which are not fully understood, usually is significant. Jaundice occurs if the cancer blocks the common bile duct. By the time the malignant tumor is identified, it often has spread (metastasized) to other parts of the body. The median survival is little more than six months from the time of diagnosis.

[0009] Current therapies for this common and difficult-to-treat disease include surgery and/or chemotherapy. Often the tumor cannot be removed by surgery, either because it has invaded vital structures that cannot be removed or because it has spread to distant sites.

[0010] Accordingly, there is a need in the art for improved treating primary and metastatic pancreatic cancers.

Figures

[0011] Figure 1 represents the mean plasma concentration of Compound Ib following i.v. in dog dosing of Compound Ib.

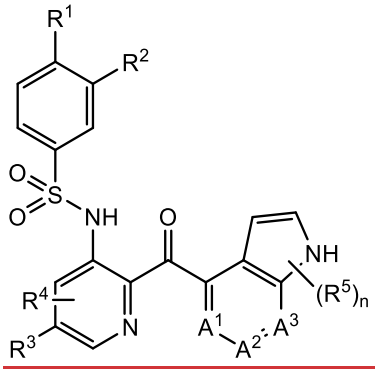
[0012] Figure 2 represents the mean plasma concentration of Compound Ib following p.o. dosing in dog of Compound Ib.

Summary

[0013] The present disclosure provides compounds that modulate CCR2 chemokine ligand activity and can be used in methods of treating pancreatic cancer. Accordingly, the compounds of the present disclosure are compounds that modulate at least one function or characteristic of mammalian CCR2, for example, a human CCR2 protein.

[0014] Thus, the present disclosure describes methods of treating pancreatic cancer in patients including administering the compounds and pharmaceutical combinations as described herein. Also described are methods of limiting over-expression of oncogenes, activating tumor suppressor genes, and regulating signaling proteins that include administering to a patient in need thereof an effective amount of any of the compounds or pharmaceutical combinations as described herein.

[0014a] Use of an effective amount of a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of pancreatic cancer or in controlling an adenocarcinoma in a patient,

wherein

R^1 is halogen or C_{1-6} alkyl;

R^2 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, or –CN;

R^3 is hydrogen, halogen, or C_{1-6} alkyl;

R^4 is hydrogen, halogen, or C_{1-6} alkyl;

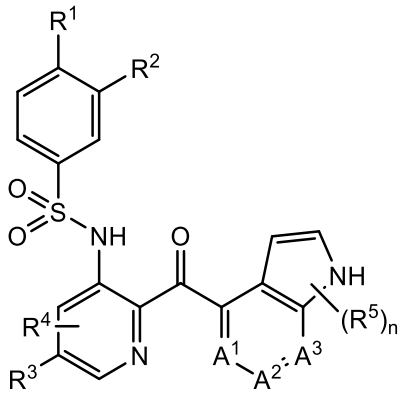
each R^5 is independently C_{1-6} alkyl, –OH, or $–NH_2$;

n is 0, 1, 2, or 3; and

each of A^1, A^2, and A^3 is –CH– or –N–, where at least one of A^1, A^2, or A^3 is –N–.

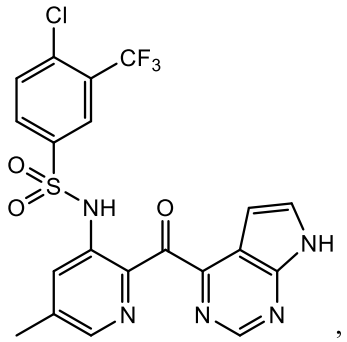
[0014b] In another aspect, there is provided the use of a pharmaceutical composition comprising a compound as defined above and a pharmaceutically acceptable excipient, in the manufacture of a medicament for the treatment of pancreatic cancer or in controlling an adenocarcinoma.

[0015] One ~~embodiment~~ example of the present disclosure includes a method of treating pancreatic cancer in a patient that includes administering to the patient in need thereof an effective amount of a compound of Formula I:



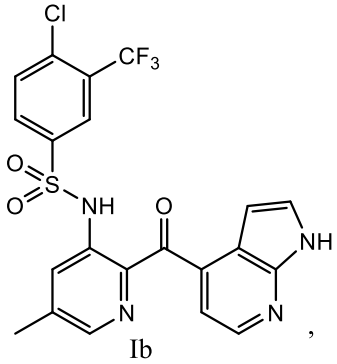
Formula I

or a pharmaceutically acceptable salt thereof wherein R^1 is halogen or C_{1-6} alkyl; R^2 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, or –CN; R^3 is hydrogen, halogen, or C_{1-6} alkyl; R^4 is hydrogen, halogen, or C_{1-6} alkyl; each R^5 is independently C_{1-6} alkyl, –OH, or $–NH_2$; n is 0, 1, 2, or 3; and each of A^1, A^2, and A^3 is –CH– or –N–, where at least one of A^1, A^2, or A^3 is –N–. In one ~~embodiment~~example, R^1 is halogen or methyl; R^2 is halogen or C_{1-6} haloalkyl; R^3 is halogen or C_{1-6} alkyl; R^4 is hydrogen; n is 0; A^1 is –CH– or –N–; A^2 is –CH–; and A^3 is –N–. In one ~~embodiment~~example, R^1 is halogen or methyl; R^2 is C_{1-3} haloalkyl; R^3 is halogen or C_{1-3} alkyl; R^4 is hydrogen; n is 0; A^1 is –CH– or –N–; A^2 is –CH–; and A^3 is –N–. In one ~~embodiment~~example, the compound is selected from the group consisting of:



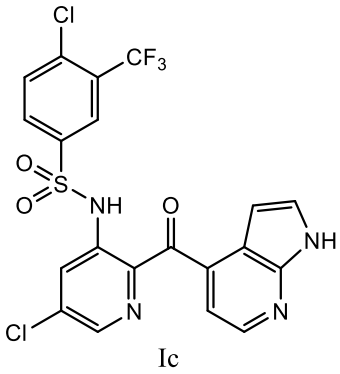
Ia

,



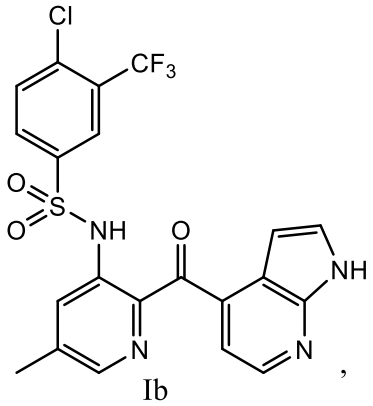
Ib

, and



Ic

or a pharmaceutically acceptable salt thereof. In one ~~embodiment~~example, the compound is the compound of Formula Ib:



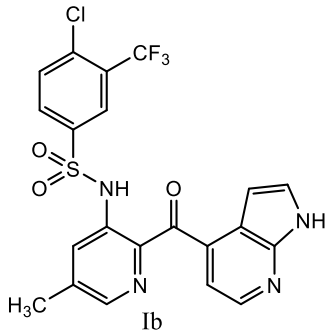
Ib,

or a pharmaceutically acceptable salt thereof. In one ~~embodiment~~example, the pancreatic cancer is Stage I, II, III, or IV. In one ~~embodiment~~example, the treatment provides one or more of a decrease in tumor size, a suppression or decrease in tumor growth, no new tumor formation, a decrease in new tumor formation, an increase in survival or progression-free survival, no metastases, an increase in treatment options, delay in time from surgery to recurrence, reduction in jaundice, suppression of spread to liver, reduction in pain, improved appetite, improved digestion, reduction of gallbladder size, and reduced incidence of blood clots. In one ~~embodiment~~example, the patient achieves a complete response. In one ~~embodiment~~example, the patient achieves a partial response. In one ~~embodiment~~example, the patient achieves stable disease. In one ~~embodiment~~example, the patient achieves a slower progressive disease. In one ~~embodiment~~example, the patient suffers from one or more of pancreatic adenocarcinoma, non-resectable pancreatic cancer, locally advanced pancreatic cancer, borderline resectable pancreatic cancer, locally advanced pancreatic ductal adenocarcinoma, borderline resectable pancreatic ductal adenocarcinoma, metastatic pancreatic cancer, chemotherapy-resistant pancreatic cancer, pancreatic ductal adenocarcinoma, squamous pancreatic cancer, pancreatic progenitor, immunogenic pancreatic cancer, aberrantly differentiated endocrine exocrine (ADEX) tumors, an exocrine pancreatic cancer, pancreatic intraepithelial neoplasia, intraductal papillary mucinous neoplasms, mucinous cystic neoplasms, mucinous pancreas cancer, adenosquamous carcinoma, signet ring cell carcinoma, hepatoid carcinoma, colloid carcinoma, undifferentiated carcinoma, undifferentiated carcinomas with osteoclast-like giant cells, a pancreatic cystic neoplasm, an islet cell tumor, a pancreas endrocrine tumor, or a pancreatic neuroendrocrine tumor. In one ~~embodiment~~example, the compound of Formula I is provided as a pharmaceutical composition for oral administration. In one ~~embodiment~~example, the

compound is administered once a day. In one ~~embodiment~~example, the compound is administered twice a day. In one ~~embodiment~~example, the method includes administering to the patient one or more additional therapeutic compounds. In one ~~embodiment~~example, the one or more additional therapeutic compound is selected from one or more of a Btk tyrosine kinase inhibitor, an Erbb2 tyrosine kinase receptor inhibitor; an Erbb4 tyrosine kinase receptor inhibitor, an mTOR inhibitor, a thymidylate synthase inhibitor, an EGFR tyrosine kinase receptor inhibitor, an epidermal growth factor antagonist, a Fyn tyrosine kinase inhibitor, a kit tyrosine kinase inhibitor, a Lyn tyrosine kinase inhibitor, a NK cell receptor modulator, a PDGF receptor antagonist, a PARP inhibitor, a poly ADP ribose polymerase inhibitor, a poly ADP ribose polymerase 1 inhibitor, a poly ADP ribose polymerase 2 inhibitor, a poly ADP ribose polymerase 3 inhibitor, a galactosyltransferase modulator, a dihydropyrimidine dehydrogenase inhibitor, an orotate phosphoribosyltransferase inhibitor, a telomerase modulator, a mucin 1 inhibitor, a mucin inhibitor, a secretin agonist, a TNF related apoptosis inducing ligand modulator, an IL17 gene stimulator, an interleukin 17E ligand, a neurokinin receptor agonist, a cyclin G1 inhibitor, a checkpoint inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a CTLA4 inhibitor, a topoisomerase I inhibitor, an Alk-5 protein kinase inhibitor, a connective tissue growth factor ligand inhibitor, a notch-2 receptor antagonist, a notch-3 receptor antagonist, a hyaluronidase stimulator, a MEK-1 protein kinase inhibitor; MEK-2 protein kinase inhibitor, a GM-CSF receptor modulator; TNF alpha ligand modulator, a mesothelin modulator, an asparaginase stimulator, a caspase-3 stimulator; caspase-9 stimulator, a PKN3 gene inhibitor, a hedgehog protein inhibitor; smoothened receptor antagonist, an AKT1 gene inhibitor, a DHFR inhibitor, a thymidine kinase stimulator, a CD29 modulator, a fibronectin modulator, an interleukin-2 ligand, a serine protease inhibitor, a D40LG gene stimulator; TNFSF9 gene stimulator, a 2-oxoglutarate dehydrogenase inhibitor, a TGF-beta type II receptor antagonist, an Erbb3 tyrosine kinase receptor inhibitor, a cholecystokinin CCK2 receptor antagonist, a Wilms tumor protein modulator, a Ras GTPase modulator, an histone deacetylase inhibitor, a cyclin-dependent kinase 4 inhibitor A modulator, an estrogen receptor beta modulator, a 4-1BB inhibitor, a 4-1BBL inhibitor, a PD-L2 inhibitor, a B7-H3 inhibitor, a B7-H4 inhibitor, a BTLA inhibitor, a HVEM inhibitor, aTIM3 inhibitor, a GAL9 inhibitor, a LAG3 inhibitor, a VISTA inhibitor, a KIR inhibitor, a 2B4 inhibitor, a CD160 inhibitor and a CD66e modulator. In one ~~embodiment~~example, the one or more additional therapeutic compounds is selected from one or more of bavituximab, IMM-101, CAP1-6D, Rexin-G , genistein, CVac, MM-D37K, PCI-27483, TG-01, mocetinostat,

vincristine, vinorelbine, zoledronate, zoledronic acid, pembrolizumab, nivolumab, IBI-308, mDX-400, BGB-108, MEDI-0680, SHR-1210, PF-06801591, PDR-001, GB-226, STI-1110, durvalumab, atezolizumab, avelumab, BMS-936559, ALN-PDL, TSR-042, KD-033, CA-170, STI-1014, FOLFIRINOX and KY-1003. In one ~~embodiment~~example, the one or more additional therapeutic compound is FOLFIRINOX. In one ~~embodiment~~example, the one or more additional therapeutic compounds are gemcitabine and paclitaxel. In one ~~embodiment~~example, the one or more additional therapeutic compounds are gemcitabine and nab-paclitaxel.

