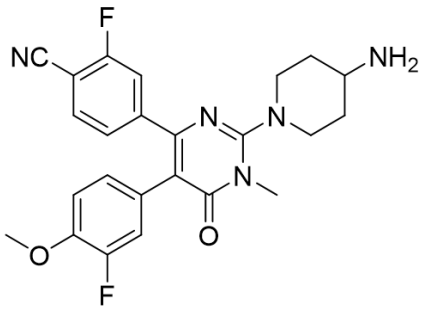
CLAIMS

WHAT IS CLAIMED IS:

1. Use of a compound having the structure of Formula (I), or a pharmaceutically acceptable salt thereof,



(I),

in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein:

(a) a patient having a cancer tumor that is a diagnostic positive cold tumor is to be identified; and

(b) a composition comprising a therapeutically effective amount of the compound having the structure of Formula (I), or a pharmaceutically acceptable salt thereof is to be administered to the patient.

2. The use of claim 1, wherein the patient:

(a) has failed single checkpoint inhibitor (CPI) therapy, has minimal response to CPI therapy, or no therapeutic effect is observed for CPI therapy; and

(b) cells of the tumor display a high gene expression of REST Corepressor 2 RCOR2 relative to the median RCOR2 gene expression of tumors in other patients having the same tumor type.

3. The use of claim 1, wherein the patient:

(a) is naïve to a CPI therapy; and

(b) cells of the tumor display a high gene expression of RCOR2 relative to the median RCOR2 gene expression of tumors in other patients having the same tumor type.

4. The use of claim 2, wherein high gene expression of RCOR2 is in the top 25% of expression of tumors in other patients having the same tumor type.

5. The use of claim 2, wherein high gene expression of RCOR2 is in the top 10% of expression of tumors in other patients having the same tumor type.

6. The use of any one of claims 1-5, wherein:

(a) the CPI therapy comprises anti-programmed cell death protein 1 (PD1) and/or

programmed death-ligand 1 (PD-L1) therapy; and

(b) the patient's cancer cells display a high gene expression of RCOR2.

7. The use of any one of claims 1-6, wherein:

(a) the patient's cancer exhibits a cold tumor signature; and

(b) the patient's cancer cells display a high gene expression of RCOR2.

8. The use of claim 7, wherein the cold tumor signature is defined by:

(a) low or no CD8 T cell infiltration within the tumor;

(b) exhibition of T cell non-inflamed or T cell excluded based on the presence of T cells within the tumor.

9. The use of claim 8, wherein the presence of T cells within the tumor is measured or estimated by gene expression levels of T cell markers in bulk RNA profiling data.

10. The use of any one of claims 1-9, wherein the patient's cancer cells exhibit an increase in the gene expression of one or more of the following genes: AK056486, NKAIN1, FAM183A, SAMD13, LINC00622, CHRNB2, MEX3A, IGSF9, C1ORF192, CCDC181, OCLM, PPFIA4, PANK1, B4GALNT4, GAS2, MS4A8, MYRF, RCOR2, FLRT1, AK313893, NXPH4, BC073932, MSI1, CCDC169, FREM2, ATP7B, AF339817, AK124233, GPX2, PAR5, PLA2G4F, IGDCC3, GOLGA6L10, UBE2Q2P2, WDR93, PDIA2, CASKIN1, AK096982, TOX3, AK057689, C16ORF3, AK127378, EFNB3, DNAH2, ANKRD13B, SOCS7, RAMP2-AS1, FAM171A2, ADAM11, METAZOA_SRP_75, CBX2, ZNF850, LOC100379224, TTYH1, VN1R1, MEIS1-AS3, LONRF2, BC022892, KLHL23, AX747067, CCDC108, IRS1, KIF1A, FLRT3, SIM2, IGSF5, CECR5-AS1, FAM227A, AX747137, FGD5P1, ACVR2B, LOC646903, FGFR3, FLJ13197, SLC10A4, TTC23L, MCIDAS, GUSBP9, GPR98, SEMA6A, PCDHGC4, USP49, TMEM151B, AK125212, PACRG, AK123300, COL28A1, SOSTDC1, AK098769, FKBP6, DPY19L2P4, EPO, CTTNBP2, KIAA1549, TAS2R5, FAM86B2, DQ595103, CHD7, AK094577, WNK2, TMEFF1, AL390170, MUM1L1, HS6ST2, and PNCK; wherein the increase in the gene expression is relative to the gene expression of a control gene.

