

PPARG INVERSE AGONISTS AND IMMUNOTHERAPIES FOR TREATING CANCER

RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional Application No. 63/546,013, filed October 27, 2023, the entire contents of which are incorporated herein by reference.

BACKGROUND

[0002] Although immune checkpoint inhibitor (ICI) approval has changed the treatment landscape of metastatic urothelial carcinoma, approximately 70% of patients succumb to refractory or acquired resistance. Tumor intrinsic mechanisms and immunoregulatory mechanisms in the tumor microenvironment (TME) are both areas of intense interrogations to identify biomarkers to ICI resistance.

[0003] Dysregulation of PPARG signaling is linked to tumor development in urothelial cancer, where PPARG signaling is essential to cell lineage determination in the luminal layers of the normal urothelium. Recurrent genetic alterations in PPARG, as well as hotspot mutations in its obligate heterodimer, retinoid X receptor alpha (RXRA), are characteristics of the luminal subtype, which responds poorly to ICI. Higher baseline PPARG expression in tumors has been significantly associated with worse overall survival (OS) of patients with hepatic carcinoma, melanoma and glioblastoma, as well as progression-free survival (PFS) in clear cell renal cell carcinoma. Moreover, tumor-cell intrinsic upregulation of PPARG is associated with an immunosuppressive TME, characterized by anti-inflammatory cytokine signaling, decreased T-cell infiltration, T-cell dysfunction and increased myeloid-derived suppressive cells.

[0004] Besides its expression in normal epithelium and tumor cells, PPARG is also expressed in certain immune cells. Studies have shown that PPARG plays an important role in the maturation and function of various immune system-related cell types, such as monocytes and macrophages. How PPARG expression impacts the cell function and cells states of these immune cells during carcinogenesis and different treatment regimens, remains a subject of interrogation.

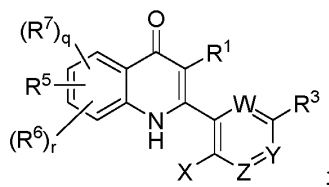
SUMMARY

[0005] We have now found that PPARG amplification is associated with a lack of response to anti-PD1 in muscle invasive urothelial cancer. See e.g., the Exemplification

section, where tumors collected from patients with muscle-invasive urothelial cancer revealed that mRNA expression level of PPARG was significantly higher in the anti-PD1 therapy group. We have also identified that PPARG is upregulated in urothelial cancer patients who were being treated with pembrolizumab, a humanized monoclonal antibody that inhibits the PD-1 receptor. See e.g., the Exemplification section below, where PPARG was found to be upregulated in urothelial cancers patients who were treated with pembrolizumab. Further, we have also found that genetically engineered mouse models of luminal urothelial cancer with intact immune systems exhibit immune filtration into tumors upon PPARG inhibition. See e.g., the Exemplification section below, where PPARG agonist treated tumors showed an increase in the number of CD45+ cells relative to tumors from animals treated with vehicle control, indicating an increase in immune cells present in the tumors after treatment. Taken together, this data suggests that PPARG may play an important role in primary resistance of immune checkpoint inhibitor therapies across different cancer indications, particularly urothelial cancers.

[0006] Provided herein, therefore, are methods of using a therapeutically effective amount of a PPARG inverse agonist with a therapeutically effective amount of an immunotherapy (IO) agent to treat cancer.

[0007] In some aspects, the PPARG inverse agonist is a compound having the Formula I:



or a polymorph thereof, or pharmaceutically acceptable salt of the compound or polymorph, wherein the variables are as described herein.

[0008] In some aspects, the present methods comprise treating subjects who are characterized as progressed/relapsed to an immunotherapeutic agent.

[0009] In some aspects, the present methods comprise treating subjects who are characterized as refractory/resistant to an immunotherapeutic agent.

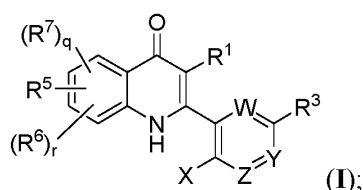
[0010] In some aspects, the present methods comprise treating cancers which are characterized as advanced cancers.

[0011] In some aspects, the immunotherapy (IO) agent described by the present methods is an immune checkpoint inhibitor.

[0012] Also provided are pharmaceutical compositions comprising a therapeutically effective amount of a PPAR γ inverse agonist (e.g., a compound of Formula I) and a therapeutically effective amount of an immunotherapy (IO) agent.

DETAILED DESCRIPTION

[0013] In one embodiment, provided herein is a method of treating cancer in a subject, comprising administering to the subject a therapeutically effective amount of an immunotherapeutic and a therapeutically effective amount of a compound having the Formula I:



or a polymorph thereof, or pharmaceutically acceptable salt of the compound or polymorph, wherein

W, Y, and Z are each independently N or $-\text{CR}^4$;

X is halo, $-\text{SR}^2$, $-\text{SOR}^2$, $-\text{SO}_2\text{R}^2$, $-\text{OR}^2$, and $-\text{SO}(=\text{NR}^2)\text{R}^{2'}$;

R^2 and $\text{R}^{2'}$ are each independently (C₁-C₄)alkyl, (C₁-C₄)alkoxy, or halo(C₁-C₄)alkyl;

R^2 is (C₁-C₄)alkyl, (C₁-C₄)alkoxy, or halo(C₁-C₄)alkyl;

R^3 is cyano or nitro;

R^4 is hydrogen, halo, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, or hydroxyl;

R^5 is halo, halo(C₁-C₄)alkyl, or cyano;

R^6 is halo, halo(C₁-C₄)alkyl, (C₁-C₄)alkyl, or cyano;

R^7 is halo, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, halo(C₁-C₄)alkyl, halo(C₁-C₄)alkoxy, $-(\text{C}_1-\text{C}_4)\text{alkylOR}^a$, $-(\text{C}_1-\text{C}_4)\text{alkylC(O)R}^a$, $-(\text{C}_1-\text{C}_4)\text{alkylC(O)OR}^a$, $-\text{C(O)NR}^a\text{R}^b$, $-(\text{C}_1-\text{C}_4)\text{alkylC(O)NR}^a\text{R}^b$, $-\text{C(O)R}^a$, $-\text{C(O)OR}^a$, $-\text{NR}^a\text{R}^b$, $-(\text{C}_1-\text{C}_4)\text{alkylNR}^a\text{R}^b$, $-\text{C(O)NR}^a\text{SO}_3\text{H}$, $-\text{NR}^a\text{C(O)R}^b$, $-\text{NR}^a\text{C(O)OR}^b$, $-\text{NR}^a\text{C(S)OR}^b$, $-\text{NR}^a\text{C(O)NR}^b$, $-\text{NR}^a\text{C(S)NR}^b$, $-\text{NR}^a\text{S(O)}_2\text{NR}^b$, $-\text{C(S)R}^a$, $-\text{S(O)}_2\text{R}^a$, $-\text{S(O)R}^a$, $-\text{C(S)OR}^a$, $-\text{C(S)NR}^a\text{R}^b$, $-\text{NR}^a\text{C(S)R}^b$, $-\text{SR}^a$, phenyl, 4- to 6-membered heterocyclyl, and 5- to 7-membered heteroaryl, wherein each of said phenyl, 4- to 6-membered heterocyclyl, and 5- to 7-membered heteroaryl are optionally and independently substituted with 1 to 3 groups selected from R^8 ;

R^8 is selected from halo, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy, halo(C₁-C₄)alkoxy, nitro, oxo, cyano, $-(\text{C}_1-\text{C}_4)\text{alkylOR}^d$, $-(\text{C}_1-\text{C}_4)\text{alkylC(O)R}^d$, $-(\text{C}_1-\text{C}_4)\text{alkylC(O)OR}^d$, $-\text{C(O)NR}^d\text{R}^e$, $-(\text{C}_1-\text{C}_4)\text{alkylC(O)NR}^d\text{R}^e$, $-\text{C(O)R}^d$, $-\text{C(O)OR}^d$, $-\text{NR}^d\text{R}^e$, -

(C₁-C₄)alkylNR^dR^e, -C(O)NR^dSO₃H, -NR^dC(O)R^e, -NR^dC(O)OR^e, -NR^dC(S)OR^e, -NR^fC(O)N^dR^e, -NR^fC(S)NR^dR^e, -NR^fS(O)₂NR^dR^e, -C(S)R^d, -S(O)₂R^d, -S(O)R^d, -C(S)OR^d, -C(S)NR^dR^e, -NR^dC(S)R^e, and -SR^d;

R^a, R^b, R^c, R^d, R^e, and R^f are each independently hydrogen or (C₁-C₄)alkyl; and
q and r are each independently 0 or 1.

[0014] In one embodiment, provided herein is a method of treating a cancer in a subject, comprising administering to the subject a therapeutically effective amount of a compound having the Formula **I** or a polymorph thereof, or pharmaceutically acceptable salt of the compound or polymorph, wherein the subject is characterized as progressed/relapsed to an immunotherapeutic agent.

[0015] In one embodiment, provided herein is a method of treating a cancer in a subject, comprising administering to the subject a therapeutically effective amount of a compound having the Formula **I** or a polymorph thereof, or pharmaceutically acceptable salt of the compound or polymorph, wherein the subject is characterized as refractory/resistant to an immunotherapeutic agent.

