COMBINATION THERAPIES FOR THE TREATMENT OF CANCER

BACKGROUND

Blocking of prostaglandin E2 (PGE2) signaling through the interaction of PGE2 with the prostaglandin E receptor 4 (EP4) by antagonists has been shown to be effective in reducing inflammation (Chen et al. (2010) *British J. Pharmacol.* **160**, 292–310). PGE2 has also been implicated as an important constituent in the immunosuppressive environment created by many solid tumors (Whiteside (2010) *Expert Opinion in Biological Therapy.* 2010. **10**, 1019–1035), and inhibition of EP4 signaling by antagonists were shown to reduce tumor growth (Terada et al. (2010) *Cancer Res.* **70**, 1606–1615) and tumor metastasis in tumor animal models (Yang et al. (2006) *Cancer Res.* **66**, 9665–9672).

Even with the most advanced cancer therapies, there continues to be a medical need for more effective treatments for solid cancers, particularly cancer that has metastasized.

SUMMARY

The anti-tumor activities of various combinations of an EP4 antagonist with: radiation; antibodies to cytotoxic t-lymphocyte antigen 4 (anti-CTLA4); antibodies to programmed death ligand 1 (anti-PDL1); antibodies to programmed cell death protein 1 (anti-PD1); and anti-metabolites have been examined. The results from this examination have indicated improved and/or synergistic anti-tumor activities by the combination of the EP4 antagonist with the other therapies as compared to single agent treatment alone, and in some embodiments this may result in a memory immune response against the tumor, even as against a different cancer.

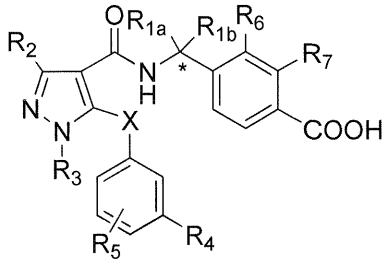
Thus, in one aspect of the invention, provided is the use of an EP4 antagonist in the manufacture of a medicament for treating cancer in a subject in need thereof wherein the medicament is to be used in combination with a therapy selected from the group consisting of: radiation therapy and an antibody therapy. In another aspect, the present invention refers to the use of an EP4 antagonist in the manufacture of a medicament for generating a memory immune response against a cancer in a subject in need thereof wherein the medicament is to be used in combination with a therapy selected from the group consisting of: radiation therapy and an antibody therapy. In still another aspect, the present invention refers to the use of an EP4 antagonist in the manufacture of a medicament for treating cancer in a subject in need thereof wherein the medicament is to be used in combination with an anti-metabolite chemotherapy.

Also described herein is a method of treating cancer in a subject in need thereof comprising administering an EP4 antagonist in combination with a therapy selected from the group consisting of radiation therapy, antibody therapy and anti-metabolite chemotherapy. In a more particular examples, the antibody therapy is selected from the group consisting of CTLA4 antibody therapy, PDL1 antibody therapy, and PD1 antibody therapy. In some embodiments, the cancer is metastatic cancer.

In another example, provided is a method of generating a memory immune response in a subject in need thereof comprising administering an amount of an EP4 antagonist in combination with a therapy selected from the group consisting of radiation therapy, antibody therapy and anti-metabolite chemotherapy. In another more particular example, the antibody therapy is selected from the group consisting of CTLA4 antibody therapy, PDL1 antibody therapy and PD1 antibody therapy.

In yet another example, the cancer treated is selected from the group consisting of breast cancers, cervical cancers, colorectal cancers, endometrial cancers, glioblastomas, head and neck cancers, kidney cancers, liver cancers, lung cancers, medulloblastomas, ovarian cancers, pancreatic cancers, prostate cancers, skin cancers and urinary tract cancers.

