

receive both positive and negative secondary co-stimulatory signals. The regulation of such positive and negative signals is critical to maximize the host's protective immune responses, while maintaining immune tolerance and preventing autoimmunity.

Negative secondary signals seem necessary for induction of T-cell tolerance, while positive signals promote T-cell activation. While the simple two-signal model still provides a valid explanation for naive lymphocytes, a host's immune response is a dynamic process, and co-stimulatory signals can also be provided to antigen-exposed T-cells.

The mechanism of co-stimulation is of therapeutic interest because the manipulation of co-stimulatory signals has shown to provide a means to either enhance or terminate cell-based immune response. Recently, it has been discovered that T cell dysfunction or anergy occurs concurrently with an induced and sustained expression of the inhibitory receptor, programmed death 1 polypeptide (PD-1). As a result, therapeutic targeting PD-1 and other molecules which signal through interactions with PD-1, such as programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PD-L2) are an area of intense interest. The inhibition of PD-L1 signaling has been proposed as a means to enhance T cell immunity for the treatment of cancer (*e.g.*, tumor immunity) and infection, including both acute and chronic (*e.g.*, persistent) infection. However, as an optimal therapeutic directed to a target in this pathway has yet to be commercialized, a significant unmet medical need exists. Antibodies against PD-L1 are described *e.g.* in WO 2010/077634.

Summary

The disclosure comprises the combination therapy of a tumor-targeted IL-2 variant immunocytokine with an antibody which binds to human PD-L1 for use in the treatment of cancer or tumor, for use in the prevention or treatment of metastasis, for use in the treatment of inflammatory diseases, for use in treating or delaying

progression of an immune related disease such as tumor immunity, or for use in stimulating an immune response or function, such as T cell activity.

The disclosure comprises the use of a tumor-targeted IL-2 variant immunocytokine for the manufacture of a medicament for use in the treatment of cancer or tumor, for use in the prevention or treatment of metastasis, for use in the treatment of inflammatory diseases, for use in treating or delaying progression of an immune related disease such as tumor immunity, or for use in stimulating an immune response or function, such as T cell activity, wherein the tumor-targeted IL-2 variant immunocytokine is administered in combination with an antibody which binds to human PD-L1.

The disclosure comprises the use of an antibody which binds to human PD-L1 for the manufacture of a medicament for use in the treatment of cancer or tumor, for use in the prevention or treatment of metastasis, for use in the treatment of inflammatory diseases, for use in treating or delaying progression of an immune related disease such as tumor immunity, or for use in stimulating an immune response or function, such as T cell activity, wherein the antibody which binds to human PD-L1 is administered in combination with a tumor-targeted IL-2 variant immunocytokine.

The disclosure comprises a method of treatment of cancer or tumor, a method of prevention or treatment of metastasis, a method of treatment of inflammatory diseases, a method of treatment or delaying progression of an immune related disease such as tumor immunity, or a method of stimulating an immune response or function, such as T cell activity, the method comprising administering the combination therapy of a tumor-targeted IL-2 variant immunocytokine with an antibody which binds to human PD-L1.

The tumor-targeted IL-2 variant immunocytokine used in the combination therapy is characterized in comprising

In an embodiment a combination therapy of a tumor-targeted IL-2 variant immunocytokine with an antibody which binds to human PD-L1 as described above is for use in the prevention or treatment of metastasis.

In an embodiment a combination therapy of a tumor-targeted IL-2 variant immunocytokine with an antibody which binds to human PD-L1 as described above is for use in the treatment of inflammatory diseases.

In an embodiment a combination therapy of a tumor-targeted IL-2 variant immunocytokine with an antibody which binds to human PD-L1 as described above is for use in treating or delaying progression of an immune related disease such as tumor immunity.

In an embodiment a combination therapy of a tumor-targeted IL-2 variant immunocytokine with an antibody which binds to human PD-L1 as described above is for use in stimulating an immune response or function, such as T cell activity.

The disclosure comprises a tumor-targeted IL-2 variant immunocytokine wherein the immunocytokine is administered in combination with an antibody which binds to human PD-L1 as described above for use in

- i) inhibition of tumor growth in a tumor expressing the target of the immunocytokine;
- ii) enhancing median and/or overall survival of subjects with a tumor expressing the target of the immunocytokine,

wherein the target may be presented on a tumor cell or in a tumor cell environment.

The disclosure comprises a CEA-targeted IL-2 variant immunocytokine wherein the immunocytokine is administered in combination with an antibody which binds to human PD-L1 for use in

- i) inhibition of tumor growth in CEA-expressing tumors;

The disclosure comprises a FAP-targeted IL-2 variant immunocytokine wherein the immunocytokine is administered in combination with an antibody which binds to human PD-L1 for use in

- i) inhibition of tumor growth in FAP-expressing tumors;
- ii) enhancing median and/or overall survival of subjects with a FAP-expressing tumor;

wherein the FAP-targeted IL-2 variant immunocytokine used in the combination therapy is characterized in comprising

- a) a heavy chain variable domain VH of SEQ ID NO:42 and a light chain variable domain VL of SEQ ID NO:41, and the polypeptide sequence of SEQ ID NO:3; or
- b) a polypeptide sequence of SEQ ID NO:79 or SEQ ID NO:80 or SEQ ID NO:81, or
- c) the polypeptide sequences of SEQ ID NO:79, and SEQ ID NO:80 and SEQ ID NO:81, or
- d) the polypeptide sequences of SEQ ID NO:124, and SEQ ID NO:125 and SEQ ID NO:126,

and the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

- a) a heavy chain variable domain VH of SEQ ID NO:89 and a light chain variable domain VL of SEQ ID NO:92, or
- b) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:93, or

- o) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:106, or
- p) a heavy chain variable domain VH of SEQ ID NO:91 and a light chain variable domain VL of SEQ ID NO:107.

