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(54) Title: METHOD FOR TREATING CANCER WITH A REVERSE TRANSCRIPTASE INHIBITOR

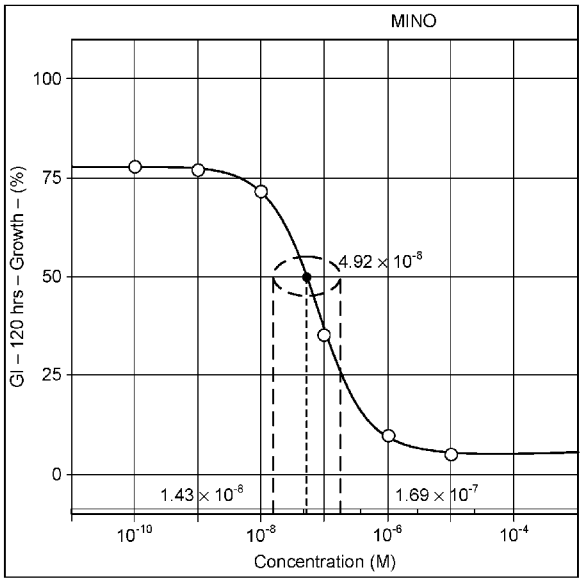

FIG. 3

(57) Abstract: Disclosed is a method for treating cancer in patient in need thereof comprising administering a therapeutically effective amount of a reverse transcriptase inhibitor (RTI) to the patient according to a continuous or an intermittent dosing schedule. RTIs include, but are not limited to, lamivudine (3TC), stavudine (d4T), emtricitabine (FTC), abacavir (ABC), tenofovir alafenamide, zidovudine (AZT), zalcitabine (ddC), didanosine (ddI), tenofovir disoproxil, adefovir dipivoxil, entecavir (ETV), telbivudine, censavudine, and islatravir.

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[Continued on next page]

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METHOD FOR TREATING CANCER WITH A REVERSE TRANSCRIPTASE INHIBITOR

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] The present disclosure is in the field of medicinal chemistry. In particular, the disclosure provides a method for treating cancer by administering a reverse transcriptase inhibitor (RTI) to a patient in need thereof according to a continuous or an intermittent dosing schedule. Exemplary RTIs include lamivudine (3TC), stavudine (d4T), emtricitabine (FTC), abacavir (ABC), tenofovir alafenamide, zidovudine (AZT), zalcitabine (ddC), didanosine (ddI), tenofovir disoproxil, adefovir dipivoxil, entecavir (ETV), censavudine, islatravir, and telbivudine. In one embodiment, the cancer is breast, colon, lung, pancreatic ductal, prostate, ovarian, or head and neck cancer.

Background

[0002] Long INterspersed Element-1 (LINE-1 or L1) retrotransposons form the only autonomously active family of transposable elements in humans. They are expressed and mobile in the germline, in embryonic stem cells, and in the early embryo, but are silenced in most somatic tissues. LINE-1 plays an important role in individual genome variations through insertional mutagenesis and sequence transduction, which occasionally lead to genetic diseases and disorders. In addition, LINE-1 is reactivated in certain cancers thus contributing to tumor genome dynamics. The LINE-1 element codes for two proteins, ORF1p and ORF2p, which are essential for its mobility. ORF1p is an RNA-binding protein with nucleic acid chaperone activity. ORF2p possesses endonuclease and reverse transcriptase activities. These proteins and the LINE-1 RNA assemble into a ribonucleoprotein particle (LINE-1 RNP) – the core of the retrotransposition machinery. The LINE-1 RNP mediates the synthesis of new LINE-1 copies upon cleavage of the target DNA and reverse transcription of the LINE-1 RNA at the target site. The LINE-1 element takes benefit of cellular host factors to complete its life cycle, however several cellular pathways also limit the cellular accumulation of LINE-1 RNPs and their deleterious activities. *See, e.g.*, Pizarro and Cristofari (2016) *Front. Cell Dev. Biol. 4:14*. doi: 10.3389/fcell.2016.00014.

[0003] LINE-1 retrotransposition is a hallmark of cancer. *See, e.g.*, Rodic, N., *Frontiers In Bioscience (Landmark Ed.) 23*:1680-1686 (2018); Xiao-Jie et al., *Genet Med 18*:431-439 (2016); and Zhang et al., *Front Cell Dev Biol. 8:657* (2020) https://doi.org/10.3389/fcell.2020.00657. Increased expression of LINE-1 promotes pathogenesis by damaging the host DNA via mutation insertions and altering target gene expression and chromosomal rearrangements. To this end, LINE-1 methylation studies have been conducted in common lethal cancers, lung cancer, colon and rectal cancers, breast cancer, prostate cancer, liver cancer, ovarian cancer, and esophageal cancer. *See, e.g.*, Ardeljan, et al, *Clinical Chemistry 63*:816-822 (2017). In non-small cell lung cancer, LINE-1 promoter hypomethylation is common and is associated with genomic instability and poor prognosis. In colon cancer, LINE-1 hypomethylation appears to be an early event also associated with poor outcomes. It is more pronounced in colon cancer liver metastases compared to matched primary tumors. In breast cancer, LINE-1 hypomethylation has been reported in preneoplastic phases of epithelial atypia with persistently low LINE-1 promoter methylation seen in in situ and invasive lesions. It has also been associated with decreased overall survival and drug resistance in younger patients. In prostate cancers, LINE-1 hypomethylation is also reported, particularly in association with chromosome 8 abnormalities; it appears to be more pronounced in metastatic lesions than in primary tumors. In hepatocellular carcinoma, several groups have associated LINE-1 hypomethylation with poor clinical outcomes, including disease recurrence after resection. In epithelial ovarian cancers, LINE-1 hypomethylation is correlated with more aggressive histology, poorer progression-free intervals, and poorer survival. Lastly, in esophageal squamous cell carcinomas, LINE-1 hypomethylation is also recognized and associated with poorer survival.

[0004] There is a need in the art for LINE-1 inhibitors for use in treating cancer.

BRIEF SUMMARY OF THE INVENTION

[0005] In some embodiments, provided is a method for treating cancer, e.g., breast, colon, lung, pancreatic ductal, prostate, ovarian, or head and neck cancer, in patient in need thereof comprising administering a therapeutically effective amount of a RTI to the patient, wherein the RTI is administered according to a continuous or an intermittent dosing schedule.

[0006] In some embodiments, provided is a method for treating cancer, e.g., breast, colon, lung, pancreatic ductal, prostate, ovarian, or head and neck cancer, in patient in need thereof comprising administering a therapeutically effective amount of censavudine to the patient in need thereof. In some embodiments, censavudine is administered according to a continuous or an intermittent dosing schedule.

[0007] In some embodiments, provided is a method for treating cancer, e.g., breast, colon, lung, pancreatic ductal, prostate, ovarian, or head and neck cancer, in patient in need thereof comprising administering a therapeutically effective amount of lamivudine (3TC), stavudine (d4T), emtricitabine (FTC), abacavir (ABC), tenofovir alafenamide, zidovudine (AZT), zalcitabine (ddC), didanosine (ddI), tenofovir disoproxil, adefovir dipivoxil, entecavir (ETV), or telbivudine to the patient in need thereof according to a continuous or an intermittent dosing schedule.

[0008] In some embodiments, provided is a method for the treatment of breast cancer. In some embodiments, provided is a method for the treatment of colon cancer. In some embodiments, provided is a method the treatment of lung cancer. In some embodiments, provided is a method for the treatment of pancreatic ductal cancer. In some embodiments, provided is a method for the treatment of prostate cancer. In some embodiments, provided is a method for the treatment high-risk localized prostate cancer. In some embodiments, provided is a method for the treatment of prostate cancer that is not metastatic. In some embodiments, provided is a method for the treatment of ovarian cancer. In some embodiments, provided is a method for the treatment of head and neck cancer.

[0009] In some embodiments, provided is a method further comprising administering a therapeutically effective amount of at least one second therapeutic agent useful for treating the cancer.

[0010] In some embodiments, provided is a method for the treatment of breast cancer, wherein the at least one second therapeutic agent is Soltamox® (tamoxifen), Arimidex® (anastrozole), Femara® (letrozole), Aromasin® (exemestane), Herceptin® (trastuzumab), Abraxane® (paclitaxel), Cytoxan® (cyclophosphamide), Taxol® (paclitaxel), Afinitor® (everolimus), Taxotere® (docetaxel), Xeloda® (capecitabine), Trexall® (methotrexate), Faslodex (fulvestrant), Adriamycin® (doxorubicin), Perjeta® (pertuzumab), Gemzar (gemcitabine), Tykerb® (lapatinib), Adrucil® (fluorouracil), Ibrance® (palbociclib), Verzenio® (abemaciclib), Fareston® (toremifene), Halaven® (eribulin), Menest,

Kadcyla® (ado-trastuzumab emtransine), Androxy® (fluoxymesterone), Avastin®(bevacizumab), esterified estrogens, Herzuma® (trastuzumab), Ixempra® (ixabepilone), Kanjinti® (trastuzumab), Kisqali® (ribociclib), Ogivri® (trastuzumab), Ontruzant® (trastuzumab), Tepadina® (thiotepa), Trazimera® (trastuzumab), Velban® (vinblastine), Piqray® (alpelisib), Tecentriq® (atezolizumab), Enhertu® (fam-trastuzumab deruxtecan), Herceptin, Hylecta™ (hyaluronidase/trastuzumab), Infugem® (gemcitabine), Kisqali® Femara® Co-Pack (ribociclib and letrozole), Talzenna® (talazoparib), Trodelvy® (sacituzumab) or Tukysa™ (tukatinib).

[0011] In some embodiments, provided is a method for the treatment of colon cancer, wherein the at least one second therapeutic agent is Xeloda® (capecitabine), Eloxatin® (oxaliplatin), fluorouracil, Avastin® (bevacizumab), leucovorin, Camptosar® (irinotecan), Stivarga® (regorafenib), Erbitux® (cetuximab), Vectibix® (panitumumab), Lonsurf® (tipiracil/trifluridine), Zaltrap® (ziv-aflibercept), Betaseron® (interferon beta-1b), Fusilev® (levoleucovorin), Wellcocorin® (methotrexate), Keytruda® (pembrolizumab), Mvasi® (bevacizumab-awwb), Cyramza® (ramucirumab), Yervoy® (ipilmumab), Opdivo® (nivolumab), Braftovi® (encorafenib), Khapzory® (levoleucovorin) or Zirabev® (bevacizumab-bvzr).

[0012] In some embodiments, provided is a method for the treatment of lung cancer, wherein the at least one second therapeutic agent is Etopophos® (etoposide), Hycamtin® (topotecan), VePesid® (etoposide), Toposar® (etoposide), Opdivo®(nivolumab), Keytruda® (pembrolizumab), Tecentriq® (atezolizumab), Imfinizi® (durvalumab), methotrexate, cyclophosphamide, Carboplatin, Cisplatin, docetaxel, Gemcitabine, Irinotecan, Paclitaxel, Pemetrexed, Vinblastine, or Vinorelbine.

[0013] In some embodiments, provided is a method for the treatment of pancreatic ductal cancer, wherein the at least one second therapeutic agent is Gemzar® (Gemcitabine), fluorouracil, Afinitor® (everolimus), Tarceva® (erlotinib), Abraxane® (paclitaxel), capecitabine, Sutent® (sunitinib), pancreatin, methotrexate, Zanosar® (streptozocin), Mutamycin® (mitomycin), Onivyde® (irinotecan), bevacizumab, cetuximab, Infugem® (gemcitabine) or Lynparza® (olaparib).

[0014] In some embodiments, provided is a method for the treatment of head and neck cancer, wherein the at least one second therapeutic agent is Erbituz® (cetuximab),

Taxotere® (docetaxel), Trexall® (methotrexate), Keytruda® (pembrolizumab) or Opdivo® (nivolumab).

[0015] In some embodiments, provided is a method for the treatment of prostate cancer, wherein the at least one second therapeutic agent is Suprefact® (buserelin), Firmagon® (degarelix), Zoladex® (goserelin), Vantas® (histrelin), Eligard® (leuprolide), Orgovyx® (relugolix), Trelstar® (triptorelin), Casodex® (bicalutamide), Eulexin® (flutamide), Nilandron® (nilutamide), Zytiga® (biraterone acetate), Erleada® (apalutamide), or Xtandi® (enzalutamide).

[0016] In some embodiments, the at least one second therapeutic agent is a STING agonist.

[0017] In some embodiments, provided is a kit for carrying out the therapeutic methods and uses of the disclosure, the kit comprising (i) a RTI; and (ii) and instructions for administering the RTI to a patient having cancer according to a continuous or an intermittent dosing schedule.

BRIEF DESCRIPTION OF DRAWINGS

[0018] Fig. 1 is a dose response curve showing the cell proliferation activity of Compound 13 in MV4-11 cells after incubation for 72 h.

[0019] Fig. 2 is a dose response curve showing the cell proliferation activity of Compound 9 in MINO cells after incubation for 72 h.

[0020] Fig. 3 is a dose response curve showing the cell proliferation activity of Compound 9 in MINO cells after incubation for 120 h.

[0021] Fig. 4 is a dose response curve showing the cell proliferation activity of Compound 9 in MINO cells after incubation for 168 h.

DETAILED DESCRIPTION OF THE INVENTION

[0022] In one embodiment, provided is a method for treating cancer in patient in need thereof comprising administering a therapeutically effective amount of a reverse transcriptase inhibitor (RTI), e.g., islatravir, censavudine, elvucitabine, lamivudine (3TC), zidovudine (AZT), tenofovir, tenofovir disoproxil, tenofovir alafenamide, stavudine (d4T), zalcitabine (ddC), didanosine (ddI), emtricitabine (FTC), entecavir (ETV) or abacavir

(ABC), to the patient, wherein the RTI is administered according to a continuous or an intermittent dosing schedule.

[0023] In another embodiment the RTI is administered to the patient on a continuous dosing schedule, e.g., the RTI is administered to the patient every day.

[0024] In another embodiment the RTI is administered to the patient on an intermittent dosing schedule, e.g., the RTI is administered to the patient every other day.

[0025] In another embodiment, the RTI is administered to the patient as an adjuvant therapy to treat cancer.

[0026] In another embodiment, the RTI is administered to the patient as a neoadjuvant therapy to treat cancer.

[0027] In one embodiment, the RTI is a nucleoside reverse transcriptase inhibitor (NRTI). Non-limiting exemplary NRTIs include abacavir (ZIAGEN™), abacavir/lamivudine (Epzicom), abacavir/lamivudine/zidovudine (TRIZIVIR™), adefovir, alovudine, amdoxovir, apricitabine, ATRIPLA®, BARACLUDE®, BIKTARVY®, COVIRACIL™, DAPD/DXG, D-D4FC, dexelvucitabine, didanosine (VIDEX™), didanosine extended-release (Videx EC), dOTC, emtricitabine (EMTRIVA™), emtricitabine/tenofovir alafenamide (DESCOVY®), emtricitabine/tenofovir disoproxil fumarate (TRUVADA®), fosalvudine, lamivudine/zidovudine (COMBIVIR™), EVIPLERA™, GENVOYA®, HIVID™, KIVEXA™, lamivudine (EPIVIR™), LODENOSINE™, ODEFSEY®, PREVEON®, racivir, stampidine, stavudine (ZERIT™), STRIBILD®, TENOFOVIR™, tenofovir disoproxil fumarate (VIREAD™), TRIUMEQ®, Trizivir, VEMLIDY®, and zidovudine (RETROVIR™).

[0028] In another embodiment, the RTI is a non-nucleoside reverse transcriptase inhibitor (NNRTI). Non-limiting exemplary NNRTIs include delavirdine, efavirenz, etravirine, nevirapine, and rilvipirine.

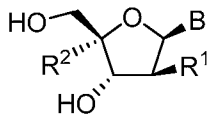
[0029] In another embodiment, the RTI is a LINE-1 inhibitor.

[0030] In another embodiment, the RTI is islatravir, censavudine, elvucitabine, lamivudine (3TC), zidovudine (AZT), tenofovir, tenofovir disoproxil, tenofovir alafenamide, stavudine (d4T), zalcitabine (ddC), didanosine (ddI), emtricitabine (FTC), entecavir (ETV), 2',3'-dideoxyguanosine (ddG), 2′,3′-dideoxyadenosine (ddA), 2′-fluoro-2′,3′-dideoxyarabinosyladenine (F-ddA), efavirenz (EFV), nevirapine (NVP), or abacavir (ABC).

[0031] In another embodiment, the RTI is lamivudine (3TC), stavudine (d4T), emtricitabine (FTC), abacavir (ABC), tenofovir alafenamide, zidovudine (AZT), zalcitabine (ddC), didanosine (ddI), tenofovir disoproxil, adefovir dipivoxil, entecavir (ETV), or telbivudine.

[0032] In another embodiment, the RTI is islatravir. In another embodiment, the RTI is censavudine. In another embodiment, the RTI is lamivudine (3TC). In another embodiment, the RTI is stavudine (d4T). In another embodiment, the RTI is emtricitabine (FTC). In another embodiment, the RTI is abacavir (ABC). In another embodiment, the RTI is tenofovir alafenamide. In another embodiment, the RTI is zidovudine (AZT). In another embodiment, the RTI is zalcitabine (ddC). In another embodiment, the RTI is didanosine (ddI). In another embodiment, the RTI is tenofovir disoproxil. In another embodiment, the RTI is adefovir dipivoxil. In another embodiment, the RTI is entecavir. In another embodiment, the RTI is telbivudine.

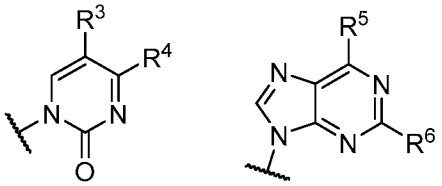
[0033] In another embodiment, the RTI is a compound of Formula **I**:



I,

or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein:

[0034] B is selected from the group consisting of:



B-1 and B-2 ;

[0035] R^1 is selected from the group consisting of hydrogen and -OH;

[0036] R^2 is selected from the group consisting of methyl, ethynyl, and -CN;

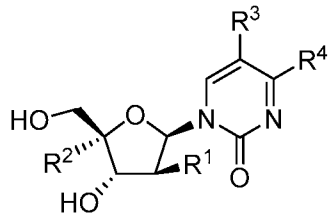
[0037] R^3 is selected from the group consisting of hydrogen, fluoro, chloro, bromo, iodo and methyl;

[0038] R^4 is selected from the group consisting of $-NH_2$ and -OH;

[0039] R^5 is selected from the group consisting of $-NH_2$ and -OH; and

[0040] R^6 is selected from the group consisting of hydrogen, fluoro, chloro, and $-NH_2$

[0041] In another embodiment, the RTI is a compound is a compound of Formula **II**:



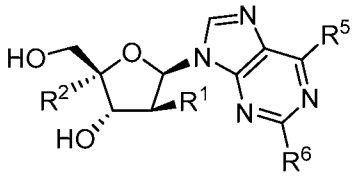
II,

or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein R^1, R^2, R^3, and R^4 are as defined in connection with Formula **I**.

[0042] In another embodiment, the RTI is a compound is a compound of Formula **II**, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein R^3 is hydrogen. In another embodiment, the RTI is a compound is a compound of Formula **II**, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein R^3 is selected from the group consisting of fluoro and chloro. In another embodiment, the RTI is a compound is a compound of Formula **II**, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein R^3 is methyl.

[0043] In another embodiment, the RTI is a compound is a compound of Formula **II**, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein R^4 is $-NH_2$. In another embodiment, the RTI is a compound is a compound of Formula **II**, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein R^4 is -OH.

[0044] In another embodiment, the RTI is a compound is a compound of Formula **III**:



III,

or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein R^1, R^2, R^5, and R^6 are as defined in connection with Formula **I**.

[0045] In another embodiment, the RTI is a compound is a compound of Formula **III**, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein R^5 is $-NH_2$. In another embodiment, the RTI is a compound is a compound of Formula **III**, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein R^5 is -OH.

[0046] In another embodiment, the RTI is a compound is a compound of Formula **III**, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein R^6 is

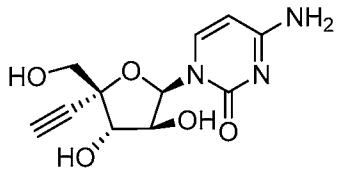
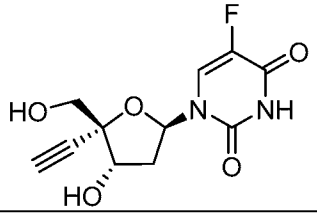
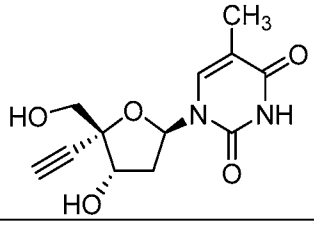
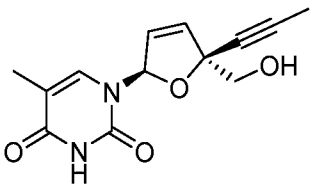
hydrogen. In another embodiment, the RTI is a compound is a compound of Formula **III**, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein R^6 is chloro. In another embodiment, the RTI is a compound is a compound of Formula **III**, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein R^6 is fluoro. In another embodiment, the RTI is a compound is a compound of Formula **III**, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein R^6 is $-NH_2$.

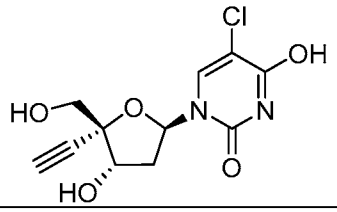
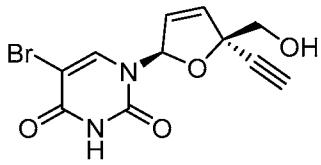
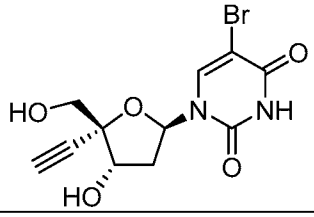
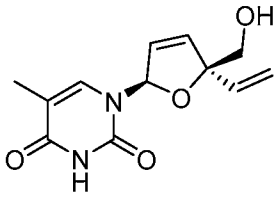
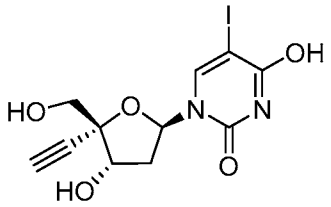
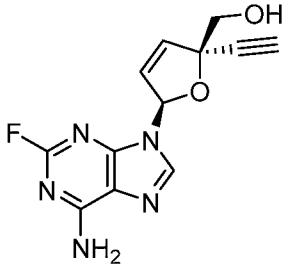
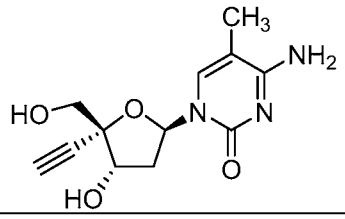
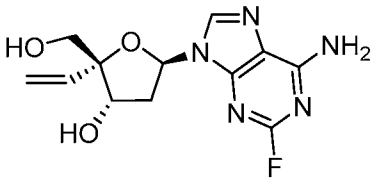
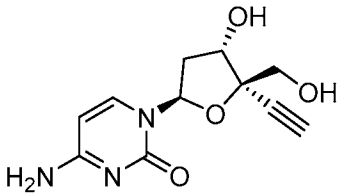
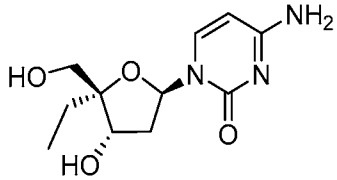
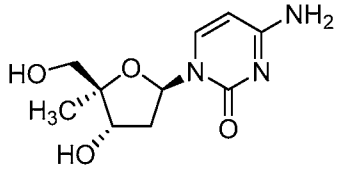
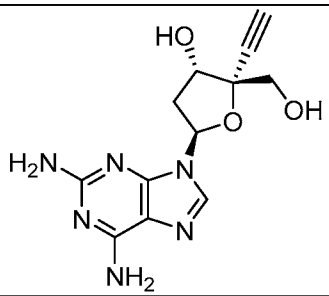
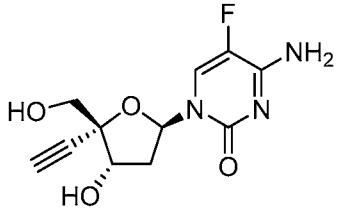
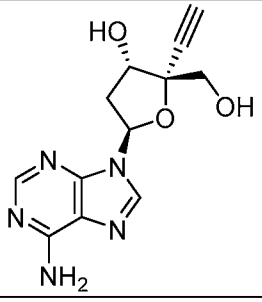
[0047] In another embodiment, the RTI is a compound is a compound of any one of Formulae **I-III**, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein R^1 is hydrogen. In another embodiment, the RTI is a compound is a compound of any one of Formulae **I-III**, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein R^1 is -OH.

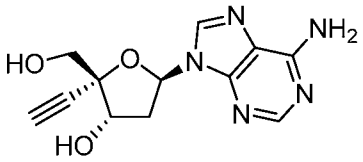
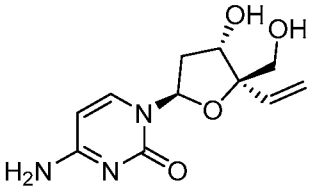
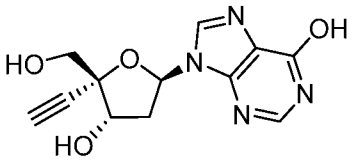
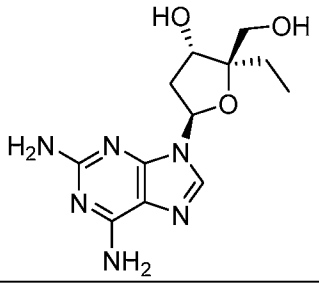
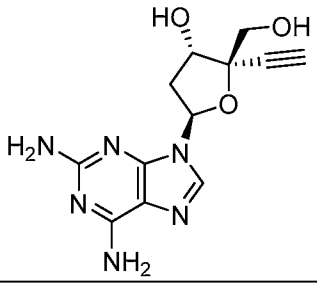
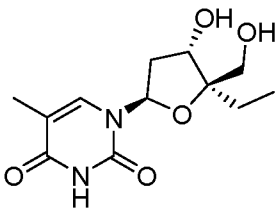
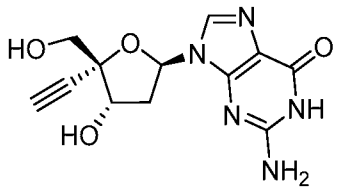
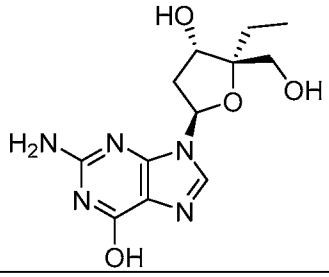
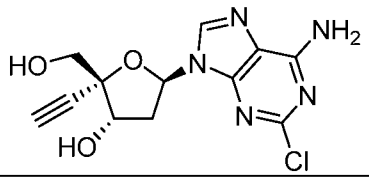
[0048] In another embodiment, the RTI is a compound is a compound of any one of Formulae **I-III**, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein R^2 is methyl. In another embodiment, the RTI is a compound is a compound of any one of Formulae **I-III**, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein R^2 is ethynyl. In another embodiment, the RTI is a compound is a compound of any one of Formulae **I-III**, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein R^2 is -CN.

[0049] In another embodiment, the RTI is any one or more of the compounds of Table 3, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.

