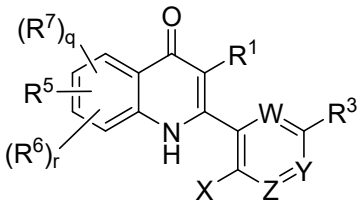
section, where tumors collected from patients with muscle-invasive urothelial cancer revealed that mRNA expression level of PPARG was significantly higher in the anti-PD1 therapy group. We have also identified that PPARG is upregulated in urothelial cancer patients who were being treated with pembrolizumab, 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.

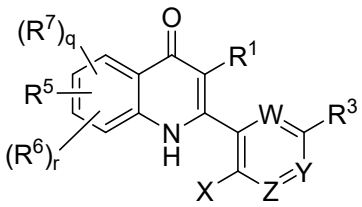
[0007] In some examples, the PPARG inverse agonist is a compound having the Formula **I**:



;

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

[0007a] In one aspect, the present disclosure relates to use of a compound having the Formula **I**:



(**I**);

or a polymorph thereof, or pharmaceutically acceptable salt of the compound or polymorph, in combination with an immunotherapeutic agent, in the manufacture of a medicament for treating cancer in a subject, wherein

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

R^1 is hydrogen, halo, $(C_1\text{-}C_4)$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 $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, or halo$(C_1\text{-}C_4)$alkyl;

R^3 is cyano or nitro;

R^4 is hydrogen, halo, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, or hydroxyl;

R^5 is halo, halo$(C_1\text{-}C_4)$alkyl, or cyano;

R^6 is halo, halo$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkyl, or cyano;

R^7 is halo, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, halo$(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkoxy, $-(C_1\text{-}C_4)$alkylOR^a, $-(C_1\text{-}C_4)$alkylC(O)R^a, $-(C_1\text{-}C_4)$alkylC(O)OR^a, $-C(O)NR^aR^b$, $-(C_1\text{-}C_4)$alkylC(O)NR^{a}R^b, $-C(O)R^a$, $-C(O)OR^a$, $-NR^aR^b$, $-(C_1\text{-}C_4)$alkylNR^{a}R^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, $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, halo$(C_1\text{-}C_4)$alkoxy, nitro, oxo, cyano, $-(C_1\text{-}C_4)$alkylOR^d, $-(C_1\text{-}C_4)$alkylC(O)R^d, $-(C_1\text{-}C_4)$alkylC(O)OR^d, $-C(O)NR^dR^e$, $-(C_1\text{-}C_4)$alkylC(O)NR^{d}R^e, $-C(O)R^d$, $-C(O)OR^d$, $-NR^dR^e$, $-(C_1\text{-}C_4)$alkylNR^{d}R^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 $(C_1\text{-}C_4)$alkyl; and

q and r are each independently 0 or 1.

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

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

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

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

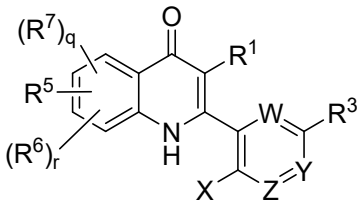
[0012] Also provided are pharmaceutical compositions comprising a therapeutically effective amount of a PPARG inverse agonist (e.g., a compound of Formula **I**) and a therapeutically effective amount of an immunotherapy (IO) agent.

[0012a] In another aspect, the present disclosure relates to a pharmaceutical composition comprising a therapeutically effective amount of a compound having the Formula **I** as described herein or a polymorph thereof, or pharmaceutically acceptable salt of the compound or polymorph; and an immune checkpoint inhibitor.

[0012b] In another aspect, the present disclosure relates to a compound having the Formula **I** as described herein or a polymorph thereof, or pharmaceutically acceptable salt of the compound or polymorph, in combination with an immunotherapeutic agent, or the pharmaceutical composition as described herein, for use in therapy.

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**:



(**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 $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, or halo$(C_1\text{-}C_4)$alkyl;

R^2 is $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, or halo$(C_1\text{-}C_4)$alkyl;

R^3 is cyano or nitro;

R^4 is hydrogen, halo, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, or hydroxyl;

R^5 is halo, halo$(C_1\text{-}C_4)$alkyl, or cyano;

R^6 is halo, halo$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkyl, or cyano;

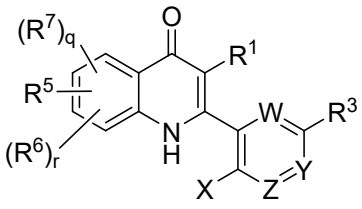
R^7 is halo, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, halo$(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkoxy, $-(C_1\text{-}C_4)$alkylOR^a, $-(C_1\text{-}C_4)$alkyl$C(O)R^a$, $-(C_1\text{-}C_4)$alkyl$C(O)OR^a$, $-C(O)NR^aR^b$, $-(C_1\text{-}C_4)$alkyl$C(O)NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-NR^aR^b$, $-(C_1\text{-}C_4)$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, $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, halo$(C_1\text{-}C_4)$alkoxy, nitro, oxo, cyano, $-(C_1\text{-}C_4)$alkylOR^d, $-(C_1\text{-}C_4)$alkyl$C(O)R^d$, $-(C_1\text{-}C_4)$alkyl$C(O)OR^d$, $-C(O)NR^dR^e$, $-(C_1\text{-}C_4)$alkyl$C(O)NR^dR^e$, $-C(O)R^d$, $-C(O)OR^d$, $-NR^dR^e$, -

