Several drugs classified as "AXL inhibitors" have entered clinical trials; however, many target multiple kinase receptors in addition to AXL.

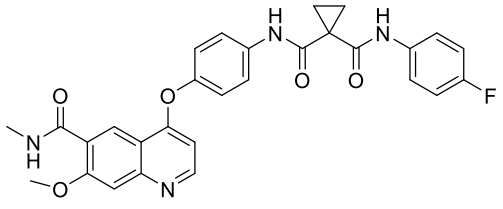
[0004] Human Axl belongs to the Tyro3, Axl, and Mer (TAM) subfamily of receptor tyrosine kinases that includes Mer. TAM kinases are characterized by an extracellular ligand binding domain consisting of two immunoglobulin-like domains and two fibronectin type III domains. Axl is overexpressed in a number of tumor cell types and was initially cloned from patients with chronic myelogenous leukemia. When overexpressed, Axl exhibits transforming potential. Axl signaling is believed to cause tumor growth through activation of proliferative and anti-apoptotic signaling pathways. Axl has been associated with cancers such as lung cancer, myeloid leukemia, uterine cancer, ovarian cancer, gliomas, melanoma, thyroid cancer, renal cell carcinoma, osteosarcoma, gastric cancer, prostate cancer, and breast cancer. The over-expression of Axl results in a poor prognosis for patients with the indicated cancers.

[0005] Activation of Mer, like Axl, conveys downstream signaling pathways that cause tumor growth and activation. Mer binds ligands such as the soluble protein Gas-6. Gas-6 binding to Mer induces autophosphorylation of Mer on its intracellular domain, resulting in downstream signal activation. Over-expression of Mer in cancer cells leads to increased metastasis, most likely by generation of soluble Mer extracellular domain protein as a decoy receptor. Tumor cells secrete a soluble form of the extracellular Mer receptor which reduces the ability of soluble Gas-6 ligand to activate Mer on endothelial cells, leading to cancer progression.

[0006] Accordingly, there is a need in the art for new therapies, including, for example, combination therapies for the treatment of cancers. Provided herein are solutions to these and other problems in the art.

SUMMARY

[0006a] In a first aspect of the present disclosure, there is provided a use of a dosage of from about 5 mg to about 100 mg of Compound 1**:**

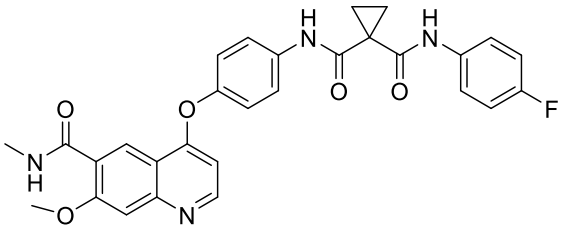


(1)

or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising Compound 1 or the pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient,

in the manufacture of a medicament for treating cancer, wherein the medicament is to be co-administered with a therapeutically effective amount of a checkpoint inhibitor or a pharmaceutical composition comprising the checkpoint inhibitor.

[0006b] In another aspect of the present disclosure, there is provided a use of a dosage of from about 5 mg to about 100 mg of Compound 1 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising Compound 1, wherein Compound 1 has the structure:



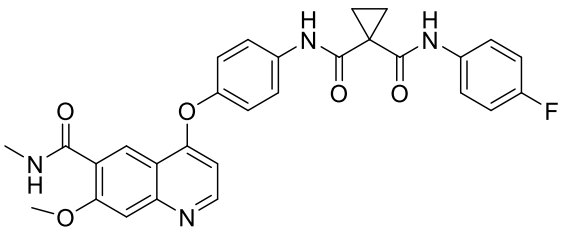
,

(1)

in the manufacture of a medicament for treating cancer, wherein the medicament is to be co-administered with a therapeutically effective amount of nivolumab or a pharmaceutical composition comprising nivolumab; and

a therapeutically effective amount of an additional immunomodulating agent or a pharmaceutical composition comprising a therapeutically effective amount of the immunomodulating agent.