Table 3

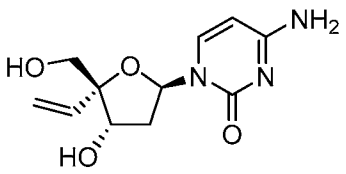
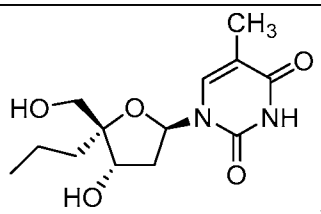
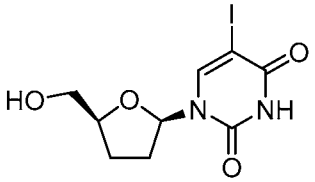
Cpd.	Structure	Cpd.	Structure
1		15	
2		16	

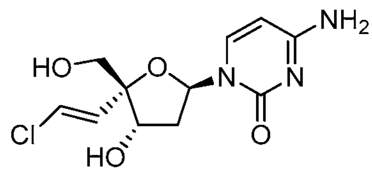
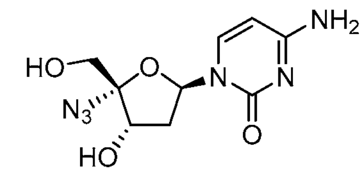
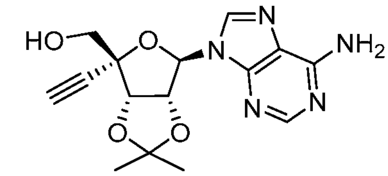
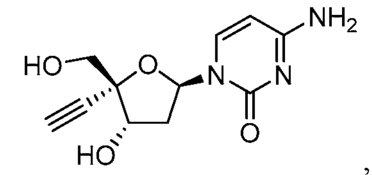
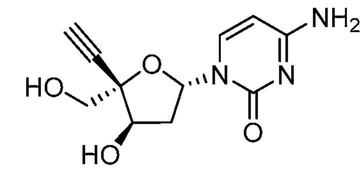
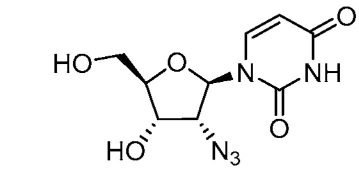
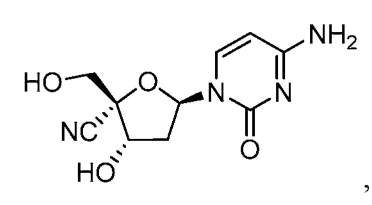
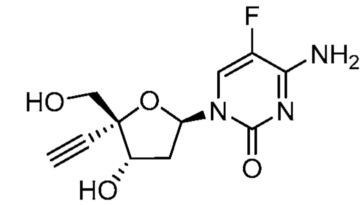
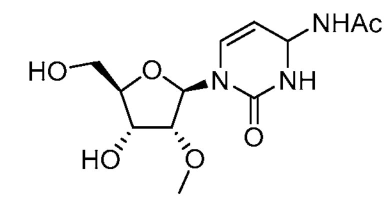
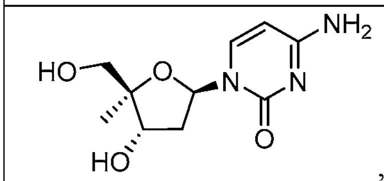
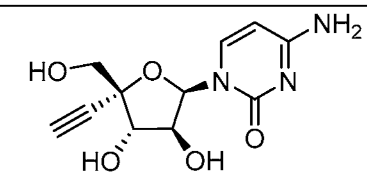
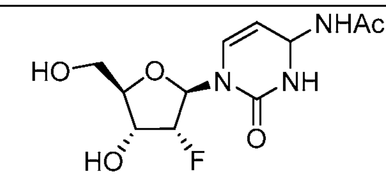
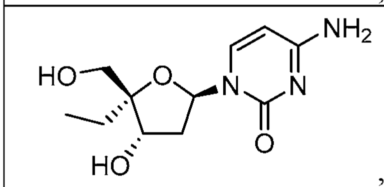
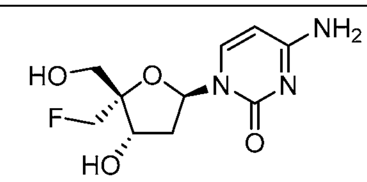
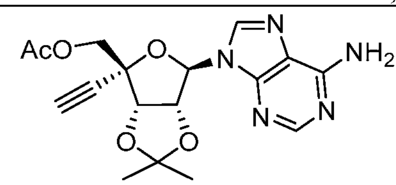
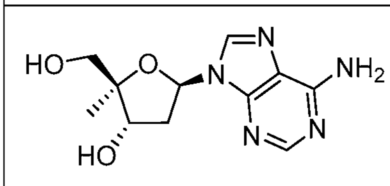
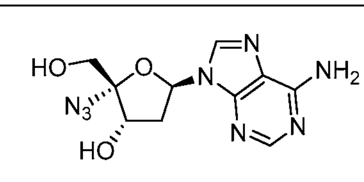
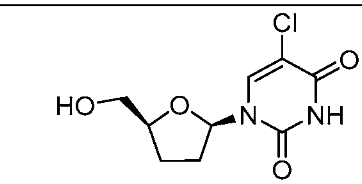
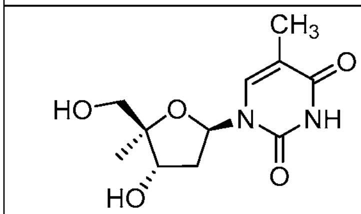
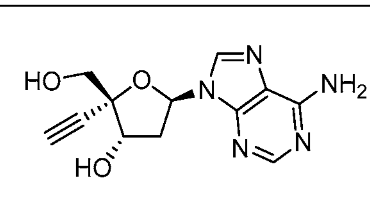
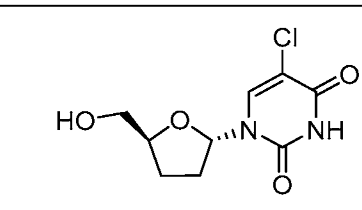
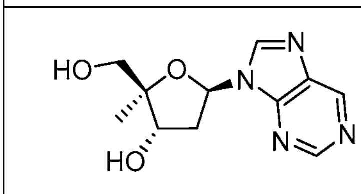
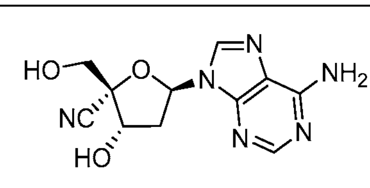
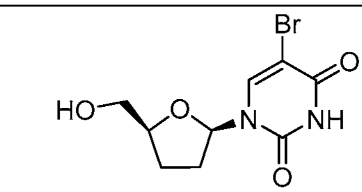
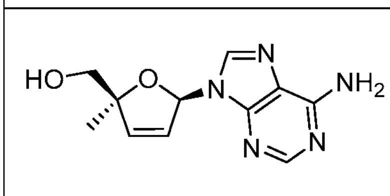
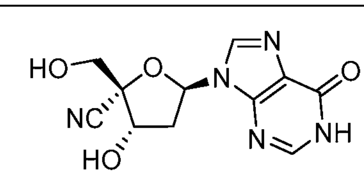
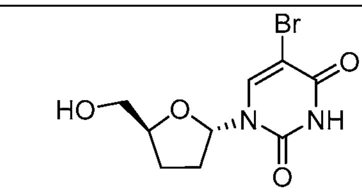
3		**17**	
4		**18**	
5		**19**	
6		**20**	
7		**21**	
8		**22**	
9		**23**	

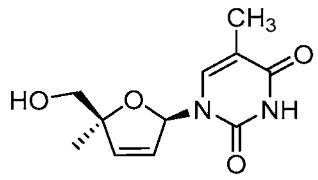
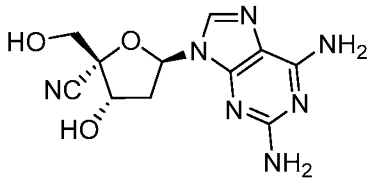
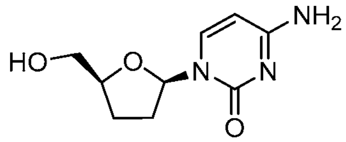
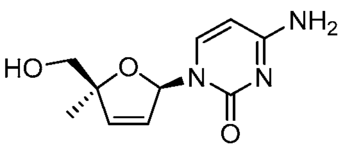
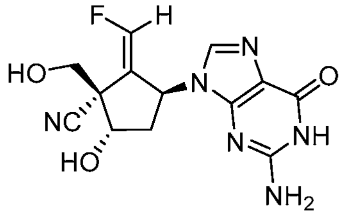
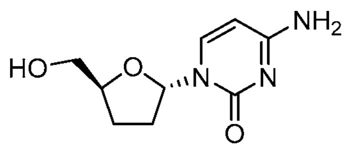
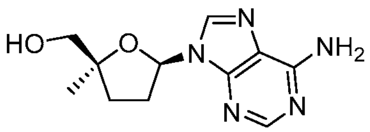
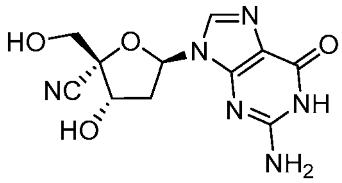
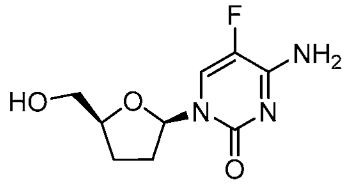
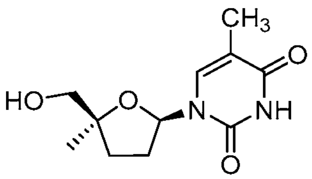
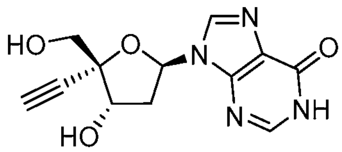
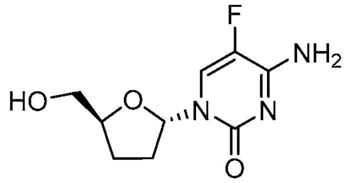
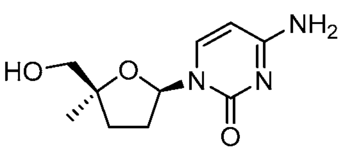
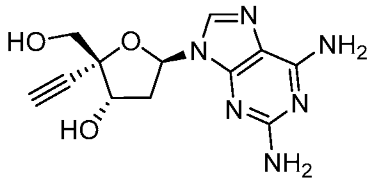
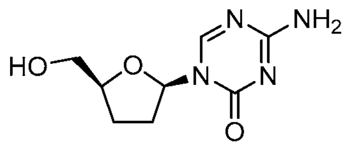
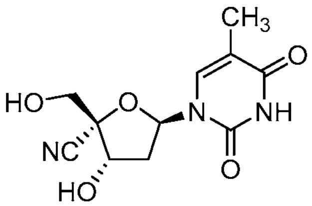
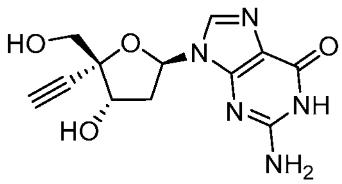
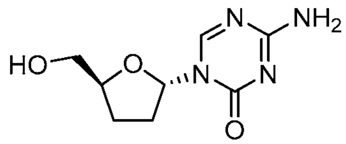
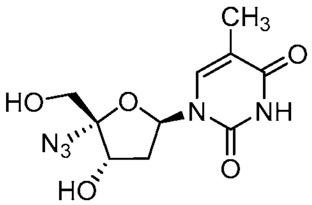
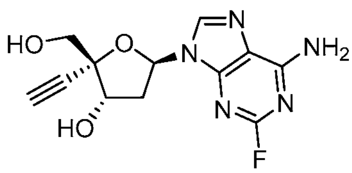
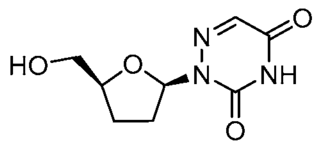
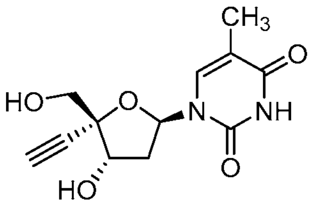
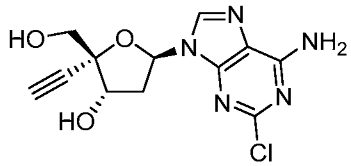
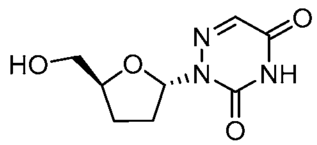
10		**24**	
11		**25**	
12		**26**	
13		**27**	
14			

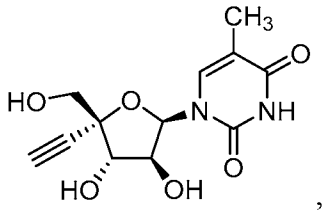
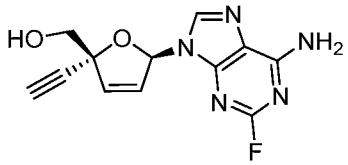
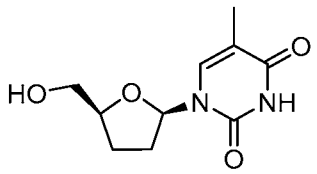
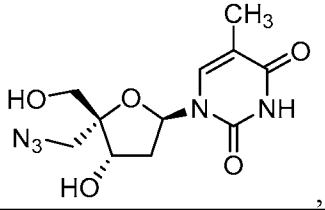
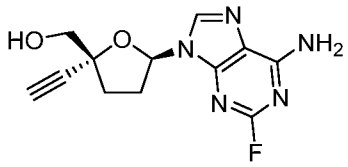
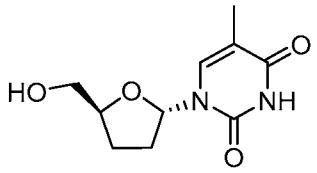
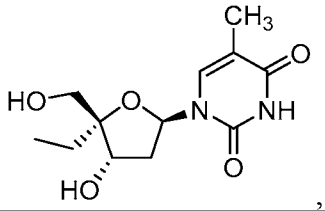
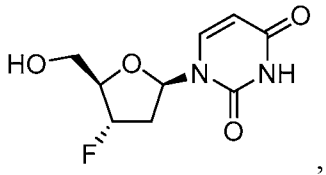
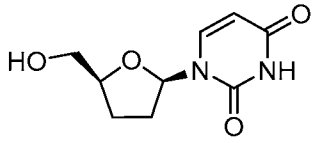
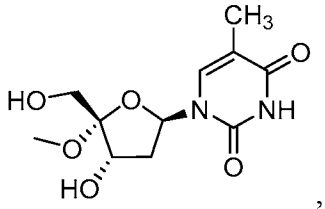
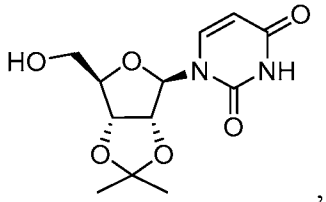
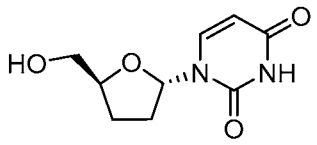
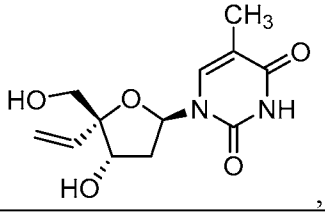
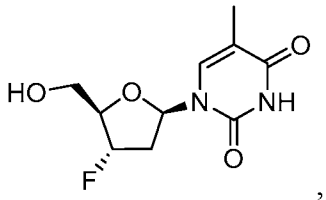
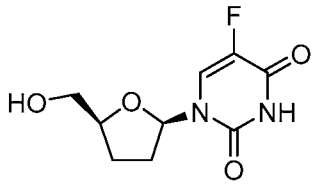
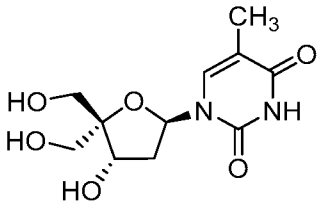
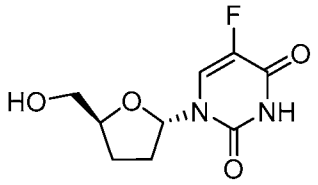
[0050] In another embodiment, the RTI is any one or more of the compounds of Table 4, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.

Table 4

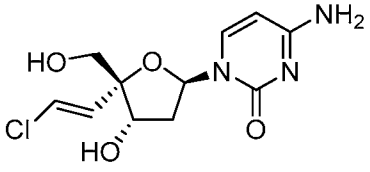
 ,	 ,	 ,

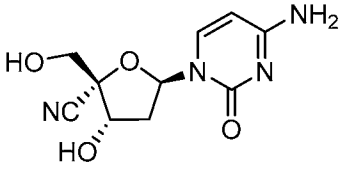
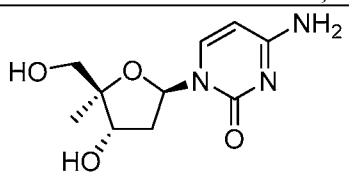
 ,	 ,	 ,
 ,	 ,	 ,
 ,	 ,	 ,
 ,	 ,	 ,
 ,	 ,	 ,
 ,	 ,	 ,
 ,	 ,	 ,
 ,	 ,	 ,
 ,	 ,	 ,

 ,	 ,	 ,
 ,	 ,	 ,
 ,	 ,	 ,
 ,	 ,	 ,
 ,	 ,	 ,
 ,	 ,	 ,
 ,	 ,	 ,
 ,	 ,	 ,

 ,	 ,	 ,
 ,	 ,	 ,
 ,	 ,	 ,
 ,	 ,	 ,
 ,	 ,	 ,
 or	 .	

[0051] In another embodiment, the RTI is a compound of Table 4, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, selected from the group consisting of:

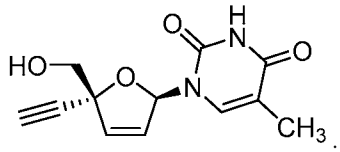
Cpd.	Structure
28	 ,

29	 , and
30	 .

[0052] The compounds of Formulae **I-III**, Table 3, and Table 4 may be found and prepared as described, for example, in Nomura et al., *J. Med. Chem. 42*:2901-2908 (1999); Ohrui et al., *J. Med. Chem. 43*:4516-4525 (2000), Ohrui, H., *Proc. Jpn. Acad. Ser. B 87*:53-65 (2011); Banuelos-Sanchez et al., *Cell Chemical Biology 26*:1095-1109 (2019); Kirby et al., *Antimicrobial Agents and Chemotherapy 57*:6254-6264 (2013), Higashi-Kuwata et al., *Journal of Hepatology 74*:1075-1086 (2021), JP Patent No. 6767011, US Patent No. 10,933,067, and/or as described in EXAMPLES 4-6, below.

[0053] The term "tautomer" as used herein refers to each of two or more isomers of a compound which exist together in equilibrium, and are interchanged by migration of an atom, e.g., a hydrogen, or group within the molecule. Certain compounds of the disclosure may exist as tautomers.

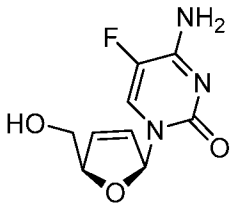
[0054] In some embodiments, provided is a method for treating cancer, e.g., breast, colon, lung, pancreatic ductal, prostate, ovarian, or head and neck cancer, by administering censavudine to a patient in need thereof. Censavudine is a compound having the following chemical structure:



Censavudine (also known as 4'-Ed4T, 4'-ethynyl-d4T, 4'-ethynylstavudine, BMS-986001, OBP-601, festinavir) and its method of synthesis is described in U.S. Pat. No. 7,589,078. In some embodiments, censavudine is administered to the subject according to an intermittent dosing schedule. In some embodiments, censavudine is administered to the subject according to a continuous dosing schedule

[0055] In some embodiments, provided is a method for treating cancer, e.g., breast, colon, lung, pancreatic ductal, prostate, ovarian, or head and neck cancer, by administering

elvucitabine a patient in need thereof. Elvucitabine is a compound having the following chemical structure:



Elvucitabine and its method of synthesis is described in U.S. Pat. No. 5,627,160. In some embodiments, elvucitabine is administered to the subject according to an intermittent dosing schedule. In some embodiments, elvucitabine is administered to the subject according to a continuous dosing schedule

[0056] The term "LINE-1 inhibitor" as used herein refers to a compound that inhibits human LINE-1 retrotransposition, e.g., with a half maximal inhibitory concentration (IC_{50}) of about 50 μM or less in a HeLa cell-based dual-luciferase assay as described in EXAMPLE 1, *see* below. *See also* Jones et al., (2008) *PLoS ONE* 3(2): e1547. doi:10.1371/journal.pone.0001547; Xie et al., (2011) *Nucleic Acids Res.* 39(3): e16. doi: 10.1093/nar/gkq1076. In another embodiment, the IC_{50} is 1 μM or less. In another embodiment, the IC_{50} is 0.5 μM or less. In another embodiment, the IC_{50} is 0.25 μM or less. In another embodiment, the IC_{50} is 0.15 μM or less. In another embodiment, the IC_{50} is 0.1 μM or less. In another embodiment, the IC_{50} is 0.05 μM or less. In another embodiment, the IC_{50} is 0.01 μM or less. In another embodiment, the IC_{50} is 0.005 μM or less. In some embodiments, the LINE-1 inhibitor is also a nucleoside reverse transcriptase inhibitor (NRTI). LINE-1 inhibitors are described, for example, in WO 2020/154656. Non-limiting exemplary LINE-1 inhibitors include islatravir, censavudine, elvucitabine, lamivudine (3TC), zidovudine (AZT), tenofovir, tenofovir disoproxil, tenofovir alaphenamide, stavudine (d4T), zalcitabine (ddC), didanosine (ddI), emtricitabine (FTC), entecavir (ETV), 2',3'-dideoxyguanosine (ddG), 2′,3′-dideoxyadenosine (ddA), 2′-fluoro-2′,3′-dideoxyarabinosyladenine (F-ddA), efavirenz (EFV), nevirapine (NVP), and abacavir (ABC).

[0057] The term "adjuvant therapy" as used herein refers to the treatment of cancer during or after a surgical intervention, radiotherapy, chemotherapy, and/or hormone therapy.

[0058] The term "neoadjuvant therapy" as used herein refers to the treatment of cancer prior to a surgical intervention, radiotherapy, chemotherapy, and/or hormone therapy. *See,*

e.g., Kent and Hussain, *Rev. Urol. 5(suppl 3)*:S28-S37 (2003). The object of neoadjuvant cancer therapy is to reduce the size or extent of the patient's tumor(s) before the primary therapy, preferably improving the likelihood of successful outcome and/or decreasing the adverse effects of more extensive treatment that would be required in the absence of neoadjuvant therapy.

[0059] There are multiple definitions used to categorize patients with high-risk prostate cancer. Pretreatment parameters, including clinical stage, prostate-specific antigen (PSA), and Gleason score, are established predictors of disease recurrence and have historically been used in high-risk disease classifications. *See, e.g.*, McKay et al, Soc Clin Oncol Ed Book 40 (2020) e241-e252. The term "high-risk localized prostate cancer" as used herein refers to prostate cancer classified as clinical T stage cT3a with a Gleason score of at least 8 and/or a PSA of at least 20 ng/mL.

[0060] The terms "intermittent dose administration," "intermittent dosing schedule," and similar terms as used herein refer to non-continuous administration of a RTI to a subject. Intermittent dose administration regimens useful in the present disclosure encompass any discontinuous administration regimen that provides a therapeutically effective amount of a RTI to a subject in need thereof. Intermittent dosing regimens can use equivalent, lower, or higher doses of a RTI than would be used in continuous dosing regimens. Advantages of intermittent dose administration include, but are not limited to, improved safety, decreased toxicity, e.g., decreased weight loss, increased exposure, increased efficacy, and/or increased subject compliance. These advantages may be realized when a RTI is administered as a single agent or when administered in combination with one or more additional therapeutic agents, e.g., a STING agonist.

[0061] In one embodiment, the RTI is administered to the subject every other day.

[0062] In another embodiment, the RTI is administered to the subject once a week.

[0063] In another embodiment, the RTI is administered to the subject twice a week on consecutive days, e.g., on Monday and Tuesday.

[0064] In another embodiment, the RTI is administered to the subject twice a week on non-consecutive days, e.g., on Monday and Wednesday.

[0065] In another embodiment, the RTI is administered to the subject three times a week on consecutive days, e.g., on Monday, Tuesday, and Wednesday.

[0066] In another embodiment, the RTI is administered to the subject three times a week on non-consecutive days, e.g., on Monday, Wednesday, and Friday.

[0067] In one embodiment, the RTI is administered to the subject for about consecutive 4 weeks in a row followed by 1 day or 2, 3, 4, 5, 6, or 7 consecutive days in a row wherein the RTI is not administered to the subject.

[0068] In one embodiment, the RTI is administered to the subject for about 3 consecutive weeks in a row followed by 1 day or 2, 3, 4, 5, 6, or 7 consecutive days in a row wherein the RTI is not administered to the subject.

[0069] In one embodiment, the RTI is administered to the subject for about 2 consecutive weeks in a row followed by 1 day or 2, 3, 4, 5, 6, or 7 consecutive days in a row wherein the RTI is not administered to the subject.

[0070] In one embodiment, the RTI is administered to the subject for 3 consecutive weeks in a row followed by 1 day or 2, 3, 4, or 5 consecutive days in a row wherein the RTI is not administered to the subject

[0071] In one embodiment, the RTI is administered to the subject for 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 consecutive days in a row followed by 1 day or 2, 3, 4, or 5 consecutive days in a row wherein the RTI is not administered to the subject.

[0072] In one embodiment, the RTI is administered to the subject for 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 consecutive days in a row followed by 1 day or 2, 3, or 4 consecutive days in a row wherein the RTI is not administered to the subject.

[0073] In one embodiment, the RTI is administered to the subject for 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 consecutive days in a row followed by about 7, 14, 21, or 28 consecutive days in a row wherein the RTI is not administered to the subject.

[0074] In one embodiment, the RTI is administered to the subject for 2, 3, 4, 5, 6, 7, 8, 9, or 10 consecutive days in a row followed by 1 day or 2, 3, or 4 consecutive days in a row wherein the RTI is not administered to the subject.

[0075] In another embodiment, the RTI is administered to the subject for 2 consecutive days in a row followed by 3 or 4 consecutive days in a row wherein the RTI is not administered.

[0076] In another embodiment, the RTI is administered to the subject for 3 consecutive days in a row followed by 3 or 4 days in a row wherein the RTI is not administered.

[0077] In another embodiment, the RTI is administered to the subject for 4 consecutive days in a row followed by 3 or 4 consecutive days in a row wherein the RTI is not administered.

[0078] In another embodiment, the RTI is administered to the subject for 5 consecutive days in a row followed by 3 or 4 consecutive days in a row wherein the RTI is not administered.

[0079] In another embodiment, the RTI is administered to the subject for 6 consecutive days in a row followed by 3 or 4 consecutive days in a row wherein the RTI is not administered.

[0080] In another embodiment, the RTI is administered to the subject for 7 consecutive days in a row followed by 3 or 4 consecutive days in a row wherein the RTI is not administered.

[0081] In another embodiment, the RTI is administered to the subject for 8 consecutive days in a row followed by 3 or 4 consecutive days in a row wherein the RTI is not administered.

[0082] In another embodiment, the RTI is administered to the subject for 9 consecutive days in a row followed by 3 or 4 consecutive days in a row wherein the RTI is not administered.

[0083] In another embodiment, the RTI is administered to the subject for 10 consecutive days in a row followed by 3 or 4 consecutive days in a row wherein the RTI is not administered.

[0084] In another embodiment, the RTI is administered to the subject for 11 consecutive days in a row followed by 3 or 4 consecutive days in a row wherein the RTI is not administered.

[0085] In another embodiment, the RTI is administered to the subject for 12 consecutive days in a row followed by 3 or 4 consecutive days in a row wherein the RTI is not administered.

[0086] In another embodiment, the RTI is administered to the subject for 13 consecutive days in a row followed by 3 or 4 consecutive days in a row wherein the RTI is not administered.

[0087] In another embodiment, the RTI is administered to the subject for 14 consecutive days in a row followed by 3 or 4 consecutive days in a row wherein the RTI is not administered.

[0088] In another embodiment, the RTI is administered to the subject for 15 consecutive days in a row followed by 3 or 4 consecutive days in a row wherein the RTI is not administered.

[0089] In another embodiment, the RTI is administered to the subject for 16 consecutive days in a row followed by 3 or 4 consecutive days in a row wherein the RTI is not administered.

[0090] In another embodiment, the RTI is administered to the subject for 17 consecutive days in a row followed by 3 or 4 consecutive days in a row wherein the RTI is not administered.

[0091] In another embodiment, the RTI is administered to the subject for 18 consecutive days in a row followed by 3 or 4 consecutive days in a row wherein the RTI is not administered.

[0092] In another embodiment, the RTI is administered to the subject for 19 consecutive days in a row followed by 3 or 4 consecutive days in a row wherein the RTI is not administered.

[0093] In another embodiment, the RTI is administered to the subject for 20 consecutive days in a row followed by 3 or 4 consecutive days in a row wherein the RTI is not administered.

[0094] In another embodiment, the RTI is administered to the subject for 21 consecutive days in a row followed by days 3 or 4 consecutive in a row wherein the RTI is not administered.

[0095] In another embodiment, the RTI is administered to the subject for 2 consecutive days in a row followed by 2 or 3 consecutive days in a row wherein the RTI is not administered.

[0096] In another embodiment, the RTI is administered to the subject for 3 consecutive days in a row followed by 2 or 3 consecutive days in a row wherein the RTI is not administered.

[0097] In another embodiment, the RTI is administered to the subject for 4 consecutive days in a row followed by 2 or 3 consecutive days in a row wherein the RTI is not administered.

[0098] In another embodiment, the RTI is administered to the subject for 5 consecutive days in a row followed by 2 or 3 consecutive days in a row wherein the RTI is not administered.

[0099] In another embodiment, the RTI is administered to the subject for 6 consecutive days in a row followed by 2 or 3 consecutive days in a row wherein the RTI is not administered.

[0100] In another embodiment, the RTI is administered to the subject for 7 consecutive days in a row followed by 2 or 3 consecutive days in a row wherein the RTI is not administered.

[0101] In another embodiment, the RTI is administered to the subject for 8 consecutive days in a row followed by 2 or 3 consecutive days in a row wherein the RTI is not administered.

[0102] In another embodiment, the RTI is administered to the subject for 9 consecutive days in a row followed by 2 or 3 consecutive days in a row wherein the RTI is not administered.

[0103] In another embodiment, the RTI is administered to the subject for 10 consecutive days in a row followed by 2 or 3 consecutive days in a row wherein the RTI is not administered.

[0104] In another embodiment, the RTI is administered to the subject for 11 consecutive days in a row followed by 2 or 3 consecutive days in a row wherein the RTI is not administered.

[0105] In another embodiment, the RTI is administered to the subject for 12 consecutive days in a row followed by 2 or 3 consecutive days in a row wherein the RTI is not administered.

[0106] In another embodiment, the RTI is administered to the subject for 13 consecutive days in a row followed by 2 or 3 consecutive days in a row wherein the RTI is not administered.

[0107] In another embodiment, the RTI is administered to the subject for 14 consecutive days in a row followed by 2 or 3 consecutive days in a row wherein the RTI is not administered.

[0108] In another embodiment, the RTI is administered to the subject for 15 consecutive days in a row followed by 2 or 3 consecutive days in a row wherein the RTI is not administered.