In more particular examples, provided are methods of treating cancer and/or generating a memory immune response comprising administering a compound of Formula (I):



(I),

wherein:

one of R_{1a} and R_{1b} is hydrogen, and the other is methyl; or R_{1a} and R_{1b} are taken together to form a cyclopropyl ring;

R_2 is methyl or fluoromethyl;

R_3 is methyl;

R_4 is hydrogen, halo, methyl, fluoromethyl, methoxy, or fluoromethoxy;

R_5 is hydrogen, halo, methyl, fluoromethyl, methoxy, or fluoromethoxy;

R_6 is hydrogen, halo, methyl, or methoxy;

R_7 is hydrogen, halo, methyl, or methoxy; and

X is oxygen;

or a pharmaceutically acceptable salt thereof,

in combination with radiation therapy; in combination with anti-CTLA4 therapy; in combination with anti-PDL1 therapy; in combination with anti-PD1 therapy; and/or in combination with anti-metabolite chemotherapy.

Further provided is the use of a combination of an EP4 antagonist and a therapy selected from the group consisting of radiation therapy, antibody therapy and/or anti-metabolite chemotherapy for treating cancer and/or generating a memory immune response as disclosed herein.

Also provided is the use of an EP4 antagonist in the preparation of a medicament for a combination therapy with a therapy selected from the group consisting of radiation therapy, antibody therapy and/or anti-metabolite chemotherapy for treating cancer and/or generating a memory immune response as disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Significantly improved anti-tumor growth activity of radiation/ER-886046 combination therapy compared with radiation alone. Panel A) Average tumor sizes of the CT26 tumor-bearing mice that received 9 Gy radiation + ER-886046, 9 Gy radiation alone, or vehicle alone. Panel B) Average animal body weight of the CT-26 tumor-bearing mice. Radiation treatment: 9 Gy single dose on day 9; ER-886046 dosing: 150 mg/kg, oral (po) administration daily from day 9 to day 32. Administration of radiation and ER-886046 to the tumor-bearing mice is indicated by the arrows and bars, respectively. N = 10-12 per group. *, $p < 0.05$, student t-test.

Figure 2. Tumor growth plots of the individual CT-26 tumors treated with radiation/ER-886046 or radiation alone. The animals are of the experiment described in Figure 1. Panel A) Vehicle treatment group. Panel B) Radiation. Panel C) Radiation plus ER-886046. N = 10-12 per group. Cure, complete tumor regression; Progression, fast tumor growth; Stable, comparable size from initial tumors before the treatment. Radiation treatment: 9 Gy single dose on day 9; ER-886046 dosing: 150 mg/kg, oral (po) administration daily from day 9 to day 32. Each line represents an individual animal.

Figure 3. Improved tumor growth suppression and animal survival by low dose radiation/ER-886046 compared with low dose radiation alone. Plots of animal survival status among indicated treatment groups. Radiation treatment: 3 Gy single dose on day 17; ER-886046 dosing: 150 mg/kg, po administration daily from days 17 to 45. Once an animal reached 20% weight loss compared its initial body weight or had a tumor volume equal to or higher than 2000 mm^3, the animal was removed from the study according to the protocol. N = 10 per group. *, $p < 0.05$; ***, $p < 0.001$; Gehan-Breslow-Wilcoxon test.

Figure 4. Long lasting anti-tumor effect with a memory immune response by ER-886046/radiation treatment. Panel A) Tumor growth in the cured mice by ER-886046 and radiation combination treatment or in the naïve BalB/c mice that received injection of CT26

WHAT IS CLAIMED IS:

1. Use of an EP4 antagonist in the manufacture of a medicament for treating cancer in a subject in need thereof wherein the medicament is to be used in combination with a therapy selected from the group consisting of: radiation therapy and an antibody therapy.

2. Use of an EP4 antagonist in the manufacture of a medicament for generating a memory immune response against a cancer in a subject in need thereof wherein the medicament is to be used in combination with a therapy selected from the group consisting of: radiation therapy and an antibody therapy.