[0006c] In a further aspect of the present disclosure, there is provided a use of a dosage of from about 5 mg to about 100 mg of Compound 1 or a pharmaceutically acceptable salt thereof, wherein Compound 1 has the structure:



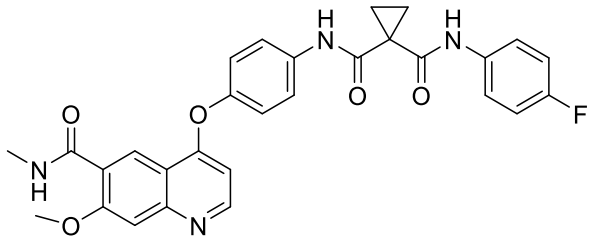
,

(1)

in the manufacture of a medicament for treating cancer, wherein the medicament is to be co-administered with a therapeutically effective amount of nivolumab and at least one additional immunomodulating agent.

[0007] In one example, the present disclosure includes a method for treating cancer in a subject, the method comprising:

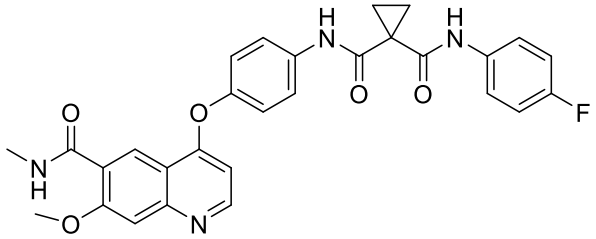
(i) administering to the subject a dosage of from about 5 mg to about 100 mg of Compound 1 or a pharmaceutically acceptable salt thereof, wherein Compound 1 has the structure:



, and

(ii) administering to the subject a therapeutically effective amount of a checkpoint inhibitor.

[0008] In another example, the present disclosure includes a method for treating cancer in a subject, the method comprising administering to the subject in need of such treatment a dosage of from about 5 mg to about 100 mg of Compound 1**:**



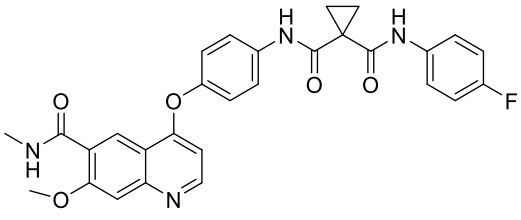
(1)

or a pharmaceutically acceptable salt thereof or a pharmaceutical composition comprising Compound 1 or the pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient,

in combination with a therapeutically effective amount of a checkpoint inhibitor or a pharmaceutical composition comprising the checkpoint inhibitor.

[0009] In one example, the present disclosure includes a method for treating urothelial carcinoma in a subject, the method comprising:

(i) administering to the subject a dosage of from about 5 mg to about 100 mg of Compound 1 or a pharmaceutically acceptable salt thereof, wherein Compound 1 has the structure:

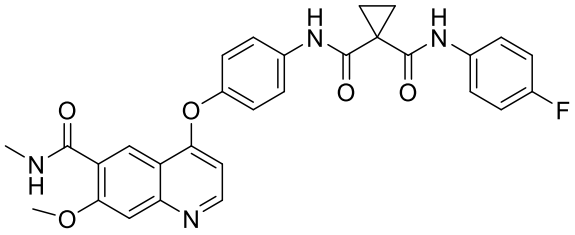


, and

(1)

(ii) administering to the subject a therapeutically effective amount of a checkpoint inhibitor.

[0010] In another example, the present disclosure includes a method for treating urothelial carcinoma in a subject, the method comprising administering to the subject in need of such treatment a dosage of from about 5 mg to about 100 mg of Compound 1**:**



(1)

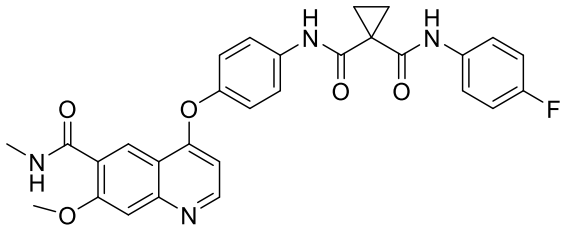
or a pharmaceutically acceptable salt thereof or a pharmaceutical composition comprising Compound 1 or the pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient,

in combination with a therapeutically effective amount of a checkpoint inhibitor or a pharmaceutical composition comprising the checkpoint inhibitor.

