid sequence of SEQ ID NO: 84, VL comprising the amino acid sequence of SEQ ID NO: 60, and CL comprising the amino acid sequence of SEQ ID NO: 63; and

(xxxviii) VH comprising the amino acid sequence of SEQ ID NO: 51, CH comprising the amino acid sequence of SEQ ID NO: 85, VL comprising the amino acid sequence of SEQ ID NO: 60, and CL comprising the amino acid sequence of SEQ ID NO: 63.

6. Use of the anticancer agent of any one of claims 1 to 5 in the manufacture of a medicament for treating a cancer in a patient, wherein the cancer is (i) a solid cancer infiltrated with one or more cells selected from a B cell, a dendritic cell, a natural killer cell, a macrophage, and a CD8⁺ T cell, and/or (ii) a solid cancer infiltrated with a regulatory T (Treg) cell or CD4⁺ T cell.

7. The use of claim 6, wherein the medicament is to be administered to a patient having a cancer refractory to treatment with an immune checkpoint inhibitor.

8. The use of claim 6 or 7, wherein the cancer is selected from the group consisting of gastric cancer, head and neck cancer, esophageal cancer, colorectal cancer, lung cancer, mesothelioma, liver cancer, ovarian cancer, breast cancer, colon cancer, kidney cancer, skin cancer, muscle tumor, pancreatic cancer, prostate cancer, testicular cancer, uterine cancer, cholangiocarcinoma, Merkel cell carcinoma, bladder cancer, thyroid cancer, schwannoma, adrenal cancer, anal cancer, central nervous system tumor, neuroendocrine tissue tumor, penile cancer, pleural tumor, salivary gland tumor, vulvar cancer, thymoma, lymphoma, myeloid leukemia and pediatric cancer.

9. The use of any one of claims 6 to 8 for use in combination therapy with at least one other anticancer agent.

10. The use of claim 9, wherein the other anticancer agent is at least one anticancer agent selected from a chemotherapeutic agent, a T cell-activating agonist agent, an immune checkpoint inhibitor, a T cell-redirecting antigen-binding molecule, an antifibrotic agent, and an angiogenesis inhibitor.

11. The use of claim 10, wherein the other anticancer agent is an immune checkpoint inhibitor.
12. The use of claim 10 or 11, wherein the other anticancer agent is at least one immune checkpoint inhibitor selected from an anti-PD1 antibody, an anti-PDL1 antibody, an anti-TIGIT antibody, an anti-TIM3 antibody, and an anti-LAG3 antibody.
13. The use of claim 10, wherein the other anticancer agent is a T cell-redirecting antigen-binding molecule.
14. The use of claim 9, wherein the other anticancer agent is an agent that depletes and/or inactivates one or more cells selected from a regulatory T cell, a CD4⁺ T cell, a B cell, a NK cell, and a macrophage.