[0016] In embodiments, the cancer treated by the present methods is urothelial cancer. In embodiments, the cancer treated by the present methods characterized as an advanced cancer. As used herein, an “advanced cancer” such as “advanced urothelial cancer” is one that is inoperable or which has metastasized. In embodiments, the cancer treated by the present is advanced urothelial cancer. In embodiments, the cancer treated by the present is muscle-invasive urothelial cancer.

[0017] In one embodiment, provided herein is a pharmaceutical composition comprising a therapeutically effective amount of a compound having the Formula **I** or a polymorph thereof, or pharmaceutically acceptable salt of the compound or polymorph; and a therapeutically effective amount of an immunotherapeutic agent.

[0018] In embodiments, the immunotherapeutic agent used in the present methods and compositions is an immune checkpoint inhibitor. In embodiments, the immunotherapeutic agent used in the present methods and compositions is selected from ipilimumab, cemiplimab, avelumab, atezolizumab, avelumab, dostarlizumab, durvalumab, ipilimumab, nivolumab, pembrolizumab, and the combination of nivolumab and relatlimab. In embodiments, the immunotherapeutic agent used in the present methods and compositions is pembrolizumab.

[0019] When used in connection to describe a chemical group that may have multiple points of attachment, a hyphen (-) designates the point of attachment of that group to the

variable to which it is defined. For example, $\text{-NR}^b\text{C(O)OR}^c$ and $\text{-NR}^b\text{C(S)OR}^c$ mean that the point of attachment for this group occurs on the nitrogen atom.

[0020] The terms “halo” and “halogen” refer to an atom selected from fluorine (fluoro, -F), chlorine (chloro, -Cl), bromine (bromo, -Br), and iodine (iodo, -I).

[0021] The term “alkyl” when used alone or as part of a larger moiety, such as “haloalkyl”, and the like, means saturated straight-chain or branched monovalent hydrocarbon radical.

[0022] “Alkoxy” means an alkyl radical attached through an oxygen linking atom, represented by -O-alkyl . For example, “(C₁-C₄)alkoxy” includes methoxy, ethoxy, propoxy, and butoxy.

[0023] The term “haloalkyl” includes mono, poly, and perhaloalkyl groups where the halogens are independently selected from fluorine, chlorine, bromine, and iodine.

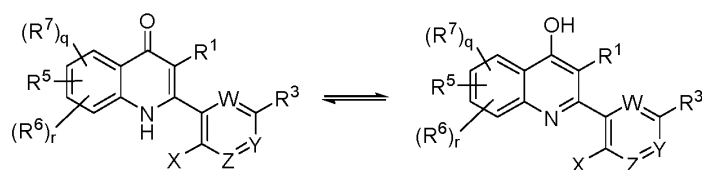
[0024] “Haloalkoxy” is a haloalkyl group which is attached to another moiety via an oxygen atom such as, e.g., -OCHF_2 or -OCF_3 .

[0025] The term oxo means the group =O .

[0026] The term “5- to 7-membered heteroaryl” used alone or as part of a larger moiety refers to a 5- to 7-membered aromatic radical containing 1-4 heteroatoms selected from N, O, and S. Monocyclic heteroaryl includes, for example, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, triazinyl, tetrazinyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, etc. Optional substituents on a heteroaryl group may be present on any substitutable position and, include, e.g., the position at which the heteroaryl is attached.

[0027] The term “4- to 6-membered heterocyclyl” means a 4- to 6-membered saturated or partially unsaturated heterocyclic ring containing 1 to 4 heteroatoms independently selected from N, O, and S. A heterocyclyl ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. Examples of monocyclic saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, pyrrolidinyl, pyrrolidonyl, piperidinyl, oxazolidinyl, piperazinyl, dioxanyl, oxetanyl, dioxolanyl, morpholinyl, dihydrofuranyl, dihydropyranyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl, and tetrahydropyrimidinyl. Optional substituents on a heterocyclyl group may be present on any substitutable position and, include, e.g., the position at which the heterocyclyl is attached.

[0028] The described compounds of Formula **I** may exist in one or more tautomeric forms, such as those below, and are included herein.



[0029] As used herein, “crystalline” refers to a solid form of a compound wherein there exists long-range atomic order in the positions of the atoms. The crystalline nature of a solid can be confirmed, for example, by examination of the X-ray powder diffraction pattern.

[0030] Unless otherwise specified, crystalline Form A of 3-(5,7-difluoro-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile is a single crystalline form, meaning that 3-(5,7-difluoro-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile is present as a single crystal or a plurality of crystals in which each crystal has the same crystal form (i.e., Form A).

[0031] The 2-theta values of the X-ray powder diffraction patterns for the crystalline form described herein may vary slightly from one instrument to another and also depending on variations in sample preparation and batch to batch variation due to factors such as temperature variation, sample displacement, and the presence or absence of an internal standard. Therefore, unless otherwise defined, the XRPD patterns / assignments recited herein are not to be construed as absolute and can vary ± 0.2 degrees. It is well known in the art that this variability will account for the above factors without hindering the unequivocal identification of a crystal form. Unless otherwise specified, the 2-theta values provided herein were obtained using Cu K α 1 radiation.

[0032] The terms “subject” and “patient” may be used interchangeably, and means a mammal in need of treatment, *e.g.*, companion animals (*e.g.*, dogs, cats, and the like), farm animals (*e.g.*, cows, pigs, horses, sheep, goats and the like) and laboratory animals (*e.g.*, rats, mice, guinea pigs and the like). Typically, the subject is a human in need of treatment.

[0033] It will be understood that unless otherwise indicated, the administrations described herein include administering a described compound of Formula I prior to, concurrently with, or after administration of the immunotherapeutic described herein. Thus, simultaneous administration is not necessary for therapeutic purposes. In one aspect, however, a described compound of Formula I inhibitor is administered concurrently with the immunotherapeutic.

[0034] As used herein, the terms “treatment,” “treat,” and “treating” refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a cancer, or one or more symptoms thereof, as described herein. In some aspects, treatment may be administered after one or more symptoms have developed, *i.e.*, therapeutic treatment. In other aspects,

treatment may be administered in the absence of symptoms. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (*e.g.*, in light of a history of symptoms and/or in light of exposure to a particular organism, or other susceptibility factors), *i.e.*, prophylactic treatment. Treatment may also be continued after symptoms have resolved, for example to delay their recurrence.

[0035] For use in medicines, the salts of the compounds described herein refer to non-toxic “pharmaceutically acceptable salts.” Pharmaceutically acceptable salt forms include pharmaceutically acceptable acidic/anionic or basic/cationic salts. Suitable pharmaceutically acceptable acid addition salts of the compounds described herein include *e.g.*, salts of inorganic acids (such as hydrochloric acid, hydrobromic, phosphoric, nitric, and sulfuric acids) and of organic acids (such as, acetic acid, benzenesulfonic, benzoic, methanesulfonic, and *p*-toluenesulfonic acids). Compounds of the present teachings with acidic groups such as carboxylic acids can form pharmaceutically acceptable salts with pharmaceutically acceptable base(s). Suitable pharmaceutically acceptable basic salts include *e.g.*, ammonium salts, alkali metal salts (such as sodium and potassium salts) and alkaline earth metal salts (such as magnesium and calcium salts). Compounds with a quaternary ammonium group also contain a counteranion such as chloride, bromide, iodide, acetate, perchlorate and the like. Other examples of such salts include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, benzoates and salts with amino acids such as glutamic acid.

[0036] The term “effective amount” or “therapeutically effective amount” refers to an amount of a compound described herein that will elicit a desired or beneficial biological or medical response of a subject *e.g.*, a dosage of between 0.01 - 100 mg/kg body weight/day.

[0037] As used herein, the term “immunotherapeutic” refers to an agent that treats diseases, such as cancer, by activating or suppressing the immune system.

Immunotherapeutics include *e.g.*, monoclonal antibodies (MABs) such as trastuzumab, pertuzumab, bevacizumab, and rituximab; immune checkpoint inhibitors such as ipilimumab, cemiplimab, avelumab, atezolizumab, avelumab, dostarlizumab, durvalumab, ipilimumab, nivolumab, pembrolizumab, and the combination of nivolumab and relatlimab; cytokines such as interferons (*e.g.*, interferon alpha) and interleukins (*e.g.*, aldesleukin); vaccines (*e.g.*, sipuleucel-T and Bacillus Calmette-Guérin); and chimeric antigen receptor T-cell therapy (CAR-T) such as tisagenlecleucel, axicabtagene ciloleucel, brexucabtagene autoleucel, lisocabtagene maraleucel, idecabtagene vicleucel, and ciltacabtagene autoleucel.