[0011] In these and other examples, the checkpoint inhibitor is selected from the group consisting of a PD-1 inhibitor, a PD-L1 inhibitor, and a CTLA-4 inhibitor. In these and other examples, the checkpoint inhibitor is selected from the group consisting of pembrolizumab, nivolumab, atezolizumab (TECENTRIQ®), durvalumab, avelumab (BAVENCIO®), cemiplimab, camrelizumab, sintilimab, tisleilizumab, toripalimab, spartalizumab, dostarlimab, KN035 (Jiangsu Alphamb Biopharmaceuticals Co.), Cosibelimab (formerly CK-301), CA-170 (Curis, Inc.), BMS-986189 (Bristol Myers Squibb Co.), and ipilimumab (Yervoy, Bristol Myers Squibb Co.).

[0012] In a further example, what is provided is a method of treating cancer in a subject, comprising:

(i) administering to the subject a dosage of from about 5 mg to about 100 mg of Compound 1 or a pharmaceutically acceptable salt thereof, wherein Compound 1 has the structure:



, and

(1)

(ii) administering to the subject a therapeutically effective amount of nivolumab and at least one additional immunomodulating agent.

[0013] In one example, the immunomodulating agent is selected from the group consisting of a PD-1 inhibitor, a PD-L1 inhibitor, a CTLA-4 inhibitor, and an IL-2 targeting agent.

[0014] In these and other examples, the subject is a human subject in need of treatment.

[0015] In these and other examples, the checkpoint inhibitor is selected from the group consisting of a PD-1 inhibitor, a PD-L1 inhibitor, and a CTLA-4 inhibitor. In these and other examples, the checkpoint inhibitor is selected from the group consisting of pembrolizumab, nivolumab, atezolizumab (TECENTRIQ®), durvalumab, avelumab (BAVENCIO®), cemiplimab, camrelizumab, sintilimab, tisleilizumab, toripalimab, spartalizumab, dostarlimab, KN035 (Jiangsu Alphamb Biopharmaceuticals Co.), Cosibelimab (formerly CK-301), CA-170 (Curis, Inc.), BMS-986189 (Bristol Myers Squibb Co.), and ipilimumab (Yervoy, Bristol Myers Squibb Co.).

[0016] In these and other examples, the IL-2 targeting agent is selected from the group consisting of a CD122-preferential IL-2 pathway agonist, a PEG-IL-2Rαβ-biased agonist, an IL-2Rβ-biased agonist, an IL-2Rβγ_c-biased agonist, an IL-2v/IL-2α fusion protein, an anti-EDB mAb (L19)/IL-2v fused to L19/TNFv, an Anti-GD2 mAb/IL-2v, an anti-FAP mAb/IL-2v, an anti-CEA mAb/IL-2v, an anti-PD-1 mAb/IL-2v, a vaccine of patient derived tumor cells + HD-IL-2, adoptive cell therapy + IL-2 infusion, adoptive cell therapy + IL-2 infusion + anti-PD-1 mAb, orthogonal IL-2v/IL-2Rβ mutant pairs, an anti-IL-2Rα mAb/PBD conjugate, a PEG-IL-2Rα-biased agonist, an IL-2v/human Fc fusion protein, a PEG-IL-2Rα-biased (N88D)/IgG1 fusion proten, an anti-IL-2 mAb/IL-2v, a recombinant plasmid encoding IL-2, PPI, TGF-β1, and IL-10, and an IL -2Rβ antagonist.

[0017] In one example, the IL-2 targeting agent is a CD122-preferential IL-2 pathway agonist. In one example, CD122-preferential IL-2 pathway agonist is bempegaldesleukin (BEMPEG; NKTR-214; Bristol Myers Squibb Co.).

[0018] In one example, the IL-2 targeting agent is a PEG-IL-2Rα-biased agonist. In one example, the PEG-IL-2Rα-biased agonist is NKTR-358 (Bristol Myers Squibb Co.).

[0019] In a further example, the present disclosure includes a method of treating cancer in a subject, the method comprising administering to the subject a dosage of from about 5 mg to about 100 mg of Compound 1 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising Compound 1.

[0020] In these and other examples, Compound 1 is administered as a free base crystalline solid or as a crystalline pharmaceutically acceptable salt. For avoidance of doubt, "Compound 1" means these crystalline free base forms as well as crystalline salt forms unless otherwise indicated.