The disclosure comprises a tumor-targeted IL-2 variant immunocytokine, for use in the treatment of a patient having a CEA-expressing tumor or a tumor characterized by expression or overexpression of CEA, having a FAP-expressing tumor or a tumor characterized by expression or overexpression of FAP or having a tumor associated with expression or overexpression of CEA or FAP, and wherein the immunocytokine is administered in combination with an antibody which binds to human PD-L1,

wherein the tumor-targeted IL-2 variant immunocytokine used in the combination therapy is characterized in comprising

- a) a heavy chain variable domain VH of SEQ ID NO:68 and a light chain variable domain VL of SEQ ID NO:67, and the polypeptide sequence of SEQ ID NO:3, or
- b) a polypeptide sequence of SEQ ID NO:84 or SEQ ID NO:86 or SEQ ID NO:88, or
- c) the polypeptide sequences of SEQ ID NO:84, and SEQ ID NO:86 and SEQ ID NO:88, or
- d) the polypeptide sequences of SEQ ID NO:108, and SEQ ID NO:109 and SEQ ID NO:110, or
- e) a heavy chain variable domain VH of SEQ ID NO:42 and a light chain variable domain VL of SEQ ID NO:41, and the polypeptide sequence of SEQ ID NO:3, or

- i) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:100, or
- j) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:101, or
- k) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:102, or
- l) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:103, or
- m) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:104, or
- n) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:105, or
- o) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:106, or
- p) a heavy chain variable domain VH of SEQ ID NO:91 and a light chain variable domain VL of SEQ ID NO:107.

In one embodiment antibody components of an immunocytokine or antibodies are of human IgG1 subclass or human IgG4 subclass.

The disclosure comprises:

A) a method for

- i) inhibition of tumor growth in CEA-expressing tumors or in FAP-expressing tumors;
- ii) enhancing median and/or overall survival of subjects with a CEA-expressing tumor or a FAP-expressing tumor;

therapy. The combination therapies of the FAP-targeted IL-2 variant immunocytokines and antibodies described herein show benefits for patients in need of a FAP-targeting therapy. The tumor-targeted IL-2 variant immunocytokines according to the disclosure show efficacy in tumor growth inhibitory activity against target-expressing tumors and are especially useful inter alia in the treatment of cancer and metastasis in combination with the anti-PD-L1 antibodies described herein. The tumor-targeted IL-2 variant immunocytokines according to the disclosure show efficacy in enhancing median and/or overall survival of subjects with a target-expressing tumor and are especially useful inter alia in the treatment of cancer and metastasis in combination with the anti-PD-L1 antibodies described herein. The specific CEA-targeted IL-2 variant immunocytokines according to the disclosure show efficacy in tumor growth inhibitory activity against CEA-expressing tumors and are especially useful inter alia in the treatment of cancer and metastasis in combination with the specific anti-PD-L1 antibodies described herein. The specific CEA-targeted IL-2 variant immunocytokines according to the disclosure show efficacy in enhancing median and/or overall survival of subjects with a CEA-expressing tumor and are especially useful inter alia in the treatment of cancer and metastasis in combination with the specific anti-PD-L1 antibodies described herein. The specific FAP-targeted IL-2 variant immunocytokines according to the disclosure show efficacy in tumor growth inhibitory activity against FAP-expressing tumors and are especially useful inter alia in the treatment of cancer and metastasis in combination with the specific anti-PD-L1 antibodies described herein. The specific FAP-targeted IL-2 variant immunocytokines according to the disclosure show efficacy in enhancing median and/or overall survival of subjects with a FAP-expressing tumor and are especially useful inter alia in the treatment of cancer and metastasis in combination with the specific anti-PD-L1 antibodies described herein. The specific antibodies which bind to human PD-L1 according to the disclosure show efficacy in enhancing median and/or overall survival of subjects with a CEA-expressing tumor or a FAP-expressing tumor and are especially useful inter alia in the treatment of cancer and metastasis in combination with the specific CEA-targeted IL-2 variant

immunocytokines or FAP-targeted IL-2 variant immunocytokines, respectively, described herein.