11. The use of claim 10, wherein the patient's cancer cells exhibit an increase in the gene expression of at least about 10% or at least about 15% of the genes where expression levels are measured.

12. The use of claim 10, wherein the patient's cancer cells exhibit an increase in the gene expression of at least about 20%, at least about 25%, at least about 30%, or at least about 35% of the genes where expression levels are measured.

13. The use of claim 10, wherein the patient's cancer cells exhibit an increase in the gene expression of at least about 40%, at least about 45%, at least about 50%, or at least about 55% of the genes where expression levels are measured.

14. The use of claim 10, wherein the patient's cancer cells exhibit an increase in the gene expression of at least about 60%, at least about 65%, at least about 70%, or at least about 75% of the genes where expression levels are measured.

15. The use of claim 10, wherein the patient's cancer cells exhibit an increase in the gene expression of at least about 80% of the genes where expression levels are measured.

16. The use of any one of claims 1-15, wherein the patient's cancer cells exhibit a decrease in the gene expression of one or more interferon response genes, wherein the decrease in the gene expression is relative to the gene expression of a control gene.

17. The use of claim 16, wherein the interferon response genes are selected from: AC124319.1, ADAR, APOL6, ARID5B, ARL4A, AUTS2, B2M, BANK1, BATF2, BPGM, BST2, BTG1, C1R, C1S, CASP1, CASP3, CASP4, CASP7, CASP8, CCL2, CCL5, CCL7, CD274, CD38, CD40, CD69, CD74, CD86, CDKN1A, CFB, CFH, CIITA, CMKLR1, CMPK2, CMTR1, CSF2RB, CXCL10, CXCL11, CXCL9, DDX58, DDX60, DHX58, EIF2AK2, EIF4E3, EPSTI1, FAS, FCGR1A, FGL2, FPR1, GBP4, GBP6, GCH1, GPR18, GZMA, HELZ2, HERC6, HIF1A, HLA-A, HLA-B, HLA-DMA, HLA-DQA1, HLA-DRB1, HLA-G, ICAM1, IDO1, IFI27, IFI30, IFI35, IFI44, IFI44L, IFIH1, IFIT1, IFIT2, IFIT3, IFITM2, IFITM3, IFNAR2, IFL10RA, IL15, IL15RA, IL18BP, IL2RB, IL4R, IL6, IL7, IRF1, IRF2, IRF4, IRF5, IRF7, IRF8, IRF9, ISG15, ISG20, ISOC1, ITGB7, JAK2, KLRK1, LAP3, LATS2, LCP2, LGALS3BP, LYSE, LYSMD2, 1-MAR, METTL7B, MT2A, MEHFD2, MVP, MX1, MX2, MYD88, NAMPT, NCOA3, NFKB1, NFKBIA, NLRC5, NMI, NOD1, NUP93, OAS2, OAS3, OASL, OGFR, P2RY14, PARP12, PARP14, PDE4B, PELI1, PFKP, PIM1, PLA2G4A, PLSCR1, PML, PNP, PNPT1, PSMA2, PSMA3, PSMB10, PSMB2, PSMB8, PSMB9, PSME1, PSME2, PTGS2, PTPN1, PTPN2, PTPN6, RAPGEF6, RBCK1, RIPK1, RIPK2, RNF31, RSAD2, RTP4, SAMD9L, SAMHD1, SECTM1, SELP, SERPING1, SLAMF7, SLC25A28, SOCS1, SOCS3, SOD2, SP110, SPPL2A, SRI, SSPN, ST3GAL5, ST8SIA4, STAT1, STAT2, STAT3, STAT4, TAP1, TAPBP, TDRD7, TNFAIP2, TNFAIP3, TNFAIP6, TNFAIP10,