[0016] One ~~embodiment~~example includes a method of treating pancreatic cancer in a patient including administering to the patient in need thereof an effective amount of a compound of Formula Ib:



Ib

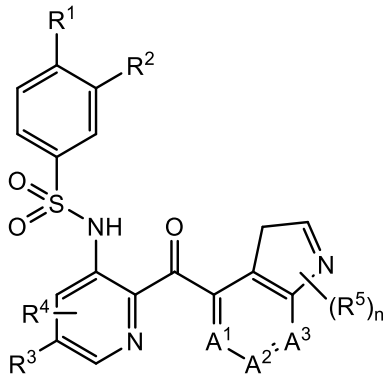
or a pharmaceutically acceptable salt thereof. In one ~~embodiment~~example, the pancreatic cancer is Stage I, II, III, or IV. In one ~~embodiment~~example, the treatment provides one or more of a decrease in tumor size, a suppression or decrease of tumor growth, no new tumor formation, a decrease in new tumor formation, an increase in survival or progression-free survival, no metastases, increase in treatment options, delay in time from surgery to recurrence, reduction in jaundice, suppression of spread to liver, reduction in pain, improved appetite, improved digestion, reduction of gallbladder size, and reduced incidence of blood clots. In one ~~embodiment~~example, the patient achieves a complete response. In one ~~embodiment~~example, the patient achieves a partial response. In one ~~embodiment~~example, the patient achieves stable disease. In one ~~embodiment~~example, the patient achieves a slower progressive disease. In one ~~embodiment~~example, the patient suffers from pancreatic adenocarcinoma, non-resectable pancreatic cancer, locally advanced pancreatic cancer, borderline resectable pancreatic cancer, locally advanced pancreatic ductal adenocarcinoma, borderline resectable pancreatic ductal adenocarcinoma, metastatic pancreatic cancer, chemotherapy-resistant pancreatic cancer, pancreatic ductal adenocarcinoma, squamous pancreatic cancer, pancreatic progenitor, immunogenic pancreatic cancer, aberrantly

differentiated endocrine exocrine (ADEX) tumors, an exocrine pancreatic cancer, pancreatic intraepithelial neoplasia, intraductal papillary mucinous neoplasms, mucinous cystic neoplasms, mucinous pancreas cancer, adenosquamous carcinoma, signet ring cell carcinoma, hepatoid carcinoma, colloid carcinoma, undifferentiated carcinoma, undifferentiated carcinomas with osteoclast-like giant cells, a pancreatic cystic neoplasm, an islet cell tumor, a pancreas endrocrine tumor, or a pancreatic neuroendrocrine tumor. In one ~~embodiment~~example, the compound of Formula Ib is provided as a pharmaceutical composition for oral administration. In one ~~embodiment~~example, the compound is administered once a day. In one ~~embodiment~~example, the compound is administered twice a day. In one ~~embodiment~~example, the effective amount is from 50 mg to 300 mg. In one ~~embodiment~~example, the effective amount is 150 mg. In one ~~embodiment~~example, the method further includes administering to the patient one or more additional therapeutic compounds. In one ~~embodiment~~example, the one or more additional therapeutic compounds is selected from one or more of a Btk tyrosine kinase inhibitor, an Erbb2 tyrosine kinase receptor inhibitor; an Erbb4 tyrosine kinase receptor inhibitor, an mTOR inhibitor, a thymidylate synthase inhibitor, an EGFR tyrosine kinase receptor inhibitor, an Epidermal growth factor antagonist, a Fyn tyrosine kinase inhibitor, a kit tyrosine kinase inhibitor, a Lyn tyrosine kinase inhibitor, a NK cell receptor modulator, a PDGF receptor antagonist, a PARP inhibitor, a poly ADP ribose polymerase inhibitor , a poly ADP ribose polymerase 1 inhibitor, a poly ADP ribose polymerase 2 inhibitor, a poly ADP ribose polymerase 3 inhibitor, a galactosyltransferase modulator, a dihydropyrimidine dehydrogenase inhibitor, an orotate phosphoribosyltransferase inhibitor, a telomerase modulator, a mucin 1 inhibitor, a mucin inhibitor, a secretin agonist, a TNF related apoptosis inducing ligand modulator, an IL17 gene stimulator, an interleukin 17E ligand, a Neurokinin receptor agonist, a cyclin G1 inhibitor, a checkpoint inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a CTLA4 inhibitor, a topoisomerase I inhibitor, an Alk-5 protein kinase inhibitor, a connective tissue growth factor ligand inhibitor, a notch-2 receptor antagonist, a notch-3 receptor antagonist, a hyaluronidase stimulator, a MEK-1 protein kinase inhibitor; MEK-2 protein kinase inhibitor, a GM-CSF receptor modulator; TNF alpha ligand modulator, a mesothelin modulator, an asparaginase stimulator, a caspase-3 stimulator; caspase-9 stimulator, a PKN3 gene inhibitor, a hedgehog protein inhibitor; Smoothened receptor antagonist, an AKT1 gene inhibitor, a DHFR inhibitor, a thymidine kinase stimulator, a CD29 modulator, a fibronectin modulator, an interleukin-2 ligand, a serine protease inhibitor, a D40LG gene stimulator; TNFSF9 gene stimulator, a 2-oxoglutarate dehydrogenase inhibitor, a

TGF-beta type II receptor antagonist, an Erbb3 tyrosine kinase receptor inhibitor, a cholecystokinin CCK2 receptor antagonist, a Wilms tumor protein modulator, a Ras GTPase modulator, an histone deacetylase inhibitor, a cyclin-dependent kinase 4 inhibitor A modulator, an estrogen receptor beta modulator, a 4-1BB inhibitor, a 4-1BBL inhibitor, a PD-L2 inhibitor, a B7-H3 inhibitor, a B7-H4 inhibitor, a BTLA inhibitor, a HVEM inhibitor, aTIM3 inhibitor, a GAL9 inhibitor, a LAG3 inhibitor, a VISTA inhibitor, a KIR inhibitor, a 2B4 inhibitor, a CD160 inhibitor and a CD66e modulator. In one ~~embodiment~~example, the the one or more additional therapeutic compound is selected from one or more of bavituximab, IMM-101, CAP1-6D, Rexin-G , genistein, CVac, MM-D37K, PCI-27483, TG-01, mocetinostat, LOAd-703, CPI-613, upamostat, CRS-207, NovaCaps, trametinib, Atu-027, sonidegib, GRASPA, trabedersen, nastorazepide, Vaccell, oregovomab, istiratumab, refametinib, regorafenib, lapatinib, selumetinib, rucaparib, pelareorep, tarextumab, PEGylated hyaluronidase, varlitinib, aglatimagene besadenovec, GBS-01, GI-4000, WF-10, galunisertib, afatinib, RX-0201, FG-3019, pertuzumab, DCVax-Direct, selinexor, glufosfamide, virulizin, yttrium (90Y) clivatuzumab tetraxetan, brivudine, nimotuzumab, algenpantucel-L, tegafur + gimeracil + oteracil potassium + calcium folinate, olaparib, ibrutinib, pirarubicin, Rh-Apo2L, tertomotide, tegafur + gimeracil + oteracil potassium, tegafur + gimeracil + oteracil potassium, masitinib, Rexin-G, mitomycin, erlotinib , adriamycin, dexamethasone, vincristine, cyclophosphamide, fluorouracil, topotecan, taxol, interferons, platinum derivatives, taxane, paclitaxel, vinca alkaloids, vinblastine, anthracyclines, doxorubicin, epipodophyllotoxins, etoposide, cisplatin, rapamycin, methotrexate, actinomycin D, dolastatin 10, colchicine, emetine, trimetrexate, metoprine, cyclosporine, daunorubicin, teniposide, amphotericin, alkylating agents, chlorambucil, 5-fluorouracil, campthothecin, cisplatin, metronidazole, Gleevec, Avastin, Vectibix, abarelix, aldesleukin, alemtuzumab, alitretinoin, allopurinol, altretamine, amifostine, anastrozole, arsenic trioxide, asparaginase, azacitidine, AZD9291, BCG Live, bevacuzimab, fluorouracil, bexarotene, bleomycin, bortezomib, busulfan, calusterone, capecitabine, camptothecin, carboplatin, carmustine, celecoxib, cetuximab, chlorambucil, cladribine, clofarabine, cyclophosphamide, cytarabine, dactinomycin, darbepoetin alfa, daunorubicin, denileukin, dexrazoxane, docetaxel, doxorubicin (neutral), doxorubicin hydrochloride, dromostanolone propionate, epirubicin, epoetin alfa, estramustine, etoposide phosphate, etoposide, exemestane, filgrastim, floxuridine fludarabine, fulvestrant, gefitinib, gemcitabine, gemtuzumab, goserelin acetate, histrelin acetate, hydroxyurea, ibritumomab, idarubicin, ifosfamide, imatinib mesylate,

interferon alfa-2a, interferon alfa-2b, irinotecan, lenalidomide, letrozole, leucovorin, leuprolide acetate, levamisole, lomustine, megestrol acetate, melphalan, mercaptopurine, 6-MP, mesna, methotrexate, methoxsalen, mitomycin C, mitotane, mitoxantrone, nandrolone, nelarabine, nofetumomab, oprelvekin, oxaliplatin, paclitaxel, palifermin, pamidronate, pegademase, pegaspargase, pegfilgrastim, pemetrexed disodium, pentostatin, pipobroman, plicamycin, porfimer sodium, procarbazine, quinacrine, rasburicase, rituximab, rociletinib, sargramostim, sorafenib, streptozocin, sunitinib maleate, talc, tamoxifen, temozolomide, teniposide, VM-26, testolactone, thioguanine, 6-TG, thiotepa, topotecan, toremifene, tositumomab, trastuzumab, tretinoin, ATRA, uracil mustard, valrubicin, vinblastine, vincristine, vinorelbine, zoledronate, zoledronic acid, pembrolizumab, nivolumab, IBI-308, mDX-400, BGB-108, MEDI-0680, SHR-1210, PF-06801591, PDR-001, GB-226, STI-1110, durvalumab, atezolizumab, avelumab, BMS-936559, ALN-PDL, TSR-042, KD-033, CA-170, STI-1014, FOLFIRINOX and KY-1003. In one ~~embodiment~~example, the one or more additional therapeutic compound is FOLFIRINOX. In one ~~embodiment~~example, the one or more additional therapeutic compounds are gemcitabine and paclitaxel. In one ~~embodiment~~example, the one or more additional therapeutic compounds are gemcitabine and nab-paclitaxel.

[0017] One ~~embodiment~~example of the present disclosure includes a pharmaceutical combination for comprising a compound of Formula I:

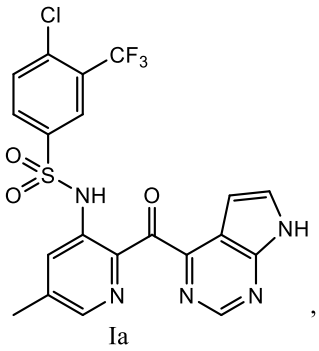


Formula I

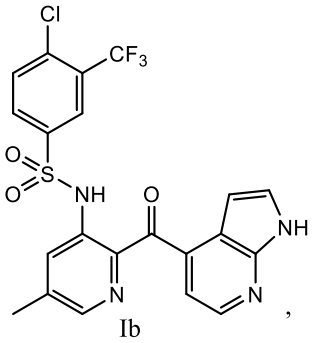
or a pharmaceutically acceptable salt thereof, wherein R^1 is halogen or C_{1-6} alkyl; R^2 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, or –CN; R^3 is hydrogen, halogen, or C_{1-6} alkyl; R^4 is hydrogen, halogen, or C_{1-6} alkyl; each R^5 is independently C_{1-6} alkyl, –OH, or $–NH_2$; n is 0, 1, 2, or 3; each of A^1, A^2, and A^3 is –CH– or –N– where at least one of A^1, A^2, or A^3 is –N–; and one or more additional therapeutic compounds. In one ~~embodiment~~example, the one or more additional therapeutic

compound is selected from one or more of a Btk tyrosine kinase inhibitor, an Erbb2 tyrosine kinase receptor inhibitor; an Erbb4 tyrosine kinase receptor inhibitor, an mTOR inhibitor, a thymidylate synthase inhibitor, an EGFR tyrosine kinase receptor inhibitor, an epidermal growth factor antagonist, a Fyn tyrosine kinase inhibitor, a kit tyrosine kinase inhibitor, a Lyn tyrosine kinase inhibitor, a NK cell receptor modulator, a PDGF receptor antagonist, a PARP inhibitor, a poly ADP ribose polymerase inhibitor, a poly ADP ribose polymerase 1 inhibitor, a poly ADP ribose polymerase 2 inhibitor, a poly ADP ribose polymerase 3 inhibitor, a galactosyltransferase modulator, a dihydropyrimidine dehydrogenase inhibitor, an orotate phosphoribosyltransferase inhibitor, a telomerase modulator, a mucin 1 inhibitor, a mucin inhibitor, a secretin agonist, a TNF related apoptosis inducing ligand modulator, an IL17 gene stimulator, an interleukin 17E ligand, a neurokinin receptor agonist, a cyclin G1 inhibitor, a checkpoint inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a CTLA4 inhibitor, a topoisomerase I inhibitor, an Alk-5 protein kinase inhibitor, a connective tissue growth factor ligand inhibitor, a notch-2 receptor antagonist, a notch-3 receptor antagonist, a hyaluronidase stimulator, a MEK-1 protein kinase inhibitor; MEK-2 protein kinase inhibitor, a GM-CSF receptor modulator; TNF alpha ligand modulator, a mesothelin modulator, an asparaginase stimulator, a caspase-3 stimulator; caspase-9 stimulator, a PKN3 gene inhibitor, a hedgehog protein inhibitor; smoothened receptor antagonist, an AKT1 gene inhibitor, a DHFR inhibitor, a thymidine kinase stimulator, a CD29 modulator, a fibronectin modulator, an interleukin-2 ligand, a serine protease inhibitor, a D40LG gene stimulator; TNFSF9 gene stimulator, a 2-oxoglutarate dehydrogenase inhibitor, a TGF-beta type II receptor antagonist, an Erbb3 tyrosine kinase receptor inhibitor, a cholecystokinin CCK2 receptor antagonist, a Wilms tumor protein modulator, a Ras GTPase modulator, an histone deacetylase inhibitor, a cyclin-dependent kinase 4 inhibitor A modulator, an estrogen receptor beta modulator, a 4-1BB inhibitor, a 4-1BBL inhibitor, a PD-L2 inhibitor, a B7-H3 inhibitor, a B7-H4 inhibitor, a BTLA inhibitor, a HVEM inhibitor, aTIM3 inhibitor, a GAL9 inhibitor, a LAG3 inhibitor, a VISTA inhibitor, a KIR inhibitor, a 2B4 inhibitor, a CD160 inhibitor and a CD66e modulator. In one ~~embodiment~~example, the one or more additional therapeutic compound is selected from one or more of bavituximab, IMM-101, CAP1-6D, Rexin-G , genistein, CVac, MM-D37K, PCI-27483, TG-01, mocetinostat, LOAd-703, CPI-613, upamostat, CRS-207, novaCaps, trametinib, Atu-027, sonidegib, GRASPA, trabedersen, nastorazepide, Vaccell , oregovomab, istiratumab, refametinib, regorafenib, lapatinib, selumetinib, rucaparib, pelareorep, tarextumab, PEGylated hyaluronidase, varlitinib,