3. The use of claim 1 or 2, wherein the therapy is radiation therapy.

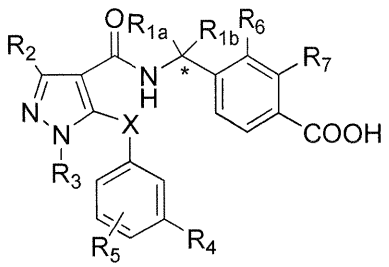
4. The use of claim 1, wherein said treating comprises an abscopal effect.

5. The use of claim 2, wherein said generating the memory immune response comprises an abscopal effect.

6. The use of claim 1 or 2, wherein the therapy is antibody therapy.

7. The use of claim 6, wherein the antibody therapy is selected from the group consisting of: CTLA4 antibody therapy, PDL1 antibody therapy and PD1 antibody therapy.

8. The use of any of claims 1–7, wherein the EP4 antagonist is a compound of Formula (I):



I

wherein:

one of R_{1a} and R_{1b} is hydrogen, and the other is methyl; or R_{1a} and R_{1b} are taken together to form a cyclopropyl ring;

R_2 is methyl or fluoromethyl;

R_3 is methyl;

R_4 is hydrogen, halo, methyl, fluoromethyl, methoxy, or fluoromethoxy;

R_5 is hydrogen, halo, methyl, fluoromethyl, methoxy, or fluoromethoxy;

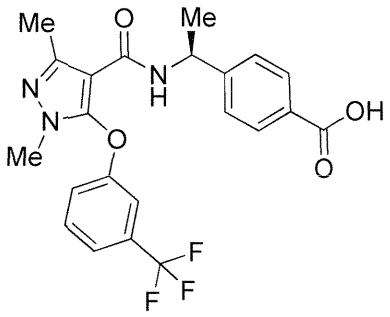
R_6 is hydrogen, halo, methyl, or methoxy;

R_7 is hydrogen, halo, methyl, or methoxy; and

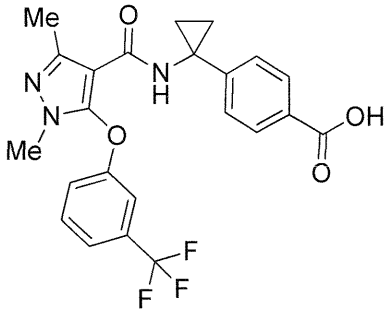
X is oxygen;

or a pharmaceutically acceptable salt thereof.

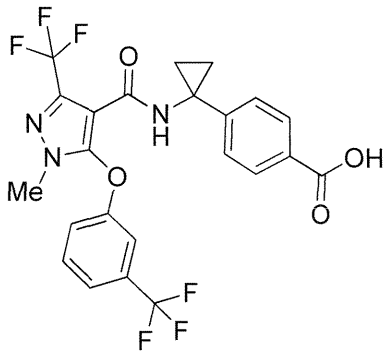
9. The use of claim 8, wherein said compound of Formula (I) is selected from the group consisting of:



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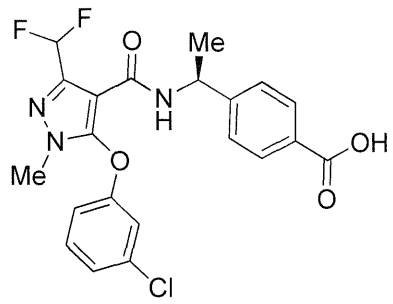
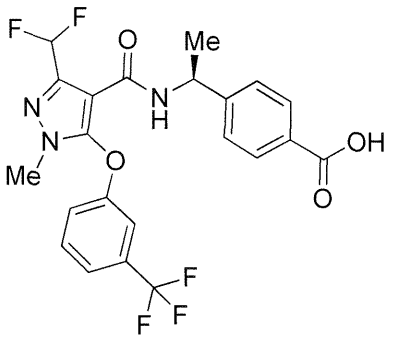
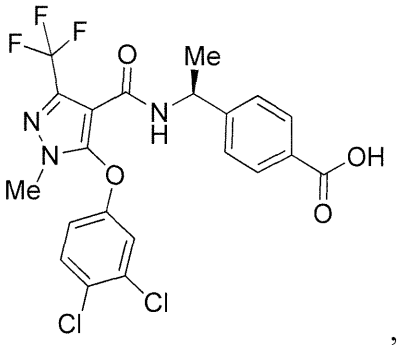