In one aspect, there is provided a tumor-targeted IL-2 variant immunocytokine in combination with an antibody which binds to human PD-L1 for use as a combination therapy in the treatment of cancer, for use as a combination therapy in the prevention or treatment of metastasis, for use as a combination therapy in the treatment of inflammatory diseases, for use as a combination therapy in treating or delaying progression of an immune related disease such as tumor immunity, or for use as a combination therapy in stimulating an immune response or function, such as T cell activity,

wherein the tumor-targeted IL-2 variant immunocytokine used in the combination therapy is characterized in comprising

- a) a heavy chain variable domain VH of SEQ ID NO:68 and a light chain variable domain VL of SEQ ID NO:67, and the polypeptide sequence of SEQ ID NO:3, or
- b) a polypeptide sequence of SEQ ID NO:84 or SEQ ID NO:86 or SEQ ID NO:88, or
- c) the polypeptide sequences of SEQ ID NO:84, and SEQ ID NO:86 and SEQ ID NO:88, or
- d) the polypeptide sequences of SEQ ID NO:108, and SEQ ID NO:109 and SEQ ID NO:110, or
- e) a heavy chain variable domain VH of SEQ ID NO:42 and a light chain variable domain VL of SEQ ID NO:41, and the polypeptide sequence of SEQ ID NO:3, or
- f) a polypeptide sequence of SEQ ID NO:79 or SEQ ID NO:80 or SEQ ID NO:81, or

g) the polypeptide sequences of SEQ ID NO:79, and SEQ ID NO:80 and SEQ ID NO:81, or

h) the polypeptide sequences of SEQ ID NO:124, and SEQ ID NO:125 and SEQ ID NO:126,

and the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

a) a heavy chain variable domain VH of SEQ ID NO:89 and a light chain variable domain VL of SEQ ID NO:92, or

b) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:93, or

c) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:94, or

d) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:95, or

e) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:96, or

f) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:97, or

g) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:98, or

h) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:99, or

i) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:100, or

- j) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:101, or
- k) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:102, or
- l) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:103, or
- m) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:104, or
- n) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:105, or
- o) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:106, or
- p) a heavy chain variable domain VH of SEQ ID NO:91 and a light chain variable domain VL of SEQ ID NO:107.

In another aspect, there is provided a tumor-targeted IL-2 variant immunocytokine in combination with an antibody which binds to human PD-L1 for use in

- i) inhibition of tumor growth in a tumor expressing the target of the immunocytokine; and/or
- ii) enhancing median and/or overall survival of subjects with a tumor expressing the target of the immunocytokine;

wherein the target is presented on a tumor cell or in a tumor cell environment,

wherein the tumor-targeted IL-2 variant immunocytokine used in the combination therapy is characterized in comprising

- a) a heavy chain variable domain VH of SEQ ID NO:68 and a light chain variable domain VL of SEQ ID NO:67, and the polypeptide sequence of SEQ ID NO:3, or
- b) a polypeptide sequence of SEQ ID NO:84 or SEQ ID NO:86 or SEQ ID NO:88, or
- c) the polypeptide sequences of SEQ ID NO:84, and SEQ ID NO:86 and SEQ ID NO:88, or
- d) the polypeptide sequences of SEQ ID NO:108, and SEQ ID NO:109 and SEQ ID NO:110, or
- e) a heavy chain variable domain VH of SEQ ID NO:42 and a light chain variable domain VL of SEQ ID NO:41, and the polypeptide sequence of SEQ ID NO:3, or
- f) a polypeptide sequence of SEQ ID NO:79 or SEQ ID NO:80 or SEQ ID NO:81, or
- g) the polypeptide sequences of SEQ ID NO:79, and SEQ ID NO:80 and SEQ ID NO:81, or
- h) the polypeptide sequences of SEQ ID NO:124, and SEQ ID NO:125 and SEQ ID NO:126;

and the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

- a) a heavy chain variable domain VH of SEQ ID NO:89 and a light chain variable domain VL of SEQ ID NO:92, or
- b) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:93, or

- c) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:94, or
- d) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:95, or
- e) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:96, or
- f) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:97, or
- g) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:98, or
- h) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:99, or
- i) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:100, or
- j) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:101, or
- k) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:102, or
- l) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:103, or
- m) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:104, or
- n) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:105, or

- o) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:106, or
- p) a heavy chain variable domain VH of SEQ ID NO:91 and a light chain variable domain VL of SEQ ID NO:107.

In another aspect, there is provided a CEA-targeted IL-2 variant immunocytokine in combination with an antibody which binds to human PD-L1 for use in

- i) inhibition of tumor growth in a CEA-expressing tumors; and/or
- ii) enhancing median and/or overall survival of subjects with a CEA-expressing tumor,

wherein the CEA-targeted IL-2 variant immunocytokine is administered in combination with an antibody which binds to human PD-L1;

wherein the CEA-targeted IL-2 variant immunocytokine used in the combination therapy is characterized in comprising

- a) a heavy chain variable domain VH of SEQ ID NO:68 and a light chain variable domain VL of SEQ ID NO:67, and the polypeptide sequence of SEQ ID NO:3, or
- b) a polypeptide sequence of SEQ ID NO:84 or SEQ ID NO:86 or SEQ ID NO:88, or
- c) the polypeptide sequences of SEQ ID NO:84, and SEQ ID NO:86 and SEQ ID NO:88, or
- d) the polypeptide sequences of SEQ ID NO:108, and SEQ ID NO:109 and SEQ ID NO:110;

and the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

- a) a heavy chain variable domain VH of SEQ ID NO:89 and a light chain variable domain VL of SEQ ID NO:92, or
- b) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:93, or
- c) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:94, or
- d) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:95, or
- e) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:96, or
- f) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:97, or
- g) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:98, or
- h) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:99, or
- i) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:100, or
- j) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:101, or
- k) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:102, or
- l) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:103, or

- m) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:104, or
- n) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:105, or
- o) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:106, or
- p) a heavy chain variable domain VH of SEQ ID NO:91 and a light chain variable domain VL of SEQ ID NO:107.