[0038] A subject who is characterized as progressed/relapsed is one who at one time responded to treatment with an immunotherapeutic (*e.g.*, an immune checkpoint inhibitor

such as ipilimumab, cemiplimab, avelumab, atezolizumab, avelumab, dostarlizumab, durvalumab, ipilimumab, nivolumab, pembrolizumab, and the combination of nivolumab and relatlimab), but who no longer responds. Similarly, a progressed/relapsed cancer is one that was initially treatable with an immunotherapeutic (e.g., an immune checkpoint inhibitor such as ipilimumab, cemiplimab, avelumab, atezolizumab, avelumab, dostarlizumab, durvalumab, ipilimumab, nivolumab, pembrolizumab, and the combination of nivolumab and relatlimab), but which has grown, spread, or come back after a certain period of time during treatment or after treatment.

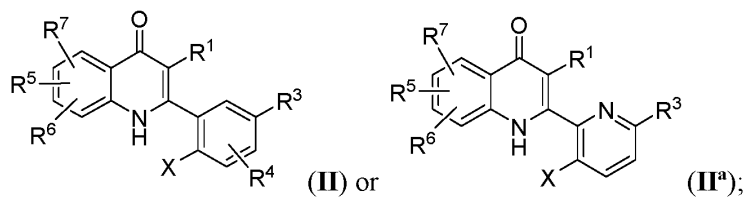
[0039] A subject who is characterized as refractory/resistant is one who is unresponsive at the beginning of treatment with an immunotherapeutic or who demonstrates worsening of cancer while on treatment with an immunotherapeutic (e.g., an immune checkpoint inhibitor such as ipilimumab, cemiplimab, avelumab, atezolizumab, avelumab, dostarlizumab, durvalumab, ipilimumab, nivolumab, pembrolizumab, and the combination of nivolumab and relatlimab). Similarly, a refractory/resistant cancer is one that does not respond to treatment either at the beginning of treatment or one that has become resistant during treatment.

[0040] Compositions and compounds described herein may be formulated for administration to a subject in need of such composition. Pharmaceutical compositions described herein may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. In some embodiments, the compositions are administered orally, intraperitoneally or intravenously. Sterile injectable forms of the pharmaceutical compositions described herein may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents.

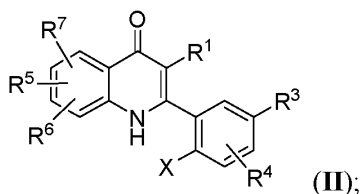
[0041] In some aspects, the pharmaceutical compositions and compounds described herein are administered orally.

[0042] A specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of a compound described herein in the composition will also depend upon the particular compound in the pharmaceutical composition.

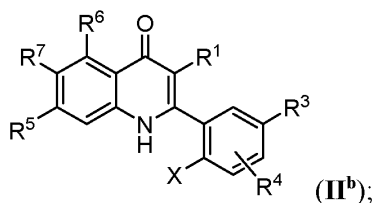
[0043] In embodiments, the compound of Formula I is of the Formula II or II^a:



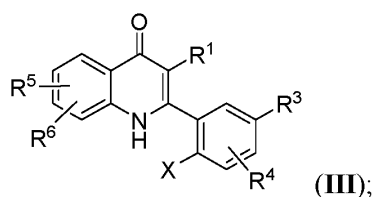
or a polymorph thereof or pharmaceutically acceptable salt of the compound or polymorph, wherein the variables are as described above for Formula I. Alternatively, in embodiments, the compound of Formula I is of the Formula II^a:



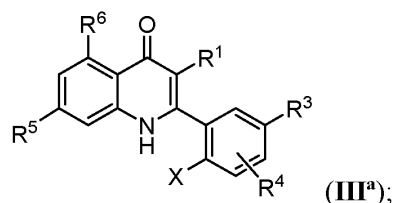
or a polymorph thereof or pharmaceutically acceptable salt of the compound or polymorph, wherein the variables are as described above for Formula I. Alternatively, in embodiments, the compound of Formula I is of the Formula II^b:



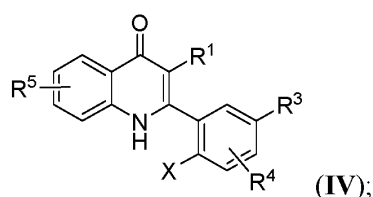
or a polymorph thereof or pharmaceutically acceptable salt of the compound or polymorph, wherein the variables are as described above for Formula I. In embodiments, the compound of Formula I is of the Formula III:



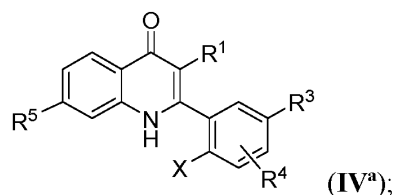
or a polymorph thereof or pharmaceutically acceptable salt of the compound or polymorph, wherein the variables are as described above for Formula I. In embodiments, the compound of Formula I is of the Formula III^a:



or a polymorph thereof or pharmaceutically acceptable salt of the compound or polymorph, wherein the variables are as described above for Formula I. In embodiments, the compound of Formula I is of the Formula IV:



or a polymorph thereof or pharmaceutically acceptable salt of the compound or polymorph, wherein the variables are as described above for Formula I. In embodiments, the compound of Formula I is of the Formula IV^a:



or a polymorph thereof or pharmaceutically acceptable salt of the compound or polymorph, wherein the variables are as described above for Formula I.

[0044] In embodiments, R¹ in the compounds described herein, or a polymorph thereof or pharmaceutically acceptable salt of the compound or polymorph is hydrogen.

[0045] In embodiments, R³ in the compounds described herein, or a polymorph thereof or pharmaceutically acceptable salt of the compound or polymorph is cyano.

[0046] In embodiments, R⁴ in the compounds described herein, or a polymorph thereof or pharmaceutically acceptable salt of the compound or polymorph is hydrogen.

[0047] In embodiments, R⁵ in the compounds described herein, or a polymorph thereof or pharmaceutically acceptable salt of the compound or polymorph is halo or cyano. In embodiments, R⁵ in the compounds described herein, or a polymorph thereof or pharmaceutically acceptable salt of the compound or polymorph is halo. In embodiments, R⁵ in the compounds described herein, or a polymorph thereof or pharmaceutically acceptable

salt of the compound or polymorph is chloro or fluoro. In embodiments, R⁵ in the compounds described herein, or a pharmaceutically acceptable salt thereof is fluoro.

[0048] In embodiments, R⁶ in the compounds described herein, or a pharmaceutically acceptable salt thereof is halo. In embodiments, R⁶ in the compounds described herein, or a polymorph thereof or pharmaceutically acceptable salt of the compound or polymorph is fluoro or chloro. In embodiments, R⁶ in the compounds described herein, or a polymorph thereof or pharmaceutically acceptable salt of the compound or polymorph is fluoro.

[0049] In embodiments, R⁷ in the compounds described herein, or a polymorph thereof or pharmaceutically acceptable salt of the compound or polymorph is halo, halo(C₁-C₄)alkyl, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, -(C₁-C₄)alkylOR^a, -C(O)NR^aR^b, phenyl, 4- to 6-membered heterocyclyl, and 5- to 7-membered heteroaryl, wherein each of said phenyl, 4- to 6-membered heterocyclyl, and 5- to 7-membered heteroaryl are optionally and independently substituted with 1 to 3 groups selected from R⁸. In embodiments, R⁷ in the compounds described herein, or a polymorph thereof or pharmaceutically acceptable salt of the compound or polymorph is halo, halo(C₁-C₄)alkyl, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, -(C₁-C₄)alkylOR^a, -C(O)NR^aR^b, phenyl, pyridinyl, piperazinyl, piperidinyl, pyrrolidinyl, thiomorpholinyl, pyrazolyl, and oxetanyl, wherein each of said phenyl, pyridinyl, pyrazolyl, pyrrolidinyl, piperazinyl, thiomorpholinyl, piperidinyl, and oxetanyl are optionally and independently substituted with 1 to 3 groups selected from R⁸. In embodiments, R⁷ in the compounds described herein, or a polymorph thereof or pharmaceutically acceptable salt of the compound or polymorph is halo, halo(C₁-C₄)alkyl, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, -(C₁-C₄)alkylOR^a, -C(O)NR^aR^b, phenyl, pyridinyl, pyrazolyl, and oxetanyl, wherein each of said phenyl, pyridinyl, pyrazolyl, and oxetanyl are optionally and independently substituted with 1 to 3 groups selected from R⁸. In embodiments, R⁷ in the compounds described herein, or a polymorph thereof or pharmaceutically acceptable salt of the compound or polymorph is pyrazolyl, pyridinyl, or piperazinyl, each of which is optionally and independently substituted with 1 to 3 groups selected from R⁸. In embodiments, R⁷ in the compounds described herein, or a polymorph thereof or pharmaceutically acceptable salt of the compound or polymorph is pyrazolyl optionally and independently substituted with 1 to 3 groups selected from R⁸.

[0050] In embodiments, R⁸ in the compounds described herein, or a polymorph thereof or pharmaceutically acceptable salt of the compound or polymorph is selected from halo, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy, halo(C₁-C₄)alkoxy, oxo, and cyano. In embodiments, R⁸ in the compounds described herein, or a polymorph thereof or pharmaceutically acceptable salt of the compound or polymorph is halo(C₁-C₄)alkyl. In

embodiments, R^8 in the compounds described herein, or a polymorph thereof or pharmaceutically acceptable salt of the compound or polymorph is (C_1-C_4) alkyl.