[0109] In another embodiment, the RTI is administered to the subject for 16 consecutive days in a row followed by 2 or 3 consecutive days in a row wherein the RTI is not administered.

[0110] In another embodiment, the RTI is administered to the subject for 17 consecutive days in a row followed by 2 or 3 consecutive days in a row wherein the RTI is not administered.

[0111] In another embodiment, the RTI is administered to the subject for 18 consecutive days in a row followed by 2 or 3 consecutive days in a row wherein the RTI is not administered.

[0112] In another embodiment, the RTI is administered to the subject for 19 consecutive days in a row followed by 2 or 3 consecutive days in a row wherein the RTI is not administered.

[0113] In another embodiment, the RTI is administered to the subject for 20 consecutive days in a row followed by 2 or 3 consecutive days in a row wherein the RTI is not administered.

[0114] In another embodiment, the RTI is administered to the subject for 21 consecutive days in a row followed by 2 or 3 consecutive days in a row wherein the RTI is not administered.

[0115] In another embodiment, the RTI is administered to the subject for 2 consecutive days in a row followed by 1 day or 2 consecutive days in a row wherein the RTI is not administered.

[0116] In another embodiment, the RTI is administered to the subject for 3 consecutive days in a row followed by 1 day or 2 consecutive days in a row wherein the RTI is not administered.

[0117] In another embodiment, the RTI is administered to the subject for 4 consecutive days in a row followed by 1 day or 2 consecutive days in a row wherein the RTI is not administered.

[0118] In another embodiment, the RTI is administered to the subject for 5 consecutive days in a row followed by 1 day or 2 consecutive days in a row wherein the RTI is not administered.

[0119] In another embodiment, the RTI is administered to the subject for 5 consecutive days in a row followed by 2 consecutive days in a row wherein the RTI is not administered.

[0120] In another embodiment, the RTI is administered to the subject for 6 consecutive days in a row followed by 1 day or 2 consecutive days in a row wherein the RTI is not administered.

[0121] In another embodiment, the RTI is administered to the subject for 7 consecutive days in a row followed by 1 day or 2 consecutive days in a row wherein the RTI is not administered.

[0122] In another embodiment, the RTI is administered to the subject for 8 consecutive days in a row followed by 1 day or 2 consecutive days in a row wherein the RTI is not administered.

[0123] In another embodiment, the RTI is administered to the subject for 9 consecutive days in a row followed by 1 day or 2 consecutive days in a row wherein the RTI is not administered.

[0124] In another embodiment, the RTI is administered to the subject for 10 consecutive days in a row followed by 1 day or 2 consecutive days in a row wherein the RTI is not administered.

[0125] In another embodiment, the RTI is administered to the subject for 11 consecutive days in a row followed by 1 day or 2 consecutive days in a row wherein the RTI is not administered.

[0126] In another embodiment, the RTI is administered to the subject for 12 consecutive days in a row followed by 1 day or 2 consecutive days in a row wherein the RTI is not administered.

[0127] In another embodiment, the RTI is administered to the subject for 13 consecutive days in a row followed by 1 day or 2 consecutive days in a row wherein the RTI is not administered.

[0128] In another embodiment, the RTI is administered to the subject for 14 consecutive days in a row followed by 1 day or 2 consecutive days in a row wherein the RTI is not administered.

[0129] In another embodiment, the RTI is administered to the subject for 15 consecutive days in a row followed by 1 day or 2 consecutive days in a row wherein the RTI is not administered.

[0130] In another embodiment, the RTI is administered to the subject for 16 consecutive days in a row followed by 1 day or 2 consecutive days in a row wherein the RTI is not administered.

[0131] In another embodiment, the RTI is administered to the subject for 17 consecutive days in a row followed by 1 day or 2 consecutive days in a row wherein the RTI is not administered.

[0132] In another embodiment, the RTI is administered to the subject for 18 consecutive days in a row followed by 1 day or 2 consecutive days in a row wherein the RTI is not administered.

[0133] In another embodiment, the RTI is administered to the subject for 19 consecutive days in a row followed by 1 day or 2 consecutive days in a row wherein the RTI is not administered.

[0134] In another embodiment, the RTI is administered to the subject for 20 consecutive days in a row followed by 1 day or 2 consecutive days in a row wherein the RTI is not administered.

[0135] In another embodiment, the RTI is administered to the subject for 21 consecutive days in a row followed by 1 day or 2 consecutive days in a row wherein the RTI is not administered.

[0136] In another embodiment, the RTI is administered to the subject for 2 consecutive days in a row followed by about 1 consecutive week wherein the RTI is not administered.

[0137] In another embodiment, the RTI is administered to the subject for 3 consecutive days in a row followed by about 1 consecutive week wherein the RTI is not administered.

[0138] In another embodiment, the RTI is administered to the subject for 4 consecutive days in a row followed by about 1 consecutive week wherein the RTI is not administered.

[0139] In another embodiment, the RTI is administered to the subject for 5 consecutive days in a row followed by about 1 consecutive week wherein the RTI is not administered.

[0140] In another embodiment, the RTI is administered to the subject for 5 consecutive days in a row followed by 2 consecutive days in a row wherein the RTI is not administered.

[0141] In another embodiment, the RTI is administered to the subject for 6 consecutive days in a row followed by about 1 consecutive week wherein the RTI is not administered.

[0142] In another embodiment, the RTI is administered to the subject for 7 consecutive days in a row followed by about 1 consecutive week wherein the RTI is not administered.

[0143] In another embodiment, the RTI is administered to the subject for 8 consecutive days in a row followed by about 1 consecutive week wherein the RTI is not administered.

[0144] In another embodiment, the RTI is administered to the subject for 9 consecutive days in a row followed by about 1 consecutive week wherein the RTI is not administered.

[0145] In another embodiment, the RTI is administered to the subject for 10 consecutive days in a row followed by about 1 consecutive week wherein the RTI is not administered.

[0146] In another embodiment, the RTI is administered to the subject for 11 consecutive days in a row followed by about 1 consecutive week wherein the RTI is not administered.

[0147] In another embodiment, the RTI is administered to the subject for 12 consecutive days in a row followed by about 1 consecutive week wherein the RTI is not administered.

[0148] In another embodiment, the RTI is administered to the subject for 13 consecutive days in a row followed by about 1 consecutive week wherein the RTI is not administered.

[0149] In another embodiment, the RTI is administered to the subject for 14 consecutive days in a row followed by about 1 consecutive week wherein the RTI is not administered.

[0150] In another embodiment, the RTI is administered to the subject for 15 consecutive days in a row followed by about 1 consecutive week wherein the RTI is not administered.

[0151] In another embodiment, the RTI is administered to the subject for 16 consecutive days in a row followed by about 1 consecutive week wherein the RTI is not administered.

[0152] In another embodiment, the RTI is administered to the subject for 17 consecutive days in a row followed by about 1 consecutive week wherein the RTI is not administered.

[0153] In another embodiment, the RTI is administered to the subject for 18 consecutive days in a row followed by about 1 consecutive week wherein the RTI is not administered.

[0154] In another embodiment, the RTI is administered to the subject for 19 consecutive days in a row followed by about 1 consecutive week wherein the RTI is not administered.

[0155] In another embodiment, the RTI is administered to the subject for 20 consecutive days in a row followed by about 1 consecutive week wherein the RTI is not administered.

[0156] In another embodiment, the RTI is administered to the subject for 21 consecutive days in a row followed by about 1 consecutive week wherein the RTI is not administered.

[0157] In another embodiment, the RTI is administered to the subject for 2 consecutive days in a row followed by about 2 consecutive weeks in a row wherein the RTI is not administered.

[0158] In another embodiment, the RTI is administered to the subject for 3 consecutive days in a row followed by about 2 consecutive weeks in a row wherein the RTI is not administered.

[0159] In another embodiment, the RTI is administered to the subject for 4 consecutive days in a row followed by about 2 consecutive weeks in a row wherein the RTI is not administered.

[0160] In another embodiment, the RTI is administered to the subject for 5 consecutive days in a row followed by about 2 consecutive weeks in a row wherein the RTI is not administered.

[0161] In another embodiment, the RTI is administered to the subject for 5 consecutive days in a row followed by 2 consecutive days in a row wherein the RTI is not administered.

[0162] In another embodiment, the RTI is administered to the subject for 6 consecutive days in a row followed by about 2 consecutive weeks in a row wherein the RTI is not administered.

[0163] In another embodiment, the RTI is administered to the subject for 7 consecutive days in a row followed by about 2 consecutive weeks in a row wherein the RTI is not administered.

[0164] In another embodiment, the RTI is administered to the subject for 8 consecutive days in a row followed by about 2 consecutive weeks in a row wherein the RTI is not administered.

[0165] In another embodiment, the RTI is administered to the subject for 9 consecutive days in a row followed by about 2 consecutive weeks in a row wherein the RTI is not administered.

[0166] In another embodiment, the RTI is administered to the subject for 10 consecutive days in a row followed by about 2 consecutive weeks in a row wherein the RTI is not administered.

[0167] In another embodiment, the RTI is administered to the subject for 11 consecutive days in a row followed by about 2 consecutive weeks in a row wherein the RTI is not administered.

[0168] In another embodiment, the RTI is administered to the subject for 12 consecutive days in a row followed by about 2 consecutive weeks in a row wherein the RTI is not administered.

[0169] In another embodiment, the RTI is administered to the subject for 13 consecutive days in a row followed by about 2 consecutive weeks in a row wherein the RTI is not administered.

[0170] In another embodiment, the RTI is administered to the subject for 14 consecutive days in a row followed by about 2 consecutive weeks in a row wherein the RTI is not administered.

[0171] In another embodiment, the RTI is administered to the subject for 15 consecutive days in a row followed by about 2 consecutive weeks in a row wherein the RTI is not administered.

[0172] In another embodiment, the RTI is administered to the subject for 16 consecutive days in a row followed by about 2 consecutive weeks in a row wherein the RTI is not administered.

[0173] In another embodiment, the RTI is administered to the subject for 17 consecutive days in a row followed by about 2 consecutive weeks in a row wherein the RTI is not administered.

[0174] In another embodiment, the RTI is administered to the subject for 18 consecutive days in a row followed by about 2 consecutive weeks in a row wherein the RTI is not administered.

[0175] In another embodiment, the RTI is administered to the subject for 19 consecutive days in a row followed by about 2 consecutive weeks in a row wherein the RTI is not administered.

[0176] In another embodiment, the RTI is administered to the subject for 20 consecutive days in a row followed by about 2 consecutive weeks in a row wherein the RTI is not administered.

[0177] In another embodiment, the RTI is administered to the subject for 21 consecutive days in a row followed by about 2 consecutive weeks in a row wherein the RTI is not administered.

[0178] In another embodiment, the RTI is administered to the subject for 2 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0179] In another embodiment, the RTI is administered to the subject for 3 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0180] In another embodiment, the RTI is administered to the subject for 4 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0181] In another embodiment, the RTI is administered to the subject for 5 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0182] In another embodiment, the RTI is administered to the subject for 5 consecutive days in a row followed by 4 consecutive days in a row wherein the RTI is not administered.

[0183] In another embodiment, the RTI is administered to the subject for 6 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0184] In another embodiment, the RTI is administered to the subject for 7 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0185] In another embodiment, the RTI is administered to the subject for 8 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0186] In another embodiment, the RTI is administered to the subject for 9 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0187] In another embodiment, the RTI is administered to the subject for 10 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0188] In another embodiment, the RTI is administered to the subject for 11 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0189] In another embodiment, the RTI is administered to the subject for 14 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0190] In another embodiment, the RTI is administered to the subject for 13 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0191] In another embodiment, the RTI is administered to the subject for 14 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0192] In another embodiment, the RTI is administered to the subject for 15 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0193] In another embodiment, the RTI is administered to the subject for 16 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0194] In another embodiment, the RTI is administered to the subject for 17 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0195] In another embodiment, the RTI is administered to the subject for 18 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0196] In another embodiment, the RTI is administered to the subject for 19 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0197] In another embodiment, the RTI is administered to the subject for 20 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0198] In another embodiment, the RTI is administered to the subject for 21 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0199] In another embodiment, the RTI is administered to the subject for 2 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0200] In another embodiment, the RTI is administered to the subject for 3 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0201] In another embodiment, the RTI is administered to the subject for 4 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0202] In another embodiment, the RTI is administered to the subject for 5 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0203] In another embodiment, the RTI is administered to the subject for 5 consecutive days in a row followed by 3 consecutive days in a row wherein the RTI is not administered.

[0204] In another embodiment, the RTI is administered to the subject for 6 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0205] In another embodiment, the RTI is administered to the subject for 7 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0206] In another embodiment, the RTI is administered to the subject for 7 consecutive days in a row followed by about 8 consecutive weeks in a row wherein the RTI is not administered.

[0207] In another embodiment, the RTI is administered to the subject for 8 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0208] In another embodiment, the RTI is administered to the subject for 9 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0209] In another embodiment, the RTI is administered to the subject for 10 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0210] In another embodiment, the RTI is administered to the subject for 11 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0211] In another embodiment, the RTI is administered to the subject for 13 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0212] In another embodiment, the RTI is administered to the subject for 13 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0213] In another embodiment, the RTI is administered to the subject for 14 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0214] In another embodiment, the RTI is administered to the subject for 15 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0215] In another embodiment, the RTI is administered to the subject for 16 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0216] In another embodiment, the RTI is administered to the subject for 17 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0217] In another embodiment, the RTI is administered to the subject for 18 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0218] In another embodiment, the RTI is administered to the subject for 19 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0219] In another embodiment, the RTI is administered to the subject for 20 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0220] In another embodiment, the RTI is administered to the subject for 21 consecutive days in a row followed by about 4 consecutive weeks in a row wherein the RTI is not administered.

[0221] In another embodiment, the RTI is administered to the subject for about 2 consecutive weeks in a row followed by about 12 consecutive weeks in a row wherein the RTI is not administered.

[0222] In another embodiment, the RTI is administered to the subject for about 3 consecutive weeks in a row followed by about 12 consecutive weeks in a row wherein the RTI is not administered.

[0223] In another embodiment, the RTI is administered to the subject for about 4 consecutive weeks in a row followed by about 12 consecutive weeks in a row wherein the RTI is not administered.

[0224] Examples of treatable cancers include, but are not limited to, any one or more of the cancers of Table 1.

Table 1

adrenal cancer	acinic cell carcinoma	acoustic neuroma	acral lentigious melanoma
acrospiroma	acute eosinophilic leukemia	acute erythroid leukemia	acute lymphoblastic leukemia
acute megakaryoblastic leukemia	acute monocytic leukemia	acute promyelocytic leukemia	adenocarcinoma
adenoid cystic carcinoma	adenoma	adenomatoid odontogenic tumor	adenosquamous carcinoma
adipose tissue neoplasm	adrenocortical carcinoma	adult T-cell leukemia/lymphoma	aggressive NK-cell leukemia
AIDS-related lymphoma	alveolar rhabdomyosarcoma	alveolar soft part sarcoma	ameloblastic fibroma
anaplastic large cell lymphoma	anaplastic thyroid cancer	angioimmunoblastic T-cell lymphoma	angiomyolipoma
angiosarcoma	astrocytoma	atypical teratoid rhabdoid tumor	B-cell chronic lymphocytic leukemia
B-cell prolymphocytic leukemia	B-cell lymphoma	basal cell carcinoma	biliary tract cancer

bladder cancer	blastoma	bone cancer	Brenner tumor
Brown tumor	Burkitt's lymphoma	breast cancer	brain cancer
carcinoma	carcinoma in situ	carcinosarcoma	cartilage tumor
cementoma	myeloid sarcoma	chondroma	chordoma
choriocarcinoma	choroid plexus papilloma	clear-cell sarcoma of the kidney	craniopharyngioma
cutaneous T-cell lymphoma	cervical cancer	colorectal cancer	Degos disease
desmoplastic small round cell tumor	diffuse large B-cell lymphoma	dysembryoplastic neuroepithelial tumor	dysgerminoma
embryonal carcinoma	endocrine gland neoplasm	endodermal sinus tumor	enteropathy-associated T-cell lymphoma
esophageal cancer	fetus in fetu	fibroma	fibrosarcoma
follicular lymphoma	follicular thyroid cancer	ganglioneuroma	gastrointestinal cancer
germ cell tumor	gestational choriocarcinoma	giant cell fibroblastoma	giant cell tumor of the bone
glial tumor	glioblastoma multiforme	glioma	gliomatosis cerebri
glucagonoma	gonadoblastoma	granulosa cell tumor	gynandroblastoma
gallbladder cancer	gastric cancer	hairy cell leukemia	hemangioblastoma
head and neck cancer	hemangiopericytoma	hematological cancer	hepatoblastoma
hepatosplenic T-cell lymphoma	Hodgkin's lymphoma	non-Hodgkin's lymphoma	invasive lobular carcinoma
intestinal cancer	kidney cancer	laryngeal cancer	lentigo maligna
lethal midline carcinoma	leukemia	leydig cell tumor	liposarcoma
lung cancer	lymphangioma	lymphangiosarcoma	lymphoepithelioma
lymphoma	acute lymphocytic leukemia	acute myelogeous leukemia	chronic lymphocytic leukemia
liver cancer	small cell lung cancer	non-small cell lung cancer	MALT lymphoma
malignant fibrous histiocytoma	malignant peripheral nerve sheath tumor	malignant triton tumor	mantle cell lymphoma
marginal zone B-cell lymphoma	mast cell leukemia	mediastinal germ cell tumor	medullary carcinoma of the breast
medullary thyroid cancer	medulloblastoma	melanoma	meningioma
merkel cell cancer	mesothelioma	metastatic urothelial carcinoma	mixed Mullerian tumor
mucinous tumor	multiple myeloma	muscle tissue neoplasm	mycosis fungoides
myxoid liposarcoma	myxoma	myxosarcoma	nasopharyngeal carcinoma
neurinoma	neuroblastoma	neurofibroma	neuroma
nodular melanoma	ocular cancer	oligoastrocytoma	oligodendroglioma

oncocytoma	optic nerve sheath meningioma	optic nerve tumor	oral cancer
osteosarcoma	ovarian cancer	Pancoast tumor	papillary thyroid cancer
paraganglioma	pinealoblastoma	pineocytoma	pituicytoma
pituitary adenoma	pituitary tumor	plasmacytoma	polyembryoma
precursor T-lymphoblastic lymphoma	primary central nervous system lymphoma	primary effusion lymphoma	preimary peritoneal cancer
prostate cancer	pancreatic cancer	pharyngeal cancer	pseudomyxoma periotonei
renal cell carcinoma	renal medullary carcinoma	retinoblastoma	rhabdomyoma
rhabdomyosarcoma	Richter's transformation	rectal cancer	sarcoma
Schwannomatosis	seminoma	Sertoli cell tumor	sex cord-gonadal stromal tumor
signet ring cell carcinoma	skin cancer	small blue round cell tumors	small cell carcinoma
soft tissue sarcoma	somatostatinoma	soot wart	spinal tumor
splenic marginal zone lymphoma	squamous cell carcinoma	synovial sarcoma	Sezary's disease
small intestine cancer	squamous carcinoma	stomach cancer	T-cell lymphoma
testicular cancer	thecoma	thyroid cancer	transitional cell carcinoma
throat cancer	urachal cancer	urogenital cancer	urothelial carcinoma
uveal melanoma	uterine cancer	verrucous carcinoma	visual pathway glioma
vulvar cancer	vaginal cancer	Waldenstrom's macroglobulinemia	Warthin's tumor
Wilms' tumor	colon cancer	pancreatic ductal cancer	

[0225] In another embodiment, the cancer is a solid tumor. In another embodiment, the cancer a hematological cancer. Exemplary hematological cancers include, but are not limited to, the cancers listed in Table 2. In another embodiment, the hematological cancer is acute lymphocytic leukemia, chronic lymphocytic leukemia (including B-cell chronic lymphocytic leukemia), or acute myeloid leukemia.

Table 2

acute lymphocytic leukemia (ALL)	acute eosinophilic leukemia
acute myeloid leukemia (AML)	acute erythroid leukemia
chronic lymphocytic leukemia (CLL)	acute lymphoblastic leukemia
small lymphocytic lymphoma (SLL)	acute megakaryoblastic leukemia
multiple myeloma (MM)	acute monocytic leukemia
Hodgkins lymphoma (HL)	acute promyelocytic leukemia

non-Hodgkin's lymphoma (NHL)	acute myelogeous leukemia
mantle cell lymphoma (MCL)	B-cell prolymphocytic leukemia
marginal zone B-cell lymphoma	B-cell lymphoma
splenic marginal zone lymphoma	MALT lymphoma
follicular lymphoma (FL)	precursor T-lymphoblastic lymphoma
Waldenstrom's macroglobulinemia (WM)	T-cell lymphoma
diffuse large B-cell lymphoma (DLBCL)	mast cell leukemia
marginal zone lymphoma (MZL)	adult T cell leukemia/lymphoma
hairy cell leukemia (HCL)	aggressive NK-cell leukemia
Burkitt's lymphoma (BL)	angioimmunoblastic T-cell lymphoma
Richter's transformation	mantle cell lymphoma

[0226] In another embodiment, the cancer is a leukemia, for example a leukemia selected from acute monocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia and mixed lineage leukemia (MLL). In another embodiment the cancer is NUT-midline carcinoma. In another embodiment the cancer is multiple myeloma. In another embodiment the cancer is a lung cancer such as small cell lung cancer (SCLC). In another embodiment the cancer is a neuroblastoma. In another embodiment the cancer is Burkitt's lymphoma. In another embodiment the cancer is cervical cancer. In another embodiment the cancer is esophageal cancer. In another embodiment the cancer is ovarian cancer. In another embodiment the cancer is colorectal cancer. In another embodiment, the cancer is prostate cancer. In another embodiment, the cancer is breast cancer.

[0227] In another embodiment, the cancer is selected from the group consisting of acute monocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia mixed lineage leukemia, NUT-midline carcinoma, multiple myeloma, small cell lung cancer, non-small cell lung cancer, neuroblastoma, Burkitt's lymphoma, cervical cancer, esophageal cancer, ovarian cancer, colorectal cancer, prostate cancer, breast cancer, bladder cancer, ovary cancer, glioma, sarcoma, esophageal squamous cell carcinoma, and papillary thyroid carcinoma.

[0228] In another embodiment, islatravir is administered to a subject in need thereof to treat breast, colon, lung, pancreatic ductal, prostate, ovarian, or head and neck cancer. In another embodiment, the cancer is breast cancer. In another embodiment, the cancer is colon cancer. In another embodiment, the cancer is lung cancer, e.g., small cell lung cancer or non-small cell lung cancer. In another embodiment, the cancer is pancreatic ductal cancer.

In another embodiment, the cancer is prostate cancer. In another embodiment, the cancer is ovarian cancer. In another embodiment, the cancer is head and neck cancer.

[0229] In some embodiments, the patient is also administered at least one second therapeutic agent useful for the treatment of cancer. In some embodiments, the second therapeutic agent is an epigenetic drug. As used herein, the term "epigenetic drug" refers to a therapeutic agent that targets an epigenetic regulator. Examples of epigenetic regulators include the histone lysine methyltransferases, histone arginine methyl transferases, histone demethylases, histone deacetylases, histone acetylases, and DNA methyltransferases. Histone deacetylase inhibitors include, but are not limited to, vorinostat.

[0230] In another embodiment, chemotherapeutic agents or other anti-proliferative agents can be combined with islatravir to treat proliferative diseases and cancer. Examples of therapies and anticancer agents that can be used in combination with islatravir include surgery, radiotherapy (e.g., gamma-radiation, neutron beam radiotherapy, electron beam radiotherapy, proton therapy, brachytherapy, and systemic radioactive isotopes), endocrine therapy, a biologic response modifier (e.g., an interferon, an interleukin, tumor necrosis factor (TNF), hyperthermia and cryotherapy, an agent to attenuate any adverse effect (e.g., an antiemetic), and any other approved chemotherapeutic drug.

[0231] Examples of antiproliferative compounds include, but are not limited to, an aromatase inhibitor; an anti-estrogen; an anti-androgen; a gonadorelin agonist; a topoisomerase I inhibitor; a topoisomerase II inhibitor; a microtubule active agent; an alkylating agent; a retinoid, a carontenoid, or a tocopherol; a cyclooxygenase inhibitor; an MMP inhibitor; an mTOR inhibitor; an antimetabolite; a platin compound; a methionine aminopeptidase inhibitor; a bisphosphonate; an antiproliferative antibody; a heparanase inhibitor; an inhibitor of Ras oncogenic isoforms; a telomerase inhibitor; a proteasome inhibitor; a compound used in the treatment of hematologic malignancies; a Flt-3 inhibitor; an Hsp90 inhibitor; a kinesin spindle protein inhibitor; a MEK inhibitor; an antitumor antibiotic; a nitrosourea; a compound targeting/decreasing protein or lipid kinase activity, a compound targeting/decreasing protein or lipid phosphatase activity, or any further anti-angiogenic compound.

[0232] Nonlimiting exemplary aromatase inhibitors include, but are not limited to, steroids, such as atamestane, exemestane, and formestane, and non-steroids, such as

aminoglutethimide, roglethimide, pyridoglutethimide, trilostane, testolactone, ketokonazole, vorozole, fadrozole, anastrozole, and letrozole.

[0233] Nonlimiting anti-estrogens include, but are not limited to, tamoxifen, fulvestrant, raloxifene, and raloxifene hydrochloride. Anti-androgens include, but are not limited to, bicalutamide. Gonadorelin agonists include, but are not limited to, abarelix, goserelin, and goserelin acetate.

[0234] Exemplary topoisomerase I inhibitors include, but are not limited to, topotecan, gimatecan, irinotecan, camptothecin and its analogues, 9-nitrocamptothecin, and the macromolecular camptothecin conjugate PNU-166148. Topoisomerase II inhibitors include, but are not limited to, anthracyclines, such as doxorubicin, daunorubicin, epirubicin, idarubicin, and nemorubicin; anthraquinones, such as mitoxantrone and losoxantrone; and podophillotoxines, such as etoposide and teniposide.

[0235] Microtubule active agents include microtubule stabilizing, microtubule destabilizing compounds, and microtubulin polymerization inhibitors including, but not limited to, taxanes, such as paclitaxel and docetaxel; vinca alkaloids, such as vinblastine, vinblastine sulfate, vincristine, and vincristine sulfate, and vinorelbine; discodermolides; cochicine and epothilones and derivatives thereof.

[0236] Exemplary nonlimiting alkylating agents include cyclophosphamide, ifosfamide, melphalan, and nitrosoureas, such as carmustine and lomustine.

[0237] Exemplary nonlimiting cyclooxygenase inhibitors include Cox-2 inhibitors, 5-alkyl substituted 2-arylaminophenylacetic acid and derivatives, such as celecoxib, rofecoxib, etoricoxib, valdecoxib, or a 5-alkyl-2-arylaminophenylacetic acid, such as lumiracoxib.

[0238] Exemplary nonlimiting matrix metalloproteinase inhibitors ("MMP inhibitors") include collagen peptidomimetic and nonpeptidomimetic inhibitors, tetracycline derivatives, batimastat, marimastat, prinomastat, metastat, BMS-279251, BAY 12-9566, TAA211, MMI270B, and AAJ996.

[0239] Exemplary nonlimiting mTOR inhibitors include compounds that inhibit the mammalian target of rapamycin (mTOR) and possess antiproliferative activity such as sirolimus, everolimus, CCI-779, and ABT578.

[0240] Exemplary nonlimiting antimetabolites include 5-fluorouracil (5-FU), capecitabine, gemcitabine, DNA demethylating compounds, such as 5-azacytidine and decitabine, methotrexate and edatrexate, and folic acid antagonists, such as pemetrexed.

[0241] Exemplary nonlimiting platin compounds include carboplatin, cis-platin, cisplatinum, and oxaliplatin.

[0242] Exemplary nonlimiting methionine aminopeptidase inhibitors include bengamide or a derivative thereof and PPI-2458.

[0243] Exemplary nonlimiting bisphosphonates include etridonic acid, clodronic acid, tiludronic acid, pamidronic acid, alendronic acid, ibandronic acid, risedronic acid, and zoledronic acid.

[0244] Exemplary nonlimiting antiproliferative antibodies include trastuzumab, trastuzumab-DMl, cetuximab, bevacizumab, rituximab, PR064553, and 2C4. The term "antibody" is meant to include intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies formed from at least two intact antibodies, and antibody fragments, so long as they exhibit the desired biological activity.

[0245] Exemplary nonlimiting heparanase inhibitors include compounds that target, decrease, or inhibit heparin sulfate degradation, such as PI-88 and OGT2115.

[0246] The term "an inhibitor of Ras oncogenic isoforms," such as H-Ras, K-Ras, or N-Ras, as used herein refers to a compound which targets, decreases, or inhibits the oncogenic activity of Ras, for example, a farnesyl transferase inhibitor, such as L-744832, DK8G557, tipifarnib, and lonafarnib.

[0247] Exemplary nonlimiting telomerase inhibitors include compounds that target, decrease, or inhibit the activity of telomerase, such as compounds that inhibit the telomerase receptor, such as telomestatin.

[0248] Exemplary nonlimiting proteasome inhibitors include compounds that target, decrease, or inhibit the activity of the proteasome including, but not limited to, bortezomid.

[0249] The phrase "compounds used in the treatment of hematologic malignancies" as used herein includes FMS-like tyrosine kinase inhibitors, which are compounds targeting, decreasing or inhibiting the activity of FMS-like tyrosine kinase receptors (Flt-3R); interferon, I-β-D-arabinofuransylcytosine (ara-c), and bisulfan; and ALK inhibitors, which are compounds which target, decrease, or inhibit anaplastic lymphoma kinase.