Listing of Claims:

1. Use of a compound having the Formula **I**:



(**I**);

or a polymorph thereof, or pharmaceutically acceptable salt of the compound or polymorph, in combination with an immunotherapeutic agent, in the manufacture of a medicament for treating cancer in a subject, wherein

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

R^1 is hydrogen, halo, $(C_1\text{-}C_4)$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 $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, or halo$(C_1\text{-}C_4)$alkyl;

R^3 is cyano or nitro;

R^4 is hydrogen, halo, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, or hydroxyl;

R^5 is halo, halo$(C_1\text{-}C_4)$alkyl, or cyano;

R^6 is halo, halo$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkyl, or cyano;

R^7 is halo, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, halo$(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkoxy, $-(C_1\text{-}C_4)$alkylOR^a, $-(C_1\text{-}C_4)$alkyl$C(O)R^a$, $-(C_1\text{-}C_4)$alkyl$C(O)OR^a$, $-C(O)NR^aR^b$, $-(C_1\text{-}C_4)$alkyl$C(O)NR^aR^b$, $-C(O)R^a$, $-C(O)OR^a$, $-NR^aR^b$, $-(C_1\text{-}C_4)$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, $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, halo$(C_1\text{-}C_4)$alkoxy, nitro, oxo, cyano, $-(C_1\text{-}C_4)$alkylOR^d, $-(C_1\text{-}C_4)$alkyl$C(O)R^d$, $-(C_1\text{-}C_4)$alkyl$C(O)OR^d$, $-C(O)NR^dR^e$, $-(C_1\text{-}C_4)$alkyl$C(O)NR^dR^e$, $-C(O)R^d$, $-C(O)OR^d$, $-NR^dR^e$, $-(C_1\text{-}C_4)$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 $(C_1\text{-}C_4)$alkyl; and

q and r are each independently 0 or 1.

2. The use of Claim 1, wherein the subject is characterized as progressed/relapsed to an immunotherapeutic agent, or the subject is characterized as refractory/resistant to an immunotherapeutic agent.

3. The use of Claim 1 or 2, wherein the cancer is urothelial cancer.

4. The use of any one of Claims 1 to 3, wherein the cancer is advanced urothelial cancer.

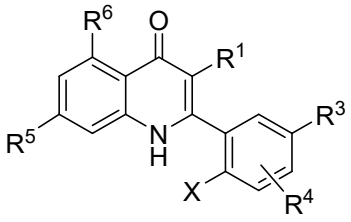
5. The use of any one of Claims 1 to 4, wherein the cancer is muscle-invasive urothelial cancer.

6. The use of any one of Claims 1 to 5, wherein the immunotherapeutic agent is an immune checkpoint inhibitor.

7. The use of any one of Claims 1 to 6, wherein the immunotherapeutic agent is selected from ipilmumab, cemiplimab, avelumab, atezolizumab, dostarlizumab, durvalumab, ipilimumab, nivolumab, pembrolizumab, and the combination of nivolumab and relatlimab.

8. The use of any one of Claims 1 to 7, wherein the immunotherapeutic agent is pembrolizumab.

9. The use of any one of Claims 1 to 8, wherein the compound is of the Formula **III^a**:



(**III^a**);

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

10. The use of any one of Claims 1 to 9, wherein

R^1 is hydrogen;

R^3 is cyano;

R^5 is halo or cyano;

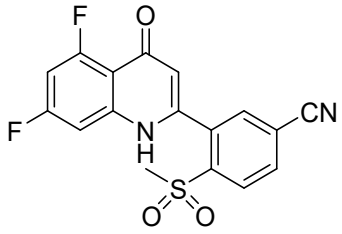
R^6 is halo;

R^4 is hydrogen;

X is halo or $-SO_2R^2$; and

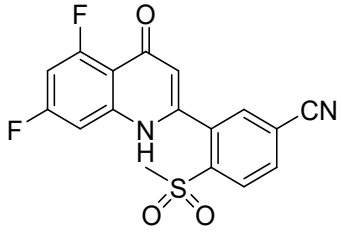
R^2 is halo(C_1-C_4)alkyl or (C_1-C_4)alkyl.

11. The use of any one of Claims 1 to 10, wherein the compound is of the structural formula:



; or pharmaceutically acceptable salt thereof.

12. The use of any one of Claims 1 to 10, 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°.

13. A pharmaceutical composition comprising a therapeutically effective amount of a compound having the Formula **I** as defined in any one of Claims 1 and 9 to 12 or a polymorph thereof, or pharmaceutically acceptable salt of the compound or polymorph; and an immune checkpoint inhibitor.

14. The pharmaceutical composition of Claim 13, wherein the immune checkpoint inhibitor is selected from ipilmumab, cemiplimab, avelumab, atezolizumab, dostarlizumab,

durvalumab, ipilimumab, nivolumab, pembrolizumab, and the combination of nivolumab and relatlimab.

15. The pharmaceutical composition of Claim 13 or 14, wherein the immune checkpoint inhibitor is pembrolizumab.

16. A compound having the Formula **I** as defined in any one of Claims 1 and 9 to 12 or a polymorph thereof, or pharmaceutically acceptable salt of the compound or polymorph, in combination with an immunotherapeutic agent, or the pharmaceutical composition of any one of Claims 13 to 15, for use in therapy.