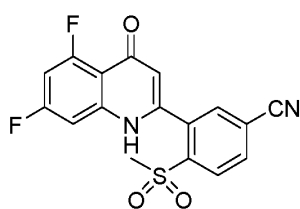
[0051] In embodiments, X in the compounds described herein, or a polymorph thereof or pharmaceutically acceptable salt of the compound or polymorph is halo or SO_2-R^2 . In

embodiments, X in the compounds described herein, or a polymorph thereof or pharmaceutically acceptable salt of the compound or polymorph is SO_2-R^2 .

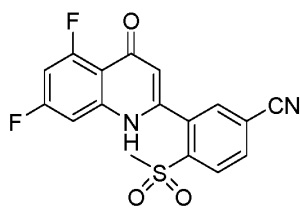
[0052] In embodiments, R^2 in the compounds described herein, or a polymorph thereof or pharmaceutically acceptable salt of the compound or polymorph is halo (C_1-C_4) alkyl or (C_1-C_4) alkyl. In embodiments, R^2 in the compounds described herein, or a polymorph thereof or pharmaceutically acceptable salt of the compound or polymorph is (C_1-C_4) alkyl. In

embodiments, R^2 in the compounds described herein, or a polymorph thereof or pharmaceutically acceptable salt of the compound or polymorph is CH_3 , CH_2CH_3 , CF_3CH_2 , CF_3 , $CH(CH_3)_2$, or $CH_2CH(CH_3)_2$. In embodiments, R^2 in the compounds described herein, or a polymorph thereof or pharmaceutically acceptable salt of the compound or polymorph is CH_3 .

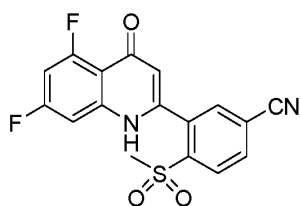
[0053] In embodiments, the compound of Formula **I** used in the present methods and compositions is of the structural formula:



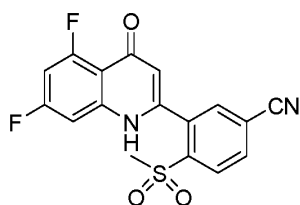
; or a polymorph thereof, or pharmaceutically acceptable salt of the compound or polymorph. In embodiments, the compound of Formula **I** used in the present methods and compositions is of the structural formula:



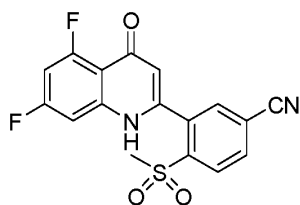
or pharmaceutically acceptable salt thereof. In embodiments, the compound of Formula **I** used in the present methods and compositions is a pharmaceutically acceptable salt of a compound having the structural formula:



. In embodiments, the compound of Formula I used in the present methods and compositions is a crystalline form of a compound having the structural formula:



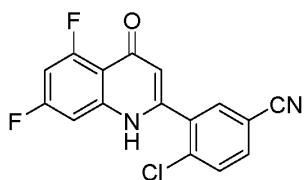
. In embodiments, the compound of Formula I used in the present methods and compositions is crystalline Form A of a compound having the structural formula:



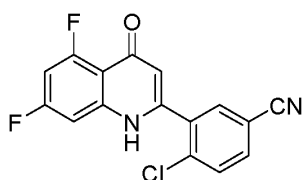
, wherein the crystalline form is characterized by at least three x-ray powder diffraction peaks at 2Θ angles selected from 6.1° , 9.3° , 12.7° , 18.8° , and 19.8° . Alternatively, crystalline Form A is characterized by at least four x-ray powder diffraction peaks at 2Θ angles selected from 6.1° , 9.3° , 12.7° , 18.8° , and 19.8° . In another alternative, crystalline Form A is characterized by x-ray powder diffraction peaks at 2Θ angles selected from 6.1° , 9.3° , 12.7° , 18.8° , and 19.8° . In yet another alternative, crystalline Form A is characterized by x-ray powder diffraction peaks at 2Θ angles selected from 6.1° , 9.3° , and 12.7° . In yet another alternative, crystalline Form A is characterized by x-ray powder diffraction peaks at 2Θ angles selected from 6.1° , 9.3° , 12.7° , and 19.8° . In yet another alternative, crystalline Form A is characterized by at least three x-ray powder diffraction peaks at 2Θ angles selected from 6.1° , 9.3° , 12.7° , 17.7° , 18.8° , 19.8° , and 22.2° . In yet another alternative, crystalline Form A is characterized by at least four x-ray powder diffraction peaks at 2Θ angles selected from 6.1° , 9.3° , 12.7° , 17.7° , 18.8° , 19.8° , and 22.2° . In yet another alternative, crystalline Form A is characterized by at least five x-ray powder diffraction peaks at 2Θ angles selected from 6.1° , 9.3° , 12.7° , 17.7° , 18.8° , 19.8° , and 22.2° . In yet another alternative, crystalline Form A is characterized by at least six x-ray powder diffraction peaks at 2Θ angles selected from 6.1° , 9.3° , 12.7° , 17.7° , 18.8° , 19.8° , and 22.2° . In

yet another alternative, crystalline Form A is characterized by x-ray powder diffraction peaks at 2θ angles selected from 6.1° , 9.3° , 12.7° , 17.7° , 18.8° , 19.8° , and 22.2° .

[0054] In embodiments, the compound of Formula I used in the present methods and compositions is of the structural formula:



; or a polymorph thereof, or pharmaceutically acceptable salt of the compound or polymorph. In embodiments, the compound of Formula I used in the present methods and compositions is of the structural formula:



; or a or pharmaceutically acceptable salt of the compound.

EXEMPLIFICATION

[0055] The representative examples that follow are intended to help illustrate the present disclosure, and are not intended to, nor should they be construed to, limit the scope of the invention.

Preparation of Compounds

[0056] The compounds according to the present methods and compositions can be prepared according to the procedures described in WO 2023/078252 and WO 2022/187203, the entire contents of each of which are incorporated herein by reference.

Biological Data

Genetically engineered mouse models of luminal urothelial cancer with intact immune systems exhibit tumor growth inhibition and immune infiltration into tumors upon PPAR γ inhibition.

[0057] **Methods:**

[0058] UPPL1541 cells, generated from a genetically engineered murine model of high-grade, muscle-invasive luminal urothelial cancer (see Saito et al., Cancer Research. 2018: 78(14) 3954-3968), were inoculated orthotopically in the bladder wall of C57BL/6J mice. After engraftment was confirmed by ultrasound, animals were dosed by oral gavage daily for

2 weeks with PPARG inverse agonists: 60 mg/kg of 4-chloro-3-(5,7-difluoro-4-oxo-1,4-dihydroquinolin-2-yl)benzonitrile (see Example 1 of WO 2022/187203, herein referred to as Compound 2) and 2 mg/kg of 3-(7-chloro-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (see Example 9 of WO 2023/078252, herein referred to as Compound 1). Tumors were harvested and fixed in formalin prior to embedding in paraffin blocks. Tumors were sectioned and stained for numerous markers, including E-cadherin and CD45. In addition, to be able to grow tumors for a longer time, and to obtain more precise measurements with calipers, we switched from the orthotopic UPPL 1541 model to a subcutaneous model, using C57B6L mice. UPPL1541 cells were introduced into the mouse upper flank, and tumor size was measured twice weekly in two dimensions using calipers. For the main experiment females were divided into 3 groups n=4 for Compound 1; n=4 for Compound 2; n=4 for vehicle. At the end of the experiment animals were sacrificed and tumors were analyzed to assess tumor proliferation.

[0059] Results:

[0060] Tumor volumes decrease with PPARG inverse agonist Compound 1 treatment compared to vehicle, indicating that the drug is slowing tumor growth. Pparg expression was decreased as was proliferation particularly in mice treated with the PPARG inverse agonist, consistent with slowed tumor growth. Also, UPPL1541 tumors were analyzed by IHC for staining of E-cadherin and CD45. E-cadherin staining was used to indicate epithelial tumor cells and CD45 is a general immune cell marker as all hematopoietic cells, excluding erythrocytes and platelets, express CD45. IHC analysis of PPARG inverse agonist treated tumors showed an increase in the number of CD45+ cells relative to tumors from animals treated with vehicle control, indicating an increase in immune cells present in the tumors after treatment.

PPARG amplification is associated with lack of response to anti-PD1 in Muscle-Invasive Urothelial Cancer

[0061] Methods:

[0062] Tumors collected from 1393 patients with muscle-invasive urothelial cancer (MIUC) were sequenced using the Tempus xT assay (DNA-seq of 648 genes at 500x coverage; RNA-seq (1389 patients both, 1365 patients DNA only). Within the dataset, 275 patients received anti-PD1 therapy. Pre-anti-PD1 treatment tissues were analyzed (threshold ≤ 90 days from start-of-treatment to tissue-collection). PD-L1 expression was assessed using the PD-L1 IHC 22C3 PharmDx assay (Combined Proportion Score [CPS] cut-off of 10%; CPS calculates the ratio of PDL1 expression including tumor cells and immune cells to the

total number of viable tumor cells). Gene expression values were normalized by transcripts-per-million (TPM). Immune infiltration was quantified with mcpCounter package in R. Patients were binned in “Amplified” (AMP) vs “Non-Amplified” (non-AMP) groups by *PPARG* copy-number cut-off of 3. Kaplan-Meier analyses were performed based on real-world progression free survival (rw-PFS) and *PPARG* amplification.