[0021] In these and other examples, Compound 1 is a crystalline solid form characterized as Form A, Form B, Form C, Form D, Form E, Form F, Form G, Form H, Form K, Form O, or Form Q.

[0022] In these and other examples, Compound 1 is a crystalline HCl salt of Compound 1.

[0023] In these and other examples, Compound 1 is a crystalline fumaric acid salt of Compound 1, or hydrate or solvate thereof.

[0024] In these and other examples, Compound 1 is a crystalline phosphoric acid salt of Compound 1 or hydrate or solvate thereof.

BRIEF DESCRIPTION OF DRAWINGS

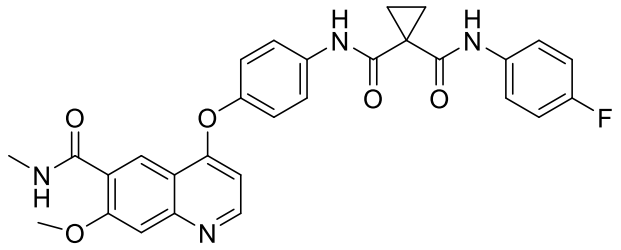
[0025] Fig. 1A shows the presence of tumor microvessels by CD31 staining after treatment with Compound 1. Horizontal bars represent mean values for n=3 tumors per condition.

[0026] Fig. 1B shows the presence of tumor microvessels by CD31 staining after treatment with Compound 1. Paraffin-embedded tumor tissue was stained with the blood vessel marker CD31 and scored for the density of blood vessels across conditions.

[0027] Fig. 2A shows the presence of cytotoxic T-cells by CD8 staining after treatment with Compound 1, PD-1, and combination of Compound 1+PD-1. Horizontal bars represent median values for n=8-12 tumors per condition.

Claims

1. Use of a dosage of from about 5 mg to about 100 mg of Compound 1**:**



(1)

or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising Compound 1 or the pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient,

in the manufacture of a medicament for treating cancer, wherein the medicament is to be co-administered with a therapeutically effective amount of a checkpoint inhibitor or a pharmaceutical composition comprising the checkpoint inhibitor.

2. The use of claim 1, wherein the checkpoint inhibitor is selected from the group consisting of a PD-1 inhibitor, a PD-L1 inhibitor, and a CTLA-4 inhibitor.

3. The use of claim 2, wherein the checkpoint inhibitor is selected from the group consisting of pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, cemiplimab, camrelizumab, sintilimab, tisleilizumab, toripalimab, spartalizumab, dostarlimab, KN035 (Jiangsu Alphamb Biopharmaceuticals Co.), Cosibelimab (formerly CK-301), CA-170 (Curis, Inc.), BMS-986189 (Bristol Myers Squibb Co.), and ipilimumab.

4. The use of any one of claims 1-3, wherein the checkpoint inhibitor is atezolizumab, avelumab, or nivolumab.

5. The use of any one of claims 1-4, wherein Compound 1 or a pharmaceutically acceptable salt thereof is to be administered orally once per day (qd) or twice per day (bid).

6. The use of claim 5, wherein the dosage of Compound 1 or a pharmaceutically acceptable salt thereof is from about 5 mg to about 80 mg.

7. The use of any one of claims 1-6, wherein the dosage of Compound 1 or a pharmaceutically acceptable salt thereof, is selected from about 10 mg, 20 mg, 40 mg, 60 mg, and 80 mg.

8. The use of any one of claims 1-7, wherein the checkpoint inhibitor is to be administered intravenously (IV) to the subject.

9. The use of any one of claims 1-8, wherein the checkpoint inhibitor is to be administered once every two weeks, once every three weeks, or once every four weeks for the duration of the treatment period.

10. The use of claim 9, wherein the dosage of the checkpoint inhibitor is from about 100 mg to about 1700 mg.

11. The use of any one of claims 1-10, wherein the checkpoint inhibitor is atezolizumab, and the dosage of atezolizumab is about 840 mg to be administered once every two weeks, about 1200 mg to be administered once every three weeks, or 1680 mg to be administered once every four weeks.

12. The use of claim 11, wherein atezolizumab is to be administered to a subject in an IV unit dosage form, wherein the dose form comprises 840 mg, 1200 mg, or 1680 mg of atezolizumab, water, glacial acetic acid, L-histidine, polysorbate 20, and sucrose.