[0250] Exemplary nonlimiting Flt-3 inhibitors include PKC412, midostaurin, a staurosporine derivative, SU11248, and MLN518.

[0251] Exemplary nonlimiting HSP90 inhibitors include compounds targeting, decreasing, or inhibiting the intrinsic ATPase activity of HSP90; or degrading, targeting, decreasing or

inhibiting the HSP90 client proteins via the ubiquitin proteosome pathway. Compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90 are especially compounds, proteins, or antibodies that inhibit the ATPase activity of HSP90, such as 17-allylamino, 17-demethoxygeldanamycin (17AAG), a geldanamycin derivative; other geldanamycin related compounds; radicicol and HDAC inhibitors.

[0252] The phrase "a compound targeting/decreasing a protein or lipid kinase activity; or a protein or lipid phosphatase activity; or any further anti-angiogenic compound" as used herein includes a protein tyrosine kinase and/or serine and/or threonine kinase inhibitor or lipid kinase inhibitor, such as a) a compound targeting, decreasing, or inhibiting the activity of the platelet- derived growth factor-receptors (PDGFR), such as a compound that targets, decreases, or inhibits the activity of PDGFR, such as an N-phenyl-2-pyrimidine-amine derivatives, such as imatinib, SUlOl, SU6668, and GFB-111; b) a compound targeting, decreasing, or inhibiting the activity of the fibroblast growth factor-receptors (FGFR); c) a compound targeting, decreasing, or inhibiting the activity of the insulin-like growth factor receptor I (IGF-IR), such as a compound that targets, decreases, or inhibits the activity of IGF-IR; d) a compound targeting, decreasing, or inhibiting the activity of the Trk receptor tyrosine kinase family, or ephrin B4 inhibitors; e) a compound targeting, decreasing, or inhibiting the activity of the Axl receptor tyrosine kinase family; f) a compound targeting, decreasing, or inhibiting the activity of the Ret receptor tyrosine kinase; g) a compound targeting, decreasing, or inhibiting the activity of the Kit/SCFR receptor tyrosine kinase, such as imatinib; h) a compound targeting, decreasing, or inhibiting the activity of the c-Kit receptor tyrosine kinases, such as imatinib; i) a compound targeting, decreasing, or inhibiting the activity of members of the c-Abl family, their gene-fusion products (e.g. Bcr-Abl kinase) and mutants, such as an N-phenyl-2-pyrimidine-amine derivative, such as imatinib or nilotinib; PD180970; AG957; NSC 680410; PD173955; or dasatinib; j) a compound targeting, decreasing, or inhibiting the activity of members of the protein kinase C (PKC) and Raf family of serine/threonine kinases, members of the MEK, SRC, JAK, FAK, PDK1, PKB/Akt, and Ras/MAPK family members, and/or members of the cyclin-dependent kinase family (CDK), such as a staurosporine derivative disclosed in U.S. Patent No. 5,093,330, such as midostaurin; examples of further compounds include UCN-01, safingol, BAY 43-9006, bryostatin 1, perifosine; ilmofosine; RO 318220 and RO 320432; GO 6976; Isis 3521; LY333531/LY379196; a isochinoline compound; a farnesyl

transferase inhibitor; PD184352 or QAN697, or AT7519; k) a compound targeting, decreasing or inhibiting the activity of a protein-tyrosine kinase, such as imatinib mesylate or a tyrphostin, such as Tyrphostin A23/RG-50810; AG 99; Tyrphostin AG 213; Tyrphostin AG 1748; Tyrphostin AG 490; Tyrphostin B44; Tyrphostin B44 (+) enantiomer; Tyrphostin AG 555; AG 494; Tyrphostin AG 556, AG957 and adaphostin (4-{[(2,5-dihydroxyphenyl)methyl]amino}-benzoic acid adamantyl ester; NSC 680410, adaphostin); 1) a compound targeting, decreasing, or inhibiting the activity of the epidermal growth factor family of receptor tyrosine kinases (EGFR, ErbB2, ErbB3, ErbB4 as homo- or heterodimers) and their mutants, such as CP 358774, ZD 1839, ZM 105180; trastuzumab, cetuximab, gefitinib, erlotinib, OSI-774, Cl-1033, EKB-569, GW-2016, antibodies El.l, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 and E7.6.3, and 7H-pyrrolo-[2,3-d]pyrimidine derivatives; and m) a compound targeting, decreasing, or inhibiting the activity of the c-Met receptor.

[0253] Exemplary compounds that target, decrease, or inhibit the activity of a protein or lipid phosphatase include inhibitors of phosphatase 1, phosphatase 2A, or CDC25, such as okadaic acid or a derivative thereof.

[0254] Further anti-angiogenic compounds include compounds having another mechanism for their activity unrelated to protein or lipid kinase inhibition, e.g., thalidomide and TNP-470.

[0255] Additional, nonlimiting, exemplary chemotherapeutic compounds, one or more of which may be used in combination with islatravir, include: daunorubicin, adriamycin, Ara-C, VP-16, teniposide, mitoxantrone, idarubicin, carboplatinum, PKC412, 6-mercaptopurine (6-MP), fludarabine phosphate, octreotide, SOM230, FTY720, 6-thioguanine, cladribine, 6-mercaptopurine, pentostatin, hydroxyurea, 2-hydroxy-lH-isoindole-l,3-dione derivatives, l-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine or a pharmaceutically acceptable salt thereof, 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine succinate, angiostatin, endostatin, anthranilic acid amides, ZD4190, ZD6474, SU5416, SU6668, bevacizumab, rhuMAb, rhuFab, macugon; FLT-4 inhibitors, FLT-3 inhibitors, VEGFR-2 IgGI antibody, RPI 4610, bevacizumab, porfimer sodium, anecortave, triamcinolone, hydrocortisone, 11-a-epihydrocotisol, cortex olone, 17a-hydroxyprogesterone, corticosterone, desoxycorticosterone, testosterone, estrone, dexamethasone, fluocinolone, a plant alkaloid, a hormonal compound and/or antagonist, a

biological response modifier, such as a lymphokine or interferon, an antisense oligonucleotide or oligonucleotide derivative, shRNA, and siRNA.

[0256] In another embodiment, the second therapeutically active agent is an immune checkpoint inhibitor. Examples of immune checkpoint inhibitors include PD-1 inhibitors, PD-L1 inhibitors, CTLA-4 inhibitors, LAG3 inhibitors, TIM3 inhibitors, cd47 inhibitors, and B7-H1 inhibitors. Thus, in one embodiment, islatravir is administered in combination with an immune checkpoint inhibitor is selected from the group consisting of a PD-1 inhibitor, a PD-L1 inhibitor, a CTLA-4 inhibitor, a LAG3 inhibitor, a TIM3 inhibitor, and a cd47 inhibitor.

[0257] In another embodiment, the immune checkpoint inhibitor is a programmed cell death (PD-1) inhibitor. PD-1 is a T-cell coinhibitory receptor that plays a pivotal role in the ability of tumor cells to evade the host's immune system. Blockage of interactions between PD-1 and PD-L1, a ligand of PD-1, enhances immune function and mediates antitumor activity. Examples of PD-1 inhibitors include antibodies that specifically bind to PD-1. Particular anti-PD-1 antibodies include, but are not limited to nivolumab, pembrolizumab, STI-A1014, and pidilzumab. For a general discussion of the availability, methods of production, mechanism of action, and clinical studies of anti-PD-1 antibodies, see U.S. 2013/0309250, U.S. 6,808,710, U.S. 7,595,048, U.S. 8,008,449, U.S. 8,728,474, U.S. 8,779,105, U.S. 8,952,136, U.S. 8,900,587, U.S. 9,073,994, U.S. 9,084,776, and Naido *et al.*, *British Journal of Cancer 111:*2214-19 (2014).

[0258] In another embodiment, the immune checkpoint inhibitor is a PD-L1 (also known as B7-H1 or CD274) inhibitor. Examples of PD-L1 inhibitors include antibodies that specifically bind to PD-L1. Particular anti-PD-L1 antibodies include, but are not limited to, avelumab, atezolizumab, durvalumab, and BMS-936559. For a general discussion of the availability, methods of production, mechanism of action, and clinical studies, see U.S. 8,217,149, U.S. 2014/0341917, U.S. 2013/0071403, WO 2015036499, and Naido *et al.*, *British Journal of Cancer 111:*2214-19 (2014).

[0259] In another embodiment, the immune checkpoint inhibitor is a CTLA-4 inhibitor. CTLA-4, also known as cytotoxic T-lymphocyte antigen 4, is a protein receptor that downregulates the immune system. CTLA-4 is characterized as a "brake" that binds costimulatory molecules on antigen-presenting cells, which prevents interaction with CD28 on T cells and also generates an overtly inhibitory signal that constrains T cell activation.

Examples of CTLA-4 inhibitors include antibodies that specifically bind to CTLA-4. Particular anti-CTLA-4 antibodies include, but are not limited to, ipilimumab and tremelimumab. For a general discussion of the availability, methods of production, mechanism of action, and clinical studies, see U.S. 6,984,720, U.S. 6,207,156, and Naido *et al.*, *British Journal of Cancer 111:*2214-19 (2014).

[0260] In another embodiment, the immune checkpoint inhibitor is a LAG3 inhibitor. LAG3, Lymphocyte Activation Gene 3, is a negative co-simulatory receptor that modulates T cell homeostatis, proliferation, and activation. In addition, LAG3 has been reported to participate in regulatory T cells (Tregs) suppressive function. A large proportion of LAG3 molecules are retained in the cell close to the microtubule-organizing center, and only induced following antigen specific T cell activation. U.S. 2014/0286935. Examples of LAG3 inhibitors include antibodies that specifically bind to LAG3. Particular anti-LAG3 antibodies include, but are not limited to, GSK2831781. For a general discussion of the availability, methods of production, mechanism of action, and studies, see, U.S. 2011/0150892, U.S. 2014/0093511, U.S. 20150259420, and Huang *et al.*, *Immunity* 21:503-13 (2004).

[0261] In another embodiment, the immune checkpoint inhibitor is a TIM3 inhibitor. TIM3, T-cell immunoglobulin and mucin domain 3, is an immune checkpoint receptor that functions to limit the duration and magnitude of T_H1 and T_C1 T-cell responses. The TIM3 pathway is considered a target for anticancer immunotherapy due to its expression on dysfunctional $CD8^+$ T cells and Tregs, which are two reported immune cell populations that constitute immunosuppression in tumor tissue. Anderson, *Cancer Immunology Research 2:*393-98 (2014). Examples of TIM3 inhibitors include antibodies that specifically bind to TIM3. For a general discussion of the availability, methods of production, mechanism of action, and studies of TIM3 inhibitors, see U.S. 20150225457, U.S. 20130022623, U.S. 8,522,156, Ngiow *et al.*, *Cancer Res 71:* 6567-71 (2011), Ngiow, *et al.*, *Cancer Res 71:*3540-51 (2011), and *Anderson*, *Cancer Immunology Res* 2:393-98 (2014).

[0262] In another embodiment, the immune checkpoint inhibitor is a cd47 inhibitor. *See* Unanue, E.R., *PNAS* 110:10886-87 (2013).

[0263] The term "antibody" is meant to include intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies formed from at least two intact antibodies, and antibody fragments, so long as they exhibit the desired biological activity. In another

embodiment, "antibody" is meant to include soluble receptors that do not possess the Fc portion of the antibody. In one embodiment, the antibodies are humanized monoclonal antibodies and fragments thereof made by means of recombinant genetic engineering.

[0264] Another class of immune checkpoint inhibitors include polypeptides that bind to and block PD-1 receptors on T-cells without triggering inhibitor signal transduction. Such peptides include B7-DC polypeptides, B7-H1 polypeptides, B7-1 polypeptides and B7-2 polypeptides, and soluble fragments thereof, as disclosed in U.S. Pat. 8,114,845.

[0265] Another class of immune checkpoint inhibitors include compounds with peptide moieties that inhibit PD-1 signaling. Examples of such compounds are disclosed in U.S. Pat. 8,907,053.

[0266] Another class of immune checkpoint inhibitors include inhibitors of certain metabolic enzymes, such as indoleamine 2,3-dioxygenase (IDO), which is expressed by infiltrating myeloid cells and tumor cells. The IDO enzyme inhibits immune responses by depleting amino acids that are necessary for anabolic functions in T cells or through the synthesis of particular natural ligands for cytosolic receptors that are able to alter lymphocyte functions. Pardoll, *Nature Reviews. Cancer 12:*252-64 (2012); Löb, *Cancer Immunol Immunother 58:*153-57 (2009). Particular IDO blocking agents include, but are not limited to levo-1-methyl typtophan (L-1MT) and 1-methyl-tryptophan (1MT). Qian *et al., Cancer Res 69:*5498-504 (2009); and Löb *et al., Cancer Immunol Immunother 58:*153-7 (2009).

[0267] In one embodiment, the immune checkpoint inhibitor is nivolumab, pembrolizumab, pidilizumab, STI-A1110, avelumab, atezolizumab, durvalumab, STI-A1014, ipilimumab, tremelimumab, GSK2831781, BMS-936559 or MED14736.

[0268] When the RTI is an FDA approved drug, the RTI may be administered in therapeutically effective amounts that are approved for therapeutic use. In other embodiments, the amounts effective can be determined with no more than routine experimentation. For example, amounts effective may range from about 1 ng/kg to about 200 mg/kg, about 1 μg/kg to about 100 mg/kg, or about 1 mg/kg to about 50 mg/kg. The dosage of a composition can be at any dosage including, but not limited to, about 1 μg/kg. The dosage of a composition may be at any dosage including, but not limited to, about 1 μg/kg, about 10 μg/kg, about 25 μg/kg, about 50 μg/kg, about 75 μg/kg, about 100 μg/kg, about 125 μg/kg, about 150 μg/kg, about 175 μg/kg, about 200 μg/kg, about 225 μg/kg,

about 250 μg/kg, about 275 μg/kg, about 300 μg/kg, about 325 μg/kg, about 350 μg/kg, about 375 μg/kg, about 400 μg/kg, about 425 μg/kg, about 450 μg/kg, about 475 μg/kg, about 500 μg/kg, about 525 μg/kg, about 550 μg/kg, about 575 μg/kg, about 600 μg/kg, about 625 μg/kg, about 650 μg/kg, about 675 μg/kg, about 700 μg/kg, about 725 μg/kg, about 750 μg/kg, about 775 μg/kg, about 800 μg/kg, about 825 μg/kg, about 850 μg/kg, about 875 μg/kg, about 900 μg/kg, about 925 μg/kg, about 950 μg/kg, about 975 μg/kg, about 1 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35 mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 60 mg/kg, about 70 mg/kg, about 80 mg/kg, about 90 mg/kg, about 100 mg/kg, about 125 mg/kg, about 150 mg/kg, about 175 mg/kg, about 200 mg/kg, or more. In other embodiments, the dosage is 1 mg-500 mg. In some embodiments, the dosage is 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, or 150 mg. These doses may be unitary or divided and may be administered one or more times per day. The above dosages are exemplary of the average case, but there can be individual instances in which higher or lower dosages are merited, and such are within the scope of this disclosure. In practice, the physician determines therapeutically effective amounts and the actual dosing regimen that is most suitable for an individual subject, which can vary with the age, weight, and response of the particular subject.

[0269] The RTI may be administered once, twice or three times per day for 1 day to the end of life, or for 1 day to 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 or more years, or until the RTI causes unacceptable side effects or is no longer useful.

[0270] In some embodiments, when the method is a method for the treatment of breast cancer, the at least one second therapeutic agent is Soltamox® (tamoxifen), Arimidex® (anastrozole), Femara® (letrozole), Aromasin® (exemestane), Herceptin® (trastuzumab), Abraxane® (paclitaxel), Cytoxan® (cyclophosphamide), Taxol® (paclitaxel), Afinitor® (everolimus), Taxotere® (docetaxel), Xeloda® (capecitabine), Trexall® (methotrexate), Faslodex (fulvestrant), Adriamycin® (doxorubicin), Perjeta® (pertuzumab), Gemzar (gemcitabine), Tykerb® (lapatinib), Adrucil® (fluorouracil), Ibrance® (palbociclib), Verzenio® (abemaciclib), Fareston® (toremifene), Halaven® (eribulin), Menest, Kadcyla® (ado-trastuzumab emtransine), Androxy® (fluoxymesterone), Avastin® (bevacizumab), esterified estrogens, Herzuma® (trastuzumab), Ixempra® (ixabepilone), Kanjinti® (trastuzumab), Kisqali® (ribociclib), Ogivri® (trastuzumab), Ontruzant®

(trastuzumab), Tepadina® (thiotepa), Trazimera® (trastuzumab), Velban® (vinblastine), Piqray® (alpelisib), Tecentriq® (atezolizumab), Enhertu® (fam-trastuzumab deruxtecan), Herceptin, Hylecta™ (hyaluronidase/trastuzumab), Infugem® (gemcitabine), Kisqali® Femara® Co-Pack (ribociclib and letrozole), Talzenna® (talazoparib), Trodelvy® (sacituzumab) or Tukysa™ (tukatinib).

[0271] In some embodiments, when the method is a method for the treatment of colon cancer, the at least one second therapeutic agent is Xeloda® (capecitabine), Eloxatin® (oxaliplatin), fluorouracil, Avastin® (bevacizumab), leucovorin, Camptosar® (irinotecan), Stivarga® (regorafenib), Erbitux® (cetuximab), Vectibix® (panitumumab), Lonsurf® (tipiracil/trifluridine), Zaltrap® (ziv-aflibercept), Betaseron® (interferon beta-1b), Fusilev® (levoleucovorin), Wellcocorin® (methotrexate), Keytruda® (pembrolizumab), Mvasi® (bevacizumab-awwb), Cyramza® (ramucirumab), Yervoy® (ipilmumab), Opdivo® (nivolumab), Braftovi® (encorafenib), Khapzory® (levoleucovorin) or Zirabev® (bevacizumab-bvzr).

[0272] In some embodiments, when the method is a method for the treatment of lung cancer, the at least one second therapeutic agent is Etopophos® (etoposide), Hycamtin® (topotecan), VePesid® (etoposide), Toposar® (etoposide), Opdivo® (nivolumab), Keytruda® (pembrolizumab), Tecentriq® (atezolizumab), Imfinizi® (durvalumab), methotrexate, cyclophosphamide, Carboplatin, Cisplatin, docetaxel, Gemcitabine, Irinotecan, Paclitaxel, Pemetrexed, Vinblastine, or Vinorelbine.

[0273] In some embodiments, when the method is a method for the treatment of pancreatic ductal cancer, the at least one second therapeutic agent is Gemzar® (Gemcitabine), fluorouracil, Afinitor® (everolimus), Tarceva® (erlotinib), Abraxane® (paclitaxel), capecitabine, Sutent® (sunitinib), pancreatin, methotrexate, Zanosar® (streptozocin), Mutamycin® (mitomycin), Onivyde® (irinotecan), bevacizumab, cetuximab, Infugem® (gemcitabine) or Lynparza® (olaparib).

[0274] In some embodiments, when the method is a method for the treatment of head and neck cancer, the at least one second therapeutic agent is Erbituz® (cetuximab), Taxotere® (docetaxel), Trexall® (methotrexate), Keytruda® (pembrolizumab) or Opdivo® (nivolumab).

[0275] In some embodiments, when the method is a method for the treatment of prostate cancer the at least one second therapeutic agent is Suprefact® (buserelin), Firmagon®

(degarelix), Zoladex® (goserelin), Vantas® (histrelin), Eligard® (leuprolide), Orgovyx® (relugolix), Trelstar® (triptorelin), Casodex® (bicalutamide), Eulexin® (flutamide), Nilandron® (nilutamide), Zytiga® (biraterone acetate), Erleada® (apalutamide), or Xtandi® (enzalutamide).

[0276] In some embodiments, the at least one second therapeutic agent is a STING agonist. Exemplary STING agonists include E7766, MIW815, SNX281, and TAK-676. *See, e.g.,* Aval et al., *Journal of Clinical Medicine 9*:3323 (2020); Su et al., *Theranostics 9*:7759-7771 (2019).

[0277] The RTI and at least one second therapeutic agent may be administered separately or together as part of a unitary pharmaceutical composition.

[0278] In some embodiments, the patient is (a) not infected with the HIV virus, (b) not suspected of being infected with the HIV virus, (c) not being treated for the HIV virus, and/or (d) not being treated to prevent the HIV virus.

[0279] The terms "patient" and "subject" as used herein are synonymous terms referring to any human or animal that is in need of or might benefit from administration of a RTI for treating cancer. Foremost among such subjects are mammals, e.g., humans, although the methods and compositions provided herein are not intended to be so limited. Other subjects include veterinary animals, e.g., cows, sheep, pigs, horses, dogs, cats and the like. In one embodiment, the subject is a human. In one embodiment, the subject is an animal.

Salts, Pharmaceutical Compositions, and Kits

[0280] The methods of the present disclosure can be accomplished by administering RTI as the neat compound or as a pharmaceutical composition. Administration of a pharmaceutical composition, or a neat RTI can be performed before, during, or after the clinical diagnosis of the cancer. Typically, the pharmaceutical compositions are sterile, and contain no toxic, carcinogenic, or mutagenic compounds that would cause an adverse reaction when administered.

[0281] Further provided are kits comprising the RTI and, optionally, at least one second therapeutic agent useful for the treatment of cancer associated, packaged separately or together, and an insert having instructions for using these active agents. In one embodiment, the RTI is packaged alone together with instructions to administered together with the at least one second therapeutic agent. The RTI and the at least one second therapeutic agent can be administered simultaneously or sequentially to achieve the desired

effect. In addition, the RTI and the at least one second therapeutic agent can be administered from a single composition or two separate compositions. The second therapeutic agent is administered in an amount to provide its desired therapeutic effect. The effective dosage range for each optional therapeutic agent is known in the art, and the optional therapeutic agent is administered to an individual in need thereof within such established ranges.

[0282] The present disclosure encompasses the preparation and use of salts of a RTI. As used herein, a "pharmaceutically acceptable salt" refers to salts or zwitterionic forms of a RTI. Salts of a RTI can be prepared during the final isolation and purification of the compound or separately by reacting the compound with a suitable acid. The pharmaceutically acceptable salts of a RTI can be acid addition salts formed with pharmaceutically acceptable acids. Examples of acids which can be employed to form pharmaceutically acceptable salts include inorganic acids such as nitric, boric, hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric. Non-limiting examples of salts of a RTI include, but are not limited to, the hydrochloride, hydrobromide, hydroiodide, sulfate, bisulfate, 2-hydroxyethansulfonate, phosphate, hydrogen phosphate, acetate, adipate, alginate, aspartate, benzoate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerolphsphate, hemisulfate, heptanoate, hexanoate, formate, succinate, fumarate, maleate, ascorbate, isethionate, salicylate, methanesulfonate, mesitylenesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylproprionate, picrate, pivalate, propionate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate, undecanoate, lactate, citrate, tartrate, gluconate, methanesulfonate, ethanedisulfonate, benzene sulfonate, and p-toluenesulfonate salts.

[0283] The present disclosure encompasses the preparation and use of solvates of a RTI. Solvates typically do not significantly alter the physiological activity or toxicity of the compounds, and as such may function as pharmacological equivalents. The term "solvate" as used herein is a combination, physical association and/or solvation of a compound with a solvent molecule such as, e.g. a disolvate, monosolvate or hemisolvate, where the ratio of solvent molecule to compound is about 2:1, about 1:1 or about 1:2, respectively. This physical association involves varying degrees of ionic and covalent bonding, including

hydrogen bonding. In certain instances, the solvate can be isolated, such as when one or more solvent molecules are incorporated into the crystal lattice of a crystalline solid. Thus, "solvate" encompasses both solution-phase and isolatable solvates. A RTI can be present as solvated forms with a pharmaceutically acceptable solvent, such as water, methanol, and ethanol. It is intended that the disclosure includes both solvated and unsolvated forms of a RTI. One type of solvate is a hydrate. A "hydrate" relates to a particular subgroup of solvates where the solvent molecule is water. Solvates typically can function as pharmacological equivalents. Preparation of solvates is known in the art. See, for example, M. Caira *et al*, *J. Pharmaceut. Sci., 93(3)*:601-611 (2004), which describes the preparation of solvates of fluconazole with ethyl acetate and with water. Similar preparation of solvates, hemisolvates, hydrates, and the like are described by E.C. van Tonder *et al.*, *AAPS Pharm. Sci. Tech., 5(1)*:Article 12 (2004), and A.L. Bingham *et al.*, *Chem. Commun.* 603-604 (2001). A typical, non-limiting, process of preparing a solvate would involve dissolving a RTI in a desired solvent (organic, water, or a mixture thereof) at temperatures above 20°C to about 25°C, then cooling the solution at a rate sufficient to form crystals, and isolating the crystals by known methods, e.g., filtration. Analytical techniques such as infrared spectroscopy can be used to confirm the presence of the solvate in a crystal of the solvate.

[0284] The RTI is typically are administered in admixture with a pharmaceutical carrier to give a pharmaceutical composition selected with regard to the intended route of administration and standard pharmaceutical practice. Pharmaceutical compositions for use in accordance with the present disclosure are formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and/or auxiliaries that facilitate processing of the RTI. These pharmaceutical compositions can be manufactured, for example, by conventional mixing, dissolving, granulating, dragee-making, emulsifying, encapsulating, entrapping, or lyophilizing processes. Proper formulation is dependent upon the route of administration chosen. When a therapeutically effective amount of a RTI is administered orally, the composition typically is in the form of a tablet, capsule, powder, solution, or elixir. When administered in tablet form, the composition additionally can contain a solid carrier, such as a gelatin or an adjuvant. The tablet, capsule, and powder contain about 0.01% to about 95%, and preferably from about 1% to about 50%, of a RTI, or a pharmaceutically acceptable salt or solvate thereof, or a

tautomer thereof. When administered in liquid form, a liquid carrier, such as water, petroleum, or oils of animal or plant origin, can be added. The liquid form of the composition can further contain physiological saline solution, dextrose or other saccharide solutions, or glycols. When administered in liquid form, the composition contains about 0.1% to about 90%, and preferably about 1% to about 50%, by weight, of a RTI.

[0285] When a therapeutically effective amount of a RTI is administered by intravenous, cutaneous, or subcutaneous injection, the composition is in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred composition for intravenous, cutaneous, or subcutaneous injection typically contains, an isotonic vehicle.

[0286] A RTI can be readily combined with pharmaceutically acceptable carriers well-known in the art. Standard pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA, 19th ed. 1995. Such carriers enable the active agents to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a subject to be treated. Pharmaceutical preparations for oral use can be obtained by adding a RTI to a solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include, for example, fillers and cellulose preparations. If desired, disintegrating agents can be added.

[0287] A RTI can be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection can be presented in unit dosage form, e.g., in ampules or in multidose containers, with an added preservative. The compositions can take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing, and/or dispersing agents.

[0288] Pharmaceutical compositions for parenteral administration include aqueous solutions of the RTI in water-soluble form. Additionally, suspensions of a compound of a RTI can be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils or synthetic fatty acid esters. Aqueous injection suspensions can contain substances which increase the viscosity of the suspension. Optionally, the

suspension also can contain suitable stabilizers or agents that increase the solubility of the compounds and allow for the preparation of highly concentrated solutions. Alternatively, a present composition can be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

[0289] In particular, a RTI can be administered orally in the form of tablets containing excipients, such as starch or lactose, or in capsules or ovules, either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavoring or coloring agents. Such liquid preparations can be prepared with pharmaceutically acceptable additives, such as suspending agents. A RTI also can be injected parenterally, for example, intravenously, intramuscularly, subcutaneously, or intracoronarily. For parenteral administration, a RTI typically used in the form of a sterile aqueous solution which can contain other substances, for example, salts or monosaccharides, such as mannitol or glucose, to make the solution isotonic with blood.

[0290] All patents, patent application, and publications cited herein are fully incorporated by reference herein.

[0291] It is to be appreciated that the Detailed Description section, and not the Summary and Abstract sections, is intended to be used to interpret the claims. The Summary and Abstract sections may set forth one or more but not all exemplary embodiments of the present invention as contemplated by the inventor(s), and thus, are not intended to limit the present invention and the appended claims in any way.

[0292] The foregoing description of the specific embodiments will so fully reveal the general nature of the invention that others can, by applying knowledge within the skill of the art, readily modify and/or adapt for various applications such specific embodiments, without undue experimentation, without departing from the general concept of the present invention. Therefore, such adaptations and modifications are intended to be within the meaning and range of equivalents of the disclosed embodiments, based on the teaching and guidance presented herein. It is to be understood that the phraseology or terminology herein is for the purpose of description and not of limitation, such that the terminology or phraseology of the present specification is to be interpreted by the skilled artisan in light of the teachings and guidance.

[0293] The disclosure also provides the following particular embodiments with respect to methods for treating cancer in a patient in need thereof.

[0294] Embodiment 1. A method for treating cancer in patient in need thereof, the method comprising administering a therapeutically effective amount of a reverse transcriptase inhibitor (RTI) to the patient, wherein the RTI is administered to the patient according to an intermittent dosing schedule.

[0295] Embodiment 2. A method for increasing the expression of ORFp2 in the cancer cells of a patient, the method comprising administering a therapeutically effective amount of a RTI to the patient, wherein the RTI is administered to the patient according to an intermittent dosing schedule.

[0296] Embodiment 3. The method of Embodiments 1 or 2, wherein the RTI is a nucleoside reverse transcriptase inhibitor (NRTI).