[0063] Results:

[0064] The median mRNA expression level of *PPARG* was significantly higher in the *PPARG* AMP group (n= 194) compared to *PPARG* non-AMP group (n= 1167) (8.81 Log₂[TPM+1] vs 7.39 Log₂[TPM+1]; p< 2.2e-16). *PPARG* expression was also higher in the PD-L1-negative tumors (CPS < 10) compared to PDL1-positive tumors (7.79 Log₂[TPM+1] vs 7.28 Log₂[TPM+1]; p=0.026). *PPARG* AMP tumors exhibited a cold immune-phenotype compared to the *PPARG* non-AMP tumors, associated with lower CD8+ T-cell infiltration signature score (3.99 Log₂[TPM+1] vs 5.73 Log₂[TPM+1]; p=0.0025) and lower expression of other immune cells (**Table 1**). Survival analysis in patients treated with anti-PD1 showed significant shorter rwPFS (p= 0.034) for patients with *PPARG* AMP (n= 41) compared to the non-AMP group (n= 222).

Table 1

Immune Signatures	Median RNA Score (Log ₂ [TPM+1])		p-value
	<i>PPARG</i> AMP (CN >3)	<i>PPARG</i> non- AMP (CN <3)	
Cytotoxic lymphocytes	1.99	2.65	<0.001
Natural killer (NK) cells	0.62	0.76	<0.001
Monocytes	25.4	33.78	<0.001
Myeloid dendritic cells	2.5	3.22	<0.001

Interrogation of *PPARG* expression in PBMCs collected from urothelial cancer patients treated with pembrolizumab

[0065] Methods:

[0066] Peripheral blood mononuclear cells (PBMCs) were collected from five (n= 5) patients with urothelial cancer that are being treated commercially with pembrolizumab and from three (n=3) normal healthy volunteer individuals. These cells were profiled at single-cell resolution following the following steps: PBMCs underwent standard 10X

Genomics processing, 3' gene expression library construction steps, and next-generation sequencing at the Discovery Life Sciences.

[0067] **Results:**

[0068] In this cohort, assessment of *PPARG* expression across blood cell populations shows that *PPARG* is mainly expressed on classical monocytes and non-classical monocytes. *PPARG* expression in other immune cell types such as T cells, B cells, NK cells, myeloid dendritic cells (mDCs) and granulocytes is very low and thus not significant. Within the classical monocyte population, comparison of *PPARG* expression across all samples shows that *PPARG* is upregulated in urothelial cancer patients compared to the healthy volunteer samples ($\log_2\text{FC} = 6.2$; adjusted $p < 0.001$). Further analysis of the myeloid cells (monocytes and mDCs) in all 8 samples revealed that classical monocytes subcluster in two populations **A**) pro-inflammatory monocytes, which are significantly enriched in the healthy volunteer samples ($n = 3$) and **B**) immunosuppressive monocytes, which are significantly enriched in the samples from the urothelial cancer patients ($n = 5$). Unbiased differential expression analysis between these two populations showed that *PPARG* is the most upregulated gene in the suppressive monocytes compared to the pro-inflammatory subset ($\log_2\text{FC} = 1.6$, adjusted $p\text{-value} < 0.001$).

3-(5,7-difluoro-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile in combination with anti-PD1 in bladder cancer patients

[0069] Three biocompatible intra-tumoral drug-releasing microdevices (IMDs; $6 \times 0.7 \text{ mm}$) comprising 3-(5,7-difluoro-4-oxo-1,4-dihydroquinolin-2-yl)-4-(methylsulfonyl)benzonitrile (see Example 1 of WO 2023/078252, herein referred to as Compound **3**); Pembrolizumab; or a combination of Pembrolizumab and Compound **3**, were implanted into a tumor from a patient suffering from clinically localized bladder cancer with histology of urothelial cancer. Nano-doses of each drug were released directly into the tumor immediately adjacent (about 0.5 to 1 mm) to the point of release. The dwelling time for the IMDs was 72 hours between implantation and removal.

[0070] Tissue slides from areas of exposure with Compound **3** (equivalent of about 350 mg), Pembrolizumab and the combination of Compound **3** and Pembrolizumab were stained for cleaved Caspase 3 (cC3). Results showed that Compound **3** alone induces apoptosis in 3.8% of cells as indicated by cC3 positivity and Pembrolizumab induced apoptosis in 11.8% of the cells. However, the combination of Compound **3** and Pembrolizumab induced apoptosis

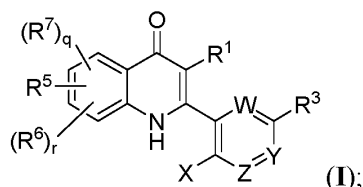
in 27% of the cells, therefore suggesting a synergistic effect of combining Compound **3** and Pembrolizumab in inducing tumor cell death in Urothelial Carcinomas.

[0071] While we have described a number of embodiments, it is apparent that our basic examples may be altered to provide other embodiments that utilize the compounds and methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims rather than by the specific embodiments that have been represented by way of example.

[0072] The contents of all references (including literature references, issued patents, published patent applications, and co-pending patent applications) cited throughout this application are hereby expressly incorporated herein in their entireties by reference. Unless otherwise defined, all technical and scientific terms used herein are accorded the meaning commonly known to one with ordinary skill in the art.

Listing of Claims:

1. A method of treating a cancer in a subject, comprising administering to the subject a therapeutically effective amount of an immunotherapeutic and a therapeutically effective amount of a compound having the Formula I:



or a polymorph thereof, or pharmaceutically acceptable salt of the compound or polymorph, wherein

W, Y, and Z are each independently N or $-CR^4$;

R^1 is hydrogen, halo, (C_1-C_4) alkyl, or hydroxyl;

X is halo, $-SR^2$, $-SOR^2$, $-SO_2R^2$, $-OR^2$, and $-SO(=NR^2)R^{2'}$;

R^2 and $R^{2'}$ are each independently (C_1-C_4) alkyl, (C_1-C_4) alkoxy, or halo (C_1-C_4) alkyl;

R^3 is cyano or nitro;

R^4 is hydrogen, halo, (C_1-C_4) alkyl, (C_1-C_4) alkoxy, or hydroxyl;

R^5 is halo, halo (C_1-C_4) alkyl, or cyano;

R^6 is halo, halo (C_1-C_4) alkyl, (C_1-C_4) alkyl, or cyano;

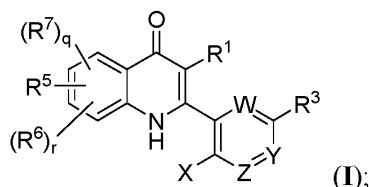
R^7 is halo, (C_1-C_4) alkyl, (C_1-C_4) alkoxy, halo (C_1-C_4) alkyl, halo (C_1-C_4) alkoxy, $-(C_1-C_4)$ alkylOR^a, $-(C_1-C_4)$ alkylC(O)R^a, $-(C_1-C_4)$ alkylC(O)OR^a, $-C(O)NR^aR^b$, $-(C_1-C_4)$ alkylC(O)NR^aR^b, $-C(O)R^a$, $-C(O)OR^a$, $-NR^aR^b$, $-(C_1-C_4)$ alkylNR^aR^b, $-C(O)NR^aSO_3H$, $-NR^aC(O)R^b$, $-NR^aC(O)OR^b$, $-NR^aC(S)OR^b$, $-NR^cC(O)N^aR^b$, $-NR^cC(S)NR^aR^b$, $-NR^cS(O)_2NR^aR^b$, $-C(S)R^a$, $-S(O)_2R^a$, $-S(O)R^a$, $-C(S)OR^a$, $-C(S)NR^aR^b$, $-NR^aC(S)R^b$, $-SR^a$, phenyl, 4- to 6-membered heterocyclyl, and 5- to 7-membered heteroaryl, wherein each of said phenyl, 4- to 6-membered heterocyclyl, and 5- to 7-membered heteroaryl are optionally and independently substituted with 1 to 3 groups selected from R^8 ;

R^8 is selected from halo, (C_1-C_4) alkyl, halo (C_1-C_4) alkyl, (C_1-C_4) alkoxy, halo (C_1-C_4) alkoxy, nitro, oxo, cyano, $-(C_1-C_4)$ alkylOR^d, $-(C_1-C_4)$ alkylC(O)R^d, $-(C_1-C_4)$ alkylC(O)OR^d, $-C(O)NR^dR^e$, $-(C_1-C_4)$ alkylC(O)NR^dR^e, $-C(O)R^d$, $-C(O)OR^d$, $-NR^dR^e$, $-(C_1-C_4)$ alkylNR^dR^e, $-C(O)NR^dSO_3H$, $-NR^dC(O)R^e$, $-NR^dC(O)OR^e$, $-NR^dC(S)OR^e$, $-NR^fC(O)N^dR^e$, $-NR^fC(S)NR^dR^e$, $-NR^fS(O)_2NR^dR^e$, $-C(S)R^d$, $-S(O)_2R^d$, $-S(O)R^d$, $-C(S)OR^d$, $-C(S)NR^dR^e$, $-NR^dC(S)R^e$, and $-SR^d$;

R^a , R^b , R^c , R^d , R^e , and R^f are each independently hydrogen or (C_1-C_4) alkyl; and

q and r are each independently 0 or 1.