TOR1B, TRAFD1, TRIM14, TRIM 21, TRIM25, TRIM 26, TXNIP, UBE2L6, UPP1, USP18, VAMP5, VAMP8, VCAM1, WARS, XAF1, XCL1, ZBP1, and ZNFX1.

18. The use of claim 13 or 14, wherein the patient's cancer cells exhibit a decrease in the gene expression of at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, or at least about 80% of the interferon response genes where expression levels are measured.

19. The use of any one of claims 1-18, wherein:

(a) the compound of Formula (I) or a pharmaceutically acceptable salt thereof is an inhibitor of Lysine-specific histone demethylase 1 (LSD-1); and/or

(b) the compound of Formula (I) or a pharmaceutically acceptable salt thereof is a reversible antagonist to LSD-1; and/or

(c) the compound of Formula (I) or a pharmaceutically acceptable salt thereof is a reversible inhibitor of LSD-1.

20. The use of claim 19, wherein when LSD-1 is blocked, infiltration of T cells is thereby enabled, thus allowing anti-PDL1 and/or anti-PD1 therapy to retard tumor growth and/or reduce tumor size.

21. The use of claim 19 or 20, wherein LSD-1 is inhibited from demethylating histone complexes, and thereby infiltration of T cells is enabled, thus allowing anti-PDL1 and/or anti-PD1 therapy to retard tumor growth and/or tumor size.

22. The use of claim 19 or 20, wherein LSD-1 is prevented from forming a functional protein complex with RCOR2, and thereby infiltration of T cells is enabled, thus allowing anti-PDL1 and/or anti-PD1 therapy to retard tumor growth and/or tumor size.

23. The use of any one of claims 1-22, wherein the subject's cancer has a high non-synonymous mutational burden.

24. The use of any one of claims 1-23, wherein:

(a) the patient is to be concurrently treated with a therapeutically effective amount of at least one CPI therapy, which can be an anti-PDL1 and/or anti-PD1 therapy; and/or

(b) the patient is to be treated sequentially with the composition comprising the compound of Formula (I) or a pharmaceutically acceptable salt thereof, and at least one CPI

therapy, which can be an anti-PDL1 and/or anti-PD1 therapy; and/or

(c) the composition comprising the compound of Formula (I) or a pharmaceutically acceptable salt thereof, additionally comprises at least one CPI therapy, which can be an anti-PDL1 and/or anti-PD1 therapy.

25. The use of claim 24, wherein the combination of treatment with a composition comprising (i) a therapeutically effective amount of the compound of Formula (I) or a pharmaceutically acceptable salt thereof, and (ii) at least one CPI therapy, which can be an anti-PDL1 and/or anti-PD1 therapy, results in an increase in survival of the patient and/or a slowing of tumor growth, as compared to administration of the composition comprising the compound of Formula (I) or a pharmaceutically acceptable salt thereof alone or the CPI therapy alone.

26. The use of claim 25, wherein tumor growth is slowed by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%, as measured by any clinically recognized method.

27. The use of claim 25 or 26, wherein the patient's survival is increased by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%, as compared to mean survival times exhibited with patients administered the composition alone and/or the anti-PDL1 and/or anti-PD1 therapy alone.

28. The use of any one of claims 24-27, wherein the CPI therapy is an anti-PD1 therapy selected from the group consisting of:

(a) nivolumab;
(b) pembrolizumab;
(c) cemiplimab;
(d) spartalizumab;
(e) camrelizumab;
(f) sintilimab;
(g) tislelizumab;
(h) toripalimab;
(i) AMP-224;
(j) MEDI0680;
(k) durvalumab; and
(l) tislelizumab.

