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(54) **Title:** COMBINATION THERAPY COMPRISING AN FGFR INHIBITOR AND A NECTIN-4 TARGETING AGENT

(57) **Abstract:** The present disclosure relates to methods of treating cancer by administering a compound, which is an Fibroblast Growth Factor Receptor (FGFR) inhibitor, in combination with enfortumab vedotin.

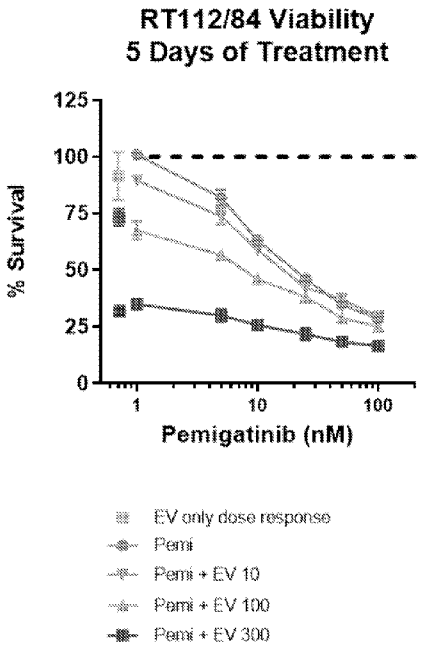


FIG. 1A

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COMBINATION THERAPY COMPRISING AN FGFR INHIBITOR AND A NECTIN-4 TARGETING AGENT

FIELD

The present disclosure relates to methods of treating cancer by administering a compound, which is an Fibroblast Growth Factor Receptor (FGFR) inhibitor, in combination with enfortumab vedotin, which is an antibody-drug conjugate targeting Nectin-4.

BACKGROUND

The Fibroblast Growth Factor Receptors (FGFR) are receptor tyrosine kinases that bind to fibroblast growth factor (FGF) ligands. There are four FGFR proteins (FGFR1-4) that are capable of binding ligands and are involved in the regulation of many physiological processes including tissue development, angiogenesis, wound healing, and metabolic regulation. Upon ligand binding, the receptors undergo dimerization and phosphorylation leading to stimulation of the protein kinase activity and recruitment of many intracellular docking proteins. These interactions facilitate the activation of an array of intracellular signaling pathways including Ras-MAPK, AKT-PI3K, and phospholipase C that are important for cellular growth, proliferation and survival (Reviewed in Eswarakumar et al. Cytokine & Growth Factor Reviews, 2005). Aberrant activation of this pathway either through overexpression of FGF ligands or FGFR or activating mutations in the FGFRs can lead to tumor development, progression, and resistance to conventional cancer therapies. In human cancer, genetic alterations including gene amplification, chromosomal translocations and somatic mutations that lead to ligand-independent receptor activation have been described. Large scale DNA sequencing of thousands of tumor samples has revealed that components of the FGFR pathway are among the most frequently mutated in human cancer. Many of these activating mutations are identical to germline mutations that lead to skeletal dysplasia syndromes. Mechanisms that lead to aberrant ligand-dependent signaling in human disease include overexpression of FGFs and changes in FGFR splicing that lead to receptors with more promiscuous ligand binding abilities (Reviewed in Knights and Cook Pharmacology & Therapeutics, 2010; Turner and Grose, Nature Reviews Cancer, 2010). Therefore, development of inhibitors targeting FGFR may be useful in the clinical treatment of diseases that have elevated FGF or FGFR activity.

The cancer types in which FGF/FGFRs are implicated include, but are not limited to: carcinomas (e.g., cholangiocarcinoma, adenocarcinoma), bladder, breast, cervical, colorectal,

endometrial, gastric, head and neck, kidney, liver, lung, ovarian, prostate); hematopoietic malignancies (e.g., multiple myeloma, chronic lymphocytic lymphoma, adult T cell leukemia, acute myelogenous leukemia, non-Hodgkin lymphoma, myeloproliferative neoplasms, and Waldenstrom's Macroglubulinemia); and other neoplasms (e.g., glioblastoma, melanoma, and rhabdosarcoma). In addition to a role in oncogenic neoplasms, FGFR activation has also been implicated in skeletal and chondrocyte disorders including, but not limited to, achrondroplasia and craniosynostosis syndromes.