In another aspect, there is provided a FAP-targeted IL-2 variant immunocytokine in combination with an antibody which binds to human PD-L1 for use in

- i) inhibition of tumor growth in a FAP-expressing tumor; and/or
- ii) enhancing median and/or overall survival of subjects with a FAP-expressing tumor;

wherein the FAP-targeted IL-2 variant immunocytokine used in the combination therapy is characterized in comprising

- a) a heavy chain variable domain VH of SEQ ID NO:42 and a light chain variable domain VL of SEQ ID NO:41, and the polypeptide sequence of SEQ ID NO:3, or
- b) a polypeptide sequence of SEQ ID NO:79 or SEQ ID NO:80 or SEQ ID NO:81, or
- c) the polypeptide sequences of SEQ ID NO:79, and SEQ ID NO:80 and SEQ ID NO:81, or
- d) the polypeptide sequences of SEQ ID NO:124, and SEQ ID NO:125 and SEQ ID NO:126;

and the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

- a) a heavy chain variable domain VH of SEQ ID NO:89 and a light chain variable domain VL of SEQ ID NO:92, or
- b) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:93, or
- c) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:94, or
- d) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:95, or
- e) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:96, or
- f) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:97, or
- g) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:98, or
- h) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:99, or
- i) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:100, or
- j) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:101, or
- k) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:102, or

- l) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:103, or
- m) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:104, or
- n) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:105, or
- o) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:106, or
- p) a heavy chain variable domain VH of SEQ ID NO:91 and a light chain variable domain VL of SEQ ID NO:107.

In another aspect, there is provided a tumor-targeted IL-2 variant immunocytokine, for use in the treatment of a patient having a CEA-expressing tumor or a tumor characterized by expression or overexpression of CEA, having a FAP-expressing tumor or a tumor characterized by expression or overexpression of FAP or having a tumor associated with expression or overexpression of CEA or FAP, and wherein the immunocytokine is administered in combination with an antibody which binds to human PD-L1,

wherein the tumor-targeted IL-2 variant immunocytokine used in the combination therapy is characterized in comprising

- a) a heavy chain variable domain VH of SEQ ID NO:68 and a light chain variable domain VL of SEQ ID NO:67, and the polypeptide sequence of SEQ ID NO:3, or
- b) a polypeptide sequence of SEQ ID NO:84 or SEQ ID NO:86 or SEQ ID NO:88, or

- c) the polypeptide sequences of SEQ ID NO:84, and SEQ ID NO:86 and SEQ ID NO:88, or
- d) the polypeptide sequences of SEQ ID NO:108, and SEQ ID NO:109 and SEQ ID NO:110, or
- e) a heavy chain variable domain VH of SEQ ID NO:42 and a light chain variable domain VL of SEQ ID NO:41, and the polypeptide sequence of SEQ ID NO:3, or
- f) a polypeptide sequence of SEQ ID NO:79 or SEQ ID NO:80 or SEQ ID NO:81, or
- g) the polypeptide sequences of SEQ ID NO:79, and SEQ ID NO:80 and SEQ ID NO:81, or
- h) the polypeptide sequences of SEQ ID NO:124, and SEQ ID NO:125 and SEQ ID NO:126;

and the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

- a) a heavy chain variable domain VH of SEQ ID NO:89 and a light chain variable domain VL of SEQ ID NO:92, or
- b) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:93, or
- c) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:94, or
- d) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:95, or

- e) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:96, or
- f) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:97, or
- g) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:98, or
- h) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:99, or
- i) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:100, or
- j) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:101, or
- k) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:102, or
- l) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:103, or
- m) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:104, or
- n) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:105, or
- o) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:106, or
- p) a heavy chain variable domain VH of SEQ ID NO:91 and a light chain variable domain VL of SEQ ID NO:107.

In another aspect, there is provided use of a tumor-targeted IL-2 variant immunocytokine in combination with an antibody which binds to human PD-L1 in the manufacture of a medicament as a combination therapy in the treatment of cancer, as a combination therapy in the prevention or treatment of metastasis, as a combination therapy in the treatment of inflammatory diseases, as a combination therapy in treating or delaying progression of an immune related disease such as tumor immunity, or as a combination therapy in stimulating an immune response or function, such as T cell activity,

wherein the tumor-targeted IL-2 variant immunocytokine used in the combination therapy is characterized in comprising