2. A method of treating a cancer in a subject, comprising administering to the subject a therapeutically effective amount of a compound having the Formula I:



or a polymorph thereof, or pharmaceutically acceptable salt of the compound or polymorph, wherein

W, Y, and Z are each independently N or $-\text{CR}^4$;

R^1 is hydrogen, halo, $(\text{C}_1\text{-C}_4)\text{alkyl}$, or hydroxyl;

X is halo, $-\text{SR}^2$, $-\text{SOR}^2$, $-\text{SO}_2\text{R}^2$, $-\text{OR}^2$, and $-\text{SO}(=\text{NR}^2)\text{R}^{2'}$;

R^2 and $\text{R}^{2'}$ are each independently $(\text{C}_1\text{-C}_4)\text{alkyl}$, $(\text{C}_1\text{-C}_4)\text{alkoxy}$, or halo $(\text{C}_1\text{-C}_4)\text{alkyl}$;

R^3 is cyano or nitro;

R^4 is hydrogen, halo, $(\text{C}_1\text{-C}_4)\text{alkyl}$, $(\text{C}_1\text{-C}_4)\text{alkoxy}$, or hydroxyl;

R^5 is halo, halo $(\text{C}_1\text{-C}_4)\text{alkyl}$, or cyano;

R^6 is halo, halo $(\text{C}_1\text{-C}_4)\text{alkyl}$, $(\text{C}_1\text{-C}_4)\text{alkyl}$, or cyano;

R^7 is halo, $(\text{C}_1\text{-C}_4)\text{alkyl}$, $(\text{C}_1\text{-C}_4)\text{alkoxy}$, halo $(\text{C}_1\text{-C}_4)\text{alkyl}$, halo $(\text{C}_1\text{-C}_4)\text{alkoxy}$, $-(\text{C}_1\text{-C}_4)\text{alkylOR}^a$, $-(\text{C}_1\text{-C}_4)\text{alkylC(O)R}^a$, $-(\text{C}_1\text{-C}_4)\text{alkylC(O)OR}^a$, $-\text{C(O)NR}^a\text{R}^b$, $-(\text{C}_1\text{-C}_4)\text{alkylC(O)NR}^a\text{R}^b$, $-\text{C(O)R}^a$, $-\text{C(O)OR}^a$, $-\text{NR}^a\text{R}^b$, $-(\text{C}_1\text{-C}_4)\text{alkylNR}^a\text{R}^b$, $-\text{C(O)NR}^a\text{SO}_3\text{H}$, $-\text{NR}^a\text{C(O)R}^b$, $-\text{NR}^a\text{C(O)OR}^b$, $-\text{NR}^a\text{C(S)OR}^b$, $-\text{NR}^c\text{C(O)N}^a\text{R}^b$, $-\text{NR}^c\text{C(S)NR}^a\text{R}^b$, $-\text{NR}^c\text{S(O)}_2\text{NR}^a\text{R}^b$, $-\text{C(S)R}^a$, $-\text{S(O)}_2\text{R}^a$, $-\text{S(O)R}^a$, $-\text{C(S)OR}^a$, $-\text{C(S)NR}^a\text{R}^b$, $-\text{NR}^a\text{C(S)R}^b$, $-\text{SR}^a$, phenyl, 4- to 6-membered heterocyclyl, and 5- to 7-membered heteroaryl, wherein each of said phenyl, 4- to 6-membered heterocyclyl, and 5- to 7-membered heteroaryl are optionally and independently substituted with 1 to 3 groups selected from R^8 ;

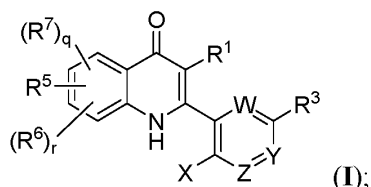
R^8 is selected from halo, $(\text{C}_1\text{-C}_4)\text{alkyl}$, halo $(\text{C}_1\text{-C}_4)\text{alkyl}$, $(\text{C}_1\text{-C}_4)\text{alkoxy}$, halo $(\text{C}_1\text{-C}_4)\text{alkoxy}$, nitro, oxo, cyano, $-(\text{C}_1\text{-C}_4)\text{alkylOR}^d$, $-(\text{C}_1\text{-C}_4)\text{alkylC(O)R}^d$, $-(\text{C}_1\text{-C}_4)\text{alkylC(O)OR}^d$, $-\text{C(O)NR}^d\text{R}^e$, $-(\text{C}_1\text{-C}_4)\text{alkylC(O)NR}^d\text{R}^e$, $-\text{C(O)R}^d$, $-\text{C(O)OR}^d$, $-\text{NR}^d\text{R}^e$, $-(\text{C}_1\text{-C}_4)\text{alkylNR}^d\text{R}^e$, $-\text{C(O)NR}^d\text{SO}_3\text{H}$, $-\text{NR}^d\text{C(O)R}^e$, $-\text{NR}^d\text{C(O)OR}^e$, $-\text{NR}^d\text{C(S)OR}^e$, $-\text{NR}^f\text{C(O)N}^d\text{R}^e$, $-\text{NR}^f\text{C(S)NR}^d\text{R}^e$, $-\text{NR}^f\text{S(O)}_2\text{NR}^d\text{R}^e$, $-\text{C(S)R}^d$, $-\text{S(O)}_2\text{R}^d$, $-\text{S(O)R}^d$, $-\text{C(S)OR}^d$, $-\text{C(S)NR}^d\text{R}^e$, $-\text{NR}^d\text{C(S)R}^e$, and $-\text{SR}^d$;

R^a , R^b , R^c , R^d , R^e , and R^f are each independently hydrogen or $(\text{C}_1\text{-C}_4)\text{alkyl}$; and

q and r are each independently 0 or 1;

wherein the subject is characterized as progressed/relapsed to an immunotherapeutic agent.

3. A method of treating a cancer in a subject, comprising administering to the subject a therapeutically effective amount of a compound having the Formula I:



or a polymorph thereof, or pharmaceutically acceptable salt of the compound or polymorph, wherein

W, Y, and Z are each independently N or $-CR^4$;

X is halo, $-SR^2$, $-SOR^2$, $-SO_2R^2$, $-OR^2$, and $-SO(=NR^2)R^{2'}$;

R^2 and $R^{2'}$ are each independently (C₁-C₄)alkyl, (C₁-C₄)alkoxy, or halo(C₁-C₄)alkyl;

R^3 is cyano or nitro;

R^4 is hydrogen, halo, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, or hydroxyl;

R^5 is halo, halo(C₁-C₄)alkyl, or cyano;

R^6 is halo, halo(C₁-C₄)alkyl, (C₁-C₄)alkyl, or cyano;

R^7 is halo, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, halo(C₁-C₄)alkyl, halo(C₁-C₄)alkoxy, $-(C_1-C_4)alkylOR^a$, $-(C_1-C_4)alkylC(O)R^a$, $-(C_1-C_4)alkylC(O)OR^a$, $-C(O)NR^aR^b$, $-(C_1-C_4)alkylC(O)NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-NR^aR^b$, $-(C_1-C_4)alkylNR^aR^b$, $-C(O)NR^aSO_3H$, $-NR^aC(O)R^b$, $-NR^aC(O)OR^b$, $-NR^aC(S)OR^b$, $-NR^cC(O)N^aR^b$, $-NR^cC(S)NR^aR^b$, $-NR^cS(O)_2NR^aR^b$, $-C(S)R^a$, $-S(O)_2R^a$, $-S(O)R^a$, $-C(S)OR^a$, $-C(S)NR^aR^b$, $-NR^aC(S)R^b$, $-SR^a$, phenyl, 4- to 6-membered heterocyclyl, and 5- to 7-membered heteroaryl, wherein each of said phenyl, 4- to 6-membered heterocyclyl, and 5- to 7-membered heteroaryl are optionally and independently substituted with 1 to 3 groups selected from R^8 ;

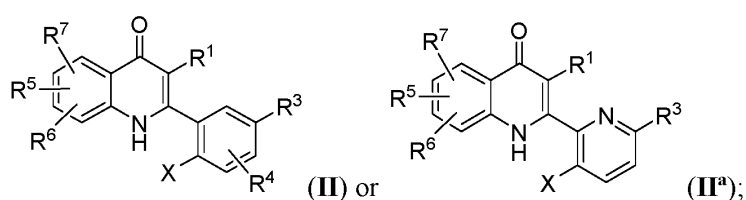
R^8 is selected from halo, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy, halo(C₁-C₄)alkoxy, nitro, oxo, cyano, $-(C_1-C_4)alkylOR^d$, $-(C_1-C_4)alkylC(O)R^d$, $-(C_1-C_4)alkylC(O)OR^d$, $-C(O)NR^dR^e$, $-(C_1-C_4)alkylC(O)NR^dR^e$, $-C(O)R^d$, $-C(O)OR^d$, $-NR^dR^e$, $-(C_1-C_4)alkylNR^dR^e$, $-C(O)NR^dSO_3H$, $-NR^dC(O)R^e$, $-NR^dC(O)OR^e$, $-NR^dC(S)OR^e$, $-NR^fC(O)N^dR^e$, $-NR^fC(S)NR^dR^e$, $-NR^fS(O)_2NR^dR^e$, $-C(S)R^d$, $-S(O)_2R^d$, $-S(O)R^d$, $-C(S)OR^d$, $-C(S)NR^dR^e$, $-NR^dC(S)R^e$, and $-SR^d$;

R^a , R^b , R^c , R^d , R^e , and R^f are each independently hydrogen or (C₁-C₄)alkyl; and

q and r are each independently 0 or 1;

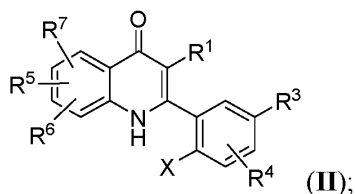
wherein the subject is characterized as refractory/resistant to an immunotherapeutic agent.