KY-1003. In one ~~embodiment~~example, the one or more additional therapeutic compound is FOLFIRINOX. In one ~~embodiment~~example, the one or more additional therapeutic compound are gemcitabine and paclitaxel. In one ~~embodiment~~example, the one or more additional therapeutic compound is gemcitabine and nab-paclitaxel. In one ~~embodiment~~example, the combination comprises a fixed dose combination or separate doses. In one ~~embodiment~~example, R^1 is halogen or methyl; R^2 is halogen or C_{1-6} haloalkyl; R^3 is halogen or C_{1-6} alkyl; R^4 is hydrogen; n is 0; A^1 is –CH– or –N–; A^2 is –CH–; and A^3 is –N–. In one ~~embodiment~~example, R^1 is halogen or methyl; R^2 is C_{1-3} haloalkyl; R^3 is halogen or C_{1-3} alkyl; R^4 is hydrogen; n is 0; A^1 is –CH– or –N–; A^2 is –CH–; and A^3 is –N–. In one ~~embodiment~~example, the combination is selected from:

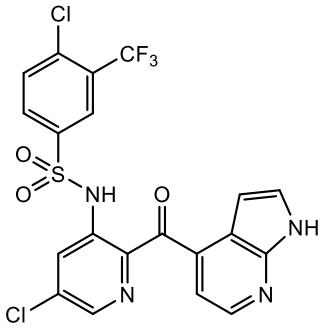


Ia ,



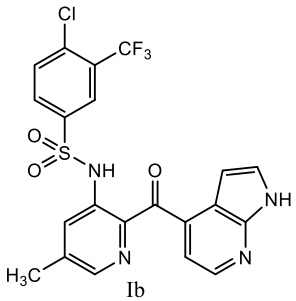
Ib ,

and



Ic

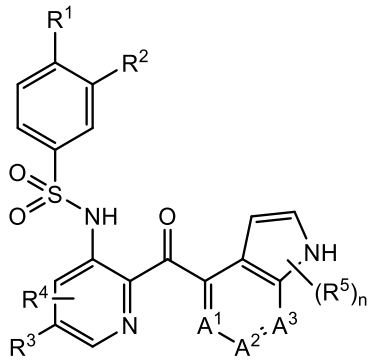
or a pharmaceutically acceptable salt thereof. In one ~~embodiment~~example, the compound is the compound of Formula 1b:



Ib

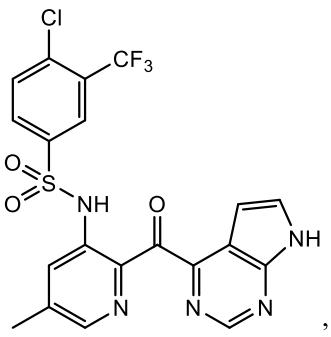
or a pharmaceutically acceptable salt thereof.

[0018] One ~~embodiment~~example includes a method of limiting over-expression of oncogenes, activating tumor suppressor genes, or regulating signaling proteins comprising administering to a patient in need thereof an effective amount of a compound of Formula I:

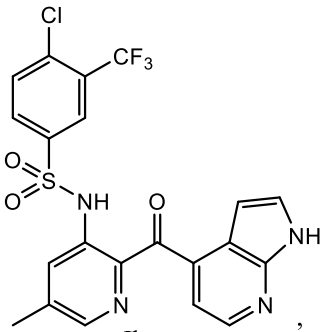


Formula I

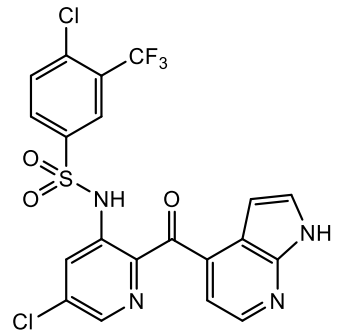
or a pharmaceutically acceptable salt thereof, wherein R^1 is halogen or C_{1-6} alkyl; R^2 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, or –CN; R^3 is hydrogen, halogen, or C_{1-6} alkyl; R^4 is hydrogen, halogen, or C_{1-6} alkyl; each R^5 is independently C_{1-6} alkyl, –OH, or $–NH_2$; n is 0, 1, 2, or 3; and each of A^1, A^2, and A^3 is –CH– or –N–, where at least one of A^1, A^2, or A^3 is –N–. In one ~~embodiment~~example, R^1 is halogen or methyl; R^2 is halogen or C_{1-6} haloalkyl; R^3 is halogen or C_{1-6} alkyl; R^4 is hydrogen; n is 0; A^1 is –CH– or –N–; A^2 is –CH–; and A^3 is –N–. In one ~~embodiment~~example, R^1 is halogen or methyl; R^2 is C_{1-3} haloalkyl; R^3 is halogen or C_{1-3} alkyl; R^4 is hydrogen; n is 0; A^1 is –CH– or –N–; A^2 is –CH–; and A^3 is –N–. In one ~~embodiment~~example, the compound is selected from:



Ia ,

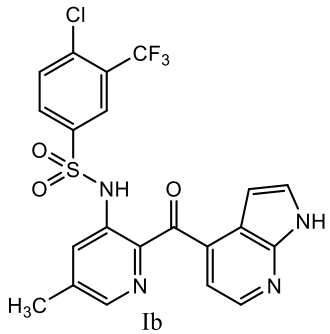


Ib ,

and 

Ic

or a pharmaceutically acceptable salt thereof. In an ~~embodiment~~example, the compound is the compound of Formula 1b:



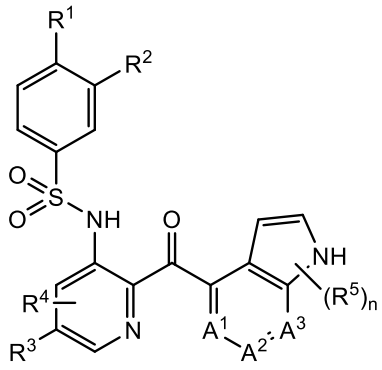
Ib

or a pharmaceutically acceptable salt thereof. In one ~~embodiment~~example, the over-expression of oncogenes, inactivation tumor suppressor genes or the deregulation of various signaling proteins resulted in diagnosis of pancreatic cancer for the patient. In one ~~embodiment~~example, the patient has been diagnosed with pancreatic adenocarcinoma, non-resectable pancreatic cancer, locally advanced pancreatic cancer, borderline resectable pancreatic cancer, locally advanced pancreatic ductal adenocarcinoma, borderline resectable pancreatic ductal adenocarcinoma, metastatic pancreatic cancer, chemotherapy-resistant pancreatic cancer, squamous pancreatic cancer, pancreatic progenitor, immunogenic pancreatic cancer, aberrantly differentiated endocrine exocrine (ADEX) tumors, pancreatic ductal adenocarcinoma. an exocrine pancreatic cancer, pancreatic intraepithelial neoplasia, intraductal papillary mucinous neoplasms, mucinous cystic neoplasms, mucinous pancreas cancer, adenosquamous carcinoma, signet ring cell carcinoma, hepatoid carcinoma, colloid carcinoma, undifferentiated carcinoma, undifferentiated carcinomas with osteoclast-like giant cells, a pancreatic cystic neoplasm, an islet cell tumor, a pancreas endrocrine tumor, or a pancreatic neuroendrocrine tumor. In one ~~embodiment~~example, the compound of Formula I is provided as a pharmaceutical composition for oral administration. In one ~~embodiment~~example, the patient achieves a complete response. In one ~~embodiment~~example, the patient achieves a partial response. In

one ~~embodiment~~example, the patient achieves stable disease. In one ~~embodiment~~example, the patient achieves a slower progressive disease. In one ~~embodiment~~example, the compound is administered once a day. In one ~~embodiment~~example, the compound is administered twice a day. In one ~~embodiment~~example, the method includes administering to the patient one or more additional therapeutic compounds. In one ~~embodiment~~example, the one or more additional therapeutic compound is selected from one or more of a Btk tyrosine kinase inhibitor, an Erbb2 tyrosine kinase receptor inhibitor; an Erbb4 tyrosine kinase receptor inhibitor, an mTOR inhibitor, a thymidylate synthase inhibitor, an EGFR tyrosine kinase receptor inhibitor, an epidermal growth factor antagonist, a Fyn tyrosine kinase inhibitor, a kit tyrosine kinase inhibitor, a Lyn tyrosine kinase inhibitor, a NK cell receptor modulator, a PDGF receptor antagonist, a PARP inhibitor, a poly ADP ribose polymerase inhibitor, a poly ADP ribose polymerase 1 inhibitor, a poly ADP ribose polymerase 2 inhibitor, a poly ADP ribose polymerase 3 inhibitor, a galactosyltransferase modulator, a dihydropyrimidine dehydrogenase inhibitor, an orotate phosphoribosyltransferase inhibitor, a telomerase modulator, a mucin 1 inhibitor, a mucin inhibitor, a secretin agonist, a TNF related apoptosis inducing ligand modulator, an IL17 gene stimulator, an interleukin 17E ligand, a neurokinin receptor agonist, a cyclin G1 inhibitor, a checkpoint inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a CTLA4 inhibitor, a topoisomerase I inhibitor, an Alk-5 protein kinase inhibitor, a connective tissue growth factor ligand inhibitor, a notch-2 receptor antagonist, a notch-3 receptor antagonist, a hyaluronidase stimulator, a MEK-1 protein kinase inhibitor; MEK-2 protein kinase inhibitor, a GM-CSF receptor modulator; TNF alpha ligand modulator, a mesothelin modulator, an asparaginase stimulator, a caspase-3 stimulator; caspase-9 stimulator, a PKN3 gene inhibitor, a hedgehog protein inhibitor; smoothened receptor antagonist, an AKT1 gene inhibitor, a DHFR inhibitor, a thymidine kinase stimulator, a CD29 modulator, a fibronectin modulator, an interleukin-2 ligand, a serine protease inhibitor, a D40LG gene stimulator; TNFSF9 gene stimulator, a 2-oxoglutarate dehydrogenase inhibitor, a TGF-beta type II receptor antagonist, an Erbb3 tyrosine kinase receptor inhibitor, a cholecystokinin CCK2 receptor antagonist, a Wilms tumor protein modulator, a Ras GTPase modulator, an histone deacetylase inhibitor, a cyclin-dependent kinase 4 inhibitor A modulator, an estrogen receptor beta modulator, a 4-1BB inhibitor, a 4-1BBL inhibitor, a PD-L2 inhibitor, a B7-H3 inhibitor, a B7-H4 inhibitor, a BTLA inhibitor, a HVEM inhibitor, aTIM3 inhibitor, a GAL9 inhibitor, a LAG3 inhibitor, a VISTA inhibitor, a KIR inhibitor, a 2B4 inhibitor, a CD160 inhibitor and a CD66e modulator. In one ~~embodiment~~example, the one or more additional therapeutic compound is

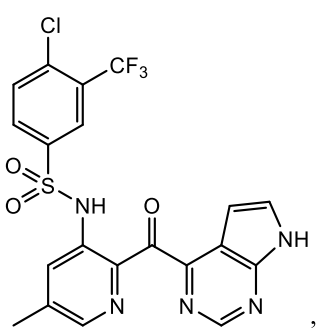
testolactone, thioguanine, 6-TG, thiotepa, topotecan, toremifene, tositumomab, trastuzumab, tretinoin, ATRA, uracil mustard, valrubicin, vinblastine, vincristine, vinorelbine, zoledronate, zoledronic acid, pembrolizumab, nivolumab, IBI-308, mDX-400, BGB-108, MEDI-0680, SHR-1210, PF-06801591, PDR-001, GB-226, STI-1110, durvalumab, atezolizumab, avelumab, BMS-936559, ALN-PDL, TSR-042, KD-033, CA-170, STI-1014, FOLFIRINOX and KY-1003. In one ~~embodiment~~example, the one or more additional therapeutic compound is FOLFIRINOX. In one ~~embodiment~~example, the one or more additional therapeutic compounds are gemcitabine and paclitaxel. In one ~~embodiment~~example, the one or more additional therapeutic compounds are gemcitabine and nab-paclitaxel.