- a) a heavy chain variable domain VH of SEQ ID NO:68 and a light chain variable domain VL of SEQ ID NO:67, and the polypeptide sequence of SEQ ID NO:3, or
- b) a polypeptide sequence of SEQ ID NO:84 or SEQ ID NO:86 or SEQ ID NO:88, or
- c) the polypeptide sequences of SEQ ID NO:84, and SEQ ID NO:86 and SEQ ID NO:88, or
- d) the polypeptide sequences of SEQ ID NO:108, and SEQ ID NO:109 and SEQ ID NO:110, or
- e) a heavy chain variable domain VH of SEQ ID NO:42 and a light chain variable domain VL of SEQ ID NO:41, and the polypeptide sequence of SEQ ID NO:3, or
- f) a polypeptide sequence of SEQ ID NO:79 or SEQ ID NO:80 or SEQ ID NO:81, or
- g) the polypeptide sequences of SEQ ID NO:79, and SEQ ID NO:80 and SEQ ID NO:81, or
- h) the polypeptide sequences of SEQ ID NO:124, and SEQ ID NO:125 and SEQ ID NO:126,

and the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

- a) a heavy chain variable domain VH of SEQ ID NO:89 and a light chain variable domain VL of SEQ ID NO:92, or
- b) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:93, or
- c) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:94, or
- d) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:95, or
- e) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:96, or
- f) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:97, or
- g) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:98, or
- h) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:99, or
- i) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:100, or
- j) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:101, or
- k) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:102, or
- l) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:103, or
- m) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:104, or
- n) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:105, or

- o) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:106, or
- p) a heavy chain variable domain VH of SEQ ID NO:91 and a light chain variable domain VL of SEQ ID NO:107.

In another aspect, there is provided use of a tumor-targeted IL-2 variant immunocytokine in combination with an antibody which binds to human PD-L1 in the manufacture of a medicament for the

- i) inhibition of tumor growth in a tumor expressing the target of the immunocytokine; and/or
- ii) enhancing median and/or overall survival of subjects with a tumor expressing the target of the immunocytokine;

wherein the target is presented on a tumor cell or in a tumor cell environment,

wherein the tumor-targeted IL-2 variant immunocytokine used in the combination therapy is characterized in comprising

- a) a heavy chain variable domain VH of SEQ ID NO:68 and a light chain variable domain VL of SEQ ID NO:67, and the polypeptide sequence of SEQ ID NO:3, or
- b) a polypeptide sequence of SEQ ID NO:84 or SEQ ID NO:86 or SEQ ID NO:88, or
- c) the polypeptide sequences of SEQ ID NO:84, and SEQ ID NO:86 and SEQ ID NO:88, or
- d) the polypeptide sequences of SEQ ID NO:108, and SEQ ID NO:109 and SEQ ID NO:110, or
- e) a heavy chain variable domain VH of SEQ ID NO:42 and a light chain variable domain VL of SEQ ID NO:41, and the polypeptide sequence of SEQ ID NO:3, or

- f) a polypeptide sequence of SEQ ID NO:79 or SEQ ID NO:80 or SEQ ID NO:81, or
- g) the polypeptide sequences of SEQ ID NO:79, and SEQ ID NO:80 and SEQ ID NO:81, or
- h) the polypeptide sequences of SEQ ID NO:124, and SEQ ID NO:125 and SEQ ID NO:126;

and the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

- a) a heavy chain variable domain VH of SEQ ID NO:89 and a light chain variable domain VL of SEQ ID NO:92, or
- b) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:93, or
- c) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:94, or
- d) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:95, or
- e) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:96, or
- f) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:97, or
- g) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:98, or
- h) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:99, or
- i) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:100, or
- j) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:101, or

- k) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:102, or
- l) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:103, or
- m) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:104, or
- n) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:105, or
- o) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:106, or
- p) a heavy chain variable domain VH of SEQ ID NO:91 and a light chain variable domain VL of SEQ ID NO:107.

In another aspect, there is provided use of a CEA-targeted IL-2 variant immunocytokine in combination with an antibody which binds to human PD-L1 in the manufacture of a medicament for the

- i) inhibition of tumor growth in a CEA-expressing tumors; and/or
- ii) enhancing median and/or overall survival of subjects with a CEA-expressing tumor,

wherein the CEA-targeted IL-2 variant immunocytokine is administered in combination with an antibody which binds to human PD-L1;

wherein the CEA-targeted IL-2 variant immunocytokine used in the combination therapy is characterized in comprising

- a) a heavy chain variable domain VH of SEQ ID NO:68 and a light chain variable domain VL of SEQ ID NO:67, and the polypeptide sequence of SEQ ID NO:3, or
- b) a polypeptide sequence of SEQ ID NO:84 or SEQ ID NO:86 or SEQ ID NO:88, or

- c) the polypeptide sequences of SEQ ID NO:84, and SEQ ID NO:86 and SEQ ID NO:88, or
- d) the polypeptide sequences of SEQ ID NO:108, and SEQ ID NO:109 and SEQ ID NO:110;

and the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

- a) a heavy chain variable domain VH of SEQ ID NO:89 and a light chain variable domain VL of SEQ ID NO:92, or
- b) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:93, or
- c) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:94, or
- d) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:95, or
- e) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:96, or
- f) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:97, or
- g) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:98, or
- h) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:99, or
- i) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:100, or
- j) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:101, or
- k) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:102, or

- l) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:103, or
- m) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:104, or
- n) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:105, or
- o) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:106, or
- p) a heavy chain variable domain VH of SEQ ID NO:91 and a light chain variable domain VL of SEQ ID NO:107.