29. The use of any one of claims 24-27, wherein the CPI therapy is an anti-PDL1 therapy selected from the group consisting of:

(a) atezolizumab;

(b) avelumab;

(c) durvalumab;

(d) KN035;

(e) CK-301;

(f) CA-170; and

(g) BMS-986189.

30. The use of any one of claims 1-29, wherein:

(a) the composition further comprises a therapeutically effective amount of etoposide; or

(b) an additional composition comprising a therapeutically effective amount of etoposide is to be administered.

31. The use of any one of claims 1-30, wherein:

(a) the composition further comprises a therapeutically effective amount of a platin, and optionally wherein the platin is selected from the group consisting of cisplatin, carboplatin, exaliplatin, nedaplatin, triplatin tetranitrate, phenanthriplantin, picoplatin, and satraplatin; or

(b) an additional composition comprising a therapeutically effective amount of a platin is to be administered, and optionally wherein the platin is selected from the group consisting of cisplatin, carboplatin, exaliplatin, nedaplatin, triplatin tetranitrate, phenanthriplantin, picoplatin, and satraplatin.

32. The use of any one of claims 1-31, wherein the patient has a cancer selected from the group consisting of: lung cancer, small cell lung cancer (SCLC), lung squamous cell carcinoma (LUSC), head and neck squamous cell carcinoma (HNSC), HPV-negative head and neck squamous cell carcinoma (HNSC HPV neg), bladder carcinoma (BLCA), bladder urothelial carcinoma, melanoma, skin cutaneous melanoma (SKCM), breast cancer, triple negative breast cancer (TNBC), ovarian cancer (OV), stomach cancer, stomach adenocarcinoma (STAD), sarcomas (SARC), glioma, neuroendocrine tumors, advanced solid tumors, prostate cancer, marginal zone lymphoma, pancreatic cancer, pancreatic adenocarcinoma (PAAD), pancreatic ductal adenocarcinoma (PDAC), pancreatic neuroendocrine tumors (PNET), low grade glioma (LGG), cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), testicular

germ cell tumors (TGCT), kidney renal clear cell carcinoma (KIRC), kidney renal papillary cell carcinoma (KIRP), and esophageal carcinoma (ESCA).

33. The use of any one of claims 1-31, wherein the patient has a cancer selected from the group consisting of melanoma, metastatic non-small cell lung cancer, head and neck squamous cell carcinoma, squamous cell lung cancer, renal cell carcinoma, Hodgkin's lymphoma, cutaneous squamous cell carcinoma (CSCC), patients with locally advanced CSCC who are not candidates for curative surgery or curative radiation, solid tumors and lymphomas, relapsed or refractory classical Hodgkin lymphoma, small cell lung cancer (SCLC), solid tumors and hematologic cancers.

34. The use of any one of claims 1-33, wherein the composition comprising the compound of Formula (I) or a pharmaceutically acceptable salt thereof, is to be administered at least once weekly.

35. The use of any one of claims 1-33, wherein the composition comprising the compound of Formula (I) or a pharmaceutically acceptable salt thereof, is to be administered daily, every other day, every 3 days, every 4 days, every 5 days, once weekly, twice weekly, three times weekly, every other week, or any other suitable dosing period.

36. The use of any one of claims 1-35, wherein the compound of Formula (I) or a pharmaceutically acceptable salt thereof, is in the form of an injectable solution.

37. The use of any one of claims 1-36, wherein the compound of Formula (I) or a pharmaceutically acceptable salt thereof is to be administered as an intravenous injection.

38. The use of any one of claims 1-35, wherein the compound of Formula (I) or a pharmaceutically acceptable salt thereof, is adapted for oral administration.