[0019] One ~~embodiment~~example includes a method for controlling an adenocarcinoma in a patient that includes administering to the patient in need thereof an effective amount of a compound of Formula I:



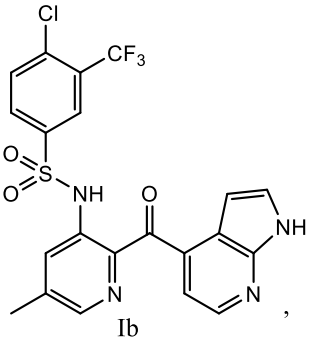
Formula I

or a pharmaceutically acceptable salt thereof. In one ~~embodiment~~example, R^1 is halogen or C_{1-6} alkyl; R^2 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, or –CN; R^3 is hydrogen, halogen, or C_{1-6} alkyl; R^4 is hydrogen, halogen, or C_{1-6} alkyl; each R^5 is independently C_{1-6} alkyl, –OH, or $–NH_2$; n is 0, 1, 2, or 3; and each of A^1, A^2, and A^3 is –CH– or –N–, where at least one of A^1, A^2, or A^3 is –N–. In one ~~embodiment~~example, R^1 is halogen or methyl; R^2 is C_{1-3} haloalkyl; R^3 is halogen or C_{1-3} alkyl; R^4 is hydrogen; n is 0; A^1 is –CH– or –N–; A^2 is –CH–; and A^3 is –N–. In one ~~embodiment~~example, the compound is selected from



Ia

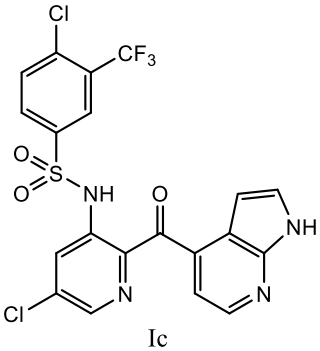
,



Ib

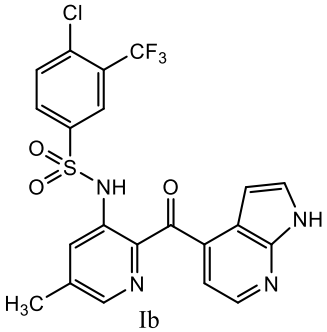
,

and



Ic

or a pharmaceutically acceptable salt thereof. In one ~~embodiment~~example, the compound is



Ib

or a pharmaceutically acceptable salt thereof. In one ~~embodiment~~example, the adenocarcinoma is pancreatic adenocarcinoma. In one ~~embodiment~~example, the patient achieves a complete response. In one ~~embodiment~~example, the patient achieves a partial response. In one ~~embodiment~~example, the patient achieves stable disease. In one ~~embodiment~~example, the patient achieves a slower progressive disease. In one ~~embodiment~~example, the patient achieves a clinical benefit. In one ~~embodiment~~example, the clinical benefit is one or more of decrease in tumor size, suppression or decrease of tumor growth, delayed time to progression, no new tumor or lesion, a decrease in new tumor formation, an increase in survival or progression-free survival , no metastases, increase in treatment options, delay in time from surgery to recurrence, reduction in jaundice, suppression of spread to liver, reduction in pain, improved appetite, improved digestion, reduction of gallbladder size, and reduced incidence of blood clots. In one ~~embodiment~~example, the compound of Formula I is provided as a pharmaceutical

composition for oral administration. In one ~~embodiment~~example, the compound is administered once a day. In one ~~embodiment~~example, the compound is administered twice a day. In one ~~embodiment~~example, the effective amount is from 50 mg to 300 mg. In one ~~embodiment~~example, the effective amount is 150 mg. In one ~~embodiment~~example, the method further comprises administering to the patient one or more additional therapeutic compound. In one ~~embodiment~~example, the the one or more additional therapeutic compound is selected from one or more of a Btk tyrosine kinase inhibitor, an Erbb2 tyrosine kinase receptor inhibitor; an Erbb4 tyrosine kinase receptor inhibitor, an mTOR inhibitor, a thymidylate synthase inhibitor, an EGFR tyrosine kinase receptor inhibitor, an Epidermal growth factor antagonist, a Fyn tyrosine kinase inhibitor, a kit tyrosine kinase inhibitor, a Lyn tyrosine kinase inhibitor, a NK cell receptor modulator, a PDGF receptor antagonist, a PARP inhibitor, a poly ADP ribose polymerase inhibitor , a poly ADP ribose polymerase 1 inhibitor, a poly ADP ribose polymerase 2 inhibitor, a poly ADP ribose polymerase 3 inhibitor, a galactosyltransferase modulator, a dihydropyrimidine dehydrogenase inhibitor, an orotate phosphoribosyltransferase inhibitor, a telomerase modulator, a mucin 1 inhibitor, a mucin inhibitor, a secretin agonist, a TNF related apoptosis inducing ligand modulator, an IL17 gene stimulator, an interleukin 17E ligand, a Neurokinin receptor agonist, a cyclin G1 inhibitor, a checkpoint inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a CTLA4 inhibitor, a topoisomerase I inhibitor, an Alk-5 protein kinase inhibitor, a connective tissue growth factor ligand inhibitor, a notch-2 receptor antagonist, a notch-3 receptor antagonist, a hyaluronidase stimulator, a MEK-1 protein kinase inhibitor; MEK-2 protein kinase inhibitor, a GM-CSF receptor modulator; TNF alpha ligand modulator, a mesothelin modulator, an asparaginase stimulator, a caspase-3 stimulator; caspase-9 stimulator, a PKN3 gene inhibitor, a hedgehog protein inhibitor; Smoothened receptor antagonist, an AKT1 gene inhibitor, a DHFR inhibitor, a thymidine kinase stimulator, a CD29 modulator, a fibronectin modulator, an interleukin-2 ligand, a serine protease inhibitor, a D40LG gene stimulator; TNFSF9 gene stimulator, a 2-oxoglutarate dehydrogenase inhibitor, a TGF-beta type II receptor antagonist, an Erbb3 tyrosine kinase receptor inhibitor, a cholecystokinin CCK2 receptor antagonist, a Wilms tumor protein modulator, a Ras GTPase modulator, an histone deacetylase inhibitor, a cyclin-dependent kinase 4 inhibitor A modulator, an estrogen receptor beta modulator, a 4-1BB inhibitor, a 4-1BBL inhibitor, a PD-L2 inhibitor, a B7-H3 inhibitor, a B7-H4 inhibitor, a BTLA inhibitor, a HVEM inhibitor, aTIM3 inhibitor, a GAL9 inhibitor, a LAG3 inhibitor, a VISTA inhibitor, a KIR inhibitor, a 2B4 inhibitor, a CD160 inhibitor and a CD66e modulator. In one ~~embodiment~~example, the one or more additional

testolactone, thioguanine, 6-TG, thiotepa, topotecan, toremifene, tositumomab, trastuzumab, tretinoin, ATRA, uracil mustard, valrubicin, vinblastine, vincristine, vinorelbine, zoledronate, zoledronic acid, pembrolizumab, nivolumab, IBI-308, mDX-400, BGB-108, MEDI-0680, SHR-1210, PF-06801591, PDR-001, GB-226, STI-1110, durvalumab, atezolizumab, avelumab, BMS-936559, ALN-PDL, TSR-042, KD-033, CA-170, STI-1014, FOLFIRINOX and KY-1003. In one ~~embodiment~~example, the one or more additional therapeutic compound is FOLFIRINOX. In one ~~embodiment~~example, the one or more additional therapeutic compounds are gemcitabine and paclitaxel. In one ~~embodiment~~example, the one or more additional therapeutic compounds are gemcitabine and nab-paclitaxel.

DETAILED DESCRIPTION

[0020] The present disclosure is directed to methods of treating pancreatic cancer in patients by administering the compounds and pharmaceutical combinations as described herein. Also described are methods of limiting over-expression of oncogenes, activating tumor suppressor genes, or regulating signaling proteins comprising administering to a patient in need thereof an effective amount of any of the compounds or pharmaceutical combinations as described herein. Accordingly, the present disclosure describes compounds which modulate at least one function or characteristic of mammalian CCR2, for example, a human CCR2 protein.

Abbreviations and definitions

[0021] The following definitions are meant to clarify, but not limit, the terms defined. If a particular term used herein is not specifically defined, such term should not be considered indefinite. Rather, terms are used within their accepted meanings by those of skill in the art.

[0022] "Alkyl" by itself or as part of another substituent refers to a hydrocarbon group which may be linear, cyclic, or branched or a combination thereof having the number of carbon atoms designated (i.e., $C_{1\text{-}8}$ means one to eight carbon atoms). Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, cyclopentyl, (cyclohexyl)methyl, cyclopropylmethyl, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, etc.

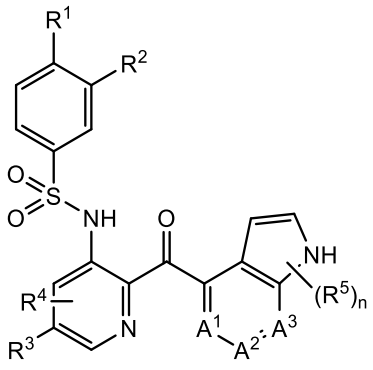
[0023] "Alkoxy" refers to –O–alkyl. Examples of an alkoxy group include methoxy, ethoxy, n-propoxy etc.

[0024] "Clinical benefit" refers to a phrase used by doctors and/or clinicians treating cancer. The term encompasses any appreciated or perceived benefit encountered by

CLAIMS

What is claimed is:

1. ~~A method of treating pancreatic cancer in a patient comprising administering to the patient in need thereof~~Use of an effective amount of a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of pancreatic cancer or in controlling an adenocarcinoma in a patient,

wherein

R^1 is halogen or C_{1-6} alkyl;

R^2 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, or –CN;

R^3 is hydrogen, halogen, or C_{1-6} alkyl;

R^4 is hydrogen, halogen, or C_{1-6} alkyl;

each R^5 is independently C_{1-6} alkyl, –OH, or $–NH_2$;

n is 0, 1, 2, or 3; and

each of A^1, A^2, and A^3 is –CH– or –N–, where at least one of A^1, A^2, or A^3 is –N–.

2. The ~~method~~ use of claim 1 wherein

R^1 is halogen or methyl;

R^2 is halogen or C_{1-6} haloalkyl;

R^3 is halogen or C_{1-6} alkyl;

R^4 is hydrogen;

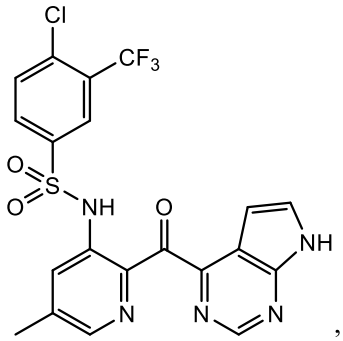
n is 0;

A^1 is –CH– or –N–;

A^2 is –CH–; and

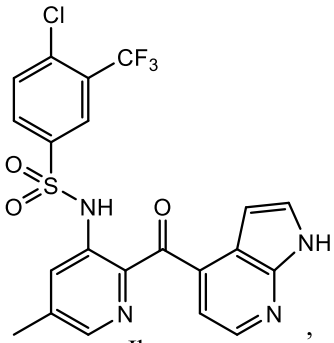
A^3 is –N–.

3. The ~~method~~ use of claim 1, wherein the compound is selected from the group consisting of:



Ia

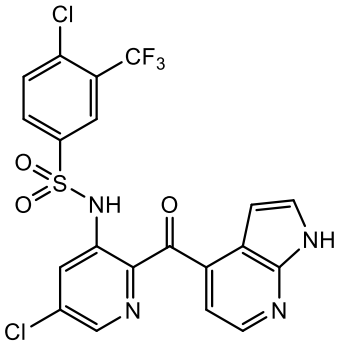
,



Ib

,

and

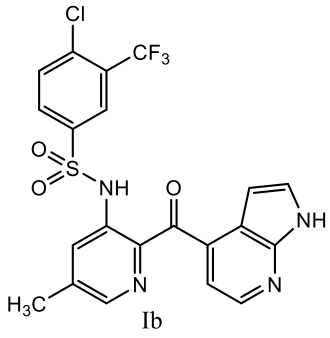


Ic

,

or a pharmaceutically acceptable salt thereof.

4. The ~~method~~ use of claim~~s~~ 1, wherein the compound is



Ib

or a pharmaceutically acceptable salt thereof.

~~5. The method of claim 1, wherein the pancreatic cancer is Stage I, II, III, or IV.~~

~~6. The method of claim 1, wherein the treatment provides one or more of a decrease in tumor size, a suppression or decrease in tumor growth, no new tumor formation, a decrease in new tumor formation, an increase in survival or progression-free survival, no metastases, an increase in treatment options, delay in time from surgery to recurrence, reduction in jaundice, suppression of spread to liver, reduction in pain, improved appetite, improved digestion, reduction of gallbladder size, and reduced incidence of blood clots.~~

~~7. The method of claim 1, wherein the patient achieves a complete response.~~

~~8. The method of claim 1, wherein the patient achieves a partial response.~~

~~9. The method of claim 1, wherein the patient achieves stable disease.~~

~~10. The method of claim 1, wherein the patient achieves a slower progressive disease.~~

~~11.~~5. The ~~method~~use of any one of claims 1 to 4, ~~wherein the patient suffers from one or more of~~in the manufacture of a medicament for controlling a pancreatic

adenocarcinoma~~, non-resectable pancreatic cancer, locally advanced pancreatic cancer, borderline resectable pancreatic cancer, locally advanced pancreatic ductal adenocarcinoma, borderline resectable pancreatic ductal adenocarcinoma, metastatic pancreatic cancer, chemotherapy-resistant pancreatic cancer, pancreatic ductal adenocarcinoma, squamous pancreatic cancer, pancreatic progenitor, immunogenic pancreatic cancer, aberrantly differentiated endocrine exocrine (ADEX) tumors, an exocrine pancreatic cancer, pancreatic intraepithelial neoplasia, intraductal papillary mucinous neoplasms, mucinous cystic neoplasms, mucinous pancreas cancer, adenosquamous carcinoma, signet ring cell carcinoma, hepatoid carcinoma, colloid carcinoma, undifferentiated carcinoma, undifferentiated carcinomas with osteoclast-like giant cells, a pancreatic cystic neoplasm, an islet cell tumor, a pancreas endrocrine tumor, or a pancreatic neuroendrocrine tumor~~.