In another aspect, there is provided use of a FAP-targeted IL-2 variant immunocytokine in combination with an antibody which binds to human PD-L1 in the manufacture of a medicament for the

- i) inhibition of tumor growth in a FAP-expressing tumor; and/or
- ii) enhancing median and/or overall survival of subjects with a FAP-expressing tumor;

wherein the FAP-targeted IL-2 variant immunocytokine used in the combination therapy is characterized in comprising

- a) a heavy chain variable domain VH of SEQ ID NO:42 and a light chain variable domain VL of SEQ ID NO:41, and the polypeptide sequence of SEQ ID NO:3, or
- b) a polypeptide sequence of SEQ ID NO:79 or SEQ ID NO:80 or SEQ ID NO:81, or
- c) the polypeptide sequences of SEQ ID NO:79, and SEQ ID NO:80 and SEQ ID NO:81, or
- d) the polypeptide sequences of SEQ ID NO:124, and SEQ ID NO:125 and SEQ ID NO:126;

and the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

- a) a heavy chain variable domain VH of SEQ ID NO:89 and a light chain variable domain VL of SEQ ID NO:92, or
- b) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:93, or
- c) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:94, or
- d) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:95, or
- e) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:96, or
- f) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:97, or
- g) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:98, or
- h) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:99, or
- i) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:100, or
- j) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:101, or
- k) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:102, or
- l) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:103, or
- m) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:104, or
- n) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:105, or

- o) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:106, or
- p) a heavy chain variable domain VH of SEQ ID NO:91 and a light chain variable domain VL of SEQ ID NO:107.

In another aspect, there is provided use of a tumor-targeted IL-2 variant immunocytokine in the manufacture of a medicament for the treatment of a patient having a CEA-expressing tumor or a tumor characterized by expression or overexpression of CEA, having a FAP-expressing tumor or a tumor characterized by expression or overexpression of FAP or having a tumor associated with expression or overexpression of CEA or FAP, and wherein the immunocytokine is to be administered in combination with an antibody which binds to human PD-L1,

wherein the tumor-targeted IL-2 variant immunocytokine used in the combination therapy is characterized in comprising

- a) a heavy chain variable domain VH of SEQ ID NO:68 and a light chain variable domain VL of SEQ ID NO:67, and the polypeptide sequence of SEQ ID NO:3, or
- b) a polypeptide sequence of SEQ ID NO:84 or SEQ ID NO:86 or SEQ ID NO:88, or
- c) the polypeptide sequences of SEQ ID NO:84, and SEQ ID NO:86 and SEQ ID NO:88, or
- d) the polypeptide sequences of SEQ ID NO:108, and SEQ ID NO:109 and SEQ ID NO:110, or
- e) a heavy chain variable domain VH of SEQ ID NO:42 and a light chain variable domain VL of SEQ ID NO:41, and the polypeptide sequence of SEQ ID NO:3, or
- f) a polypeptide sequence of SEQ ID NO:79 or SEQ ID NO:80 or SEQ ID NO:81, or

- g) the polypeptide sequences of SEQ ID NO:79, and SEQ ID NO:80 and SEQ ID NO:81, or
- h) the polypeptide sequences of SEQ ID NO:124, and SEQ ID NO:125 and SEQ ID NO:126;

and the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

- a) a heavy chain variable domain VH of SEQ ID NO:89 and a light chain variable domain VL of SEQ ID NO:92, or
- b) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:93, or
- c) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:94, or
- d) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:95, or
- e) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:96, or
- f) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:97, or
- g) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:98, or
- h) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:99, or
- i) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:100, or
- j) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:101, or
- k) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:102, or

- l) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:103, or
- m) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:104, or
- n) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:105, or
- o) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:106, or
- p) a heavy chain variable domain VH of SEQ ID NO:91 and a light chain variable domain VL of SEQ ID NO:107.

Description of the Figures

Fig. 1. Presents the results of an efficacy experiment with CEA-IL2v and PD-L1 Mab as single agents and in a combination setting. The MC38-CEA transfectant colorectal carcinoma cell line was injected into the portal vein in Black 6-huCEA-hu Fcγ RIII tg mice to study survival in a liver metastatic model. The amount of antibodies injected per mouse in mg/kg is indicated in the figure legend.

Fig. 2. Presents the results of an efficacy experiment with CEA-IL2v and PD-L1 Mab as single agents and in a combination setting. The MC38-CEA transfectant colorectal carcinoma cell line was injected subcutaneously in Black 6-huCEA-huFcγ RIII tg mice to study tumor growth inhibition in a subcutaneous model, tumor size was measured using a caliper. The amount of antibodies injected per mouse in mg/kg is indicated in the figure legend.

Fig. 3. Presents the results of an efficacy experiment with CEA-IL2v and PD-L1 Mab as single agents and in a combination setting. The Panc02-H7-CEA transfectant pancreatic carcinoma cell line was injected into the pancreas in Black 6-huCEA-huFcγ RIII tg mice to study survival in a pancreatic orthotopic syngeneic model. The amount of antibodies injected per mouse in mg/kg is indicated in the figure legend.

Fig. 4. Presents (A) the results of an efficacy experiment with CEA-targeted CEA-IL2v and PD-L1 Mab or untargeted DP47-IL2v and PD-L1 Mab as single agents and in a combination setting. The Panc02-H7-CEA transfectant pancreatic carcinoma cell line was injected into the pancreas in Black 6-huCEA-huFcγRIII tg mice to study survival in a pancreatic orthotopic syngeneic model. The amount of antibodies injected per mouse in mg/kg is

claims, wherein the minimal effector function results from an effectorless Fc mutation.