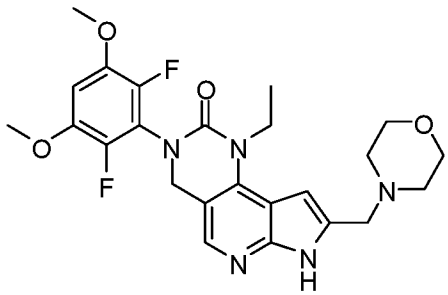
Inhibitors of FGFR are currently being developed for the treatment of cancer. For example, pemigatinib, or 3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-8-(morpholin-4-ylmethyl)-1,3,4,7-tetrahydro-2H-pyrrolo[3',2':5,6]pyrido[4,3-d]pyrimidin-2-one, and other small molecule inhibitors of FGFR are reported in e.g., US Patent No. 9,611,267, and US Publication Nos.: 2012/0165305; 2014/0045814; 2013/0338134; 2014/0171405; 2014/0315902; 2016/0115164; 2016/0244448; 2016/0244449, 2016/0244450, 2019/0337948, and 2020/0002338.

There remains a need for new treatment regimens for cancer using inhibitors of FGFR in combination with additional therapeutic agents. The present disclosure is directed toward this need and others.

SUMMARY

The present application provides, *inter alia*, methods of treating cancer in a patient, comprising administering to said patient:

(i) pemigatinib, having the structure:



Pemigatinib;

or a pharmaceutically acceptable salt thereof; and

(ii) enfortumab vedotin.

The present application further provides methods of treating cancer in a patient, comprising administering to the patient, pemigatinib, or a pharmaceutically acceptable salt thereof, and enfortumab vedotin.

The present application also provides use of pemigatinib, or a pharmaceutically acceptable salt thereof, and enfortumab vedotin, for preparation of a medicament for treatment of cancer.

The present application further provides pemigatinib, or a pharmaceutically acceptable salt thereof, and enfortumab vedotin, for use in any of the methods described herein.

DESCRIPTION OF DRAWINGS

FIG. 1A is a graph depicting the effects on cell proliferation on RT112/84 bladder cancer cell lines treated with different concentrations of pemigatinib ranging from 1 to 100 nM alone or in combination with either 300, 100 or 10 ng/mL of EV.

FIG. 1B is a graph depicting the effects on cell proliferation on UM-UC-14 bladder cancer cell lines treated with different concentrations of pemigatinib ranging from 1 to 100 nM alone or in combination with either 300, 100 or 10 ng/mL of EV.

FIG. 2A is a graph depicting the Nectin-4 receptor density in RT112/84 cell treated with (i) 100 nM of pemigatinib, (ii) 100 nM of enfortumab vedotin (EV), or (iii) 100 nM of pemigatinib and 100 nM of EV.

FIG. 2B is a graph depicting the Nectin-4 receptor density in tumor cells obtained from RT112/84 tumor bearing mice that were administered (i) vehicle, (ii) 0.3 mg/kg of pemigatinib, (iii) 1 mg/kg of pemigatinib, (iv) 3 mg/kg of EV, (v) 0.3 mg/kg of pemigatinib and 3 mg/kg of EV, or (vi) 1 mg/kg of pemigatinib and 3 mg/kg of EV.

FIG. 3 is a graph depicting the phosphorylation of ERK in tumor cells obtained from RT112/84 tumor bearing mice that were administered (i) vehicle, (ii) 1 mg/kg of pemigatinib, (iii) 3 mg/kg of EV, or (iv) 1 mg/kg of pemigatinib and 3 mg/kg of EV.

FIG. 4 is a graph depicting the tumor volume of RT112/84 tumor bearing mice administered (i) vehicle, (ii) 0.3 mg/kg of pemigatinib, (iii) 1 mg/kg of pemigatinib, (iv) 3 mg/kg of EV, (v) 0.3 mg/kg of pemigatinib and 3 mg/kg of EV, or (vi) 1 mg/kg of pemigatinib and 3 mg/kg of EV.

FIG. 5 is a graph depicting the tumor volume of RT112/84 tumor bearing mice administered (i) vehicle, (ii) 0.3 mg/kg of pemigatinib, (iii) 1 mg/kg of pemigatinib, (iv) 3 mg/kg of EV; (v) 10 mg/kg of EV, (vi) 0.3 mg/kg of pemigatinib and 3 mg/kg of EV, (vii) 0.3 mg/kg of pemigatinib and 10 mg/kg of EV, (viii) 1 mg/kg of pemigatinib and 3 mg/kg of EV, or (ix) 1 mg/kg of pemigatinib and 10 mg/kg of EV.