~~12.~~6. The ~~method~~ use of any one of claims 1 to 5, wherein the compound of Formula I is provided as a pharmaceutical composition ~~for~~ to be administered orally ~~administration~~.

7. The use of any one of claims 1 to 6, wherein the effective amount is from 50 mg to 300 mg, preferably 150 mg.

~~13.~~8. The ~~method~~ use of any one of claims 1 to 7, wherein the compound is to be administered once a day or twice a day.

~~14. The method of claim 1, wherein the compound is administered twice a day.~~

~~15.~~ The ~~method~~ use of any one of claims 1 to 8, further comprising ~~administering to the patient~~ one or more additional therapeutic compound to be administered to the patient~~.~~

~~16.~~9. ~~The method of claim 15,~~ wherein the one or more additional therapeutic compound is selected from one or more of a Btk tyrosine kinase inhibitor, an Erbb2 tyrosine kinase receptor inhibitor; an Erbb4 tyrosine kinase receptor inhibitor, an mTOR inhibitor, a thymidylate synthase inhibitor, an EGFR tyrosine kinase receptor inhibitor, an Epidermal growth factor antagonist, a Fyn tyrosine kinase inhibitor, a kit tyrosine kinase inhibitor, a Lyn tyrosine kinase inhibitor, a NK cell receptor modulator, a PDGF receptor antagonist, a PARP inhibitor, a poly ADP ribose polymerase inhibitor , a poly ADP ribose polymerase 1 inhibitor, a poly ADP ribose polymerase 2 inhibitor, a poly ADP ribose polymerase 3 inhibitor, a galactosyltransferase modulator, a dihydropyrimidine dehydrogenase inhibitor, an orotate phosphoribosyltransferase inhibitor, a telomerase modulator, a mucin 1 inhibitor, a mucin inhibitor, a secretin agonist, a TNF related apoptosis inducing ligand modulator, an IL17 gene stimulator, an interleukin 17E ligand, a Neurokinin receptor agonist, a cyclin G1 inhibitor, a checkpoint inhibitor, a PD-1

inhibitor, a PD-L1 inhibitor, a CTLA4 inhibitor, a topoisomerase I inhibitor, an Alk-5 protein kinase inhibitor, a connective tissue growth factor ligand inhibitor, a notch-2 receptor antagonist, a notch-3 receptor antagonist, a hyaluronidase stimulator, a MEK-1 protein kinase inhibitor; MEK-2 protein kinase inhibitor, a GM-CSF receptor modulator; TNF alpha ligand modulator, a mesothelin modulator, an asparaginase stimulator, a caspase-3 stimulator; caspase-9 stimulator, a PKN3 gene inhibitor, a hedgehog protein inhibitor; Smoothened receptor antagonist, an AKT1 gene inhibitor, a DHFR inhibitor, a thymidine kinase stimulator, a CD29 modulator, a fibronectin modulator, an interleukin-2 ligand, a serine protease inhibitor, a D40LG gene stimulator; TNFSF9 gene stimulator, a 2-oxoglutarate dehydrogenase inhibitor, a TGF-beta type II receptor antagonist, an Erbb3 tyrosine kinase receptor inhibitor, a cholecystokinin CCK2 receptor antagonist, a Wilms tumor protein modulator, a Ras GTPase modulator, an histone deacetylase inhibitor, a cyclin-dependent kinase 4 inhibitor A modulator, an estrogen receptor beta modulator, a 4-1BB inhibitor, a 4-1BBL inhibitor, a PD-L2 inhibitor, a B7-H3 inhibitor, a B7-H4 inhibitor, a BTLA inhibitor, a HVEM inhibitor, aTIM3 inhibitor, a GAL9 inhibitor, a LAG3 inhibitor, a VISTA inhibitor, a KIR inhibitor, a 2B4 inhibitor, a CD160 inhibitor and a CD66e modulator.

~~17. The method of claim 15 wherein the one or more additional therapeutic compound is selected from one or more of bavituximab, IMM-101, CAP1-6D, Rexin-G , genistein, CVac, MM-D37K, PCI-27483, TG-01, mocetinostat, LOAd-703, CPI-613, upamostat, CRS-207, NovaCaps, trametinib, Atu-027, sonidegib, GRASPA, trabedersen, nastorazepide, Vaccell , oregovomab, istiratumab, refametinib, regorafenib, lapatinib, selumetinib, rucaparib, pelareorep, tarextumab, PEGylated hyaluronidase, varlitinib, aglatimagene besadenovec, GBS-01, GI-4000, WF-10, galunisertib, afatinib, RX-0201, FG-3019, pertuzumab, DCVax-Direct, selinexor, glufosfamide, virulizin, yttrium (90Y) clivatuzumab tetraxetan, brivudine, nimotuzumab, algenpantucel-L, tegafur + gimeracil + oteracil potassium + calcium folinate, olaparib, ibrutinib, pirarubicin, Rh-Apo2L, tertomotide, tegafur + gimeracil + oteracil potassium, tegafur + gimeracil + oteracil potassium, masitinib, Rexin-G, mitomycin, erlotinib , adriamycin, dexamethasone, vincristine, cyclophosphamide, fluorouracil, topotecan, taxol, interferons, platinum derivatives, taxane, paclitaxel, vinca alkaloids, vinblastine, anthracyclines, doxorubicin, epipodophyllotoxins, etoposide, cisplatin, rapamycin, methotrexate, actinomycin D, dolastatin 10, colchicine, emetine, trimetrexate, metoprine, cyclosporine, daunorubicin, teniposide, amphotericin, alkylating agents, chlorambucil, 5-fluorouracil, campthothecin,~~

metronidazole, Gleevec, Avastin, Vectibix, abarelix, aldesleukin, alemtuzumab, alitretinoin, allopurinol, altretamine, amifostine, anastrozole, arsenic trioxide, asparaginase, azacitidine, AZD9291, BCG Live, bevacuzimab, fluorouracil, bexarotene, bleomycin, bortezomib, busulfan, calusterone, capecitabine, camptothecin, carboplatin, carmustine, celecoxib, cetuximab, chlorambucil, cladribine, clofarabine, cyclophosphamide, cytarabine, dactinomycin, darbepoetin alfa, daunorubicin, denileukin, dexrazoxane, docetaxel, doxorubicin (neutral), doxorubicin hydrochloride, dromostanolone propionate, epirubicin, epoetin alfa, estramustine, etoposide phosphate, etoposide, exemestane, filgrastim, floxuridine fludarabine, fulvestrant, gefitinib, gemcitabine, gemtuzumab, goserelin acetate, histrelin acetate, hydroxyurea, ibritumomab, idarubicin, ifosfamide, imatinib mesylate, interferon alfa-2a, interferon alfa-2b, irinotecan, lenalidomide, letrozole, leucovorin, leuprolide acetate, levamisole, lomustine, megestrol acetate, melphalan, mercaptopurine, 6-MP, mesna, methotrexate, methoxsalen, mitomycin C, mitotane, mitoxantrone, nandrolone, nelarabine, nofetumomab, oprelvekin, oxaliplatin, paclitaxel, palifermin, pamidronate, pegademase, pegaspargase, pegfilgrastim, pemetrexed disodium, pentostatin, pipobroman, plicamycin, porfimer sodium, procarbazine, quinacrine, rasburicase, rituximab, rociletinib, sargramostim, sorafenib, streptozocin, sunitinib maleate, talc, tamoxifen, temozolomide, teniposide, VM-26, testolactone, thioguanine, 6-TG, thiotepa, topotecan, toremifene, tositumomab, trastuzumab, tretinoin, ATRA, uracil mustard, valrubicin, vinblastine, vincristine, vinorelbine, zoledronate, zoledronic acid, pembrolizumab, nivolumab, IBI-308, mDX-400, BGB-108, MEDI-0680, SHR-1210, PF-06801591, PDR-001, GB-226, STI-1110, durvalumab, atezolizumab, avelumab, BMS-936559, ALN-PDL, TSR-042, KD-033, CA-170, STI-1014, FOLFIRINOX and KY-1003.

18. The use method of claim 9 15, wherein the one or more additional therapeutic compound is FOLFIRINOX.

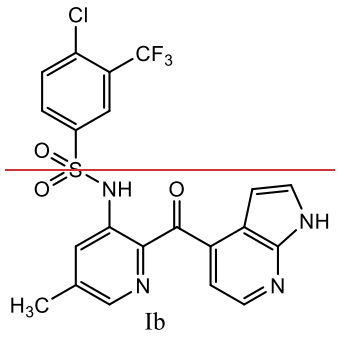
19. 10. The method of claim 15, or wherein the one or more additional therapeutic compounds are gemcitabine and paclitaxel.

11. Use of a pharmaceutical composition comprising a compound as defined in any one of claims 1 to 5 and a pharmaceutically acceptable excipient, in the manufacture of a medicament for the treatment of pancreatic cancer or in controlling an adenocarcinoma.

12. The use according to claim 11, comprising one or more additional therapeutic compound in addition to the compound as defined in any one of claims 1 to 5, wherein the one or

more additional therapeutic compound is FOLFIRINOX, or wherein the one or more additional therapeutic compounds are gemcitabine and paclitaxel.

~~20. A method of treating pancreatic cancer in a patient comprising administering to the patient in need thereof an effective amount of a compound of Formula Ib:~~



Ib

~~or a pharmaceutically acceptable salt thereof.~~

~~21. The method of claim 20, wherein the pancreatic cancer is Stage I, II, III, or IV.~~

~~22. The method of claim 20, wherein the treatment provides one or more of a decrease in tumor size, a suppression or decrease of tumor growth, no new tumor formation, a decrease in new tumor formation, an increase in survival or progression-free survival, no metastases, increase in treatment options, delay in time from surgery to recurrence, reduction in jaundice, suppression of spread to liver, reduction in pain, improved appetite, improved digestion, reduction of gallbladder size, and reduced incidence of blood clots.~~

~~23. The method of claim 20, wherein the patient achieves a complete response.~~

~~24. The method of claim 20, wherein the patient achieves a partial response.~~

~~25. The method of claim 20, wherein the patient achieves stable disease.~~

~~26. The method of claim 20, wherein the patient achieves a slower progressive disease.~~

~~27. The method of claim 20, wherein the patient suffers from pancreatic adenocarcinoma, non-resectable pancreatic cancer, locally advanced pancreatic cancer, borderline resectable pancreatic cancer, locally advanced pancreatic ductal adenocarcinoma, borderline resectable pancreatic ductal adenocarcinoma, metastatic pancreatic cancer, chemotherapy-resistant pancreatic cancer, pancreatic ductal adenocarcinoma, squamous pancreatic cancer, pancreatic progenitor, immunogenic pancreatic cancer, aberrantly differentiated endocrine exocrine (ADEX) tumors, an exocrine pancreatic cancer, pancreatic intraepithelial neoplasia, intraductal papillary mucinous neoplasms, mucinous cystic neoplasms, mucinous pancreas cancer, adenosquamous carcinoma,~~

signet ring cell carcinoma, hepatoid carcinoma, colloid carcinoma, undifferentiated carcinoma, undifferentiated carcinomas with osteoclast-like giant cells, a pancreatic cystic neoplasm, an islet cell tumor, a pancreas endrocrine tumor, or a pancreatic neuroendrocrine tumor.

28. The method of claim 20, wherein the compound of Formula Ib is provided as a pharmaceutical composition for oral administration.

29. The method of claim 20, wherein the compound is administered once a day.

30. The method of claim 20, wherein the compound is administered twice a day.

31. The method of claim 20, wherein the effective amount is from 50 mg to 300 mg.

32. The method of claim 20, wherein the effective amount is 150 mg.

33. The method of claim 20, further comprising administering to the patient one or more additional therapeutic compound.

34. The method of claim 33 wherein the one or more additional therapeutic compound is selected from one or more of a Btk tyrosine kinase inhibitor, an Erbb2 tyrosine kinase receptor inhibitor; an Erbb4 tyrosine kinase receptor inhibitor, an mTOR inhibitor, a thymidylate synthase inhibitor, an EGFR tyrosine kinase receptor inhibitor, an Epidermal growth factor antagonist, a Fyn tyrosine kinase inhibitor, a kit tyrosine kinase inhibitor, a Lyn tyrosine kinase inhibitor, a NK cell receptor modulator, a PDGF receptor antagonist, a PARP inhibitor, a poly ADP ribose polymerase inhibitor , a poly ADP ribose polymerase 1 inhibitor, a poly ADP ribose polymerase 2 inhibitor, a poly ADP ribose polymerase 3 inhibitor, a galactosyltransferase modulator, a dihydropyrimidine dehydrogenase inhibitor, an orotate phosphoribosyltransferase inhibitor, a telomerase modulator, a mucin 1 inhibitor, a mucin inhibitor, a secretin agonist, a TNF related apoptosis inducing ligand modulator, an IL17 gene stimulator, an interleukin 17E ligand, a Neurokinin receptor agonist, a cyclin G1 inhibitor, a checkpoint inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a CTLA4 inhibitor, a topoisomerase I inhibitor, an Alk-5 protein kinase inhibitor, a connective tissue growth factor ligand inhibitor, a notch-2 receptor antagonist, a notch-3 receptor antagonist, a hyaluronidase stimulator, a MEK-1 protein kinase inhibitor; MEK-2 protein kinase inhibitor, a GM-CSF receptor modulator; TNF alpha ligand modulator, a mesothelin modulator, an asparaginase stimulator, a caspase-3 stimulator; caspase-9 stimulator, a PKN3 gene inhibitor, a hedgehog protein inhibitor; Smoothened receptor antagonist, an AKT1 gene inhibitor, a DHFR inhibitor, a thymidine kinase stimulator, a CD29 modulator, a fibronectin modulator, an interleukin-2 ligand, a serine protease inhibitor, a D40LG gene stimulator; TNFSF9 gene stimulator, a

2-oxoglutarate dehydrogenase inhibitor, a TGF-beta type II receptor antagonist, an Erbb3 tyrosine kinase receptor inhibitor, a cholecystokinin CCK2 receptor antagonist, a Wilms tumor protein modulator, a Ras GTPase modulator, an histone deacetylase inhibitor, a cyclin-dependent kinase 4 inhibitor A modulator, an estrogen receptor beta modulator, a 4-1BB inhibitor, a 4-1BBL inhibitor, a PD-L2 inhibitor, a B7-H3 inhibitor, a B7-H4 inhibitor, a BTLA inhibitor, a HVEM inhibitor, aTIM3 inhibitor, a GAL9 inhibitor, a LAG3 inhibitor, a VISTA inhibitor, a KIR inhibitor, a 2B4 inhibitor, a CD160 inhibitor and a CD66e modulator.