[0297] Embodiment 4. The method of Embodiments 1 or 2, wherein the RTI is a non-nucleoside reverse transcriptase inhibitor (NNRTI).

[0298] Embodiment 5. The method of Embodiments 1 or 2, wherein the RTI is a LINE-1 inhibitor.

[0299] Embodiment 6. The method of Embodiments 1 or 2, wherein the RTI is islatravir, censavudine, elvucitabine, lamivudine (3TC), zidovudine (AZT), tenofovir, tenofovir disoproxil, tenofovir alafenamide, stavudine (d4T), zalcitabine (ddC), didanosine (ddI), emtricitabine (FTC), entecavir (ETV), 2',3'-dideoxyguanosine (ddG), 2′,3′-dideoxyadenosine (ddA), 2′-fluoro-2′,3′-dideoxyarabinosyladenine (F-ddA), efavirenz (EFV), nevirapine (NVP), or abacavir (ABC), adefovir dipivoxil, or telbivudine.

[0300] Embodiment 7. The method of Embodiment 6, wherein the RTI is lamivudine, stavudine, emtricitabine, abacavir, tenofovir alafenamide, zidovudine, zalcitabine, didanosine, tenofovir disoproxil, adefovir dipivoxil, entecavir, or telbivudine.

[0301] Embodiment 8. The method of Embodiment 6, wherein the RTI is lamivudine.

[0302] Embodiment 9. The method of Embodiment 6, wherein the RTI is stavudine.

[0303] Embodiment 10. The method of Embodiment 6, wherein the RTI is emtricitabine.

[0304] Embodiment 11. The method of Embodiment 6, wherein the RTI is abacavir.

[0305] Embodiment 12. The method of Embodiment 6, wherein the RTI is tenofovir alafenamide.

[0306] Embodiment 13. The method of Embodiment 6, wherein the RTI is zidovudine.

[0307] Embodiment 14. The method of Embodiment 6, wherein the RTI is zalcitabine.

[0308] Embodiment 15. The method of Embodiment 6, wherein the RTI is didanosine.

[0309] Embodiment 16. The method of Embodiment 6, wherein the RTI is tenofovir disoproxil.

[0310] Embodiment 17. The method of Embodiment 6, wherein the RTI is adefovir dipivoxil.

[0311] Embodiment 18. The method of Embodiment 6, wherein the RTI is entecavir.

[0312] Embodiment 19. The method of Embodiment 6, wherein the RTI is telbivudin.

[0313] Embodiment 20. The method of any one of Embodiments 1-19, wherein the cancer is any one or more of the cancers of Table 1, e.g., breast cancer, colon cancer, lung cancer, pancreatic ductal cancer, prostate cancer, ovarian cancer, or head and neck cancer.

[0314] Embodiment 21. The method of Embodiment 20, wherein the cancer is breast cancer.

[0315] Embodiment 22. The method of Embodiment 20, wherein the cancer is colon cancer.

[0316] Embodiment 23. The method of Embodiment 20, wherein the cancer is lung cancer.

[0317] Embodiment 24. The method of Embodiment 20, wherein the cancer is pancreatic ductal cancer.

[0318] Embodiment 25. The method of Embodiment 20, wherein the cancer is prostate cancer.

[0319] Embodiment 26. The method of Embodiment 20, wherein the cancer is ovarian cancer.

[0320] Embodiment 27. The method of Embodiment 20, wherein the cancer is head and neck cancer.

[0321] Embodiment 28. The method of any one of Embodiments 1-27, further comprising administering a therapeutically effective amount of at least one second therapeutic agent useful for treating the cancer.

[0322] Embodiment 29. The method of Embodiment 28 for the treatment of breast cancer, wherein the at least one second therapeutic agent is Soltamox® (tamoxifen), Arimidex® (anastrozole), Femara® (letrozole), Aromasin® (exemestane), Herceptin® (trastuzumab), Abraxane® (paclitaxel), Cytoxan® (cyclophosphamide), Taxol® (paclitaxel), Afinitor® (everolimus), Taxotere® (docetaxel), Xeloda® (capecitabine), Trexall® (methotrexate), Faslodex (fulvestrant), Adriamycin® (doxorubicin), Perjeta® (pertuzumab), Gemzar (gemcitabine), Tykerb® (lapatinib), Adrucil® (fluorouracil), Ibrance® (palbociclib), Verzenio® (abemaciclib), Fareston® (toremifene), Halaven® (eribulin), Menest, Kadcyla® (ado-trastuzumab emtransine), Androxy® (fluoxymesterone), Avastin® (bevacizumab), esterified estrogens, Herzuma® (trastuzumab), Ixempra® (ixabepilone), Kanjinti® (trastuzumab), Kisqali® (ribociclib), Ogivri® (trastuzumab), Ontruzant® (trastuzumab), Tepadina® (thiotepa), Trazimera® (trastuzumab), Velban® (vinblastine), Piqray® (alpelisib), Tecentriq® (atezolizumab), Enhertu® (fam-trastuzumab deruxtecan), Herceptin, Hylecta™ (hyaluronidase/trastuzumab), Infugem® (gemcitabine), Kisqali® Femara® Co-Pack (ribociclib and letrozole), Talzenna® (talazoparib), Trodelvy® (sacituzumab) or Tukysa™ (tukatinib).

[0323] Embodiment 30. The method of Embodiment 28 for the treatment of colon cancer, wherein the at least one second therapeutic agent is Xeloda® (capecitabine), Eloxatin® (oxaliplatin), fluorouracil, Avastin® (bevacizumab), leucovorin, Camptosar® (irinotecan), Stivarga® (regorafenib), Erbitux® (cetuximab), Vectibix® (panitumumab), Lonsurf® (tipiracil/trifluridine), Zaltrap® (ziv-aflibercept), Betaseron® (interferon beta-1b), Fusilev® (levoleucovorin), Wellcocorin® (methotrexate), Keytruda® (pembrolizumab), Mvasi® (bevacizumab-awwb), Cyramza® (ramucirumab), Yervoy® (ipilmumab), Opdivo® (nivolumab), Braftovi® (encorafenib), Khapzory® (levoleucovorin) or Zirabev® (bevacizumab-bvzr).

[0324] Embodiment 31. The method of Embodiment 28 for the treatment of lung cancer, wherein the at least one second therapeutic agent is Etopophos® (etoposide), Hycamtin® (topotecan), VePesid® (etoposide), Toposar® (etoposide), Opdivo® (nivolumab), Keytruda® (pembrolizumab), Tecentriq® (atezolizumab), Imfinizi® (durvalumab), methotrexate, cyclophosphamide, Carboplatin, Cisplatin, docetaxel, Gemcitabine, Irinotecan, Paclitaxel, Pemetrexed, Vinblastine, or Vinorelbine.

[0325] Embodiment 32. The method of Embodiment 28 for the treatment of pancreatic ductal cancer, wherein the at least one second therapeutic agent is Gemzar® (Gemcitabine), fluorouracil, Afinitor® (everolimus), Tarceva® (erlotinib), Abraxane® (paclitaxel), capecitabine, Sutent® (sunitinib), pancreatin, methotrexate, Zanosar® (streptozocin), Mutamycin® (mitomycin), Onivyde® (irinotecan), bevacizumab, cetuximab, Infugem® (gemcitabine) or Lynparza® (olaparib).

[0326] Embodiment 33. The method of Embodiment 28 for the treatment of head and neck cancer, wherein the at least one second therapeutic agent is Erbituz® (cetuximab), Taxotere® (docetaxel), Trexall® (methotrexate), Keytruda® (pembrolizumab) or Opdivo® (nivolumab).

[0327] Embodiment 34. The method of Embodiment 28 for the treatment of prostate cancer, wherein the at least one second therapeutic agent is Suprefact® (buserelin), Firmagon® (degarelix), Zoladex® (goserelin), Vantas® (histrelin), Eligard® (leuprolide), Orgovyx® (relugolix), Trelstar® (triptorelin), Casodex® (bicalutamide), Eulexin® (flutamide), Nilandron® (nilutamide), Zytiga® (biraterone acetate), Erleada® (apalutamide), or Xtandi® (enzalutamide).

[0328] Embodiment 35. The method of Embodiment 28, wherein the at least one second therapeutic agent is a STING agonist.

[0329] Embodiment 36. The method of any one of Embodiments 1-35, wherein the patient is (a) not infected with the HIV virus, (b) not suspected of being infected with the HIV virus, (c) not being treated for the HIV virus, and/or (d) not being treated to prevent the HIV virus.

[0330] Embodiment 37. A kit for carrying out the method of any one Embodiments 1-35, the kit comprising (i) a RTI; and (ii) and instructions for administering the RTI to a patient having cancer according to an intermittent dosing schedule.

[0331] Embodiment 38. The kit of Embodiment 36 further comprising at least one second therapeutic agent.

[0332] The disclosure also provides the following particular embodiments with respect to RTIs (and compositions thereof) for use to treat cancer in a subject.

[0333] Embodiment 1. A RTI for use in treating cancer in patient in need thereof, wherein the RTI is to be administered according to an intermittent dosing schedule.

[0334] Embodiment 2. A RTI for use in increasing the expression of ORFp2 in the cancer cells of a patient, wherein the RTI is to be administered to the patient according to an intermittent dosing schedule.

[0335] Embodiment 3. The RTI for use of Embodiments 1 or 2, wherein the RTI is a nucleoside reverse transcriptase inhibitor (NRTI).

[0336] Embodiment 4. The RTI for use of Embodiments 1 or 2, wherein the RTI is a non-nucleoside reverse transcriptase inhibitor (NNRTI).

[0337] Embodiment 5. The RTI for use of Embodiments 1 or 2, wherein the RTI is a LINE-1 inhibitor.

[0338] Embodiment 6. The RTI for use of Embodiments 1 or 2, wherein the RTI is islatravir, censavudine, elvucitabine, lamivudine (3TC), zidovudine (AZT), tenofovir, tenofovir disoproxil, tenofovir alafenamide, stavudine (d4T), zalcitabine (ddC), didanosine (ddI), emtricitabine (FTC), entecavir (ETV), 2',3'-dideoxyguanosine (ddG), 2′,3′-dideoxyadenosine (ddA), 2′-fluoro-2′,3′-dideoxyarabinosyladenine (F-ddA), efavirenz (EFV), nevirapine (NVP), or abacavir (ABC), adefovir dipivoxil, or telbivudine.

[0339] Embodiment 7. The RTI for use of Embodiment 6, wherein the RTI is lamivudine, stavudine, emtricitabine, abacavir, tenofovir alafenamide, zidovudine, zalcitabine, didanosine, tenofovir disoproxil, adefovir dipivoxil, entecavir, or telbivudine.

[0340] Embodiment 8. The RTI for use of Embodiment 6, wherein the RTI is lamivudine.

[0341] Embodiment 9. The RTI for use of Embodiment 6, wherein the RTI is stavudine.

[0342] Embodiment 10. The RTI for use of Embodiment 6, wherein the RTI is emtricitabine.

[0343] Embodiment 11. The RTI for use of Embodiment 6, wherein the RTI is abacavir.

[0344] Embodiment 12. The RTI for use of Embodiment 6, wherein the RTI is tenofovir alafenamide.

[0345] Embodiment 13. The RTI for use of Embodiment 6, wherein the RTI is zidovudine.

[0346] Embodiment 14. The RTI for use of Embodiment 6, wherein the RTI is zalcitabine.

[0347] Embodiment 15. The RTI for use of Embodiment 6, wherein the RTI is didanosine.

[0348] Embodiment 16. The RTI for use of Embodiment 6, wherein the RTI is tenofovir disoproxil.

[0349] Embodiment 17. The RTI for use of Embodiment 6, wherein the RTI is adefovir dipivoxil.

[0350] Embodiment 18. The RTI for use of Embodiment 6, wherein the RTI is entecavir.

[0351] Embodiment 19. The RTI for use of Embodiment 6, wherein the RTI is telbivudine.

[0352] Embodiment 20. The RTI for use of any one of Embodiments 1-19, wherein the cancer is any one or more of the cancers of Table 1, e.g., breast cancer, colon cancer, lung cancer, pancreatic ductal cancer, prostate cancer, ovarian cancer, or head and neck cancer.

[0353] Embodiment 21. The RTI for use of Embodiment 20, wherein the cancer is breast cancer.

[0354] Embodiment 22. The RTI for use of Embodiment 20, wherein the cancer is colon cancer.

[0355] Embodiment 23. The RTI for use of Embodiment 20, wherein the cancer is lung cancer.

[0356] Embodiment 24. The RTI for use of Embodiment 20, wherein the cancer is pancreatic ductal cancer.

[0357] Embodiment 25. The RTI for use of Embodiment 20, wherein the cancer is prostate cancer.

[0358] Embodiment 26. The RTI for use of Embodiment 20, wherein the cancer is ovarian cancer.

[0359] Embodiment 27. The RTI for use of Embodiment 20, wherein the cancer is head and neck cancer.

[0360] Embodiment 28. The RTI for use of any one of Embodiments 1-27, further comprising administering a therapeutically effective amount of at least one second therapeutic agent useful for treating the cancer.

[0361] Embodiment 29. The RTI for use of Embodiment 28 for the treatment of breast cancer, wherein the at least one second therapeutic agent is Soltamox® (tamoxifen), Arimidex® (anastrozole), Femara® (letrozole), Aromasin® (exemestane), Herceptin® (trastuzumab), Abraxane® (paclitaxel), Cytoxan® (cyclophosphamide), Taxol® (paclitaxel), Afinitor® (everolimus), Taxotere® (docetaxel), Xeloda® (capecitabine), Trexall® (methotrexate), Faslodex (fulvestrant), Adriamycin® (doxorubicin), Perjeta® (pertuzumab), Gemzar (gemcitabine), Tykerb® (lapatinib), Adrucil® (fluorouracil), Ibrance® (palbociclib), Verzenio® (abemaciclib), Fareston® (toremifene), Halaven® (eribulin), Menest, Kadcyla® (ado-trastuzumab emtransine), Androxy® (fluoxymesterone), Avastin® (bevacizumab), esterified estrogens, Herzuma® (trastuzumab), Ixempra® (ixabepilone), Kanjinti® (trastuzumab), Kisqali® (ribociclib), Ogivri® (trastuzumab), Ontruzant® (trastuzumab), Tepadina® (thiotepa), Trazimera® (trastuzumab), Velban® (vinblastine), Piqray® (alpelisib), Tecentriq® (atezolizumab), Enhertu® (fam-trastuzumab deruxtecan), Herceptin, Hylecta™ (hyaluronidase/trastuzumab), Infugem® (gemcitabine), Kisqali® Femara® Co-Pack (ribociclib and letrozole), Talzenna® (talazoparib), Trodelvy® (sacituzumab) or Tukysa™ (tukatinib).

[0362] Embodiment 30. The RTI for use of Embodiment 28 for the treatment of colon cancer, wherein the at least one second therapeutic agent is Xeloda® (capecitabine), Eloxatin® (oxaliplatin), fluorouracil, Avastin® (bevacizumab), leucovorin, Camptosar® (irinotecan), Stivarga® (regorafenib), Erbitux® (cetuximab), Vectibix® (panitumumab), Lonsurf® (tipiracil/trifluridine), Zaltrap® (ziv-aflibercept), Betaseron® (interferon beta-1b), Fusilev® (levoleucovorin), Wellcocorin® (methotrexate), Keytruda® (pembrolizumab), Mvasi® (bevacizumab-awwb), Cyramza® (ramucirumab), Yervoy® (ipilmumab), Opdivo® (nivolumab), Braftovi® (encorafenib), Khapzory® (levoleucovorin) or Zirabev® (bevacizumab-bvzr).

[0363] Embodiment 31. The RTI for use of Embodiment 28 for the treatment of lung cancer, wherein the at least one second therapeutic agent is Etopophos® (etoposide), Hycamtin® (topotecan), VePesid® (etoposide), Toposar® (etoposide), Opdivo® (nivolumab), Keytruda® (pembrolizumab), Tecentriq® (atezolizumab), Imfinizi® (durvalumab), methotrexate, cyclophosphamide, Carboplatin, Cisplatin, docetaxel, Gemcitabine, Irinotecan, Paclitaxel, Pemetrexed, Vinblastine, or Vinorelbine.

[0364] Embodiment 32. The RTI for use of Embodiment 28 for the treatment of pancreatic ductal cancer, wherein the at least one second therapeutic agent is Gemzar® (Gemcitabine), fluorouracil, Afinitor® (everolimus), Tarceva® (erlotinib), Abraxane® (paclitaxel), capecitabine, Sutent® (sunitinib), pancreatin, methotrexate, Zanosar® (streptozocin), Mutamycin® (mitomycin), Onivyde® (irinotecan), bevacizumab, cetuximab, Infugem® (gemcitabine) or Lynparza® (olaparib).

[0365] Embodiment 33. The RTI for use of Embodiment 28 for the treatment of head and neck cancer, wherein the at least one second therapeutic agent is Erbituz® (cetuximab), Taxotere® (docetaxel), Trexall® (methotrexate), Keytruda® (pembrolizumab) or Opdivo® (nivolumab).

[0366] Embodiment 34. The RTI for use of Embodiment 28 for the treatment of prostate cancer, wherein the at least one second therapeutic agent is Suprefact® (buserelin), Firmagon® (degarelix), Zoladex® (goserelin), Vantas® (histrelin), Eligard® (leuprolide), Orgovyx® (relugolix), Trelstar® (triptorelin), Casodex® (bicalutamide), Eulexin® (flutamide), Nilandron® (nilutamide), Zytiga® (biraterone acetate), Erleada® (apalutamide), or Xtandi® (enzalutamide).

[0367] Embodiment 35. The RTI for use of Embodiment 28, wherein the at least one second therapeutic agent is a STING agonist.

[0368] Embodiment 36. The RTI for use of any one of Embodiments 1-35, wherein the patient is (a) not infected with the HIV virus, (b) not suspected of being infected with the HIV virus, (c) not being treated for the HIV virus, and/or (d) not being treated to prevent the HIV virus.

[0369] The disclosure also provides the following particular embodiments with respect to uses of a RTI in the manufacture of a medicament for treating cancer.

[0370] Embodiment 1. Use of a RTI in the manufacture of a medicament for treating cancer in patient in need thereof, wherein the RTI is to be administered according to an intermittent dosing schedule.

[0371] Embodiment 2. Use of a RTI in the manufacture of a medicament for increasing the expression of ORFp2 in the cancer cells of a patient, wherein the RTI is to be administered to the patient according to an intermittent dosing schedule.

[0372] Embodiment 3. The use of Embodiments 1 or 2, wherein the RTI is a nucleoside reverse transcriptase inhibitor (NRTI).

[0373] Embodiment 4. The use of Embodiments 1 or 2, wherein the RTI is a non-nucleoside reverse transcriptase inhibitor (NNRTI).

[0374] Embodiment 5. The use of Embodiments 1 or 2, wherein the RTI is a LINE-1 inhibitor.

[0375] Embodiment 6. The use of Embodiments 1 or 2, wherein the RTI is islatravir, censavudine, elvucitabine, lamivudine (3TC), zidovudine (AZT), tenofovir, tenofovir disoproxil, tenofovir alafenamide, stavudine (d4T), zalcitabine (ddC), didanosine (ddI), emtricitabine (FTC), entecavir (ETV), 2',3'-dideoxyguanosine (ddG), 2′,3′-dideoxyadenosine (ddA), 2′-fluoro-2′,3′-dideoxyarabinosyladenine (F-ddA), efavirenz (EFV), nevirapine (NVP), or abacavir (ABC), adefovir dipivoxil, or telbivudine.

[0376] Embodiment 7. The use of Embodiment 6, wherein the RTI is lamivudine, stavudine, emtricitabine, abacavir, tenofovir alafenamide, zidovudine, zalcitabine, didanosine, tenofovir disoproxil, adefovir dipivoxil, entecavir, or telbivudine.

[0377] Embodiment 8. The use of Embodiment 6, wherein the RTI is lamivudine.

[0378] Embodiment 9. The use of Embodiment 6, wherein the RTI is stavudine.

[0379] Embodiment 10. The use of Embodiment 6, wherein the RTI is emtricitabine.

[0380] Embodiment 11. The use of Embodiment 6, wherein the RTI is abacavir.

[0381] Embodiment 12. The use of Embodiment 6, wherein the RTI is tenofovir alafenamide.

[0382] Embodiment 13. The use of Embodiment 6, wherein the RTI is zidovudine.

[0383] Embodiment 14. The use of Embodiment 6, wherein the RTI is zalcitabine.

[0384] Embodiment 15. The use of Embodiment 6, wherein the RTI is didanosine.

[0385] Embodiment 16. The RTI for use of Embodiment 6, wherein the RTI is tenofovir disoproxil.

[0386] Embodiment 17. The use of Embodiment 6, wherein the RTI is adefovir dipivoxil.

[0387] Embodiment 18. The use of Embodiment 6, wherein the RTI is entecavir.

[0388] Embodiment 19. The use of Embodiment 6, wherein the RTI is telbivudine.

[0389] Embodiment 20. The use of any one of Embodiments 1-19, wherein the cancer is any one or more of the cancers of Table 1, e.g., breast cancer, colon cancer, lung cancer, pancreatic ductal cancer, prostate cancer, ovarian cancer, or head and neck cancer.

[0390] Embodiment 21. The use of Embodiment 20, wherein the cancer is breast cancer.

[0391] Embodiment 22. The use of Embodiment 20, wherein the cancer is colon cancer.

[0392] Embodiment 23. The use of Embodiment 20, wherein the cancer is lung cancer.

[0393] Embodiment 24. The use of Embodiment 20, wherein the cancer is pancreatic ductal cancer.

[0394] Embodiment 25. The use of Embodiment 20, wherein the cancer is prostate cancer.

[0395] Embodiment 26. The use of Embodiment 20, wherein the cancer is ovarian cancer.

[0396] Embodiment 27. The use of Embodiment 20, wherein the cancer is head and neck cancer.

[0397] Embodiment 28. The RTI for use of any one of Embodiments 1-27, further comprising administering a therapeutically effective amount of at least one second therapeutic agent useful for treating the cancer.

[0398] Embodiment 29. The use of Embodiment 28 for the treatment of breast cancer, wherein the at least one second therapeutic agent is Soltamox® (tamoxifen), Arimidex® (anastrozole), Femara® (letrozole), Aromasin® (exemestane), Herceptin® (trastuzumab), Abraxane® (paclitaxel), Cytoxan® (cyclophosphamide), Taxol® (paclitaxel), Afinitor® (everolimus), Taxotere® (docetaxel), Xeloda® (capecitabine), Trexall® (methotrexate), Faslodex (fulvestrant), Adriamycin® (doxorubicin), Perjeta® (pertuzumab), Gemzar (gemcitabine), Tykerb® (lapatinib), Adrucil® (fluorouracil), Ibrance® (palbociclib), Verzenio® (abemaciclib), Fareston® (toremifene), Halaven® (eribulin), Menest, Kadcyla® (ado-trastuzumab emtransine), Androxy® (fluoxymesterone), Avastin® (bevacizumab), esterified estrogens, Herzuma® (trastuzumab), Ixempra® (ixabepilone), Kanjinti® (trastuzumab), Kisqali® (ribociclib), Ogivri® (trastuzumab), Ontruzant® (trastuzumab), Tepadina® (thiotepa), Trazimera® (trastuzumab), Velban® (vinblastine), Piqray® (alpelisib), Tecentriq® (atezolizumab), Enhertu® (fam-trastuzumab deruxtecan), Herceptin, Hylecta™ (hyaluronidase/trastuzumab), Infugem® (gemcitabine), Kisqali®

Femara® Co-Pack (ribociclib and letrozole), Talzenna® (talazoparib), Trodelvy® (sacituzumab) or Tukysa™ (tukatinib).

[0399] Embodiment 30. The use of Embodiment 28 for the treatment of colon cancer, wherein the at least one second therapeutic agent is Xeloda® (capecitabine), Eloxatin® (oxaliplatin), fluorouracil, Avastin® (bevacizumab), leucovorin, Camptosar® (irinotecan), Stivarga® (regorafenib), Erbitux® (cetuximab), Vectibix® (panitumumab), Lonsurf® (tipiracil/trifluridine), Zaltrap® (ziv-aflibercept), Betaseron® (interferon beta-1b), Fusilev® (levoleucovorin), Wellcocorin® (methotrexate), Keytruda® (pembrolizumab), Mvasi® (bevacizumab-awwb), Cyramza® (ramucirumab), Yervoy® (ipilmumab), Opdivo® (nivolumab), Braftovi® (encorafenib), Khapzory® (levoleucovorin) or Zirabev® (bevacizumab-bvzr).

[0400] Embodiment 31. The use of Embodiment 28 for the treatment of lung cancer, wherein the at least one second therapeutic agent is Etopophos® (etoposide), Hycamtin® (topotecan), VePesid® (etoposide), Toposar® (etoposide), Opdivo® (nivolumab), Keytruda® (pembrolizumab), Tecentriq® (atezolizumab), Imfinizi® (durvalumab), methotrexate, cyclophosphamide, Carboplatin, Cisplatin, docetaxel, Gemcitabine, Irinotecan, Paclitaxel, Pemetrexed, Vinblastine, or Vinorelbine.

[0401] Embodiment 32. The use of Embodiment 28 for the treatment of pancreatic ductal cancer, wherein the at least one second therapeutic agent is Gemzar® (Gemcitabine), fluorouracil, Afinitor® (everolimus), Tarceva® (erlotinib), Abraxane® (paclitaxel), capecitabine, Sutent® (sunitinib), pancreatin, methotrexate, Zanosar® (streptozocin), Mutamycin® (mitomycin), Onivyde® (irinotecan), bevacizumab, cetuximab, Infugem® (gemcitabine) or Lynparza® (olaparib).

[0402] Embodiment 33. The use of Embodiment 28 for the treatment of head and neck cancer, wherein the at least one second therapeutic agent is Erbituz® (cetuximab), Taxotere® (docetaxel), Trexall® (methotrexate), Keytruda® (pembrolizumab) or Opdivo® (nivolumab).

[0403] Embodiment 34. The use of Embodiment 28 for the treatment of prostate cancer, wherein the at least one second therapeutic agent is Suprefact® (buserelin), Firmagon® (degarelix), Zoladex® (goserelin), Vantas® (histrelin), Eligard® (leuprolide), Orgovyx® (relugolix), Trelstar® (triptorelin), Casodex® (bicalutamide), Eulexin®

(flutamide), Nilandron® (nilutamide), Zytiga® (biraterone acetate), Erleada® (apalutamide), or Xtandi® (enzalutamide).

[0404] Embodiment 35. The use of Embodiment 28, wherein the at least one second therapeutic agent is a STING agonist.

[0405] Embodiment 36. The use of any one of Embodiments 1-35, wherein the patient is (a) not infected with the HIV virus, (b) not suspected of being infected with the HIV virus, (c) not being treated for the HIV virus, and/or (d) not being treated to prevent the HIV virus.

[0406] The disclosure also provides the following particular embodiments with respect to methods for treating cancer in a patient in need thereof.

[0407] Embodiment 1'. A method for treating cancer in patient in need thereof, the method comprising administering a therapeutically effective amount of a reverse transcriptase inhibitor (RTI) to the patient, wherein the RTI is administered according to a continuous or an intermittent dosing schedule.

[0408] Embodiment 2'. The method of Embodiment 1', wherein the RTI is a nucleoside reverse transcriptase inhibitor (NRTI).

[0409] Embodiment 3'. The method of Embodiment 1', wherein the RTI is a non-nucleoside reverse transcriptase inhibitor (NNRTI).

[0410] Embodiment 4'. The method of Embodiment 1', wherein the RTI is a LINE-1 inhibitor.

[0411] Embodiment 5'. The method of Embodiment 1', wherein the RTI is elvucitabine, lamivudine (3TC), zidovudine (AZT), tenofovir, tenofovir disoproxil, tenofovir alafenamide, stavudine (d4T), zalcitabine (ddC), didanosine (ddI), emtricitabine (FTC), entecavir (ETV), 2',3'-dideoxyguanosine (ddG), 2′,3′-dideoxyadenosine (ddA), 2′-fluoro-2′,3′-dideoxyarabinosyladenine (F-ddA), efavirenz (EFV), nevirapine (NVP), or abacavir (ABC), adefovir dipivoxil, telbivudine, censavudine, or islatravir.

[0412] Embodiment 6'. The method of Embodiment 5', wherein the RTI is lamivudine, stavudine, emtricitabine, abacavir, tenofovir alafenamide, zidovudine, zalcitabine, didanosine, tenofovir disoproxil, adefovir dipivoxil, entecavir, telbivudine, censavudine, or islatravir.

[0413] Embodiment 7'. The method of Embodiment 5', wherein the RTI is lamivudine.

[0414] Embodiment 8'. The method of Embodiment 5', wherein the RTI is stavudine.

[0415] Embodiment 9'. The method of Embodiment 5', wherein the RTI is emtricitabine.

[0416] Embodiment 10'. The method of Embodiment 5', wherein the RTI is abacavir.

[0417] Embodiment 11'. The method of Embodiment 5', wherein the RTI is tenofovir alafenamide.

[0418] Embodiment 12'. The method of Embodiment 5', wherein the RTI is zidovudine.

[0419] Embodiment 13'. The method of Embodiment 5', wherein the RTI is zalcitabine.

[0420] Embodiment 14'. The method of Embodiment 5', wherein the RTI is didanosine.

[0421] Embodiment 15'. The method of Embodiment 5', wherein the RTI is tenofovir disoproxil.

[0422] Embodiment 16'. The method of Embodiment 5', wherein the RTI is adefovir dipivoxil.

[0423] Embodiment 17'. The method of Embodiment 5', wherein the RTI is entecavir.