16. The tumor-targeted IL-2 variant immunocytokine in combination with an antibody which binds to human PD-L1 according to any one of the preceding claims, wherein the effectorless Fc mutation is L234A/L235A or L234A/L235A/P329G or N297A or D265A/N297A. 17. Use of a tumor-targeted IL-2 variant immunocytokine in combination with an antibody which binds to human PD-L1 in the manufacture of a medicament as a combination therapy in the treatment of cancer, as a combination therapy in the prevention or treatment of metastasis, as a combination therapy in the treatment of inflammatory diseases, as a combination therapy in treating or delaying progression of an immune related disease such as tumor immunity, or as a combination therapy in stimulating an immune response or function, such as T cell activity,

wherein the tumor-targeted IL-2 variant immunocytokine used in the combination therapy is characterized in comprising

- a) a heavy chain variable domain VH of SEQ ID NO:68 and a light chain variable domain VL of SEQ ID NO:67, and the polypeptide sequence of SEQ ID NO:3, or
- b) a polypeptide sequence of SEQ ID NO:84 or SEQ ID NO:86 or SEQ ID NO:88, or
- c) the polypeptide sequences of SEQ ID NO:84, and SEQ ID NO:86 and SEQ ID NO:88, or
- d) the polypeptide sequences of SEQ ID NO:108, and SEQ ID NO:109 and SEQ ID NO:110, or
- e) a heavy chain variable domain VH of SEQ ID NO:42 and a light chain variable domain VL of SEQ ID NO:41, and the polypeptide sequence of SEQ ID NO:3, or

- f) a polypeptide sequence of SEQ ID NO:79 or SEQ ID NO:80 or SEQ ID NO:81, or
- g) the polypeptide sequences of SEQ ID NO:79, and SEQ ID NO:80 and SEQ ID NO:81, or
- h) the polypeptide sequences of SEQ ID NO:124, and SEQ ID NO:125 and SEQ ID NO:126,

and the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

- a) a heavy chain variable domain VH of SEQ ID NO:89 and a light chain variable domain VL of SEQ ID NO:92, or
- b) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:93, or
- c) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:94, or
- d) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:95, or
- e) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:96, or
- f) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:97, or
- g) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:98, or
- h) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:99, or
- i) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:100, or

- j) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:101, or
- k) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:102, or
- l) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:103, or
- m) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:104, or
- n) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:105, or
- o) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:106, or
- p) a heavy chain variable domain VH of SEQ ID NO:91 and a light chain variable domain VL of SEQ ID NO:107.

18. Use of a tumor-targeted IL-2 variant immunocytokine in combination with an antibody which binds to human PD-L1 in the manufacture of a medicament for the

- i) inhibition of tumor growth in a tumor expressing the target of the immunocytokine; and/or
- ii) enhancing median and/or overall survival of subjects with a tumor expressing the target of the immunocytokine;

wherein the target is presented on a tumor cell or in a tumor cell environment,

wherein the tumor-targeted IL-2 variant immunocytokine used in the combination therapy is characterized in comprising

- a) a heavy chain variable domain VH of SEQ ID NO:68 and a light chain variable domain VL of SEQ ID NO:67, and the polypeptide sequence of SEQ ID NO:3, or
- b) a polypeptide sequence of SEQ ID NO:84 or SEQ ID NO:86 or SEQ ID NO:88, or
- c) the polypeptide sequences of SEQ ID NO:84, and SEQ ID NO:86 and SEQ ID NO:88, or
- d) the polypeptide sequences of SEQ ID NO:108, and SEQ ID NO:109 and SEQ ID NO:110, or
- e) a heavy chain variable domain VH of SEQ ID NO:42 and a light chain variable domain VL of SEQ ID NO:41, and the polypeptide sequence of SEQ ID NO:3, or
- f) a polypeptide sequence of SEQ ID NO:79 or SEQ ID NO:80 or SEQ ID NO:81, or
- g) the polypeptide sequences of SEQ ID NO:79, and SEQ ID NO:80 and SEQ ID NO:81, or
- h) the polypeptide sequences of SEQ ID NO:124, and SEQ ID NO:125 and SEQ ID NO:126;

and the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

- a) a heavy chain variable domain VH of SEQ ID NO:89 and a light chain variable domain VL of SEQ ID NO:92, or
- b) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:93, or
- c) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:94, or

- d) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:95, or
- e) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:96, or
- f) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:97, or
- g) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:98, or
- h) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:99, or
- i) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:100, or
- j) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:101, or
- k) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:102, or
- l) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:103, or
- m) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:104, or
- n) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:105, or
- o) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:106, or
- p) a heavy chain variable domain VH of SEQ ID NO:91 and a light chain variable domain VL of SEQ ID NO:107.