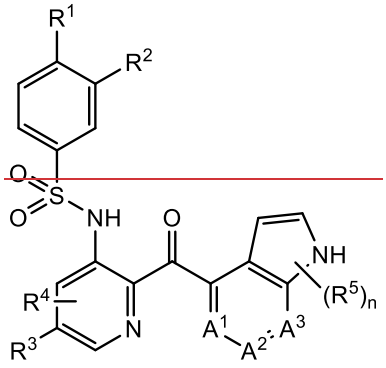
35. The method of claim 33 wherein the one or more additional therapeutic compound is selected from one or more of bavituximab, IMM-101, CAP1-6D, Rexin-G , genistein, CVac, MM-D37K, PCI-27483, TG-01, mocetinostat, LOAd-703, CPI-613, upamostat, CRS-207, NovaCaps, trametinib, Atu-027, sonidegib, GRASPA, trabedersen, nastorazepide, Vaccell , oregovomab, istiratumab, refametinib, regorafenib, lapatinib, selumetinib, rucaparib, pelareorep, tarextumab, PEGylated hyaluronidase, varlitinib, aglatimagene besadenovec, GBS-01, GI-4000, WF-10, galunisertib, afatinib, RX-0201, FG-3019, pertuzumab, DCVax-Direct, selinexor, glufosfamide, virulizin, yttrium (90Y) clivatuzumab tetraxetan, brivudine, nimotuzumab, algenpantucel-L, tegafur + gimeracil + oteracil potassium + calcium folinate, olaparib, ibrutinib, pirarubicin, Rh-Apo2L, tertomotide, tegafur + gimeracil + oteracil potassium, tegafur + gimeracil + oteracil potassium, masitinib, Rexin-G, mitomycin, erlotinib , adriamycin, dexamethasone, vincristine, cyclophosphamide, fluorouracil, topotecan, taxol, interferons, platinum derivatives, taxane, paclitaxel, vinca alkaloids, vinblastine, anthracyclines, doxorubicin, epipodophyllotoxins, etoposide, cisplatin, rapamycin, methotrexate, actinomycin D, dolastatin 10, colchicine, emetine, trimetrexate, metoprine, cyclosporine, daunorubicin, teniposide, amphotericin, alkylating agents, chlorambucil, 5-fluorouracil, campthothecin, cisplatin, metronidazole, Gleevec, Avastin, Vectibix, abarelix, aldesleukin, alemtuzumab, alitretinoin, allopurinol, altretamine, amifostine, anastrozole, arsenic trioxide, asparaginase, azacitidine, AZD9291, BCG Live, bevacuzimab, fluorouracil, bexarotene, bleomycin, bortezomib, busulfan, calusterone, capecitabine, camptothecin, carboplatin, carmustine, celecoxib, cetuximab, chlorambucil, cladribine, clofarabine, cyclophosphamide, cytarabine, dactinomycin, darbepoetin alfa, daunorubicin, denileukin, dexrazoxane, docetaxel, doxorubicin (neutral), doxorubicin hydrochloride, dromostanolone propionate, epirubicin, epoetin alfa, estramustine, etoposide phosphate, etoposide, exemestane, filgrastim, floxuridine fludarabine, fulvestrant, gefitinib,

gemcitabine, gemtuzumab, goserelin acetate, histrelin acetate, hydroxyurea, ibritumomab, idarubicin, ifosfamide, imatinib mesylate, interferon alfa-2a, interferon alfa-2b, irinotecan, lenalidomide, letrozole, leucovorin, leuprolide acetate, levamisole, lomustine, megestrol acetate, melphalan, mercaptopurine, 6-MP, mesna, methotrexate, methoxsalen, mitomycin C, mitotane, mitoxantrone, nandrolone, nelarabine, nofetumomab, oprelvekin, oxaliplatin, paclitaxel, palifermin, pamidronate, pegademase, pegaspargase, pegfilgrastim, pemetrexed disodium, pentostatin, pipobroman, plicamycin, porfimer sodium, procarbazine, quinacrine, rasburicase, rituximab, rociletinib, sargramostim, sorafenib, streptozocin, sunitinib maleate, talc, tamoxifen, temozolomide, teniposide, VM-26, testolactone, thioguanine, 6-TG, thiotepa, topotecan, toremifene, tositumomab, trastuzumab, tretinoin, ATRA, uracil mustard, valrubicin, vinblastine, vincristine, vinorelbine, zoledronate, zoledronic acid, pembrolizumab, nivolumab, IBI-308, mDX-400, BGB-108, MEDI-0680, SHR-1210, PF-06801591, PDR-001, GB-226, STI-1110, durvalumab, atezolizumab, avelumab, BMS-936559, ALN-PDL, TSR-042, KD-033, CA-170, STI-1014, FOLFIRINOX and KY-1003.

36. The method of claim 33, wherein the one or more additional therapeutic compound is FOLFIRINOX.

37. The method of claim 33, wherein the one or more additional therapeutic compounds are gemcitabine and paclitaxel.

38. A pharmaceutical combination comprising a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, wherein

R^1 is halogen or C_{1-6} alkyl;

R^2 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, or –CN;

R^3 is hydrogen, halogen, or C_{1-6} alkyl;

R^4 is hydrogen, halogen, or C_{1-6} alkyl;

each R^5 is independently C_{1-6} alkyl, –OH, or $–NH_2$;

n is 0, 1, 2, or 3;

each of A^1, A^2, and A^3 is –CH– or –N–, where at least one of A^1, A^2, or A^3 is –N–; and

one or more additional therapeutic compound.

39. The pharmaceutical combination of claim 38, wherein the one or more additional therapeutic compound is selected from one or more of a Btk tyrosine kinase inhibitor, an Erbb2 tyrosine kinase receptor inhibitor; an Erbb4 tyrosine kinase receptor inhibitor, an mTOR inhibitor, a thymidylate synthase inhibitor, an EGFR tyrosine kinase receptor inhibitor, an Epidermal growth factor antagonist, a Fyn tyrosine kinase inhibitor, a kit tyrosine kinase inhibitor, a Lyn tyrosine kinase inhibitor, a NK cell receptor modulator, a PDGF receptor antagonist, a PARP inhibitor, a poly ADP ribose polymerase inhibitor , a poly ADP ribose polymerase 1 inhibitor, a poly ADP ribose polymerase 2 inhibitor, a poly ADP ribose polymerase 3 inhibitor, a galactosyltransferase modulator, a dihydropyrimidine dehydrogenase inhibitor, an orotate phosphoribosyltransferase inhibitor, a telomerase modulator, a mucin 1 inhibitor, a mucin inhibitor, a secretin agonist, a TNF related apoptosis inducing ligand modulator, an IL17 gene stimulator, an interleukin 17E ligand, a Neurokinin receptor agonist, a cyclin G1 inhibitor, a checkpoint inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a CTLA4 inhibitor, a topoisomerase I inhibitor, an Alk-5 protein kinase inhibitor, a connective tissue growth factor ligand inhibitor, a notch-2 receptor antagonist, a notch-3 receptor antagonist, a hyaluronidase stimulator, a MEK-1 protein kinase inhibitor; MEK-2 protein kinase inhibitor, a GM-CSF receptor modulator; TNF alpha ligand modulator, a mesothelin modulator, an asparaginase stimulator, a caspase-3 stimulator; caspase-9 stimulator, a PKN3 gene inhibitor, a hedgehog protein inhibitor; Smoothened receptor antagonist, an AKT1 gene inhibitor, a DHFR inhibitor, a thymidine kinase stimulator, a CD29 modulator, a fibronectin modulator, an interleukin-2 ligand, a serine protease inhibitor, a D40LG gene stimulator; TNFSF9 gene stimulator, a 2-oxoglutarate dehydrogenase inhibitor, a TGF-beta type II receptor antagonist, an Erbb3 tyrosine kinase receptor inhibitor, a cholecystokinin CCK2 receptor antagonist, a Wilms tumor protein modulator, a Ras GTPase modulator, an histone deacetylase inhibitor, a cyclin-dependent kinase 4 inhibitor A modulator, an estrogen receptor beta modulator, a 4-1BB inhibitor, a 4-1BBL inhibitor, a PD-L2 inhibitor, a B7-H3 inhibitor, a B7-H4 inhibitor, a BTLA inhibitor, a

HVEM inhibitor, aTIM3 inhibitor, a GAL9 inhibitor, a LAG3 inhibitor, a VISTA inhibitor, a KIR inhibitor, a 2B4 inhibitor, a CD160 inhibitor and a CD66e modulator.

40. The pharmaceutical combination of claim 38, wherein the one or more additional therapeutic compound is selected from one or more of bavituximab, IMM-101, CAP1-6D, Rexin-G , genistein, CVac, MM-D37K, PCI-27483, TG-01, mocetinostat, LOAd-703, CPI-613, upamostat, CRS-207, NovaCaps, trametinib, Atu-027, sonidegib, GRASPA, trabedersen, nastorazepide, Vaccell , oregovomab, istiratumab, refametinib, regorafenib, lapatinib, selumetinib, rucaparib, pelareorep, tarextumab, PEGylated hyaluronidase, varlitinib, aglatimagene besadenovec, GBS-01, GI-4000, WF-10, galunisertib, afatinib, RX-0201, FG-3019, pertuzumab, DCVax-Direct, selinexor, glufosfamide, virulizin, yttrium (90Y) clivatuzumab tetraxetan, brivudine, nimotuzumab, algenpantucel-L, tegafur + gimeracil + oteracil potassium + calcium folinate, olaparib, ibrutinib, pirarubicin, Rh-Apo2L, tertomotide, tegafur + gimeracil + oteracil potassium, tegafur + gimeracil + oteracil potassium, masitinib, Rexin-G, mitomycin, erlotinib , adriamycin, dexamethasone, vincristine, cyclophosphamide, fluorouracil, topotecan, taxol, interferons, platinum derivatives, taxane, paclitaxel, vinca alkaloids, vinblastine, anthracyclines, doxorubicin, epipodophyllotoxins, etoposide, cisplatin, rapamycin, methotrexate, actinomycin D, dolastatin 10, colchicine, emetine, trimetrexate, metoprine, cyclosporine, daunorubicin, teniposide, amphotericin, alkylating agents, chlorambucil, 5-fluorouracil, campthothecin, cisplatin, metronidazole, Gleevec, Avastin, Vectibix, abarelix, aldesleukin, alemtuzumab, alitretinoin, allopurinol, altretamine, amifostine, anastrozole, arsenic trioxide, asparaginase, azacitidine, AZD9291, BCG Live, bevacuzimab, fluorouracil, bexarotene, bleomycin, bortezomib, busulfan, calusterone, capecitabine, camptothecin, carboplatin, carmustine, celecoxib, cetuximab, chlorambucil, cladribine, clofarabine, cyclophosphamide, cytarabine, dactinomycin, darbepoetin alfa, daunorubicin, denileukin, dexrazoxane, docetaxel, doxorubicin (neutral), doxorubicin hydrochloride, dromostanolone propionate, epirubicin, epoetin alfa, estramustine, etoposide phosphate, etoposide, exemestane, filgrastim, floxuridine fludarabine, fulvestrant, gefitinib, gemcitabine, gemtuzumab, goserelin acetate, histrelin acetate, hydroxyurea, ibritumomab, idarubicin, ifosfamide, imatinib mesylate, interferon alfa-2a, interferon alfa-2b, irinotecan, lenalidomide, letrozole, leucovorin, leuprolide acetate, levamisole, lomustine, megestrol acetate, melphalan, mercaptopurine, 6-MP, mesna, methotrexate, methoxsalen, mitomycin C, mitotane, mitoxantrone, nandrolone, nelarabine, nofetumomab, oprelvekin, oxaliplatin, paclitaxel, palifermin, pamidronate,

pegademase, pegaspargase, pegfilgrastim, pemetrexed disodium, pentostatin, pipobroman, plicamycin, porfimer sodium, procarbazine, quinacrine, rasburicase, rituximab, rociletinib, sargramostim, sorafenib, streptozocin, sunitinib maleate, talc, tamoxifen, temozolomide, teniposide, VM-26, testolactone, thioguanine, 6-TG, thiotepa, topotecan, toremifene, tositumomab, trastuzumab, tretinoin, ATRA, uracil mustard, valrubicin, vinblastine, vincristine, vinorelbine, zoledronate, zoledronic acid, pembrolizumab, nivolumab, IBI-308, mDX-400, BGB-108, MEDI-0680, SHR-1210, PF-06801591, PDR-001, GB-226, STI-1110, durvalumab, atezolizumab, avelumab, BMS-936559, ALN-PDL, TSR-042, KD-033, CA-170, STI-1014, FOLFIRINOX and KY-1003.