4. The method of any one of Claims 1 to 3, wherein the cancer is urothelial cancer.
5. The method of any one of Claims 1 to 4, wherein the cancer is advanced urothelial cancer.
6. The method of any one of Claims 1 to 5, wherein the cancer is muscle-invasive urothelial cancer.
7. The method of any one of Claims 1 to 6, wherein the immunotherapeutic agent is an immune checkpoint inhibitor.
8. The method of any one of Claims 1 to 7, wherein the immunotherapeutic agent is selected from ipilimumab, cemiplimab, avelumab, atezolizumab, avelumab, dostarlizumab, durvalumab, ipilimumab, nivolumab, pembrolizumab, and the combination of nivolumab and relatlimab.
9. The method of any one of Claims 1 to 8, wherein the immunotherapeutic agent is pembrolizumab.
10. The method of any one of Claims 1 to 9, wherein the compound is of the Formula **II** or **II^a**:



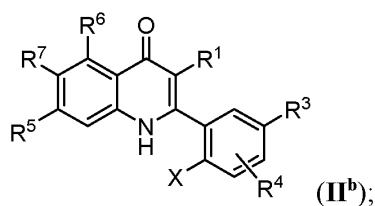
or a polymorph thereof, or pharmaceutically acceptable salt of the compound or polymorph.

11. The method of any one of Claims 1 to 10, wherein the compound is of the Formula **II**:



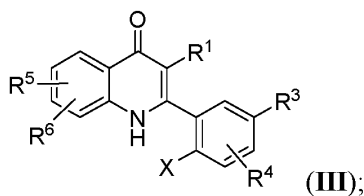
or a polymorph thereof, or pharmaceutically acceptable salt of the compound or polymorph.

12. The method of any one of Claims 1 to 11, wherein the compound is of the Formula **II^b**:



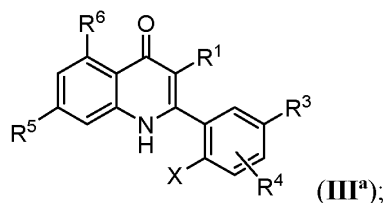
or a polymorph thereof, or pharmaceutically acceptable salt of the compound or polymorph.

13. The method of any one of Claims 1 to 11, wherein the compound is of the Formula **III**:



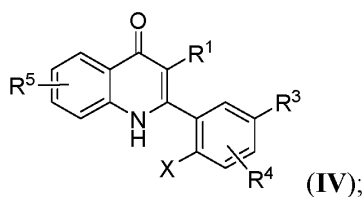
or a polymorph thereof, or pharmaceutically acceptable salt of the compound or polymorph.

14. The method of any one of Claims 1 to 11, wherein the compound is of the Formula **III^a**:



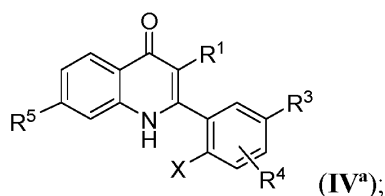
or a polymorph thereof, or pharmaceutically acceptable salt of the compound or polymorph.

15. The method of any one of Claims 1 to 11, wherein the compound is of the Formula **IV**:



or a polymorph thereof, or pharmaceutically acceptable salt of the compound or polymorph.

16. The method of any one of Claims 1 to 11, wherein the compound is of the Formula **IV^a**:

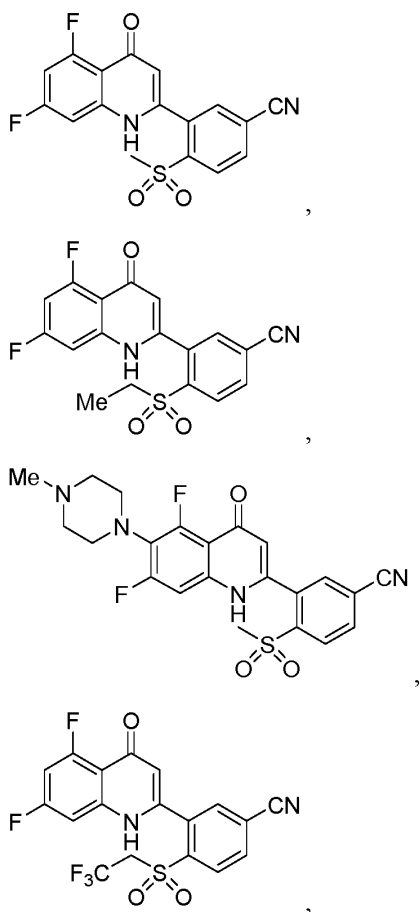


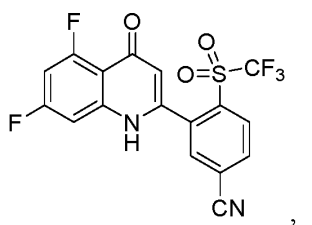
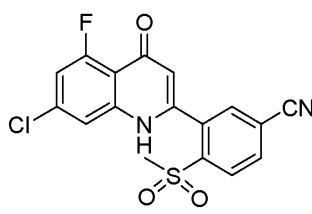
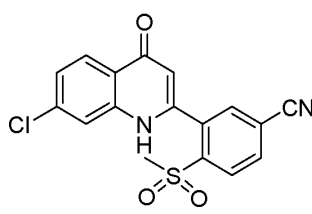
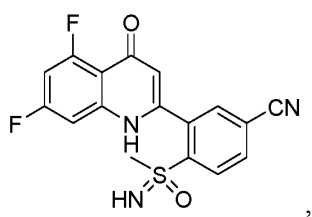
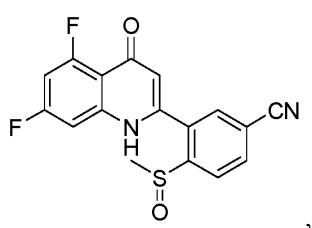
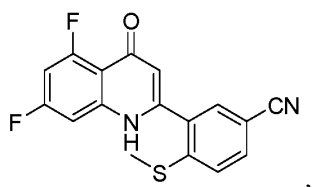
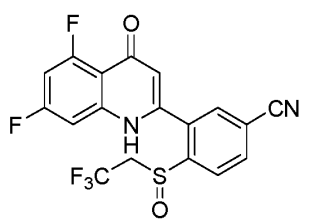
or a polymorph thereof, or pharmaceutically acceptable salt of the compound or polymorph.

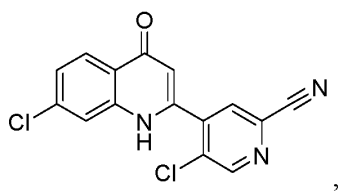
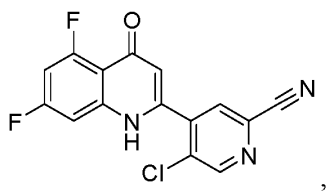
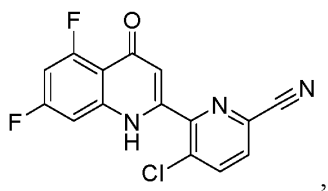
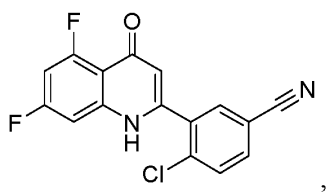
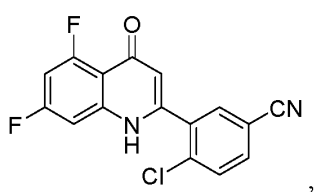
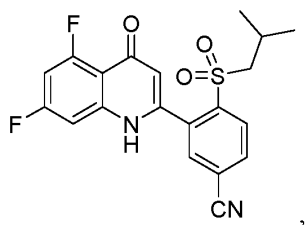
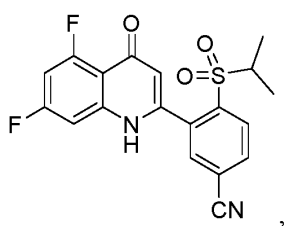
17. The method of any one of Claims 1 to 16, wherein R¹ is hydrogen.
18. The method of any one of Claims 1 to 17, wherein R³ is cyano.
19. The method of any one of Claims 1 to 18, wherein R⁵ is halo or cyano.
20. The method of any one of Claims 1 to 19, wherein R⁵ is halo.
21. The method of any one of Claims 1 to 20, wherein R⁵ is chloro or fluoro.
22. The method of any one of Claims 1 to 21, wherein R⁵ is fluoro.
23. The method of any one of Claims 1 to 14, wherein R⁶ is halo.
24. The method of any one of Claims 1 to 14, wherein R⁶ is fluoro or chloro.
25. The method of any one of Claims 1 to 14, wherein R⁶ is fluoro.