[0424] Embodiment 18'. The method of Embodiment 5', wherein the RTI is telbivudine.

[0425] Embodiment 19'. The method of Embodiment 5', wherein the RTI is censavudine.

[0426] Embodiment 20'. The method of Embodiment 5', wherein the RTI is islatravir.

[0427] Embodiment 21'. The method of Embodiment 1', wherein the RTI is a compound of Formula I, *see* above, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein:

[0428] B is selected from the group consisting of B-1 and B-2, *see* above;

[0429] R^1 is selected from the group consisting of hydrogen and -OH;

[0430] R^2 is selected from the group consisting of methyl, ethynyl, and -CN;

[0431] R^3 is selected from the group consisting of hydrogen, fluoro, chloro, bromo, iodo and methyl;

[0432] R^4 is selected from the group consisting of $-NH_2$ and -OH;

[0433] R^5 is selected from the group consisting of $-NH_2$ and -OH; and

[0434] R^6 is selected from the group consisting of hydrogen, fluoro, chloro, and $-NH_2$.

[0435] Embodiment 22'. The method of Embodiment 21', wherein the RTI is a compound of Formula II, *see* above, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.

[0436] Embodiment 23'. The method of Embodiment 22', wherein R^3 is hydrogen.

[0437] Embodiment 24'. The method of Embodiment 22', wherein R^3 is selected from the group consisting of fluoro and chloro.

[0438] Embodiment 25'. The method of Embodiment 22', wherein R^3 is methyl.

[0439] Embodiment 26'. The method of any one of Embodiments 22'-25', wherein R^4 is $-NH_2$.

[0440] Embodiment 27'. The method of any one of Embodiments 22'-25', wherein R^4 is -OH.

[0441] Embodiment 28'. The method of Embodiment 21', wherein the RTI is a compound is a compound of Formula III, *see* above, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.

[0442] Embodiment 29'. The method of Embodiment 28', wherein R^5 is $-NH_2$.

[0443] Embodiment 30'. The method of Embodiment 28', wherein R^5 is -OH.

[0444] Embodiment 31'. The method of any one of Embodiments 28'-30', wherein R^6 is hydrogen.

[0445] Embodiment 32'. The method of any one of Embodiments 28'-30', wherein R^6 is chloro.

[0446] Embodiment 33'. The method of any one of Embodiments 28'-30', wherein R^6 is fluoro.

[0447] Embodiment 34'. The method of any one of Embodiments 28'-30', wherein R^6 is $-NH_2$.

[0448] Embodiment 35'. The method of any one of Embodiments 21'-34', wherein R^1 is hydrogen.

[0449] Embodiment 36'. The method of any one of Embodiments 21'-34', wherein R^1 is -OH.

[0450] Embodiment 37'. The method of any one of Embodiments 21'-36', wherein R^2 is methyl.

[0451] Embodiment 38'. The method of any one of Embodiments 21'-36', wherein R^2 is ethynyl.

[0452] Embodiment 39'. The method of any one of Embodiments 21'-36', wherein R^2 is -CN.

[0453] Embodiment 40'. The method of Embodiment 1', wherein the RTI is a compound of Table 3, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.

[0454] Embodiment 41'. The method of Embodiment 1', wherein the RTI is a compound of Table 4, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.

[0455] Embodiment 42. The method of any one of Embodiments 1'-41', wherein the cancer is breast cancer, colon cancer, lung cancer, pancreatic ductal cancer, prostate cancer, ovarian cancer, or head and neck cancer.

[0456] Embodiment 43'. The method of Embodiment 42', wherein the cancer is breast cancer.

[0457] Embodiment 44'. The method of Embodiment 42', wherein the cancer is colon cancer.

[0458] Embodiment 45'. The method of Embodiment 42', wherein the cancer is lung cancer.

[0459] Embodiment 46'. The method of Embodiment 42', wherein the cancer is pancreatic ductal cancer.

[0460] Embodiment 47'. The method of Embodiment 42', wherein the cancer is prostate cancer.

[0461] Embodiment 48'. The method of Embodiment 47', wherein the prostate cancer is high-risk localized prostate cancer.

[0462] Embodiment 49'. The method of Embodiment 42', wherein the cancer is ovarian cancer.

[0463] Embodiment 50'. The method of Embodiment 42', wherein the cancer is head and neck cancer.

[0464] Embodiment 51'. The method of any one of Embodiments 1'-41', wherein the patient has prostate cancer and the RTI is administered as an adjuvant therapy.

[0465] Embodiment 52'. The method of any one of Embodiments 1'-41', wherein the patient has prostate cancer and the RTI is administered as a neoadjuvant therapy.

[0466] Embodiment 53'. The method of any one of Embodiment 1'-52', further comprising administering a therapeutically effective amount of at least one second therapeutic agent useful for treating the cancer.

[0467] Embodiment 54'. The method of Embodiment 53 for the treatment of breast cancer, wherein the at least one second therapeutic agent is Soltamox® (tamoxifen), Arimidex® (anastrozole), Femara® (letrozole), Aromasin® (exemestane), Herceptin® (trastuzumab), Abraxane® (paclitaxel), Cytoxan® (cyclophosphamide), Taxol® (paclitaxel), Afinitor® (everolimus), Taxotere® (docetaxel), Xeloda® (capecitabine), Trexall® (methotrexate), Faslodex (fulvestrant), Adriamycin® (doxorubicin), Perjeta® (pertuzumab), Gemzar (gemcitabine), Tykerb® (lapatinib), Adrucil® (fluorouracil), Ibrance® (palbociclib), Verzenio® (abemaciclib), Fareston® (toremifene), Halaven® (eribulin), Menest, Kadcyla® (ado-trastuzumab emtransine), Androxy® (fluoxymesterone), Avastin® (bevacizumab), esterified estrogens, Herzuma® (trastuzumab), Ixempra® (ixabepilone), Kanjinti® (trastuzumab), Kisqali® (ribociclib), Ogivri® (trastuzumab), Ontruzant® (trastuzumab), Tepadina® (thiotepa), Trazimera® (trastuzumab), Velban® (vinblastine), Piqray® (alpelisib), Tecentriq® (atezolizumab), Enhertu® (fam-trastuzumab deruxtecan), Herceptin, Hylecta™ (hyaluronidase/trastuzumab), Infugem® (gemcitabine), Kisqali® Femara® Co-Pack (ribociclib and letrozole), Talzenna® (talazoparib), Trodelvy® (sacituzumab) or Tukysa™ (tukatinib).

[0468] Embodiment 55'. The method of Embodiment 53 for the treatment of colon cancer, wherein the at least one second therapeutic agent is Xeloda® (capecitabine), Eloxatin® (oxaliplatin), fluorouracil, Avastin® (bevacizumab), leucovorin, Camptosar® (irinotecan), Stivarga® (regorafenib), Erbitux® (cetuximab), Vectibix® (panitumumab), Lonsurf® (tipiracil/trifluridine), Zaltrap® (ziv-aflibercept), Betaseron® (interferon beta-1b), Fusilev® (levoleucovorin), Wellcocorin® (methotrexate), Keytruda® (pembrolizumab), Mvasi® (bevacizumab-awwb), Cyramza® (ramucirumab), Yervoy® (ipilmumab), Opdivo® (nivolumab), Braftovi® (encorafenib), Khapzory® (levoleucovorin) or Zirabev® (bevacizumab-bvzr).

[0469] Embodiment 56'. The method of Embodiment 53 for the treatment of lung cancer, wherein the at least one second therapeutic agent is Etopophos® (etoposide), Hycamtin® (topotecan), VePesid® (etoposide), Toposar® (etoposide), Opdivo® (nivolumab), Keytruda® (pembrolizumab), Tecentriq® (atezolizumab), Imfinizi® (durvalumab), methotrexate, cyclophosphamide, Carboplatin, Cisplatin, docetaxel, Gemcitabine, Irinotecan, Paclitaxel, Pemetrexed, Vinblastine, or Vinorelbine.

[0470] Embodiment 57'. The method of Embodiment 53 for the treatment of pancreatic ductal cancer, wherein the at least one second therapeutic agent is Gemzar® (Gemcitabine), fluorouracil, Afinitor® (everolimus), Tarceva® (erlotinib), Abraxane® (paclitaxel), capecitabine, Sutent® (sunitinib), pancreatin, methotrexate, Zanosar® (streptozocin), Mutamycin® (mitomycin), Onivyde® (irinotecan), bevacizumab, cetuximab, Infugem® (gemcitabine) or Lynparza® (olaparib).

[0471] Embodiment 58'. The method of Embodiment 53 for the treatment of head and neck cancer, wherein the at least one second therapeutic agent is Erbituz® (cetuximab), Taxotere® (docetaxel), Trexall® (methotrexate), Keytruda® (pembrolizumab) or Opdivo® (nivolumab).

[0472] Embodiment 59'. The method of Embodiment 53 for the treatment of prostate cancer, wherein the at least one second therapeutic agent is Suprefact® (buserelin), Firmagon® (degarelix), Zoladex® (goserelin), Vantas® (histrelin), Eligard® (leuprolide), Orgovyx® (relugolix), Trelstar® (triptorelin), Casodex® (bicalutamide), Eulexin® (flutamide), Nilandron® (nilutamide), Zytiga® (biraterone acetate), Erleada® (apalutamide), or Xtandi® (enzalutamide).

[0473] Embodiment 60'. The method of Embodiment 53', wherein the at least one second therapeutic agent is a STING agonist.

[0474] Embodiment 61'. The method of any one of Embodiments 1'-60', wherein the patient is (a) not infected with the HIV virus, (b) not suspected of being infected with the HIV virus, (c) not being treated for the HIV virus, and/or (d) not being treated to prevent the HIV virus.

[0475] Embodiment 62' The method of any one of Embodiments 1'-61', wherein the RTI is administered according to a continuous dosing schedule.

[0476] Embodiment 63' The method of any one of Embodiments 1'-61', wherein the RTI is administered according to an intermittent dosing schedule.

[0477] Embodiment 64'. A kit for carrying out the method of any one Embodiments 1'-63', the kit comprising (i) a RTI; and (ii) and instructions for administering the RTI to a patient having cancer.

[0478] Embodiment 65'. The kit of Embodiment 64' further comprising at least one second therapeutic agent.

[0479] The disclosure also provides the following particular embodiments with respect to RTIs (and compositions thereof) for use to treat cancer in a subject.

[0480] Embodiment 1'. A RTI for use in treating cancer in patient in need thereof, wherein the RTI is to be administered according to a continuous or an intermittent dosing schedule.

[0481] Embodiment 2'. The RTI for use of Embodiment 1', wherein the RTI is a nucleoside reverse transcriptase inhibitor (NRTI).

[0482] Embodiment 3'. The RTI for use of Embodiment 1', wherein the RTI is a non-nucleoside reverse transcriptase inhibitor (NNRTI).

[0483] Embodiment 4'. The RTI for use of Embodiment 1', wherein the RTI is a LINE-1 inhibitor.

[0484] Embodiment 5'. The RTI for use of Embodiment 1', wherein the RTI is elvucitabine, lamivudine (3TC), zidovudine (AZT), tenofovir, tenofovir disoproxil, tenofovir alafenamide, stavudine (d4T), zalcitabine (ddC), didanosine (ddI), emtricitabine (FTC), entecavir (ETV), 2',3'-dideoxyguanosine (ddG), 2′,3′-dideoxyadenosine (ddA), 2′-fluoro-2′,3′-dideoxyarabinosyladenine (F-ddA), efavirenz (EFV), nevirapine (NVP), or abacavir (ABC), adefovir dipivoxil, telbivudine, censavudine, or islatravir.

[0485] Embodiment 6'. The RTI for use of Embodiment 5', wherein the RTI is lamivudine, stavudine, emtricitabine, abacavir, tenofovir alafenamide, zidovudine, zalcitabine, didanosine, tenofovir disoproxil, adefovir dipivoxil, entecavir, telbivudine, censavudine, or islatravir.

[0486] Embodiment 7'. The RTI for use of Embodiment 5', wherein the RTI is lamivudine.

[0487] Embodiment 8'. The RTI for use of Embodiment 5', wherein the RTI is stavudine.

[0488] Embodiment 9'. The RTI for use of Embodiment 5', wherein the RTI is emtricitabine.

[0489] Embodiment 10'. The RTI for use of Embodiment 5', wherein the RTI is abacavir.

[0490] Embodiment 11'. The RTI for use of Embodiment 5', wherein the RTI is tenofovir alafenamide.

[0491] Embodiment 12'. The RTI for use of Embodiment 5', wherein the RTI is zidovudine.

[0492] Embodiment 13'. The RTI for use of Embodiment 5', wherein the RTI is zalcitabine.

[0493] Embodiment 14'. The RTI for use of Embodiment 5', wherein the RTI is didanosine.

[0494]

[0495] Embodiment 15'. The RTI for use of Embodiment 5', wherein the RTI is tenofovir disoproxil.

[0496] Embodiment 16'. The RTI for use of Embodiment 5', wherein the RTI is adefovir dipivoxil.

[0497] Embodiment 17'. The RTI for use of Embodiment 5', wherein the RTI is entecavir.

[0498] Embodiment 18'. The RTI for use of Embodiment 5', wherein the RTI is telbivudine.

[0499] Embodiment 19'. The RTI for use of Embodiment 5', wherein the RTI is censavudine.

[0500] Embodiment 20'. The RTI for use of Embodiment 5', wherein the RTI is islatravir.

[0501] Embodiment 21'. The RTI for use of Embodiment 1', wherein the RTI is a compound of Formula, *see* above, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein:

[0502] B is selected from the group consisting of B-1 and B-2, *see* above;

[0503] R^1 is selected from the group consisting of hydrogen and -OH;

[0504] R^2 is selected from the group consisting of methyl, ethynyl, and -CN;

[0505] R^3 is selected from the group consisting of hydrogen, fluoro, chloro, bromo, iodo and methyl;

[0506] R^4 is selected from the group consisting of $-NH_2$ and -OH;

[0507] R^5 is selected from the group consisting of -NH_2 and -OH; and

[0508] R^6 is selected from the group consisting of hydrogen, fluoro, chloro, and -NH_2.

[0509] Embodiment 22'. The method of Embodiment 21', wherein the RTI is a compound of Formula II *see* above, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.

[0510] Embodiment 23'. The RTI for use of Embodiment 22', wherein R^3 is hydrogen.

[0511] Embodiment 24'. The RTI for use of f Embodiment 22', wherein R^3 is selected from the group consisting of fluoro and chloro.

[0512] Embodiment 25'. The RTI for use of Embodiment 22', wherein R^3 is methyl.

[0513] Embodiment 26'. The RTI for use of any one of Embodiments 22'-25', wherein R^4 is -NH_2.

[0514] Embodiment 27'. The RTI for use of any one of Embodiments 22'-25', wherein R^4 is -OH.

[0515] Embodiment 28'. The RTI for use of Embodiment 21', wherein the RTI is a compound is a compound of Formula III *see* above, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.

[0516] Embodiment 29'. The RTI for use of Embodiment 28', wherein R^5 is -NH_2.

[0517] Embodiment 30'. The RTI for use of Embodiment 28', wherein R^5 is -OH.

[0518] Embodiment 31'. The RTI for use of any one of Embodiments 28'-30', wherein R^6 is hydrogen.

[0519] Embodiment 32'. The RTI for use of any one of Embodiments 28'-30', wherein R^6 is chloro.

[0520] Embodiment 33'. The RTI for use of any one of Embodiments 28'-30', wherein R^6 is fluoro.

[0521] Embodiment 34'. The RTI for use of any one of Embodiments 28'-30', wherein R^6 is -NH_2.

[0522] Embodiment 35'. The RTI for use of any one of Embodiments 21'-34', wherein R^1 is hydrogen.

[0523] Embodiment 36'. The RTI for use of any one of Embodiments 21'-34', wherein R^1 is -OH.

[0524] Embodiment 37'. The RTI for use of any one of Embodiments 21'-36', wherein R^2 is methyl.

[0525] Embodiment 38'. The RTI for use of any one of Embodiments 21'-36', wherein R^2 is ethynyl.

[0526] Embodiment 39'. The RTI for use of any one of Embodiments 21'-36', wherein R^2 is -CN.

[0527] Embodiment 40'. The RTI for use of Embodiment 1', wherein the RTI is a compound of Table 3, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.

[0528] Embodiment 41'. The RTI for use of Embodiment 1', wherein the RTI is a compound of Table 4, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.

[0529] Embodiment 42. The RTI for use of any one of Embodiments 1'-41', wherein the cancer is breast cancer, colon cancer, lung cancer, pancreatic ductal cancer, prostate cancer, ovarian cancer, or head and neck cancer.

[0530] Embodiment 43'. The RTI for use of Embodiment 42', wherein the cancer is breast cancer.

[0531] Embodiment 44'. The RTI for use of Embodiment 42', wherein the cancer is colon cancer.

[0532] Embodiment 45'. The RTI for use of Embodiment 42', wherein the cancer is lung cancer.

[0533] Embodiment 46'. The RTI for use of Embodiment 42', wherein the cancer is pancreatic ductal cancer.

[0534] Embodiment 47'. The RTI for use of Embodiment 42', wherein the cancer is prostate cancer.

[0535] Embodiment 48'. The RTI for use of Embodiment 47', wherein the prostate cancer is high-risk localized prostate cancer.

[0536] Embodiment 49'. The RTI for use of Embodiment 42', wherein the cancer is ovarian cancer.

[0537] Embodiment 50'. The RTI for use of Embodiment 42', wherein the cancer is head and neck cancer.

[0538] Embodiment 51'. The RTI for use of any one of Embodiments 1'-41', wherein the patient has prostate cancer and the RTI is administered as an adjuvant therapy.

[0539] Embodiment 52'. The RTI for use of any one of Embodiments 1'-41', wherein the patient has prostate cancer and the RTI is administered as a neoadjuvant therapy.

[0540] Embodiment 53'. The RTI for use of any one of Embodiment 1'-52', further comprising administering a therapeutically effective amount of at least one second therapeutic agent useful for treating the cancer.

[0541] Embodiment 54'. The RTI for use of Embodiment 53' for the treatment of breast cancer, wherein the at least one second therapeutic agent is Soltamox® (tamoxifen), Arimidex® (anastrozole), Femara® (letrozole), Aromasin® (exemestane), Herceptin® (trastuzumab), Abraxane® (paclitaxel), Cytoxan® (cyclophosphamide), Taxol® (paclitaxel), Afinitor® (everolimus), Taxotere® (docetaxel), Xeloda® (capecitabine), Trexall® (methotrexate), Faslodex (fulvestrant), Adriamycin® (doxorubicin), Perjeta® (pertuzumab), Gemzar (gemcitabine), Tykerb® (lapatinib), Adrucil® (fluorouracil), Ibrance® (palbociclib), Verzenio® (abemaciclib), Fareston® (toremifene), Halaven® (eribulin), Menest, Kadcyla® (ado-trastuzumab emtransine), Androxy® (fluoxymesterone), Avastin® (bevacizumab), esterified estrogens, Herzuma® (trastuzumab), Ixempra® (ixabepilone), Kanjinti® (trastuzumab), Kisqali® (ribociclib), Ogivri® (trastuzumab), Ontruzant® (trastuzumab), Tepadina® (thiotepa), Trazimera® (trastuzumab), Velban® (vinblastine), Piqray® (alpelisib), Tecentriq® (atezolizumab), Enhertu® (fam-trastuzumab deruxtecan), Herceptin, Hylecta™ (hyaluronidase/trastuzumab), Infugem® (gemcitabine), Kisqali® Femara® Co-Pack (ribociclib and letrozole), Talzenna® (talazoparib), Trodelvy® (sacituzumab) or Tukysa™ (tukatinib).

[0542] Embodiment 55'. The RTI for use of Embodiment 53' for the treatment of colon cancer, wherein the at least one second therapeutic agent is Xeloda® (capecitabine), Eloxatin® (oxaliplatin), fluorouracil, Avastin® (bevacizumab), leucovorin, Camptosar® (irinotecan), Stivarga® (regorafenib), Erbitux® (cetuximab), Vectibix® (panitumumab), Lonsurf® (tipiracil/trifluridine), Zaltrap® (ziv-aflibercept), Betaseron® (interferon beta-1b), Fusilev® (levoleucovorin), Wellcocorin® (methotrexate), Keytruda® (pembrolizumab), Mvasi® (bevacizumab-awwb), Cyramza® (ramucirumab), Yervoy® (ipilmumab), Opdivo® (nivolumab), Braftovi® (encorafenib), Khapzory® (levoleucovorin) or Zirabev® (bevacizumab-bvzr).

[0543] Embodiment 56'. The method of Embodiment 53' for the treatment of lung cancer, wherein the at least one second therapeutic agent is Etopophos® (etoposide), Hycamtin® (topotecan), VePesid® (etoposide), Toposar® (etoposide), Opdivo® (nivolumab), Keytruda® (pembrolizumab), Tecentriq® (atezolizumab), Imfinizi® (durvalumab), methotrexate, cyclophosphamide, Carboplatin, Cisplatin, docetaxel, Gemcitabine, Irinotecan, Paclitaxel, Pemetrexed, Vinblastine, or Vinorelbine.

[0544] Embodiment 57'. The RTI for use of Embodiment 53 for the treatment of pancreatic ductal cancer, wherein the at least one second therapeutic agent is Gemzar® (Gemcitabine), fluorouracil, Afinitor® (everolimus), Tarceva® (erlotinib), Abraxane® (paclitaxel), capecitabine, Sutent® (sunitinib), pancreatin, methotrexate, Zanosar® (streptozocin), Mutamycin® (mitomycin), Onivyde® (irinotecan), bevacizumab, cetuximab, Infugem® (gemcitabine) or Lynparza® (olaparib).

[0545] Embodiment 58'. The method of Embodiment 53' for the treatment of head and neck cancer, wherein the at least one second therapeutic agent is Erbituz® (cetuximab), Taxotere® (docetaxel), Trexall® (methotrexate), Keytruda® (pembrolizumab) or Opdivo® (nivolumab).

[0546] Embodiment 59'. The RTI for use of Embodiment 53' for the treatment of prostate cancer, wherein the at least one second therapeutic agent is Suprefact® (buserelin), Firmagon® (degarelix), Zoladex® (goserelin), Vantas® (histrelin), Eligard® (leuprolide), Orgovyx® (relugolix), Trelstar® (triptorelin), Casodex® (bicalutamide), Eulexin® (flutamide), Nilandron® (nilutamide), Zytiga® (biraterone acetate), Erleada® (apalutamide), or Xtandi® (enzalutamide).

[0547] Embodiment 60'. The RTI for use of Embodiment 53', wherein the at least one second therapeutic agent is a STING agonist.

[0548] Embodiment 61'. The RTI for use of any one of Embodiments 1'-60', wherein the patient is (a) not infected with the HIV virus, (b) not suspected of being infected with the HIV virus, (c) not being treated for the HIV virus, and/or (d) not being treated to prevent the HIV virus.

[0549] Embodiment 62' The RTI for use of any one of Embodiments 1'-61', wherein the RTI is to be administered according to a continuous dosing schedule.

[0550] Embodiment 63' The RTI for use of any one of Embodiments 1'-61', wherein the RTI is to be administered according to an intermittent dosing schedule.

[0551] The disclosure also provides the following particular embodiments with respect to uses of a RTI in the manufacture of a medicament for treating cancer.

[0552] Embodiment 1'. Use of a RTI in the manufacture of a medicament for treating cancer in patient in need thereof, wherein the RTI is to be administered according to a continuous or an intermittent dosing schedule.

[0553] Embodiment 2'. The use of Embodiment 1', wherein the RTI is a nucleoside reverse transcriptase inhibitor (NRTI).

[0554] Embodiment 3'. The use of Embodiment 1', wherein the RTI is a non-nucleoside reverse transcriptase inhibitor (NNRTI).

[0555] Embodiment 4'. The use of Embodiment 1', wherein the RTI is a LINE-1 inhibitor.

[0556] Embodiment 5'. The use of Embodiment 1', wherein the RTI is elvucitabine, lamivudine (3TC), zidovudine (AZT), tenofovir, tenofovir disoproxil, tenofovir alafenamide, stavudine (d4T), zalcitabine (ddC), didanosine (ddI), emtricitabine (FTC), entecavir (ETV), 2',3'-dideoxyguanosine (ddG), 2′,3′-dideoxyadenosine (ddA), 2′-fluoro-2′,3′-dideoxyarabinosyladenine (F-ddA), efavirenz (EFV), nevirapine (NVP), or abacavir (ABC), adefovir dipivoxil, telbivudine, censavudine, or islatravir.

[0557] Embodiment 6'. The use of Embodiment 5', wherein the RTI is lamivudine, stavudine, emtricitabine, abacavir, tenofovir alafenamide, zidovudine, zalcitabine, didanosine, tenofovir disoproxil, adefovir dipivoxil, entecavir, telbivudine, censavudine, or islatravir.

[0558] Embodiment 7'. The use of Embodiment 5', wherein the RTI is lamivudine.

[0559] Embodiment 8'. The use of Embodiment 5', wherein the RTI is stavudine.

[0560] Embodiment 9'. The use of Embodiment 5', wherein the RTI is emtricitabine.

[0561] Embodiment 10'. The use of Embodiment 5', wherein the RTI is abacavir.

[0562] Embodiment 11'. The use of Embodiment 5', wherein the RTI is tenofovir alafenamide.

[0563] Embodiment 12'. The use of Embodiment 5', wherein the RTI is zidovudine.

[0564] Embodiment 13'. The use of Embodiment 5', wherein the RTI is zalcitabine.

[0565] Embodiment 14'. The use of Embodiment 5', wherein the RTI is didanosine.

[0566] Embodiment 15'. The use of Embodiment 5', wherein the RTI is tenofovir disoproxil.

[0567] Embodiment 16'. The use of Embodiment 5', wherein the RTI is adefovir dipivoxil.

[0568] Embodiment 17'. The use of Embodiment 5', wherein the RTI is entecavir.

[0569] Embodiment 18'. The use of Embodiment 5', wherein the RTI is telbivudine.

[0570] Embodiment 19'. The use of Embodiment 5', wherein the RTI is censavudine.

[0571] Embodiment 20'. The use of Embodiment 5', wherein the RTI is islatravir.

[0572] Embodiment 21'. The use of Embodiment 1', wherein the RTI is a compound of Formula I, *see* above, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein:

[0573] B is selected from the group consisting of B-1 and B-2, *see* above;

[0574] R^1 is selected from the group consisting of hydrogen and -OH;

[0575] R^2 is selected from the group consisting of methyl, ethynyl, and -CN;

[0576] R^3 is selected from the group consisting of hydrogen, fluoro, chloro, bromo, iodo and methyl;

[0577] R^4 is selected from the group consisting of $-NH_2$ and -OH;

[0578] R^5 is selected from the group consisting of $-NH_2$ and -OH; and

[0579] R^6 is selected from the group consisting of hydrogen, fluoro, chloro, and $-NH_2$.

[0580] Embodiment 22'. The method of Embodiment 21', wherein the RTI is a compound of Formula II, *see* above, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.

[0581] Embodiment 23'. The use of Embodiment 22', wherein R^3 is hydrogen.

[0582] Embodiment 24'. The use of Embodiment 22', wherein R^3 is selected from the group consisting of fluoro and chloro.

[0583] Embodiment 25'. The use of Embodiment 22', wherein R^3 is methyl.

[0584] Embodiment 26'. The use of any one of Embodiments 22'-25', wherein R^4 is $-NH_2$.

[0585] Embodiment 27'. The use of any one of Embodiments 22'-25', wherein R^4 is -OH.

[0586] Embodiment 28'. The use of Embodiment 21', wherein the RTI is a compound is a compound of Formula III, *see* above, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.

[0587] Embodiment 29'. The use of Embodiment 28', wherein R^5 is $-NH_2$.

[0588] Embodiment 30'. The use of Embodiment 28', wherein R^5 is -OH.

[0589] Embodiment 31'. The use of any one of Embodiments 28'-30', wherein R^6 is hydrogen.

[0590] Embodiment 32'. The use of any one of Embodiments 28'-30', wherein R^6 is chloro.

[0591] Embodiment 33'. The use of any one of Embodiments 28'-30', wherein R^6 is fluoro.

[0592] Embodiment 34'. The use of any one of Embodiments 28'-30', wherein R^6 is -NH_2.

[0593] Embodiment 35'. The use of any one of Embodiments 21'-34', wherein R^1 is hydrogen.

[0594] Embodiment 36'. The use of any one of Embodiments 21'-34', wherein R^1 is -OH.

[0595] Embodiment 37'. The use of any one of Embodiments 21'-36', wherein R^2 is methyl.

[0596] Embodiment 38'. The use of any one of Embodiments 21'-36', wherein R^2 is ethynyl.

[0597] Embodiment 39'. The use of any one of Embodiments 21'-36', wherein R^2 is -CN.

[0598] Embodiment 40'. The use of Embodiment 1', wherein the RTI is a compound of Table 3, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.

[0599] Embodiment 41'. The use of Embodiment 1', wherein the RTI is a compound of Table 4, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.

[0600] Embodiment 42'. The use of any one of Embodiments 1'-41', wherein the cancer is breast cancer, colon cancer, lung cancer, pancreatic ductal cancer, prostate cancer, ovarian cancer, or head and neck cancer.

[0601] Embodiment 43'. The use of Embodiment 42', wherein the cancer is breast cancer.

[0602] Embodiment 44'. The use of Embodiment 42', wherein the cancer is colon cancer.

[0603] Embodiment 45'. The use of Embodiment 42', wherein the cancer is lung cancer.

[0604] Embodiment 46'. The use of Embodiment 42', wherein the cancer is pancreatic ductal cancer.