41. The pharmaceutical combination of claim 38, wherein the one or more additional therapeutic compound is FOLFIRINOX.

42. The pharmaceutical combination of claim 38, wherein the one or more additional therapeutic compounds are gemcitabine and paclitaxel.

43. The pharmaceutical combination of claim 38, wherein the combination comprises a fixed dose combination or separate doses.

44. The pharmaceutical combination of claim 38, wherein

R^1 is halogen or methyl;

R^2 is halogen or C_{1-6} haloalkyl;

R^3 is halogen or C_{1-6} alkyl;

R^4 is hydrogen;

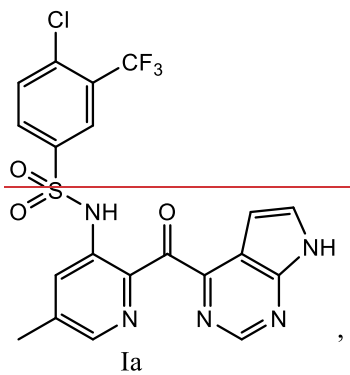
n is 0;

A^1 is –CH– or –N–;

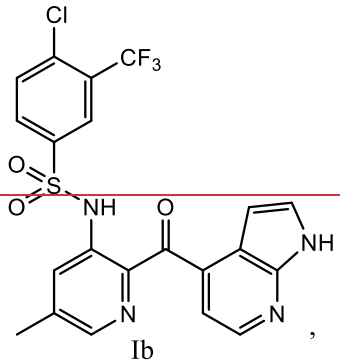
A^2 is –CH–; and

A^3 is –N–.

45. The pharmaceutical combination of claim 38, wherein the compound is selected from:

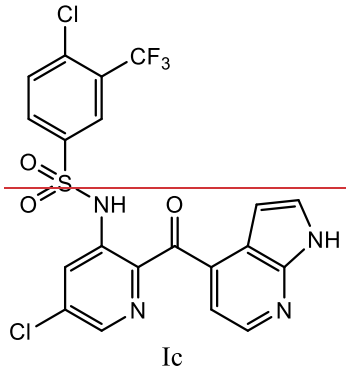


Ia ,



Ib ,

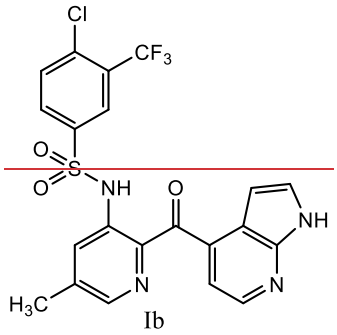
and



Ic ,

or a pharmaceutically acceptable salt thereof.

46. The pharmaceutical combination of claim 38, wherein the compound is

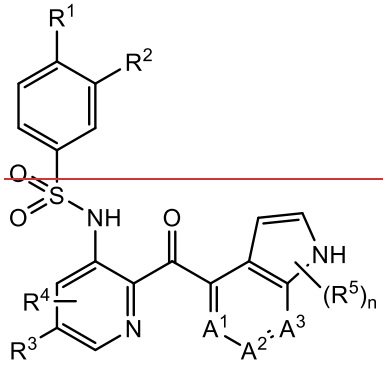


Ib

or a pharmaceutically acceptable salt thereof.

47. A method of treating pancreatic cancer comprising administration of the pharmaceutical combination of claim 38.

48. A method of limiting over-expression of oncogenes, activating tumor suppressor genes, or regulating signaling proteins comprising administering to a patient in need thereof an effective amount of a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, wherein

R^1 is halogen or C_{1-6} alkyl;

R^2 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, or –CN;

R^3 is hydrogen, halogen, or C_{1-6} alkyl;

R^4 is hydrogen, halogen, or C_{1-6} alkyl;

each R^5 is independently C_{1-6} alkyl, –OH, or $–NH_2$;

n is 0, 1, 2, or 3; and

each of A^1, A^2, and A^3 is –CH– or –N–, where at least one of A^1, A^2, or A^3 is –N–.

49. The method of claim 48, wherein

R^1 is halogen or methyl;

R^2 is halogen or C_{1-6} haloalkyl;

R^3 is halogen or C_{1-6} alkyl;

R^4 is hydrogen;

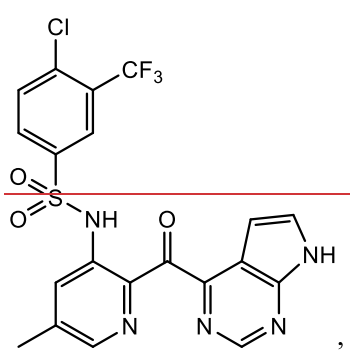
n is 0;

A^1 is –CH– or –N–;

A^2 is –CH–; and

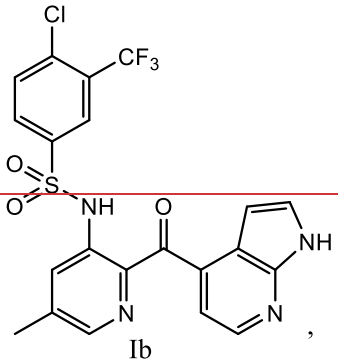
A^3 is –N–.

50. The method of claim 48, wherein the compound is selected from:



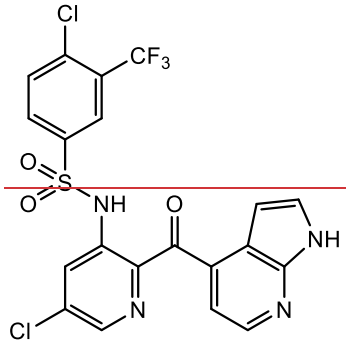
Ia

,



Ib

, and

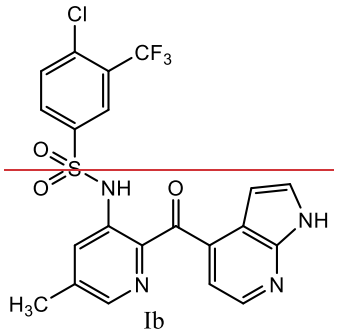


Ic

,

or a pharmaceutically acceptable salt thereof.

51. The method of claim 48, wherein the compound is



Ib

or a pharmaceutically acceptable salt thereof.

52. The method of claim 48, wherein the over-expression of oncogenes, inactivation tumor suppressor genes or the deregulation of various signaling proteins resulted in diagnosis of pancreatic cancer for the patient.

53. The method of claim 48, wherein the patient has been diagnosed with pancreatic adenocarcinoma, non-resectable pancreatic cancer, locally advanced pancreatic cancer, borderline resectable pancreatic cancer, locally advanced pancreatic ductal adenocarcinoma, borderline resectable pancreatic ductal adenocarcinoma, metastatic

pancreatic cancer, chemotherapy-resistant pancreatic cancer, squamous pancreatic cancer, pancreatic progenitor, immunogenic pancreatic cancer, aberrantly differentiated endocrine exocrine (ADEX) tumors, pancreatic ductal adenocarcinoma. an exocrine pancreatic cancer, pancreatic intraepithelial neoplasia, intraductal papillary mucinous neoplasms, mucinous cystic neoplasms, mucinous pancreas cancer, adenosquamous carcinoma, signet ring cell carcinoma, hepatoid carcinoma, colloid carcinoma, undifferentiated carcinoma, undifferentiated carcinomas with osteoclast-like giant cells, a pancreatic cystic neoplasm, an islet cell tumor, a pancreas endrocrine tumor, or a pancreatic neuroendrocrine tumor.

54. The method of claim 48, wherein the compound of Formula I is provided as a pharmaceutical composition for oral administration.

55. The method of claim 48, wherein the patient achieves a complete response.

56. The method of claim 48, wherein the patient achieves a partial response.

57. The method of claim 48, wherein the patient achieves stable disease.

58. The method of claim 48, wherein the patient achieves a slower progressive disease.

59. The method of claim 48, wherein the compound is administered once a day.

60. The method of claim 48, wherein the compound is administered twice a day.

61. The method of claim 48, further comprising administering to the patient one or more additional therapeutic compound.

62. The method of claim 61 wherein the one or more additional therapeutic compound is selected from one or more of a Btk tyrosine kinase inhibitor, an Erbb2 tyrosine kinase receptor inhibitor; an Erbb4 tyrosine kinase receptor inhibitor, an mTOR inhibitor, a thymidylate synthase inhibitor, an EGFR tyrosine kinase receptor inhibitor, an Epidermal growth factor antagonist, a Fyn tyrosine kinase inhibitor, a kit tyrosine kinase inhibitor, a Lyn tyrosine kinase inhibitor, a NK cell receptor modulator, a PDGF receptor antagonist, a PARP inhibitor, a poly ADP ribose polymerase inhibitor , a poly ADP ribose polymerase 1 inhibitor, a poly ADP ribose polymerase 2 inhibitor, a poly ADP ribose polymerase 3 inhibitor, a galactosyltransferase modulator, a dihydropyrimidine dehydrogenase inhibitor, an orotate phosphoribosyltransferase inhibitor, a telomerase modulator, a mucin 1 inhibitor, a mucin inhibitor, a secretin agonist, a TNF related apoptosis inducing ligand modulator, an IL17 gene stimulator, an interleukin 17E ligand, a Neurokinin receptor agonist, a cyclin G1 inhibitor, a checkpoint inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a CTLA4 inhibitor, a topoisomerase I inhibitor, an Alk-5 protein kinase inhibitor, a connective tissue growth factor ligand inhibitor, a notch-2

receptor antagonist, a notch-3 receptor antagonist, a hyaluronidase stimulator, a MEK-1 protein kinase inhibitor; MEK-2 protein kinase inhibitor, a GM-CSF receptor modulator; TNF-alpha ligand modulator, a mesothelin modulator, an asparaginase stimulator, a caspase-3 stimulator; caspase-9 stimulator, a PKN3 gene inhibitor, a hedgehog protein inhibitor; Smoothened receptor antagonist, an AKT1 gene inhibitor, a DHFR inhibitor, a thymidine kinase stimulator, a CD29 modulator, a fibronectin modulator, an interleukin-2 ligand, a serine protease inhibitor, a D40LG gene stimulator; TNFSF9 gene stimulator, a 2-oxoglutarate dehydrogenase inhibitor, a TGF-beta type II receptor antagonist, an Erbb3 tyrosine kinase receptor inhibitor, a cholecystokinin CCK2 receptor antagonist, a Wilms tumor protein modulator, a Ras GTPase modulator, an histone deacetylase inhibitor, a cyclin-dependent kinase 4 inhibitor A modulator, an estrogen receptor beta modulator, a 4-1BB inhibitor, a 4-1BBL inhibitor, a PD-L2 inhibitor, a B7-H3 inhibitor, a B7-H4 inhibitor, a BTLA inhibitor, a HVEM inhibitor, aTIM3 inhibitor, a GAL9 inhibitor, a LAG3 inhibitor, a VISTA inhibitor, a KIR inhibitor, a 2B4 inhibitor, a CD160 inhibitor and a CD66e modulator.

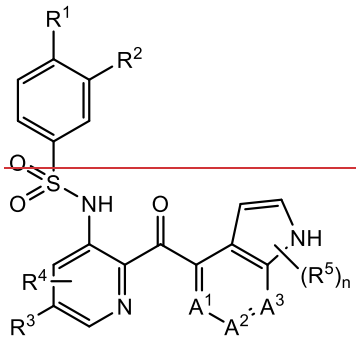
63. The method of claim 61 wherein the one or more additional therapeutic compound is selected from one or more of bavituximab, IMM-101, CAP1-6D, Rexin-G , genistein, CVac, MM-D37K, PCI-27483, TG-01, mocetinostat, LOAd-703, CPI-613, upamostat, CRS-207, NovaCaps, trametinib, Atu-027, sonidegib, GRASPA, trabedersen, nastorazepide, Vaccell , oregovomab, istiratumab, refametinib, regorafenib, lapatinib, selumetinib, rucaparib, pelareorep, tarextumab, PEGylated hyaluronidase, varlitinib, aglatimagene besadenovec, GBS-01, GI-4000, WF-10, galunisertib, afatinib, RX-0201, FG-3019, pertuzumab, DCVax-Direct, selinexor, glufosfamide, virulizin, yttrium (90Y) clivatuzumab tetraxetan, brivudine, nimotuzumab, algenpantucel-L, tegafur + gimeracil + oteracil potassium + calcium folinate, olaparib, ibrutinib, pirarubicin, Rh-Apo2L, tertomotide, tegafur + gimeracil + oteracil potassium, tegafur + gimeracil + oteracil potassium, masitinib, Rexin-G, mitomycin, erlotinib , adriamycin, dexamethasone, vincristine, cyclophosphamide, fluorouracil, topotecan, taxol, interferons, platinum derivatives, taxane, paclitaxel, vinca alkaloids, vinblastine, anthracyclines, doxorubicin, epipodophyllotoxins, etoposide, cisplatin, rapamycin, methotrexate, actinomycin D, dolastatin 10, colchicine, emetine, trimetrexate, metoprine, cyclosporine, daunorubicin, teniposide, amphotericin, alkylating agents, chlorambucil, 5-fluorouracil, campthothecin, cisplatin, metronidazole, Gleevec, Avastin, Vectibix, abarelix, aldesleukin, alemtuzumab, alitretinoin, allopurinol, altretamine, amifostine, anastrozole, arsenic

trioxide, asparaginase, azacitidine, AZD9291, BCG Live, bevacuzimab, fluorouracil, bexarotene, bleomycin, bortezomib, busulfan, calusterone, capecitabine, camptothecin, carboplatin, carmustine, celecoxib, cetuximab, chlorambucil, cladribine, clofarabine, cyclophosphamide, cytarabine, dactinomycin, darbepoetin alfa, daunorubicin, denileukin, dexrazoxane, docetaxel, doxorubicin (neutral), doxorubicin hydrochloride, dromostanolone propionate, epirubicin, epoetin alfa, estramustine, etoposide phosphate, etoposide, exemestane, filgrastim, floxuridine fludarabine, fulvestrant, gefitinib, gemcitabine, gemtuzumab, goserelin acetate, histrelin acetate, hydroxyurea, ibritumomab, idarubicin, ifosfamide, imatinib mesylate, interferon alfa-2a, interferon alfa-2b, irinotecan, lenalidomide, letrozole, leucovorin, leuprolide acetate, levamisole, lomustine, megestrol acetate, melphalan, mercaptopurine, 6-MP, mesna, methotrexate, methoxsalen, mitomycin C, mitotane, mitoxantrone, nandrolone, nelarabine, nofetumomab, oprelvekin, oxaliplatin, paclitaxel, palifermin, pamidronate, pegademase, pegaspargase, pegfilgrastim, pemetrexed disodium, pentostatin, pipobroman, plicamycin, porfimer sodium, procarbazine, quinacrine, rasburicase, rituximab, rociletinib, sargramostim, sorafenib, streptozocin, sunitinib maleate, talc, tamoxifen, temozolomide, teniposide, VM-26, testolactone, thioguanine, 6-TG, thiotepa, topotecan, toremifene, tositumomab, trastuzumab, tretinoin, ATRA, uracil mustard, valrubicin, vinblastine, vincristine, vinorelbine, zoledronate, zoledronic acid, pembrolizumab, nivolumab, IBI-308, mDX-400, BGB-108, MEDI-0680, SHR-1210, PF-06801591, PDR-001, GB-226, STI-1110, durvalumab, atezolizumab, avelumab, BMS-936559, ALN-PDL, TSR-042, KD-033, CA-170, STI-1014, FOLFIRINOX and KY-1003.