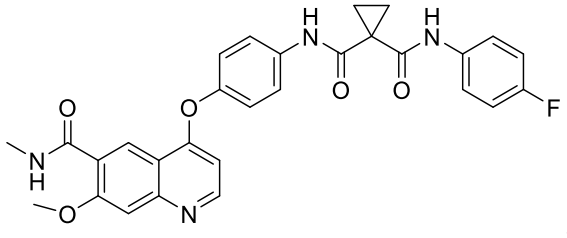
13. The use of claim 11 or 12, wherein atezolizumab is to be administered to a subject in an IV unit dosage form, wherein the dosage form is sold as Tecentriq®.

14. The use of any one of claims 1-10, wherein the checkpoint inhibitor is avelumab, and the dosage of avelumab is about 800 mg to be administered once every two weeks, about 1200 mg to be administered once every three weeks, or 1600 mg to be administered once every four weeks.

15. The use of claim 14, wherein avelumab is to be administered at about 800 mg once every two weeks as an intravenous infusion.

16. The use of claims 1-10, wherein the checkpoint inhibitor is nivolumab and the dose of nivolumab is about 360 mg to be administered every three weeks.

17. Use of a dosage of from about 5 mg to about 100 mg of Compound 1 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising Compound 1, wherein Compound 1 has the structure:



,

(1)

in the manufacture of a medicament for treating cancer, wherein the medicament is to be co-administered with a therapeutically effective amount of nivolumab or a pharmaceutical composition comprising nivolumab; and

a therapeutically effective amount of an additional immunomodulating agent or a pharmaceutical composition comprising a therapeutically effective amount of the immunomodulating agent.

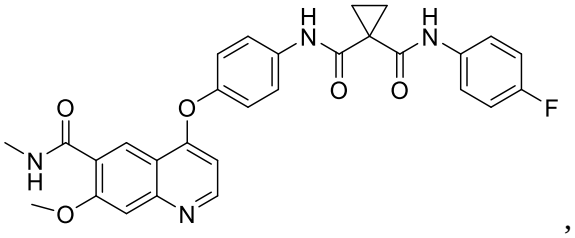
18. The use of claim 17, wherein the additional immunomodulating agent is ipilimumab.

19. The use of claim 18 wherein the ipilimumab is to be administered as four IV doses at about 1 mg/kg IV mg every three weeks.

20. The use of claim 17, wherein the additional immunomodulating agent is BEMPEG.

21. The use of claim 18 wherein the BEMPEG is to be administered at about 0.006 mg/kg IV mg every three weeks.

22. Use of a dosage of from about 5 mg to about 100 mg of Compound 1 or a pharmaceutically acceptable salt thereof, wherein Compound 1 has the structure:



(1)

in the manufacture of a medicament for treating cancer, wherein the medicament is to be co-administered with a therapeutically effective amount of nivolumab and at least one additional immunomodulating agent.

23. The use of claim 22, wherein the immunomodulating agent is selected from the group consisting of a PD-1 inhibitor, a PD-L1 inhibitor, a CTLA-4 inhibitor, and an IL-2 targeting agent.

24. The use of claim 23, wherein the PD-1 inhibitor, PD-L1 inhibitor, and CTLA-4 inhibitor is selected from the group consisting of pembrolizumab, atezolizumab (TECENTRIQ®), durvalumab, avelumab (BAVENCIO®), cemiplimab, camrelizumab, sintilimab, tisleilizumab, toripalimab, spartalizumab, dostarlimab, KN035 (Jiangsu Alphamb Biopharmaceuticals Co.), Cosibelimab (formerly CK-301), CA-170 (Curis, Inc.), BMS-986189 (Bristol Myers Squibb Co.), and ipilimumab (Yervoy, Bristol Myers Squibb Co.).