[0605] Embodiment 47'. The use of Embodiment 42', wherein the cancer is prostate cancer.

[0606] Embodiment 48'. The use of Embodiment 47', wherein the prostate cancer is high-risk localized prostate cancer.

[0607] Embodiment 49'. The use of Embodiment 42', wherein the cancer is ovarian cancer.

[0608] Embodiment 50'. The use of Embodiment 42', wherein the cancer is head and neck cancer.

[0609] Embodiment 51'. The use of any one of Embodiments 1'-41', wherein the patient has prostate cancer and the RTI is administered as an adjuvant therapy.

[0610] Embodiment 52'. The use of any one of Embodiments 1'-41', wherein the patient has prostate cancer and the RTI is administered as a neoadjuvant therapy.

[0611] Embodiment 53'. The use of any one of Embodiment 1'-52', further comprising administering a therapeutically effective amount of at least one second therapeutic agent useful for treating the cancer.

[0612] Embodiment 54'. The use of Embodiment 53' for the treatment of breast cancer, wherein the at least one second therapeutic agent is Soltamox® (tamoxifen), Arimidex® (anastrozole), Femara® (letrozole), Aromasin® (exemestane), Herceptin® (trastuzumab), Abraxane® (paclitaxel), Cytoxan® (cyclophosphamide), Taxol® (paclitaxel), Afinitor® (everolimus), Taxotere® (docetaxel), Xeloda® (capecitabine), Trexall® (methotrexate), Faslodex (fulvestrant), Adriamycin® (doxorubicin), Perjeta® (pertuzumab), Gemzar (gemcitabine), Tykerb® (lapatinib), Adrucil® (fluorouracil), Ibrance® (palbociclib), Verzenio® (abemaciclib), Fareston® (toremifene), Halaven® (eribulin), Menest, Kadcyla® (ado-trastuzumab emtransine), Androxy® (fluoxymesterone), Avastin® (bevacizumab), esterified estrogens, Herzuma® (trastuzumab), Ixempra® (ixabepilone), Kanjinti® (trastuzumab), Kisqali® (ribociclib), Ogivri® (trastuzumab), Ontruzant® (trastuzumab), Tepadina® (thiotepa), Trazimera® (trastuzumab), Velban® (vinblastine), Piqray® (alpelisib), Tecentriq® (atezolizumab), Enhertu® (fam-trastuzumab deruxtecan), Herceptin, Hylecta™ (hyaluronidase/trastuzumab), Infugem® (gemcitabine), Kisqali® Femara® Co-Pack

(ribociclib and letrozole), Talzenna® (talazoparib), Trodelvy® (sacituzumab) or Tukysa™ (tukatinib).

[0613] Embodiment 55'. The use of Embodiment 53' for the treatment of colon cancer, wherein the at least one second therapeutic agent is Xeloda® (capecitabine), Eloxatin® (oxaliplatin), fluorouracil, Avastin® (bevacizumab), leucovorin, Camptosar® (irinotecan), Stivarga® (regorafenib), Erbitux® (cetuximab), Vectibix® (panitumumab), Lonsurf® (tipiracil/trifluridine), Zaltrap® (ziv-aflibercept), Betaseron® (interferon beta-1b), Fusilev® (levoleucovorin), Wellcocorin® (methotrexate), Keytruda® (pembrolizumab), Mvasi® (bevacizumab-awwb), Cyramza® (ramucirumab), Yervoy® (ipilmumab), Opdivo® (nivolumab), Braftovi® (encorafenib), Khapzory® (levoleucovorin) or Zirabev® (bevacizumab-bvzr).

[0614] Embodiment 56'. The method of Embodiment 53' for the treatment of lung cancer, wherein the at least one second therapeutic agent is Etopophos® (etoposide), Hycamtin® (topotecan), VePesid® (etoposide), Toposar® (etoposide), Opdivo® (nivolumab), Keytruda® (pembrolizumab), Tecentriq® (atezolizumab), Imfinizi® (durvalumab), methotrexate, cyclophosphamide, Carboplatin, Cisplatin, docetaxel, Gemcitabine, Irinotecan, Paclitaxel, Pemetrexed, Vinblastine, or Vinorelbine.

[0615] Embodiment 57'. The use of Embodiment 53 for the treatment of pancreatic ductal cancer, wherein the at least one second therapeutic agent is Gemzar® (Gemcitabine), fluorouracil, Afinitor® (everolimus), Tarceva® (erlotinib), Abraxane® (paclitaxel), capecitabine, Sutent® (sunitinib), pancreatin, methotrexate, Zanosar® (streptozocin), Mutamycin® (mitomycin), Onivyde® (irinotecan), bevacizumab, cetuximab, Infugem® (gemcitabine) or Lynparza® (olaparib).

[0616] Embodiment 58'. The method of Embodiment 53' for the treatment of head and neck cancer, wherein the at least one second therapeutic agent is Erbituz® (cetuximab), Taxotere® (docetaxel), Trexall® (methotrexate), Keytruda® (pembrolizumab) or Opdivo® (nivolumab).

[0617] Embodiment 59'. The use of Embodiment 53' for the treatment of prostate cancer, wherein the at least one second therapeutic agent is Suprefact® (buserelin), Firmagon® (degarelix), Zoladex® (goserelin), Vantas® (histrelin), Eligard® (leuprolide), Orgovyx® (relugolix), Trelstar® (triptorelin), Casodex® (bicalutamide), Eulexin®

(flutamide), Nilandron® (nilutamide), Zytiga® (biraterone acetate), Erleada® (apalutamide), or Xtandi® (enzalutamide).

[0618] Embodiment 60'. The use of Embodiment 53', wherein the at least one second therapeutic agent is a STING agonist.

[0619] Embodiment 61'. The use of any one of Embodiments 1'-60', wherein the patient is (a) not infected with the HIV virus, (b) not suspected of being infected with the HIV virus, (c) not being treated for the HIV virus, and/or (d) not being treated to prevent the HIV virus.

[0620] Embodiment 62' The use of any one of Embodiments 1'-61', wherein the RTI is to be administered according to a continuous dosing schedule.

[0621] Embodiment 63' The use of any one of Embodiments 1'-61', wherein the RTI is to be administered according to an intermittent dosing schedule.

EXAMPLE 1

[0622] Representative compounds were tested for inhibition of retrotransposition activity of human LINE-1 (L1) retrotransposition reporter assay in HeLa cells according to the following procedure.

[0623] Human Cervical Adenocarcinoma Cells (HeLa) were cultured in Dulbecco's Modified Eagle's Medium (DMEM) containing 4500 mg/L glucose, L-glutamine, sodium pyruvate and sodium bicarbonate, supplemented with 10 % of heat inactivated fetal bovine serum (FBS). Cells were grown at 37°C in an atmosphere of 5% $C0_2$. The dual luciferase-encoding plasmid pYX017 was provided by Prof. Wenfeng An (Xie, et al., 2011, Nucleic Acids Res).

[0624] The reporter assay was performed in 96-well white, optical bottom plates (Thermo Fisher, 165306). 24 hours prior to transfection, HeLa cells were seeded in a density of 2,500 cells per well, in 50 µL of DMEM, 10% FBS media volume. Cells were incubated at 37°C in an atmosphere of 5% C02. Seeding was optimized to achieve approximately 30% cell confluency on the day of transfection. A transfection mix was prepared by combining transfection reagent FuGENE® HD (Promega, E2311) and plasmid DNA (100 ng per well) in a 3:1 ratio, in OpiMEM media (Thermo Fisher, 31985062). Next, 5 µL of the transfection mix was combined with 20 µL of DMEM, 10% FBS media, and 25 µL of this mix was added into each well of an assay plate. In each assay plate one column remained untransfected to serve as a blank luminescence signal.

[0625] Serial dilution of test compounds was performed in DMSO and transferred to medium. Next, 25 µL of media-diluted compounds series were transferred to an assay plate containing cells and transfection media. The final concentration of DMSO in treated wells was 0.2 %. Serial dilutions of compounds were added to an assay plate immediately after transfection. Compounds were tested in triplicates. The assay plate was then incubated with transfection reagent and compounds at 37°C in an atmosphere of 5% $C0_2$ for 72 hours.

[0626] Luciferase reporter activity was quantified with the Dual-Luciferase® Reporter Assay System (Promega) following the manufacturer's manual, with a passive lysis buffer volume increased to 30 µL and lysis incubation time increased to 20 min at room temperature with gentle shaking, to ensure complete cell lysis. Luminescence was measured using a SpectraMax i3x Multi-Mode Microplate Reader, with integration times of 100 ms and 10 ms applied to measure FLuc and RLuc signals, respectively. Relative LNE-1 activity was calculated as Firefly signal/Renilla signal *10,000. In order to determine IC_{50} values for each compound, dose response data were fit to a logistic using non-linear regression.

[0627] The results for representative compounds of the disclosure are provided in Table 5.

Table 5: Human L1 activity inhibition

Cpd.	Human LINE-1 IC_{50} (µM)	Name	Human LINE-1 IC_{50} (µM)
2	0.39	Islatravir (EFdA)	0.0011
4	0.49	Zalcitabine	0.066
6	18.56	Censavudine	0.070
7	0.0097	Elvucitabine	0.092
9	0.021	Emtricitabine (FTC)	0.48
12	0.0062	Tenofovir Disoproxil	0.19
13	0.00051	Didanosine	0.53
15	0.8333	AZT	0.63
16	>25	Lamivudine	0.66
17	0.91	Stavudine	0.75
18	12.5	Entecavir	1.45
19	>12.5	Tenofovir	2.7
20	0.011	Adefovir	>6.25
21	0.043	Apricitabine	6.34
22	23.4	Abacavir sulfate	17.1
23	>50	Efavirenz	>50
24	0.010	Nevirapine	>50
25	0.0036	Tenofovir Alafenamide (TAF)	0.01

26	2.05		
27	0.0026		

EXAMPLE 2

Cancer Cell Proliferation Activity of Compound 13

[0628] A dose response relationship on cell proliferation was assessed for Compound 13 on 140 tumor cell lines. Briefly, compound treatment of cells started one day after seeding with a final DMSO concentration of 0.1%, and was performed by nanodrop-dispensing using a Tecan Dispenser. 0.1% DMSO (solvent) and Staurosporine (10 μM) served as high control (100% viability) and low control (0% viability), respectively. Compound 13 was tested at 10, 3, 1, 0.3, 0.1, 0.03, 0.01, and 0.003 μM.

[0629] Cells were cultured in the appropriate media. For the assays, cells were seeded in white cell culture-treated flat and clear bottom multiwell plates and incubated at 37 °C overnight before compound was added. After incubation for 72 h at 37°C at 5% or 10% CO_2 dependent on the medium, cell plates were equilibrated to room temperature for one hour, CellTiterGlo reagent (Promega) was added and luminescence was measured approximately an hour later using a luminometer.

[0630] Raw data were converted into percent cell viability relative to the high and low control, which were set to 100% and 0%, respectively. IC_{50} calculation was performed using GraphPad Prism software with a variable slope sigmoidal response fitting model using 0% viability as bottom constraint and 100% viability as top constraint.

[0631] The IC_{50} values are summarized in Table 6. A representative dose response curve in MV4-11 cells is provided in Fig. 1.

Table 6

No.	Entity	Cancer Cell Line	IC_{50} (μM)	No.	Entity	Cancer Cell Line	IC_{50} (μM)
1	Kidney	786-O	5.81	**71**	Pancreas	Mia PaCA 2	>10
2	Brain	A172	>10	**72**	Stomach	MKN-1	8.76
3	Skin	A2058	>10	**73**	Stomach	MKN-45	>10
4	Ovary	A2780	4.58	**74**	Blood	MOLM-13	0.46
5	Skin	A375	2.37	**75**	Blood	MOLT-4	0.51
6	Lung	A427	0.55	**76**	Blood	MV4-11	0.21
7	Skin	A431	5.06	**77**	Blood	NALM-6	0.25
8	Kidney	A498	>10	**78**	Lung	NCI-H1048	2.49
9	Lung	A549	>10	**79**	Lung	NCI-H1437	>10
10	Pancreas	AsPC-1	>10	**80**	Lung	NCI-H1563	>10
11	Lung	BEN	>10	**81**	Lung	NCI-H1573	8.59
12	Breast	BT-20	>10	**82**	Lung	NCI-H1581	2.97

13	Pancreas	BxPC-3	5.43	**83**	Lung	NCI-H1703	9.16
14	Kidney	Caki-1	9.76	**84**	Lung	NCI-H1838	7.53
15	Kidney	Caki-2	>10	**85**	Lung	NCI-H2009	1.23
16	Lung	Calu-6	>10	**86**	Lung	NCI-H2110	3.41
17	Colon	Colo 205	1.50	**87**	Lung	NCI-H2286	5.69
18	Lung	COR-L279	>10	**88**	Lung	NCI-H292	8.56
19	Ovary	COV434	4.41	**89**	Lung	NCI-H441	3.64
20	Head/Neck	Detroit562	4.79	**90**	Lung	NCI-H82	6.46
21	Colon	DLD-1	>10	**91**	Lung	NCI-H838	>10
22	Prostate	DU-145	5.73	**92**	Stomach	NCI-N87	3.60
23	Lung	DV90	1.59	**93**	Blood	OCI-AML3	7.15
24	Breast	EFM-19	2.65	**94**	Blood	OCI-AML5	1.37
25	Breast	EFM-192A	>10	**95**	Blood	OCI-LY19	0.56
26	Ovary	EFO-27	9.90	**96**	Blood	OPM-2	>10
27	Lung	EPLC-272H	6.63	**97**	Ovary	OV56	1.99
28	Lung	H1299	7.68	**98**	Ovary	OVCAR-3	1.16
29	Lung	H2228	>10	**99**	Ovary	OVK18	2.21
30	Brain	H4	>10	**100**	Blood	P31/FUJ	0.40
31	Lung	H460	5.68	**101**	Pancreas	PANC-1	>10
32	Breast	HCC 1569	>10	**102**	Prostate	PC3	4.01
33	Breast	HCC202	>10	**103**	Lung	PC-9	>10
34	Breast	HCC38	6.37	**104**	Lung	RERF-LC-Ad2	2.58
35	Lung	HCC827	4.47	**105**	Lung	RERF-LC-MS	>10
36	Colon	HCT116	5.84	**106**	Colon	RKO	4.51
37	Colon	HCT-15	>10	**107**	Endometrium	RL95-2	5.38
38	Endometrium	HEC-1-A	>10	**108**	Blood	RPMI 8226	>10
39	Endometrium	HEC-1-B	>10	**109**	Bone	Saos-2 EC	3.99
40	Ovary	HeLa	1.30	**110**	Stomach	SCH	0.29
41	Liver	Hep3B2.1-7	0.82	**111**	Lung	SCLC-21H	6.78
42	Blood	HL-60	1.13	**112**	Ovary	SiHa	2.45
43	Stomach	Hs 746T	5.39	**113**	Bone	SJSA-1	6.44
44	Fibrosarcoma	HT-1080	7.16	**114**	Breast	SK-BR-3	>10
45	Colon	HT-29	>10	**115**	Bone	SK-ES-1	4.99
46	Liver	HuH7	1.24	**116**	Lung	SK-LU-1	>10
47	Duodenum	Hutu 80	1.44	**117**	Skin	SK-MEL-3	>10
48	Endometrium	Ishikawa	6.07	**118**	Brain	SK-N-FI	>10
49	Bladder	J82	5.73	**119**	Brain	SK-N-MC	3.19
50	Breast	JIMT-1	7.00	**120**	Brain	SK-N-SH	6.47
51	Blood	Jurkat	1.17	**121**	Ovary	SK-OV3	4.00
52	Blood	JVM-3	2.45	**122**	Stomach	SNU-1	2.89
53	Blood	K562	>10	**123**	Stomach	SNU-16	1.95
54	Blood	KARPAS 299	4.07	**124**	Stomach	SNU-216	1.74
55	Stomach	Kato III	4.86	**125**	Ovary	SNU840	4.23
56	Blood	KG-1	>10	**126**	Blood	SU-DHL-5	3.74
57	Blood	KG-1 a	5.86	**127**	Brain	SW-1783	2.25
58	Blood	KMS-12-BM	0.96	**128**	Colon	SW480	>10
59	Brain	LN229	2.23	**129**	Colon	SW620	7.21
60	Prostate	LnCap	>10	**130**	Colon	SW948	5.02

61	Lung	LOU-NH91	>10	**131**	Breast	T-47D	>10
62	Colon	LOVO	8.21	**132**	Colon	T84	>10
63	Blood	LP-1	3.15	**133**	Brain	T98G	>10
64	Blood	M07e	4.07	**134**	Brain	U118MG	5.74
65	Ovary	MCAS	>10	**135**	Brain	U251MG	>10
66	Breast	MCF-7	>10	**136**	Blood	U-266	>10
67	Breast	MDA MB 231	3.85	**137**	Bone	U2OS	2.18
68	Skin	MDA MB 435	>10	**138**	Brain	U87MG	6.39
69	Breast	MDA-MB-468	>10	**139**	Blood	U-937	1.12
70	Blood	MEC-1	9.85	**140**	Breast	ZR-75-1	>10

EXAMPLE 3

Cancer Cell Proliferation Activity of Compounds

[0632] A dose response relationship on cell proliferation is assessed for Compounds 2, 6, 7, 9, 12, 15, 20, 21, 24, 28-30, zalcitabine, tenofovir alafenamide, and islatravir on 95 tumor cell lines after incubation for 168 h using the same basic protocol as described in EXAMPLE 2. The IC_{50} values for Compound 9 are summarized in Table 7. Representative dose response curves in MINO cells at 72 h, 120 h, and 168 h for Compound 9 are provided in Figs. 2-4.

Table 7

Number	**Cancer Cell Line**	**IC_{50} (μM)**		
		72 h	**120 h**	**168 h**
1	22RV1	3.80	3.28	3.69
2	5637	>10	>10	>10
3	786O	>10	>10	>10
4	A204	>10	>10	>10
5	A2780	>10	>10	>10
6	A375	>10	>10	>10
7	A431	>10	3.18	1.42
8	A549	>10	>10	>10
9	A673	>10	>10	>10
10	ACHN	>10	0.91	0.94
11	ASPC1	>10	0.72	0.49
12	BT20	>10	>10	>10
13	BXPC3	>10	1.29	0.59
14	C33A	>10	2.93	3.07
15	CACO2	>10	>10	>10
16	CAKI1	>10	>10	>10
17	CALU6	>10	>10	>10
18	CASKI	>10	>10	>10

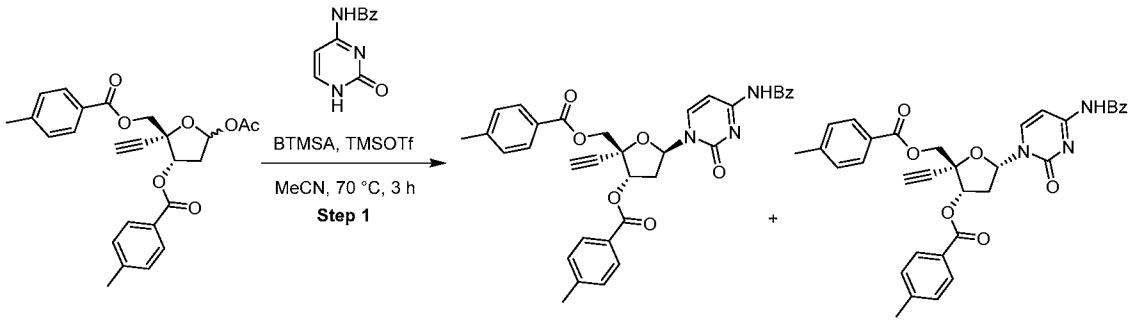
19	CLS439	>10	>10	>10
20	COLO205	>10	1.15	0.87
21	COLO678	>10	>10	>10
22	DLD1	>10	>10	>10
23	DU145	>10	>10	>10
24	EFO21	>10	>10	>10
25	EJ28	>10	>10	>10
26	GRANTA-519	4.98	0.24	0.35
27	HCT116	>10	>10	>10
28	HCT15	>10	>10	>10
29	HEK293	>10	>10	>10
30	HELA	>10	>10	>10
31	HEPG2	>10	>10	>10
32	HL-60	>10	>10	>10
33	HS578T	>10	>10	>10
34	HS729	>10	>10	>10
35	HT1080	>10	>10	>10
36	HT29	>10	>10	>10
37	IGROV1	>10	>10	>10
38	IMR90	>10	>10	>10
39	J82	>10	>10	>10
40	JAR	>10	>10	>10
41	JEG3	>10	>10	>10
42	JIMT1	>10	>10	>10
43	K-562	>10	>10	>10
44	KASUMI	>10	>10	>10
45	L363	>10	>10	>10
46	LOVO	>10	3.28	2.06
47	MCF7	>10	>10	>10
48	MDAMB231	>10	>10	>10
49	MDAMB435	>10	>10	>10
50	MDAMB436	>10	>10	>10
51	MDAMB468	>10	>10	>10
52	MG63	>10	>10	>10
53	MHHES1	>10	>10	>10
54	MIAPACA2	>10	>10	>10
55	MINO	0.34	0.049	0.065
56	MT3	>10	3.04	>10
57	MV4-11	2.48	0.251	1.72
58	NCI-H23	>10	>10	>10
59	NCI-H292	>10	>10	>10
60	NCIH358M	>10	>10	0.67
61	NCIH460	>10	>10	>10
62	NCIH82	>10	9.1	>10
63	OVCAR3	>10	>10	>10
64	OVCAR4	>10	>10	>10
65	PANC1	>10	>10	>10

66	PANC1005	>10	>10	>10
67	PBMC	>10	>10	>10
68	PC3	>10	>10	>10
69	PLCPRF5	>10	>10	>10
70	RAMOS	4.04	0.004	1.18
71	RD	>10	>10	>10
72	RDES	>10	>10	>10
73	SAOS2	>10	>10	>10
74	SF268	>10	>10	>10
75	SF295	>10	>10	>10
76	SKBR3	1.45	0.96	0.37
77	SKHEP1	>10	>10	>10
78	SKLMS1	>10	>10	>10
79	SKMEL28	>10	>10	>10
80	SKMEL5	>10	>10	>10
81	SKNAS	>10	>10	>10
82	SKNSH	>10	>10	>10
83	SKOV3	>10	>10	>10
84	SNB75	>10	>10	>10
85	SU-DHL-10	0.14	61.5	3.86
86	SU-DHL-6	>10	4.99	1.3
87	SW620	>10	>10	>10
88	T24	>10	>10	>10
89	TE671	>10	>10	>10
90	THP-1	>10	>10	>10
91	U2OS	>10	>10	>10
92	U87MG	>10	>10	>10
93	UMUC3	>10	>10	>10
94	UO31	>10	>10	>10
95	WSU-NHL	3.01	0.42	0.87

EXAMPLE 4

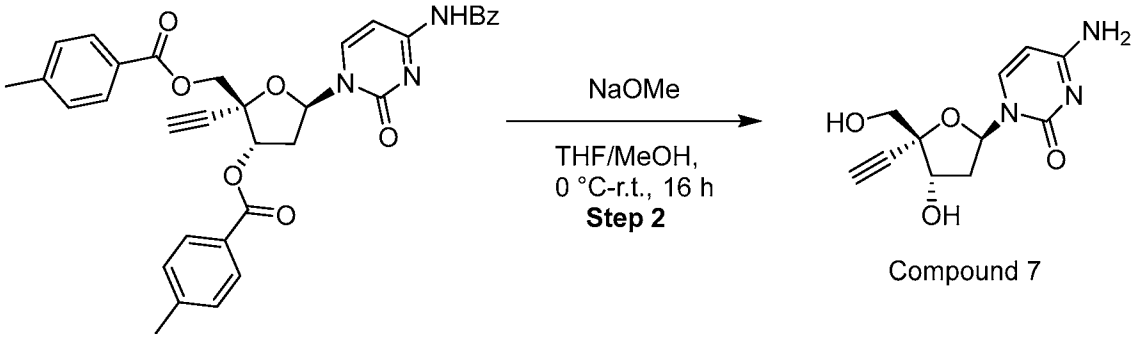
Synthesis of 4-amino-1-((2*R*,4*S*,5*R*)-5-ethynyl-4-hydroxy-5 (hydroxymethyl)tetrahydrofuran-2-yl)pyrimidin-2(1*H*)-one (Compound 7)

[0633] Step 1: Synthesis of (2*R*,3*S*,5*R*)-5-(4-benzamido-2-oxopyrimidin-1(2*H*)-yl)-2-ethynyl-2-(((4-methylbenzoyl)oxy)methyl)tetrahydrofuran-3-yl 4-methylbenzoate and (2*R*,3*S*,5*S*)-5-(4-benzamido-2-oxopyrimidin-1(2*H*)-yl)-2-ethynyl-2-(((4-methylbenzoyl) oxy)methyl)tetrahydrofuran-3-yl 4-methylbenzoate



[0634] To a solution of *N*-(2-oxo-1*H*-pyrimidin-4-yl)benzamide (118 mg, 0.55 mmol) in MeCN (20 mL) was added BTMSA (234 mg, 1.37 mmol) at room temperature. The resulting mixture was heated at 70 °C for 1 h. After cooling to room temperature, TMSOTf (122 mg, 0.55 mmol) was added and the mixture was reheated to 70 °C, then a solution of [(2*R*,3*S*)-5-acetoxy-2-ethynyl-3-(4-methylbenzoyl)oxy-tetrahydrofuran-2-yl]methyl4-methylbenzoate (200 mg, 0.46 mmol) in MeCN (5 mL) was added dropwise. After stirring at 70 °C for 2 h, the reaction mixture was poured into water (50 mL) and extracted with EtOAc (50 mL x 2). The layers were separated, and the organic layer was concentrated. The residue was purified by prep-TLC eluting with 50 % EtOAc in petroleum ether to give [(2*R*,3*S*,5*R*)-5-(4-benzamido-2-oxo-pyrimidin-1-yl)-2-ethynyl-3-(4-methylbenzoyl)oxy-tetrahydrofuran-2-yl]methyl 4-methylbenzoate (R_f = 0.5) (60 mg, 22% yield) as a white solid and [(2*R*,3*S*,5*S*)-5-(4-benzamido-2-oxo-pyrimidin-1-yl)-2-ethynyl-3-(4-methyl benzoyl)oxy-tetrahydrofuran-2-yl]methyl 4-methylbenzoate (R_f = 0.4) (60 mg, 22% yield) as a white solid.

[0635] Step 2: Synthesis of 4-amino-1-((2*R*,4*S*,5*R*)-5-ethynyl-4-hydroxy-5 (hydroxymethyl)tetrahydrofuran-2-yl)pyrimidin-2(1*H*)-one



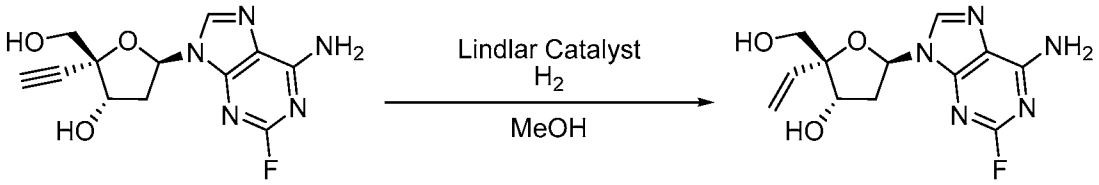
Compound 7

[0636] To a mixture of [(2*R*,3*S*,5*R*)-5-(4-benzamido-2-oxo-pyrimidin-1-yl)-2-ethynyl-3-(4-methylbenzoyl)oxy-tetrahydrofuran-2-yl]methyl4-methylbenzoate (60 mg, 0.1 mmol) in THF (5 mL) was added dropwise a solution of NaOMe (7 mg, 0.13 mmol) in MeOH (2 mL) at 0 °C, then the resulting mixture was stirred at room temperature for 16 h. After

that, the reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC to afford Compound 7 (8.8 mg, 34% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.77 (d, J = 7.2 Hz, 1H), 7.17 - 7.11 (m, 2H), 6.15 - 6.12 (m, 1H), 5.71 (d, J = 7.2 Hz, 1H), 5.46 (s, 1H), 5.39 (s, 1H), 4.30 - 4.29 (m, 1H), 3.60 - 3.50 (m, 2H), 3.48 (s, 1H), 2.26 - 2.20 (m, 1H), 2.10 - 2.01 (m, 1H). LCMS (ESI): m/z 252.2 $(M+H)^+$.