64. The method of claim 61, wherein the one or more additional therapeutic compound is FOLFIRINOX.

65. The method of claim 61, wherein the one or more additional therapeutic compounds are gemcitabine and paclitaxel.

66. A method for controlling an adenocarcinoma in a patient comprising administering to the patient in need thereof an effective amount of a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, wherein

R^1 is halogen or C_{1-6} alkyl;

R^2 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, or –CN;

R^3 is hydrogen, halogen, or C_{1-6} alkyl;

R^4 is hydrogen, halogen, or C_{1-6} alkyl;

each R^5 is independently C_{1-6} alkyl, –OH, or $–NH_2$;

n is 0, 1, 2, or 3; and

each of A^1, A^2, and A^3 is –CH– or –N–, where at least one of A^1, A^2, or A^3 is –N–.

67. The method of claim 66, wherein

R^1 is halogen or methyl;

R^2 is halogen or C_{1-6} haloalkyl;

R^3 is halogen or C_{1-6} alkyl;

R^4 is hydrogen;

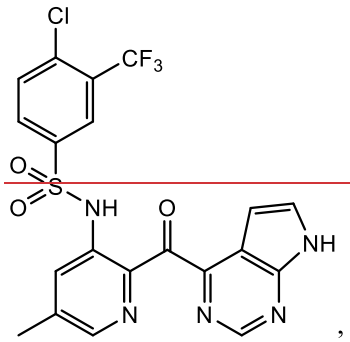
n is 0;

A^1 is –CH– or –N–;

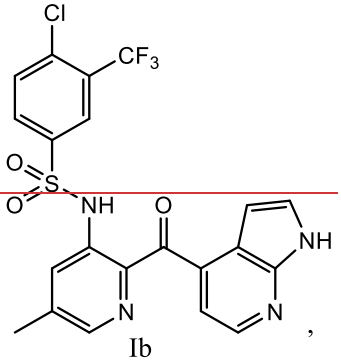
A^2 is –CH–; and

A^3 is –N–.

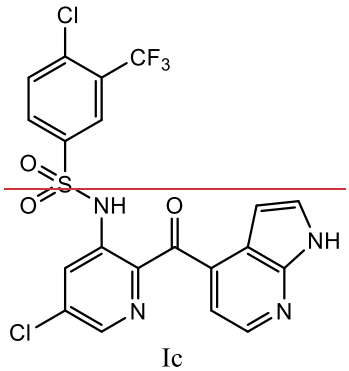
68. The method of claim 66, wherein the compound is selected from:



Ia ,



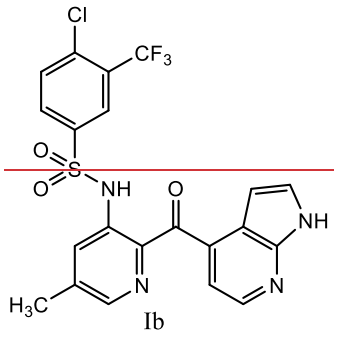
Ib ,



Ic and ,

or a pharmaceutically acceptable salt thereof.

69. The method of claim 66, wherein the compound is



Ib

or a pharmaceutically acceptable salt thereof.

70. The method of claim 66, wherein the adenocarcinoma is pancreatic adenocarcinoma.

71. The method of claim 66, wherein the patient achieves a complete response.

72. The method of claim 66, wherein the patient achieves a partial response.

73. The method of claim 66, wherein the patient achieves stable disease.

74. The method of claim 66, wherein the patient achieves a slower progressive disease.

75. The method of claim 66, wherein the patient achieves a clinical benefit.

76. The method of claim 75, wherein the clinical benefit is one or more of decrease in tumor size, suppression or decrease of tumor growth, delayed time to progression, no new tumor or lesion, a decrease in new tumor formation, an increase in survival or progression-free survival , no metastases, increase in treatment options, delay in time from surgery to recurrence, reduction in jaundice, suppression of spread to liver, reduction in pain, improved appetite, improved digestion, reduction of gallbladder size, and reduced incidence of blood clots.

77. The method of claim 66, wherein the compound of Formula I is provided as a pharmaceutical composition for oral administration.

78. The method of claim 66, wherein the compound is administered once a day.

79. The method of claim 66, wherein the compound is administered twice a day.

80. The method of claim 66, wherein the effective amount is from 50 mg to 300 mg.

81. The method of claim 66, wherein the effective amount is 150 mg.

82. The method of claim 66, further comprising administering to the patient one or more additional therapeutic compound.

83. The method of claim 82 wherein the one or more additional therapeutic compound is selected from one or more of a Btk tyrosine kinase inhibitor, an Erbb2 tyrosine kinase receptor inhibitor; an Erbb4 tyrosine kinase receptor inhibitor, an mTOR inhibitor, a thymidylate synthase inhibitor, an EGFR tyrosine kinase receptor inhibitor, an Epidermal growth factor antagonist, a Fyn tyrosine kinase inhibitor, a kit tyrosine kinase inhibitor, a Lyn tyrosine kinase inhibitor, a NK cell receptor modulator, a PDGF receptor antagonist, a PARP inhibitor, a poly ADP ribose polymerase inhibitor , a poly ADP ribose polymerase 1 inhibitor, a poly ADP ribose polymerase 2 inhibitor, a poly ADP ribose polymerase 3 inhibitor, a galactosyltransferase modulator, a dihydropyrimidine dehydrogenase inhibitor, an orotate phosphoribosyltransferase inhibitor, a telomerase modulator, a mucin 1 inhibitor, a mucin inhibitor, a secretin agonist, a TNF related apoptosis inducing ligand modulator, an IL17 gene stimulator, an interleukin 17E ligand, a Neurokinin receptor agonist, a cyclin G1 inhibitor, a checkpoint inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a CTLA4 inhibitor, a topoisomerase I inhibitor, an Alk-5 protein kinase inhibitor, a connective tissue growth factor ligand inhibitor, a notch-2 receptor antagonist, a notch-3 receptor antagonist, a hyaluronidase stimulator, a MEK-1 protein kinase inhibitor; MEK-2 protein kinase inhibitor, a GM-CSF receptor modulator; TNF alpha ligand modulator, a mesothelin modulator, an asparaginase stimulator, a caspase-3 stimulator; caspase-9 stimulator, a PKN3 gene inhibitor, a hedgehog protein inhibitor; Smoothened receptor antagonist, an AKT1 gene inhibitor, a DHFR inhibitor, a thymidine kinase stimulator, a CD29 modulator, a fibronectin modulator, an interleukin-2 ligand, a serine protease inhibitor, a D40LG gene stimulator; TNFSF9 gene stimulator, a 2-oxoglutarate dehydrogenase inhibitor, a TGF-beta type II receptor antagonist, an Erbb3 tyrosine kinase receptor inhibitor, a cholecystokinin CCK2 receptor antagonist, a Wilms tumor protein modulator, a Ras GTPase modulator, an histone deacetylase inhibitor, a cyclin-dependent kinase 4 inhibitor A modulator, an estrogen receptor beta modulator, a 4-1BB inhibitor, a 4-1BBL inhibitor, a PD-L2 inhibitor, a B7-H3 inhibitor, a B7-H4 inhibitor, a BTLA inhibitor, a HVEM inhibitor, aTIM3 inhibitor, a GAL9 inhibitor, a

LAG3 inhibitor, a VISTA inhibitor, a KIR inhibitor, a 2B4 inhibitor, a CD160 inhibitor and a CD66e modulator.

84. The method of claim 82 wherein the one or more additional therapeutic compound is selected from one or more of bavituximab, IMM-101, CAP1-6D, Rexin-G , genistein, CVac, MM-D37K, PCI-27483, TG-01, mocetinostat, LOAd-703, CPI-613, upamostat, CRS-207, NovaCaps, trametinib, Atu-027, sonidegib, GRASPA, trabedersen, nastorazepide, Vaccell , oregovomab, istiratumab, refametinib, regorafenib, lapatinib, selumetinib, rucaparib, pelareorep, tarextumab, PEGylated hyaluronidase, varlitinib, aglatimagene besadenovec, GBS-01, GI-4000, WF-10, galunisertib, afatinib, RX-0201, FG-3019, pertuzumab, DCVax-Direct, selinexor, glufosfamide, virulizin, yttrium (90Y) clivatuzumab tetraxetan, brivudine, nimotuzumab, algenpantucel-L, tegafur + gimeracil + oteracil potassium + calcium folinate, olaparib, ibrutinib, pirarubicin, Rh-Apo2L, tertomotide, tegafur + gimeracil + oteracil potassium, tegafur + gimeracil + oteracil potassium, masitinib, Rexin-G, mitomycin, erlotinib , adriamycin, dexamethasone, vincristine, cyclophosphamide, fluorouracil, topotecan, taxol, interferons, platinum derivatives, taxane, paclitaxel, vinca alkaloids, vinblastine, anthracyclines, doxorubicin, epipodophyllotoxins, etoposide, cisplatin, rapamycin, methotrexate, actinomycin D, dolastatin 10, colchicine, emetine, trimetrexate, metoprine, cyclosporine, daunorubicin, teniposide, amphotericin, alkylating agents, chlorambucil, 5-fluorouracil, campthothecin, cisplatin, metronidazole, Gleevec, Avastin, Vectibix, abarelix, aldesleukin, alemtuzumab, alitretinoin, allopurinol, altretamine, amifostine, anastrozole, arsenic trioxide, asparaginase, azacitidine, AZD9291, BCG Live, bevacuzimab, fluorouracil, bexarotene, bleomycin, bortezomib, busulfan, calusterone, capecitabine, camptothecin, carboplatin, carmustine, celecoxib, cetuximab, chlorambucil, cladribine, clofarabine, cyclophosphamide, cytarabine, dactinomycin, darbepoetin alfa, daunorubicin, denileukin, dexrazoxane, docetaxel, doxorubicin (neutral), doxorubicin hydrochloride, dromostanolone propionate, epirubicin, epoetin alfa, estramustine, etoposide phosphate, etoposide, exemestane, filgrastim, floxuridine fludarabine, fulvestrant, gefitinib, gemcitabine, gemtuzumab, goserelin acetate, histrelin acetate, hydroxyurea, ibritumomab, idarubicin, ifosfamide, imatinib mesylate, interferon alfa-2a, interferon alfa-2b, irinotecan, lenalidomide, letrozole, leucovorin, leuprolide acetate, levamisole, lomustine, megestrol acetate, melphalan, mercaptopurine, 6-MP, mesna, methotrexate, methoxsalen, mitomycin C, mitotane, mitoxantrone, nandrolone, nelarabine, nofetumomab, oprelvekin, oxaliplatin, paclitaxel, palifermin, pamidronate, pegademase,

pegaspargase, pegfilgrastim, pemetrexed disodium, pentostatin, pipobroman, plicamycin, porfimer sodium, procarbazine, quinacrine, rasburicase, rituximab, rociletinib, sargramostim, sorafenib, streptozocin, sunitinib maleate, talc, tamoxifen, temozolomide, teniposide, VM-26, testolactone, thioguanine, 6-TG, thiotepa, topotecan, toremifene, tositumomab, trastuzumab, tretinoin, ATRA, uracil mustard, valrubicin, vinblastine, vincristine, vinorelbine, zoledronate, zoledronic acid, pembrolizumab, nivolumab, IBI-308, mDX-400, BGB-108, MEDI-0680, SHR-1210, PF-06801591, PDR-001, GB-226, STI-1110, durvalumab, atezolizumab, avelumab, BMS-936559, ALN-PDL, TSR-042, KD-033, CA-170, STI-1014, FOLFIRINOX and KY-1003.

85. The method of claim 82, wherein the one or more additional therapeutic compound is FOLFIRINOX.

86. The method of claim 82, wherein the one or more additional therapeutic compounds are gemcitabine and paclitaxel.