25. The use of claim 23, wherein the IL-2 targeting agent is selected from the group consisting of a CD122-preferential IL-2 pathway agonist, a PEG-IL-2Rαβ-biased agonist, an IL-2Rβ-biased agonist, an IL-2Rβγ_c-biased agonist, an IL-2v/IL-2α fusion protein, an anti-EDB mAb (L19)/IL-2v fused to L19/TNFv, an Anti-GD2 mAb/IL-2v, an anti-FAP mAb/IL-2v, an anti-CEA mAb/IL-2v, an anti-PD-1 mAb/IL-2v, a vaccine of patient derived tumor cells + HD-IL-2, adoptive cell therapy + IL-2 infusion, adoptive cell therapy + IL-2 infusion + anti-PD-1 mAb, orthogonal IL-2v/IL-2Rβ mutant pairs, an anti-IL-2Rα mAb/PBD conjugate, a PEG-IL-2Rα-biased agonist, an IL-2v/human Fc fusion protein, a PEG-IL-2Rα-biased (N88D)/IgG1 fusion proten, an anti-IL-2 mAb/IL-2v, a recombinant plasmid encoding IL-2, PPI, TGF-β1, and IL-10, and an IL -2Rβ antagonist.

26. The use of any one of claims 1-25, wherein Compound 1 or the pharmaceutically acceptable is a crystalline fumaric acid salt of Compound 1, or hydrate or solvate thereof.

27. The use of any one of claims 1-26, wherein Compound 1 is to be administered as a pharmaceutical composition comprising:

a. about 25 percent to about 35 percent by weight of Compound 1 or a pharmaceutically acceptable salt thereof;
b. about 37 percent to about 43 percent by weight of microcrystalline cellulose;
c. about 18 to about 22 percent by weight of anhydrous lactose;
d. about 2 to about 6 percent by weight of hydroxypropyl cellulose;
e. about 5 to about 7 percent by weight of croscarmellose sodium;
f. about 0.2 to about 0.4 percent by weight of colloidal silicon dioxide;
g. about 0.5 to about 3.5 percent by weight magnesium stearate; and optionally
h. a film coating.

28. The use of any one of claims 1-26, wherein Compound 1 is to be administered as a pharmaceutical composition comprising:

a. about 25 percent to about 35 percent by weight of Compound 1 or a pharmaceutically acceptable salt thereof;

b. about 35 percent to about 40 percent by weight of microcrystalline cellulose;
c. about 16 to about 22 percent by weight of anhydrous lactose;
d. about 3 to about 7 percent by weight of hydroxypropyl cellulose;
e. about 3 to about 7 percent by weight of croscarmellose sodium
f. about 0.1 to about 0.5 percent by weight of colloidal silicon dioxide;
g. about 0.5 to about 3.5 percent by weight stearic acid; and optionally
h. a film coating.

29. The use of any one of claims 1-28, wherein the cancer is selected from cardiac cancer, head and neck cancer, lung cancer, non-small cell lung cancer, small cell lung cancer, non-clear cell renal cell carcinoma, advanced or metastatic clear cell renal cell carcinoma, castration-resistant prostate cancer, hormone receptor-positive breast cancer, prostate cancer, colon cancer, gastrointestinal cancer, breast cancer, genitourinary tract cancer, liver cancer, bone cancer, thyroid cancer, cancer of the nervous system, gynecological cancer, hematologic cancer, skin cancer, urothelial carcinoma, cancer of the adrenal glands, endometrial cancer, sarcoma, neuroendocrine tumor, ovarian cancer, hepatocellular carcinoma, gastric cancer, colorectal cancer, and melanoma.

30. The use of any one of claims 1-29, wherein the cancer is solid tumor that is inoperable, locally advanced, metastatic, or recurrent.

31. The use of claim 30, wherein the solid tumor is unresectable or metastatic and life-prolonging therapies do not exist or available therapies are intolerable or no longer effective.

32. The use of any one of claims 29-31, wherein the cancer is non-clear cell renal cell carcinoma, advanced or metastatic clear cell renal cell carcinoma, hormone receptor positive breast cancer, colorectal cancer, or castration resistant prostate cancer.

33. The use of claim 32, wherein the cancer is advanced metastatic clear cell renal cell carcinoma, unresectable advanced or metastatic renal cell carcinoma with a clear-cell component, cancer with a sarcomatoid feature, advanced non-clear cell renal cell carcinoma,

unresectable advanced or metastatic non-clear cell renal cell carcinoma, Papillary renal cell carcinoma, unclassified renal cell carcinoma, or sarcomatoid renal cell carcinoma.

34. The use of any one of claims 17-31, wherein Compound 1, nivolumab, and the additional immunomodulating agent are to be administered concurrently, sequentially, or separately.