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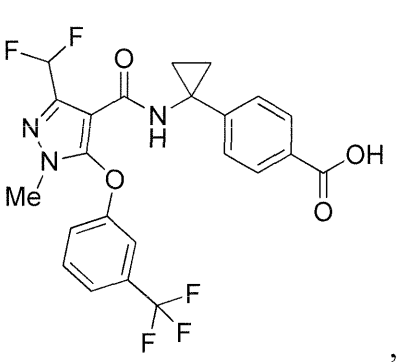
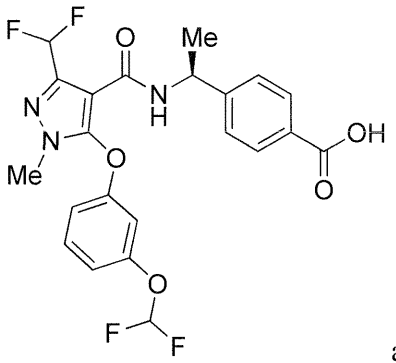


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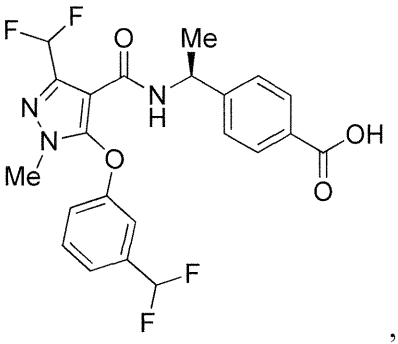
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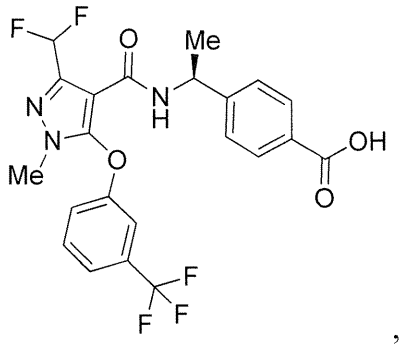
and



ER-885290 ER-885740 ER-885741

or a pharmaceutically acceptable salt thereof.

10. The use of claim 8, wherein said compound of Formula (I) is:



ER-886046 (E7046)

or a pharmaceutically acceptable salt thereof.

11. The use of any of claims 1-10, wherein the cancer is selected from the group consisting of breast cancers, cervical cancers, colorectal cancers, endometrial cancers, glioblastomas, head and neck cancers, kidney cancers, liver cancers, lung cancers, medulloblastomas, ovarian cancers, pancreatic cancers prostate cancers, skin cancers (e.g., melanoma) and urinary tract cancers.

12. The use of any of claims 1–11, wherein the cancer is metastatic cancer.

13. The use of any of claims 2–12, wherein the memory immune response comprises epitope spreading.

14. The use of any one of the preceding claims, wherein the use further comprises that an anti-metabolite chemotherapy is to be administered in combination with the EP4 antagonist and therapy selected from the group consisting of: radiation therapy and an antibody therapy.

15. The use of claim 14, wherein the anti-metabolite is a deoxynucleoside analog.

16. The use of claim 15, wherein the deoxynucleoside analog is gemcitabine or capecitabine.

17. Use of an EP4 antagonist in the manufacture of a medicament for treating cancer in a subject in need thereof wherein the medicament is to be used in combination with an anti-metabolite chemotherapy.

18. The use of claim 17, wherein the anti-metabolite is a deoxynucleoside analog.

19. The use of claim 18, wherein the deoxynucleoside analog is gemcitabine.

20. The use of claim 18, wherein the deoxynucleoside analog is capecitabine.