EXAMPLE 5

Synthesis of (2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-(hydroxymethyl)-2-vinyltetrahydrofuran-3-ol (Compound 20)

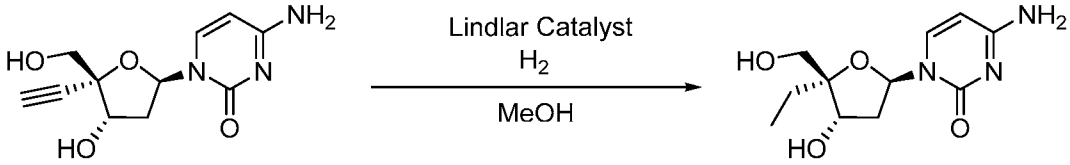


Compound 20

[0637] (2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-ethynyl-2-(hydroxymethyl)tetrahydrofuran-3-ol (79.3 mg, 270 μmol) and Lindlar Catalyst (10.0 mg, 270 μmol) were solubilized in MeOH (5.00 mL) at room temperature. Nitrogen atmosphere was bubbled through the solution for 10 min and then hydrogen was bubbled through the solution for 1 h using a balloon. The reaction was sealed and stirred for 18 h at room temperature. Then, nitrogen atmosphere was bubbled through the solution for 5 min, then the resulting mixture was filtered over a Celite® pad and it was rinsed with MeOH (15 mL). The filtrate was concentrated. The desired product was purified by prep-HPLC using a XBridge Prep C18, 5μm 19 x 10 mm pre-column, CSH Prep C18 OBD, 5 μm, 30 x 75 mm column with MeOH (Eluent B) and AmF pH 3.8 (Eluent A) using an isocratic at 5% B for 1min pre-run and a gradient of 5% B isocratic for 1min, 5% B to 25% B for 11 minutes, 25% B to 100% B for 0.1 minute, hold 100% B for 2.9 minutes with a 45 mL/min flowrate and a 15 min runtime, affording (2R,3S,5R)-5-(6-amino-2-fluoro-9H-purin-9-yl)-2-(hydroxymethyl)-2-vinyltetrahydrofuran-3-ol (42.4 mg, 59%). LC-MS (ESI) m/z calcd for $C_{12}H_{14}FN_5O_3$: 295.1. Found 296.2 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.36 (s, 1H), 7.82 (br s, 1H), 6.24 - 6.22 (m, 1H), 5.99 - 5.92 (m, 1H), 5.41 - 5.36 (m, 1H), 5.31 - 5.30 (m, 1H), 5.23 - 5.20 (m, 1H), 5.11 (m, 1H), 4.64 (q, J = 6.0 Hz, 1H), 3.52 - 3.48 (m, 2H), 2.60 - 2.57 (m, 1H), 2.29 - 2.22 (m, 1H).

EXAMPLE 6

Synthesis of 4-amino-1-((2R,4S,5R)-5-ethyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)pyrimidin-2(1H)-one (Compound 21)



Compound 21

[0638] 4-amino-1-((2R,4S,5R)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)pyrimidin-2(1H)-one (7.20 mg, 28.7 μmol) was dissolved in MeOH in a 5-mL vial with a rubber septum. Then solid Lindlar Catalyst (7.20 mg, 28.7 μmol) was added and the reaction mixture was flushed with H_2 balloon for 30 min. This reaction was stirred till full conversion to the title compound was observed by LC-MS. Then the reaction mixture was filtered through Celite® and washed with MeOH and the solvent was removed under reduced pressure, affording 4-amino-1-((2R,4S,5R)-5-ethyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)pyrimidin-2(1H)-one (2.85 mg, 39 %) as an off-white powder. LC-MS (ESI) m/z calcd for $C_{11}H_{16}N_3O_4$: 254.12. Found 254.4 [M-H]-. 1H-NMR (400 MHz, CD3OD) δ 8.05 (d, J = 7.6 Hz, 1H), 6.21 – 6.06 (m, 1H), 5.95 – 5.77 (d, J=5.8 Hz, 1H), 4.41 – 4.33 (m, 1H), 3.73 – 3.60 (m, 1H), 3.60 – 3.47 (m, 1H), 2.52 – 2.11 (m, 1H), 1.85 – 1.47 (m, 1H), 1.04 – 0.84 (m, 5H).

[0639] The breadth and scope of the present disclosure should not be limited by any of the above-described exemplary embodiments, but should be defined only in accordance with the following claims and their equivalents.

WHAT IS CLAIMED IS:

1. A method for treating cancer in patient in need thereof, the method comprising administering a therapeutically effective amount of a reverse transcriptase inhibitor (RTI) to the patient, wherein the RTI is administered according to an intermittent dosing schedule.

2. The method of claim 1, wherein the RTI is a nucleoside reverse transcriptase inhibitor (NRTI).

3. The method of claim 1, wherein the RTI is a non-nucleoside reverse transcriptase inhibitor (NNRTI).

4. The method of claim 1, wherein the RTI is a LINE-1 inhibitor.

5. The method of claim 1, wherein the RTI is censavudine, islatravir, elvucitabine, lamivudine (3TC), zidovudine (AZT), tenofovir, tenofovir disoproxil, tenofovir alafenamide, stavudine (d4T), zalcitabine (ddC), didanosine (ddI), emtricitabine (FTC), entecavir (ETV), 2',3'-dideoxyguanosine (ddG), 2′,3′-dideoxyadenosine (ddA), 2′-fluoro-2′,3′-dideoxyarabinosyladenine (F-ddA), efavirenz (EFV), nevirapine (NVP), abacavir (ABC), adefovir dipivoxil, or telbivudine.

6. The method of claim 5, wherein the RTI is censavudine, islatravir, lamivudine, stavudine, emtricitabine, abacavir, tenofovir alafenamide, zidovudine, zalcitabine, didanosine, tenofovir disoproxil, adefovir dipivoxil, entecavir, or telbivudine.

7. The method of claim 5, wherein the RTI is lamivudine.

8. The method of claim 5, wherein the RTI is stavudine.

9. The method of claim 5, wherein the RTI is emtricitabine.

10. The method of claim 5, wherein the RTI is abacavir.

11. The method of claim 5, wherein the RTI is tenofovir alafenamide.

12. The method of claim 5, wherein the RTI is zidovudine.

13. The method of claim 5, wherein the RTI is zalcitabine.

14. The method of claim 5, wherein the RTI is didanosine.

15. The method of claim 5, wherein the RTI is tenofovir disoproxil.

16. The method of claim 5, wherein the RTI is adefovir dipivoxil.

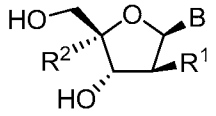
17. The method of claim 5, wherein the RTI is entecavir.

18. The method of claim 5, wherein the RTI is telbivudine.

19. The method of claim 5, wherein the RTI is censavudine.

20. The method of claim 5, wherein the RTI is islatravir.

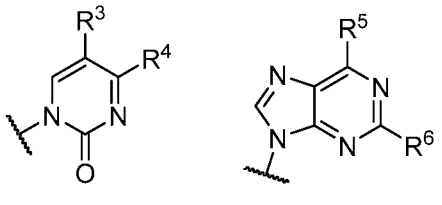
21. The method of claim 1, wherein the RTI is a compound of Formula **I**:



I,

or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof, wherein:

B is selected from the group consisting of:



B-1 and B-2 ;

R^1 is selected from the group consisting of hydrogen and -OH;

R^2 is selected from the group consisting of methyl, ethynyl, and -CN;

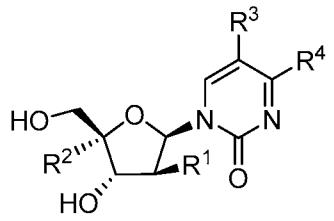
R^3 is selected from the group consisting of hydrogen, fluoro, chloro, bromo, iodo and methyl;

R^4 is selected from the group consisting of $-NH_2$ and -OH;

R^5 is selected from the group consisting of $-NH_2$ and -OH; and

R^6 is selected from the group consisting of hydrogen, fluoro, chloro, and $-NH_2$.

22. The method of claim 21, wherein the RTI is a compound of Formula **II**:



II,

or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.

23. The method of claim 22, wherein R^3 is hydrogen.

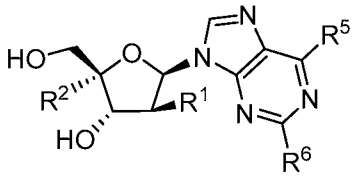
24. The method of claim 22, wherein R^3 is selected from the group consisting of fluoro and chloro.

25. The method of claim 22, wherein R^3 is methyl.

26. The method of any one of claims 2-5, wherein R^4 is $-NH_2$.

27. The method of any one of claims 22-25, wherein R^4 is -OH.

28. The method of claim 21, wherein the RTI is a compound is a compound of Formula **III**:



III,

or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.

29. The method of claim 28, wherein R^5 is $-NH_2$.

30. The method of claim 28, wherein R^5 is -OH.

31. The method of any one of claims 28-30, wherein R^6 is hydrogen.

32. The method of any one of claims 28-30, wherein R^6 is chloro.

33. The method of any one of claims 28-30, wherein R^6 is fluoro.

34. The method of any one of claims 28-30, wherein R^6 is $-NH_2$.

35. The method of any one of claims 21-34, wherein R^1 is hydrogen.

36. The method of any one of claims 21-34, wherein R^1 is -OH.

37. The method of any one of claims 21-36, wherein R^2 is methyl.

38. The method of any one of claims 21-36, wherein R^2 is ethynyl.

39. The method of any one of claims 21-36, wherein R^2 is -CN.

40. The method of claim 1, wherein the RTI is a compound of Table 3, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.

41. The method of claim 1, wherein the RTI is a compound of Table 4, or a pharmaceutically acceptable salt or solvate thereof, or a tautomer thereof.

42. The method of any one of claims 1-41, wherein the cancer is breast cancer, colon cancer, lung cancer, pancreatic ductal cancer, prostate cancer, ovarian cancer, or head and neck cancer.

43. The method of claim 42, wherein the cancer is breast cancer.

44. The method of claim 42, wherein the cancer is colon cancer.

45. The method of claim 42, wherein the cancer is lung cancer.

46. The method of claim 42, wherein the cancer is pancreatic ductal cancer.

47. The method of claim 42, wherein the cancer is prostate cancer.

48. The method of claim 47, wherein the prostate cancer is high-risk localized prostate cancer.

49. The method of claim 42, wherein the cancer is ovarian cancer.

50. The method of claim 42, wherein the cancer is head and neck cancer.

51. The method of any one of claims 1-41, wherein the patient has prostate cancer and the RTI is administered as an adjuvant therapy.

52. The method of any one of claims 1-41, wherein the patient has prostate cancer and the RTI is administered as a neoadjuvant therapy.

53. The method of any one of claims 1-52, further comprising administering a therapeutically effective amount of at least one second therapeutic agent useful for treating the cancer.

54. The method of claim 53 for the treatment of breast cancer, wherein the at least one second therapeutic agent is Soltamox® (tamoxifen), Arimidex® (anastrozole), Femara® (letrozole), Aromasin® (exemestane), Herceptin® (trastuzumab), Abraxane® (paclitaxel), Cytoxan® (cyclophosphamide), Taxol® (paclitaxel), Afinitor® (everolimus), Taxotere®

(docetaxel), Xeloda® (capecitabine), Trexall® (methotrexate), Faslodex (fulvestrant), Adriamycin® (doxorubicin), Perjeta® (pertuzumab), Gemzar (gemcitabine), Tykerb® (lapatinib), Adrucil® (fluorouracil), Ibrance® (palbociclib), Verzenio® (abemaciclib), Fareston® (toremifene), Halaven® (eribulin), Menest, Kadcyla® (ado-trastuzumab emtransine), Androxy® (fluoxymesterone), Avastin® (bevacizumab), esterified estrogens, Herzuma® (trastuzumab), Ixempra® (ixabepilone), Kanjinti® (trastuzumab), Kisqali® (ribociclib), Ogivri® (trastuzumab), Ontruzant® (trastuzumab), Tepadina® (thiotepa), Trazimera® (trastuzumab), Velban® (vinblastine), Piqray® (alpelisib), Tecentriq® (atezolizumab), Enhertu® (fam-trastuzumab deruxtecan), Herceptin, Hylecta™ (hyaluronidase/trastuzumab), Infugem® (gemcitabine), Kisqali® Femara® Co-Pack (ribociclib and letrozole), Talzenna® (talazoparib), Trodelvy® (sacituzumab) or Tukysa™ (tukatinib).

55. The method of claim 53 for the treatment of colon cancer, wherein the at least one second therapeutic agent is Xeloda® (capecitabine), Eloxatin® (oxaliplatin), fluorouracil, Avastin® (bevacizumab), leucovorin, Camptosar® (irinotecan), Stivarga® (regorafenib), Erbitux® (cetuximab), Vectibix® (panitumumab), Lonsurf® (tipiracil/trifluridine), Zaltrap® (ziv-aflibercept), Betaseron® (interferon beta-1b), Fusilev® (levoleucovorin), Wellcocorin® (methotrexate), Keytruda® (pembrolizumab), Mvasi® (bevacizumab-awwb), Cyramza® (ramucirumab), Yervoy® (ipilmumab), Opdivo® (nivolumab), Braftovi® (encorafenib), Khapzory® (levoleucovorin) or Zirabev® (bevacizumab-bvzr).

56. The method of claim 53 for the treatment of lung cancer, wherein the at least one second therapeutic agent is Etopophos® (etoposide), Hycamtin® (topotecan), VePesid® (etoposide), Toposar® (etoposide), Opdivo® (nivolumab), Keytruda® (pembrolizumab), Tecentriq® (atezolizumab), Imfinizi® (durvalumab), methotrexate, cyclophosphamide, Carboplatin, Cisplatin, docetaxel, Gemcitabine, Irinotecan, Paclitaxel, Pemetrexed, Vinblastine, or Vinorelbine.

57. The method of claim 53 for the treatment of pancreatic ductal cancer, wherein the at least one second therapeutic agent is Gemzar® (Gemcitabine), fluorouracil, Afinitor® (everolimus), Tarceva® (erlotinib), Abraxane® (paclitaxel), capecitabine, Sutent® (sunitinib),

pancreatin, methotrexate, Zanosar® (streptozocin), Mutamycin® (mitomycin), Onivyde® (irinotecan), bevacizumab, cetuximab, Infugem® (gemcitabine) or Lynparza® (olaparib).

58. The method of claim 53 for the treatment of head and neck cancer, wherein the at least one second therapeutic agent is Erbituz® (cetuximab), Taxotere® (docetaxel), Trexall® (methotrexate), Keytruda® (pembrolizumab) or Opdivo® (nivolumab).

59. The method of claim 53 for the treatment of prostate cancer, wherein the at least one second therapeutic agent is Suprefact® (buserelin), Firmagon® (degarelix), Zoladex® (goserelin), Vantas® (histrelin), Eligard® (leuprolide), Orgovyx® (relugolix), Trelstar® (triptorelin), Casodex® (bicalutamide), Eulexin® (flutamide), Nilandron® (nilutamide), Zytiga® (biraterone acetate), Erleada® (apalutamide), or Xtandi® (enzalutamide).

60. The method of claim 53, wherein the at least one second therapeutic agent is a STING agonist.

61. The method of any one of claims 1-60, wherein the patient is (a) not infected with the HIV virus, (b) not suspected of being infected with the HIV virus, (c) not being treated for the HIV virus, and/or (d) not being treated to prevent the HIV virus.

62. A kit for carrying out the method of any one claims 1-61, the kit comprising (i) a RTI; and (ii) and instructions for administering the RTI to a patient having cancer.

63. The kit of claim 62 further comprising at least one second therapeutic agent.

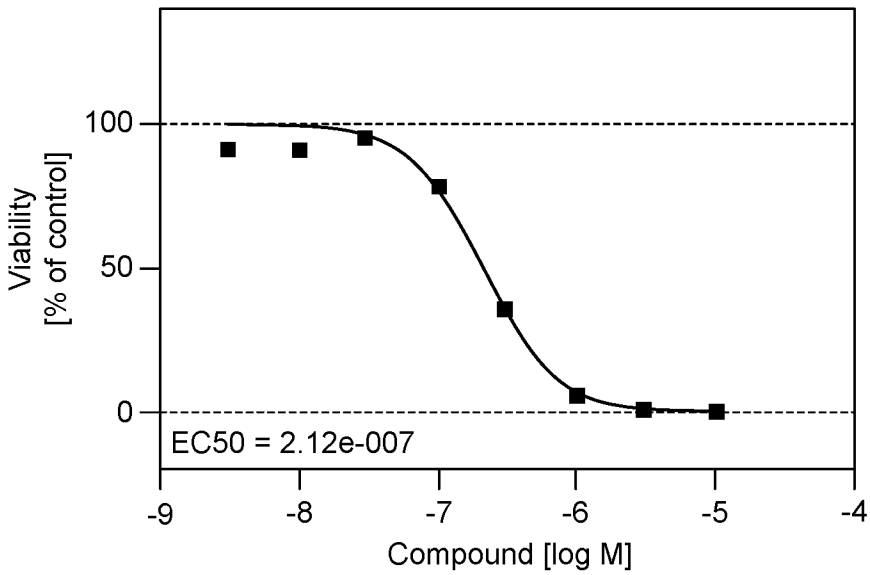

100
50
0
Viability
[% of control]
EC50 = 2.12e-007
-9
-8
-7
-6
-5
-4
Compound [log M]

FIG. 1

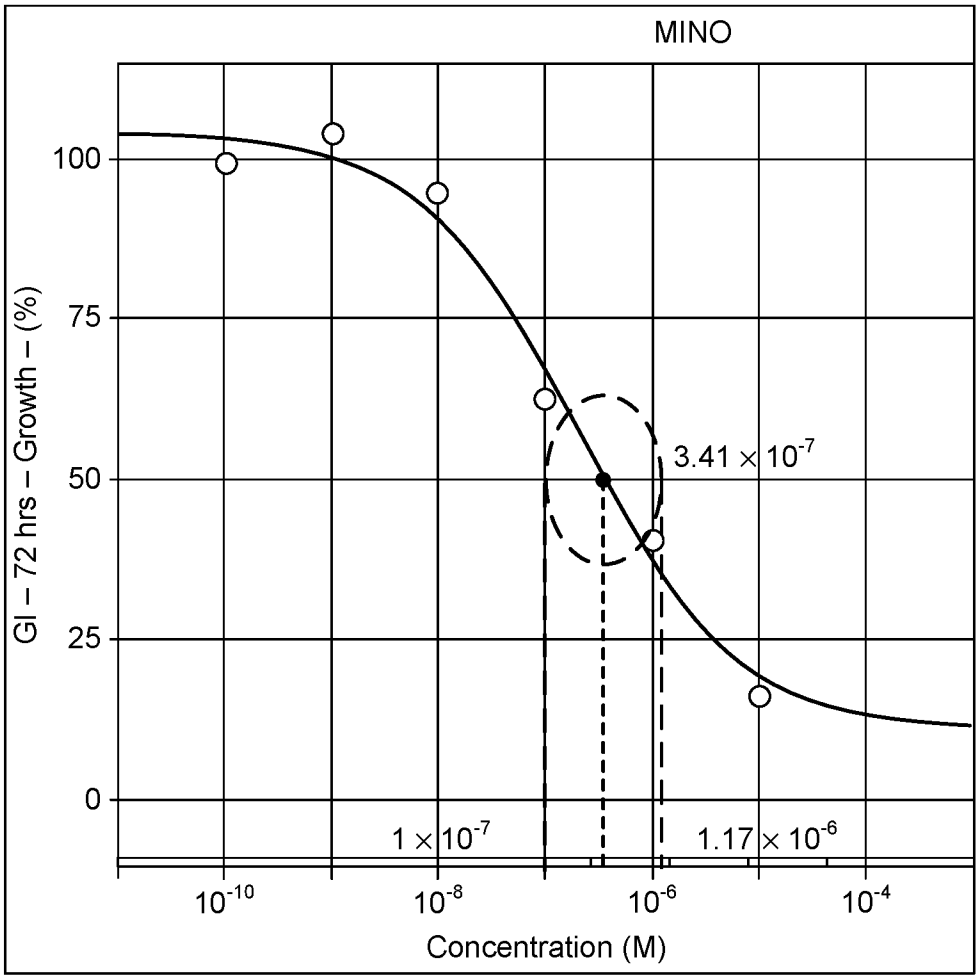

MINO
100
75
50
25
0
GI – 72 hrs – Growth – (%)
3.41 × 10-7
1 × 10-7
1.17 × 10-6
10-10
10-8
10-6
10-4
Concentration (M)

FIG. 2

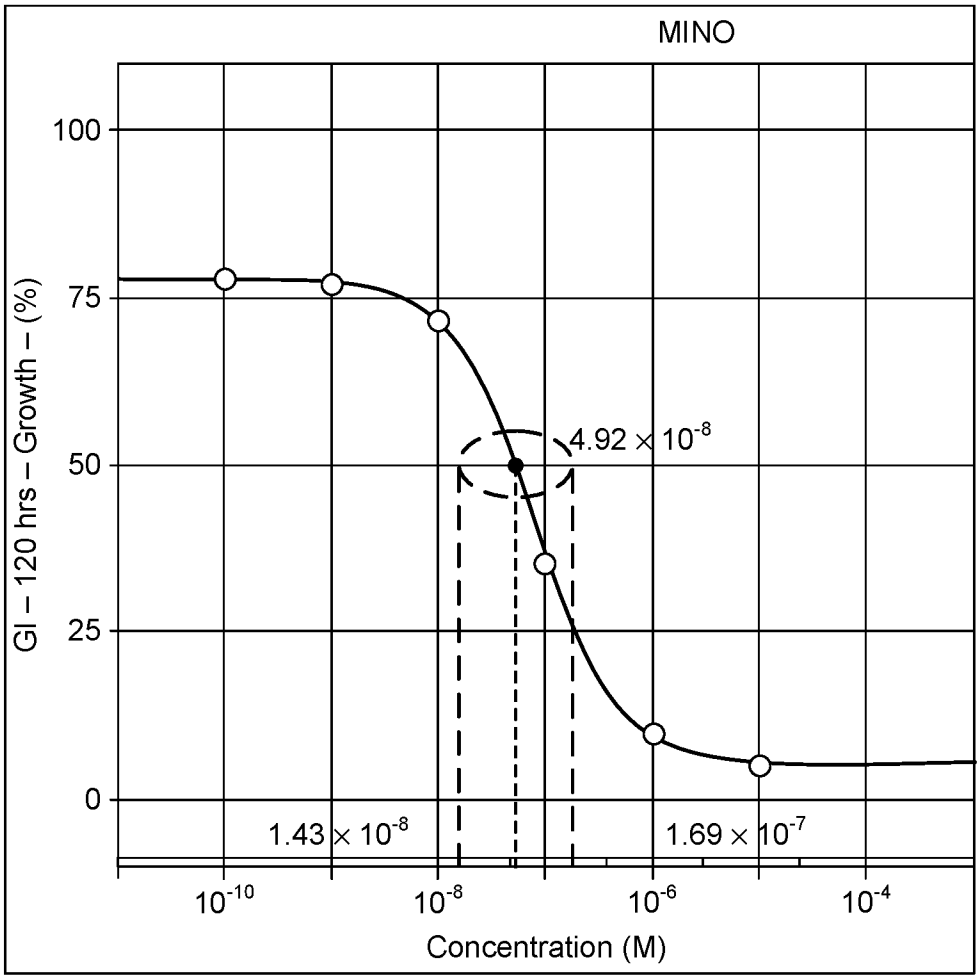

MINO
100
75
50
25
0
GI – 120 hrs – Growth – (%)
4.92 × 10-8
1.43 × 10-8
1.69 × 10-7
10-10
10-8
10-6
10-4
Concentration (M)

FIG. 3

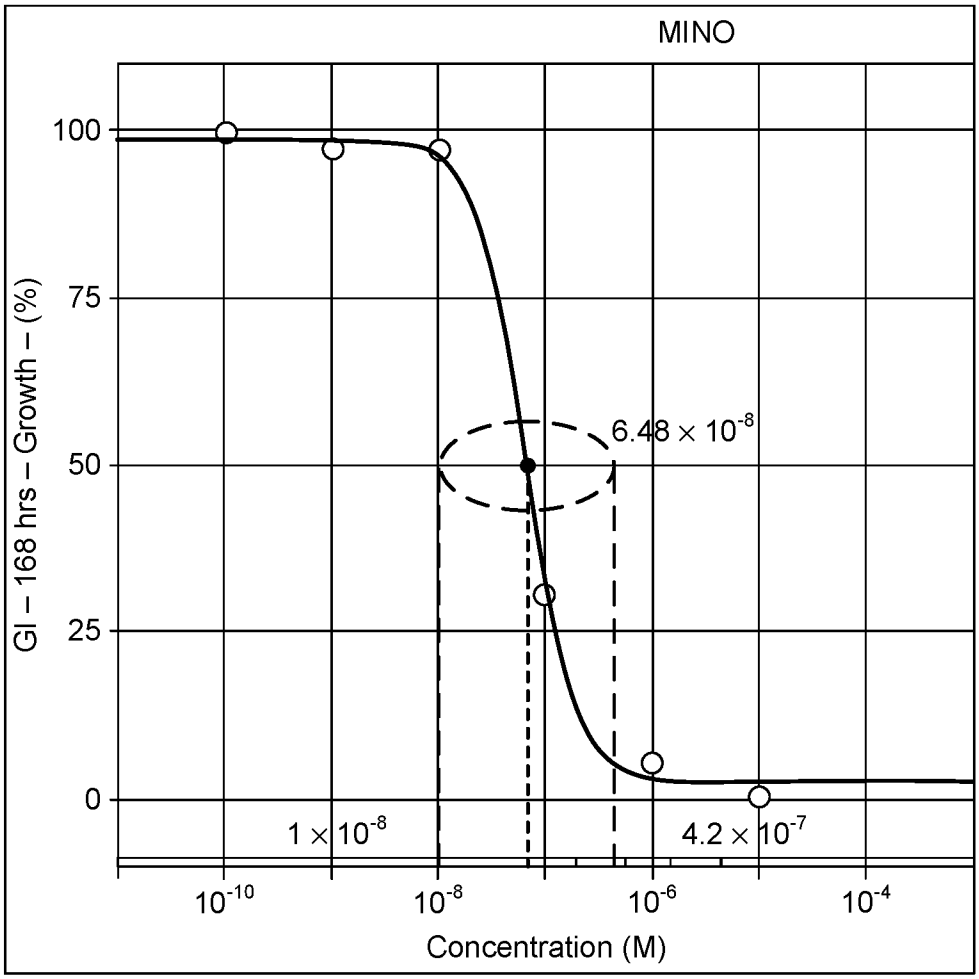

MINO
100
75
50
25
0
GI – 168 hrs – Growth – (%)
6.48 × 10-8
1 × 10-8
4.2 × 10-7
10-10
10-8
10-6
10-4
Concentration (M)

FIG. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2021/051718

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K; A61K 31/7072; A61K 31/7088; A61K 39/395; A61K 45/00; A61K 45/06 (2021.01)
CPC - A61K 39/395; A61K 45/06; A61K 2039/505; A61P 3/10; A61P 31/12; A61P 31/18; A61P 33/00; A61P 35/00; A61P 37/00; A61P 37/02; A61P 43/00; C07K 16/28; C07K 16/2878; C07K 2317/622; C07K 2317/73 (2021.08)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
see Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
see Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
see Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2020/142629 A1 (THE GENERAL HOSPITAL CORPORATION) 09 July 2020 (09.07.2020) entire document	1, 4-6, 19
A	US 5,223,490 A (HART et al) 29 June 1993 (29.06.1993) entire document	1, 4-6, 19
A	WO 2020/154656 A1 (BROWN UNIVERSITY) 30 July 2020 (30.07.2020) entire document	1, 4-6, 19
A	US 2015/0290235 A1 (AB SCIENCE) 15 October 2015 (15.10.2015) entire document	1, 4-6, 19
A	WO 2019/157087 A1 (THE GENERAL HOSPITAL CORPORATION et al) 15 August 2019 (15.08.2019) entire documont	1, 4-6, 19
E, X	WO 2021/188910 A1 (UNIVERSITY OF VIRGINIA PATENT FOUNDATION) 23 September 2021 (23.09.2021) entire document	1, 4-6, 19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 December 2021	JAN 27 2022
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Harry Kim Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2021/051718

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 35-39, 42-63
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See extra sheet(s).

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 4-6, 19

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2021/051718

Continued from Box No. III Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-34, 40, and 41 are drawn to a method for treating cancer in patient in need thereof.

The first invention of Group I+ is restricted to a method and a reverse transcriptase inhibitor (RTI), wherein the RTI is censavudine. It is believed that claims 1, 4-6, and 19 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect RTIs for each method to be searched in a specific combination by paying an additional fee for each set of election. An exemplary election would be a method and an RTI, wherein the RTI is islatravir. Additional RTIs will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

Groups I+ RTIs do not share a significant structural element, requiring the selection of alternatives for the RTIs, where the RTI is "censavudine, islatravir, elvucitabine, lamivudine (3TC), zidovudine (AZT), tenofovir, tenofovir disoproxil, tenofovir alafenamide, stavudine (d4T), zalcitabine (ddC), didanosine (ddI), emtricitabine (FTC), entecavir (ETV), 2',3'-dideoxyguanosine (ddG), 2',3'-dideoxyadenosine (ddA), 2'-fluoro-2',3'-dideoxyarabinosyladenine (F-ddA), efavirenz (EFV), nevirapine (NVP), abacavir (ABC), adefovir, dipivoxil, or telbivudine".

Additionally, even if Groups I+ were considered to share the technical features of a method for treating cancer in patient in need thereof, the method comprising administering a therapeutically effective amount of a reverse transcriptase inhibitor (RTI) to the patient, wherein the RTI is administered according to an intermittent dosing schedule, these shared technical features do not represent a contribution over the prior art as disclosed by US 5,223,490 A to Hart et al. (hereinafter, "Hart").

Hart teaches a method for treating cancer in patient in need thereof, the method comprising administering a therapeutically effective amount of a reverse transcriptase inhibitor (RTI) to the patient (Col. 1, Ln. 65 to Col. 2, Ln. 4, a method for the treatment or prophylaxis of retrovirus-associated adenocarcinoma in a human which comprises the administration of reverse transcriptase inhibitor or a pharmaceutically acceptable derivative thereof to the human in an amount effective to treat said adenocarcinoma), wherein the RTI is administered according to an intermittent dosing schedule (Col. 3, Lns. 57-68, dose should be administered to achieve peak plasma concentrations of the active compound...blood levels may be maintained by a continuous infusion to provide about 0.01 to about 5.0 mg/kg/hour or by intermittent infusions containing about 0.4 to about 15 mg/kg of the active ingredient).

The Inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.