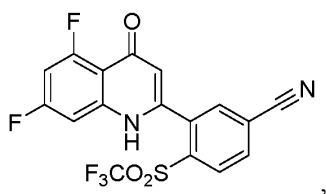
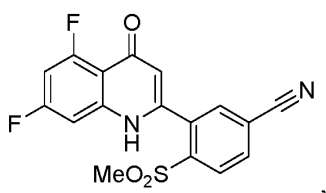
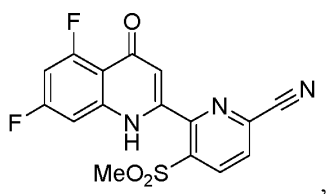
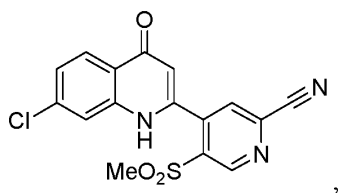
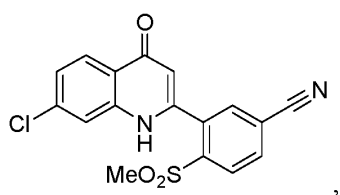
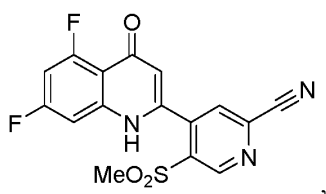
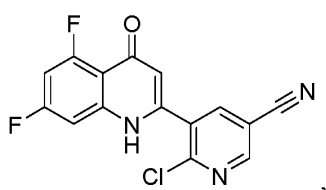
26. The method of any one of Claims 1 to 25, wherein R^4 is hydrogen.
27. The method of any one of Claims 1 to 12 and 17 to 26, wherein R^7 is halo, halo(C_1 - C_4)alkyl, (C_1 - C_4)alkyl, (C_1 - C_4)alkoxy, $-(C_1-C_4)alkylOR^a$, $-C(O)NR^aR^b$, phenyl, 4- to 6-membered heterocyclyl, and 5- to 7-membered heteroaryl, wherein each of said phenyl, 4- to 6-membered heterocyclyl, and 5- to 7-membered heteroaryl are optionally and independently substituted with 1 to 3 groups selected from R^8 .
28. The method of any one of Claims 1 to 12 and 17 to 27, wherein R^7 is halo, halo(C_1 - C_4)alkyl, (C_1 - C_4)alkyl, (C_1 - C_4)alkoxy, $-(C_1-C_4)alkylOR^a$, $-C(O)NR^aR^b$, phenyl, pyridinyl, piperazinyl, piperidinyl, pyrrolidinyl, thiomorpholinyl, pyrazolyl, and oxetanyl, wherein each of said phenyl, pyridinyl, pyrazolyl, pyrrolidinyl, piperazinyl, thiomorpholinyl, piperidinyl, and oxetanyl are optionally and independently substituted with 1 to 3 groups selected from R^8 .
29. The method of any one of Claims 1 to 12 and 17 to 28, wherein R^7 is pyrazolyl, pyridinyl, or piperazinyl, each of which are optionally and independently substituted with 1 to 3 groups selected from R^8 .
30. The method of any one of Claims 1 to 12 and 17 to 29, wherein R^7 is pyrazolyl optionally and independently substituted with 1 to 3 groups selected from R^8 .
31. The method of any one of Claims 1 to 12 and 17 to 30, wherein R^8 is selected from halo, (C_1 - C_4)alkyl, halo(C_1 - C_4)alkyl, (C_1 - C_4)alkoxy, halo(C_1 - C_4)alkoxy, oxo, and cyano.
32. The method of any one of Claims 1 to 12 and 17 to 31, wherein R^8 is halo(C_1 - C_4)alkyl.
33. The method of any one of Claims 1 to 12 and 17 to 32, wherein R^8 is (C_1 - C_4)alkyl.
34. The method of any one of Claims 1 to 12 and 17 to 33, wherein X is halo or $-SO_2R^2$.
35. The method of any one of Claims 1 to 12 and 17 to 34, wherein X is $-SO_2R^2$.

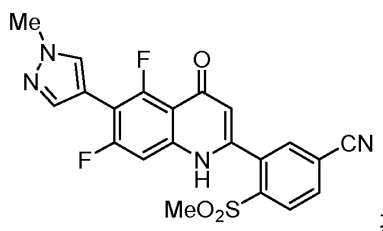
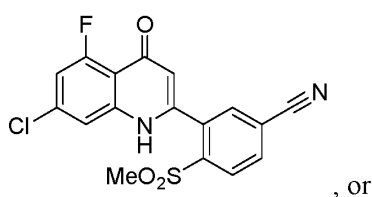
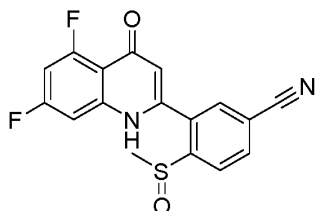
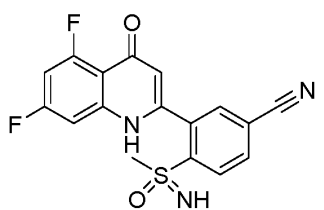
36. The method of any one of Claims 1 to 35, wherein R² is halo(C₁-C₄)alkyl or (C₁-C₄)alkyl.
37. The method of any one of Claims 1 to 36, wherein R² is CH₃, CH₂CH₃, CF₃CH₂, CF₃, CH(CH₃)₂, or CH₂CH(CH₃)₂.
38. The method of any one of Claims 1 to 36, wherein R² is (C₁-C₄)alkyl.
39. The method of any one of Claims 1 to 36, wherein R² is CH₃.
40. The method of any one of Claims 1 to 9, wherein the compound is of the structural formula:





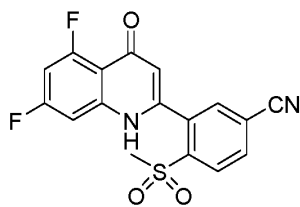






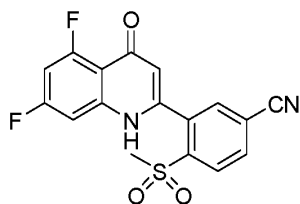
or a polymorph thereof of any of the foregoing, or pharmaceutically acceptable salt of the compound or polymorph of any of the foregoing.

41. The method of any one of Claims 1 to 9, wherein the compound is of the structural formula:



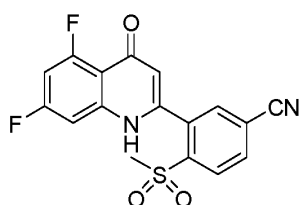
; or a polymorph thereof, or pharmaceutically acceptable salt of the compound or polymorph.

42. The method of any one of Claims 1 to 9, wherein the compound is of the structural formula:



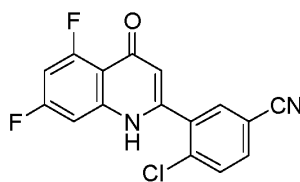
; or pharmaceutically acceptable salt thereof.

43. The method of any one of Claims 1 to 9, wherein the compound is of the structural formula:



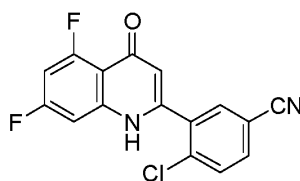
and wherein the compound is crystalline Form A characterized by at least three x-ray powder diffraction peaks at 2θ angles selected from 6.1° , 9.3° , 12.7° , 18.8° , and 19.8° .

44. The method of any one of Claims 1 to 9, wherein the compound is of the structural formula:



; or a polymorph thereof, or pharmaceutically acceptable salt of the compound or polymorph.

45. The method of any one of Claims 1 to 9, wherein the compound is of the structural formula:



; or pharmaceutically acceptable salt thereof.

46. A pharmaceutical composition comprising a therapeutically effective amount of a compound having the Formula I as defined in any one of Claims 1 and 10 to 45 or a polymorph thereof, or pharmaceutically acceptable salt of the compound or polymorph; and an immunotherapeutic agent.
47. The pharmaceutical composition of Claim 46, wherein the immunotherapeutic agent is an immune checkpoint inhibitor.
48. The pharmaceutical composition of Claim 46 or 47, wherein the immunotherapeutic agent is selected from ipilimumab, cemiplimab, avelumab, atezolizumab, avelumab, dostarlizumab, durvalumab, ipilimumab, nivolumab, pembrolizumab, and the combination of nivolumab and relatlimab.
49. The pharmaceutical composition of any one of Claims 46 to 48, wherein the immunotherapeutic agent is pembrolizumab.