19. Use of a CEA-targeted IL-2 variant immunocytokine in combination with an antibody which binds to human PD-L1 in the manufacture of a medicament for the

- i) inhibition of tumor growth in a CEA-expressing tumors; and/or
- ii) enhancing median and/or overall survival of subjects with a CEA-expressing tumor,

wherein the CEA-targeted IL-2 variant immunocytokine is administered in combination with an antibody which binds to human PD-L1;

wherein the CEA-targeted IL-2 variant immunocytokine used in the combination therapy is characterized in comprising

- a) a heavy chain variable domain VH of SEQ ID NO:68 and a light chain variable domain VL of SEQ ID NO:67, and the polypeptide sequence of SEQ ID NO:3, or
- b) a polypeptide sequence of SEQ ID NO:84 or SEQ ID NO:86 or SEQ ID NO:88, or
- c) the polypeptide sequences of SEQ ID NO:84, and SEQ ID NO:86 and SEQ ID NO:88, or
- d) the polypeptide sequences of SEQ ID NO:108, and SEQ ID NO:109 and SEQ ID NO:110;

and the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

- a) a heavy chain variable domain VH of SEQ ID NO:89 and a light chain variable domain VL of SEQ ID NO:92, or
- b) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:93, or

- c) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:94, or
- d) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:95, or
- e) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:96, or
- f) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:97, or
- g) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:98, or
- h) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:99, or
- i) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:100, or
- j) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:101, or
- k) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:102, or
- l) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:103, or
- m) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:104, or
- n) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:105, or
- o) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:106, or

- p) a heavy chain variable domain VH of SEQ ID NO:91 and a light chain variable domain VL of SEQ ID NO:107.

20. Use of a FAP-targeted IL-2 variant immunocytokine in combination with an antibody which binds to human PD-L1 in the manufacture of a medicament for the

- i) inhibition of tumor growth in a FAP-expressing tumor; and/or
- ii) enhancing median and/or overall survival of subjects with a FAP-expressing tumor;

wherein the FAP-targeted IL-2 variant immunocytokine used in the combination therapy is characterized in comprising

- a) a heavy chain variable domain VH of SEQ ID NO:42 and a light chain variable domain VL of SEQ ID NO:41, and the polypeptide sequence of SEQ ID NO:3, or
- b) a polypeptide sequence of SEQ ID NO:79 or SEQ ID NO:80 or SEQ ID NO:81, or
- c) the polypeptide sequences of SEQ ID NO:79, and SEQ ID NO:80 and SEQ ID NO:81, or
- d) the polypeptide sequences of SEQ ID NO:124, and SEQ ID NO:125 and SEQ ID NO:126;

and the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

- a) a heavy chain variable domain VH of SEQ ID NO:89 and a light chain variable domain VL of SEQ ID NO:92, or
- b) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:93, or

- c) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:94, or
- d) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:95, or
- e) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:96, or
- f) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:97, or
- g) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:98, or
- h) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:99, or
- i) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:100, or
- j) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:101, or
- k) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:102, or
- l) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:103, or
- m) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:104, or
- n) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:105, or
- o) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:106, or

- p) a heavy chain variable domain VH of SEQ ID NO:91 and a light chain variable domain VL of SEQ ID NO:107.

21. Use of a tumor-targeted IL-2 variant immunocytokine in the manufacture of a medicament for the treatment of a patient having a CEA-expressing tumor or a tumor characterized by expression or overexpression of CEA, having a FAP-expressing tumor or a tumor characterized by expression or overexpression of FAP or having a tumor associated with expression or overexpression of CEA or FAP, and wherein the immunocytokine is to be administered in combination with an antibody which binds to human PD-L1,

wherein the tumor-targeted IL-2 variant immunocytokine used in the combination therapy is characterized in comprising

- a) a heavy chain variable domain VH of SEQ ID NO:68 and a light chain variable domain VL of SEQ ID NO:67, and the polypeptide sequence of SEQ ID NO:3, or
- b) a polypeptide sequence of SEQ ID NO:84 or SEQ ID NO:86 or SEQ ID NO:88, or
- c) the polypeptide sequences of SEQ ID NO:84, and SEQ ID NO:86 and SEQ ID NO:88, or
- d) the polypeptide sequences of SEQ ID NO:108, and SEQ ID NO:109 and SEQ ID NO:110, or
- e) a heavy chain variable domain VH of SEQ ID NO:42 and a light chain variable domain VL of SEQ ID NO:41, and the polypeptide sequence of SEQ ID NO:3, or
- f) a polypeptide sequence of SEQ ID NO:79 or SEQ ID NO:80 or SEQ ID NO:81, or
- g) the polypeptide sequences of SEQ ID NO:79, and SEQ ID NO:80 and SEQ ID NO:81, or

- h) the polypeptide sequences of SEQ ID NO:124, and SEQ ID NO:125 and SEQ ID NO:126;

and the antibody which binds to human PD-L1 used in the combination therapy is characterized in comprising

- a) a heavy chain variable domain VH of SEQ ID NO:89 and a light chain variable domain VL of SEQ ID NO:92, or
- b) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:93, or
- c) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:94, or
- d) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:95, or
- e) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:96, or
- f) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:97, or
- g) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:98, or
- h) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:99, or
- i) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:100, or
- j) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:101, or
- k) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:102, or

- l) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:103, or
- m) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:104, or
- n) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:105, or
- o) a heavy chain variable domain VH of SEQ ID NO:90 and a light chain variable domain VL of SEQ ID NO:106, or
- p) a heavy chain variable domain VH of SEQ ID NO:91 and a light chain variable domain VL of SEQ ID NO:107.