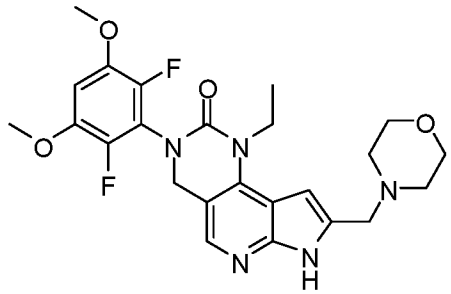
FIG. 6A is a Kaplan-Meier graph depicting the overall survival of RT112/84 tumor bearing mice administered (i) vehicle, (ii) 0.3 mg/kg of pemigatinib, (iii) 1 mg/kg of pemigatinib, (iv) 3 mg/kg of EV; (v) 10 mg/kg of EV, (vi) 0.3 mg/kg of pemigatinib and 3 mg/kg of EV, (vii) 0.3 mg/kg of pemigatinib and 10 mg/kg of EV, (viii) 1 mg/kg of pemigatinib and 3 mg/kg of EV, or (ix) 1 mg/kg of pemigatinib and 10 mg/kg of EV.

FIG. 6B is a Kaplan-Meier graph depicting the overall survival of RT112/84 tumor bearing mice administered (i) vehicle, (ii) 0.3 mg/kg of pemigatinib, (iii) 1 mg/kg of pemigatinib, (iv) 3 mg/kg of EV; (v) 10 mg/kg of EV, (vi) 0.3 mg/kg of pemigatinib and 3 mg/kg of EV, (vii) 0.3 mg/kg of pemigatinib and 10 mg/kg of EV, (viii) 1 mg/kg of pemigatinib and 3 mg/kg of EV, or (ix) 1 mg/kg of pemigatinib and 10 mg/kg of EV, over a period of 100 days after inoculation.

FIG. 7 is a graph depicting the tumor volume of UM-UC-14 tumor bearing mice administered (i) vehicle, (ii) 0.3 mg/kg of pemigatinib, (iii) 1 mg/kg of pemigatinib, (iv) 3 mg/kg of EV, (v) 0.3 mg/kg of pemigatinib and 3 mg/kg of EV, or (vi) 1 mg/kg of pemigatinib and 3 mg/kg of EV.

DETAILED DESCRIPTION

The present application provides, *inter alia*, a method of treating cancer in a patient, comprising administering pemigatinib, which is 3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-8-(morpholin-4-ylmethyl)-1,3,4,7-tetrahydro-2H-pyrrolo[3',2':5,6]pyrido[4,3-d]pyrimidin-2-one, having the structure shown below:



Pemigatinib,

in combination with enfortumab vedotin.

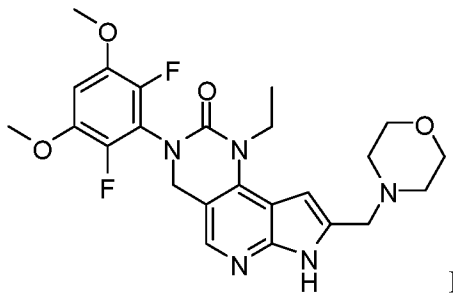
Pemigatinib is described in US Patent No. 9,611,267, the entirety of which is incorporated herein by reference. Pemigatinib is further described in US Publication Nos.: 2019/0337948 and 2020/0002338, the entireties of which are incorporated herein by reference. Pemigatinib can be referred to as "pemi." Pemigatinib as described herein can inhibit the activity of the FGFR enzyme. For example, pemigatinib can be used to inhibit

activity of an FGFR enzyme in a cell or in an individual or patient in need of inhibition of the enzyme by administering an inhibiting amount of pemigatinib to the cell, individual, or patient. As an FGFR inhibitor, pemigatinib is useful in the treatment of various diseases associated with abnormal expression or activity of the FGFR enzyme or FGFR ligands. Compounds which inhibit FGFR will be useful in providing a means of preventing the growth or inducing apoptosis in tumors, particularly by inhibiting angiogenesis. The methods disclosed herein can be useful in treating or preventing proliferative disorders such as cancers. In particular tumors with activating mutants of receptor tyrosine kinases or upregulation of receptor tyrosine kinases may be particularly sensitive to the methods desribed herein.

Enfortumab vedotin is an antibody-drug conjugate that is approved by the U.S. Food & Drug Administration for the treatment of cancer expressing Nectin-4, including urothelial cancer (e.g., bladder cancer), in adult patients who have previously received a PD-1 or PD-L1 inhibitor and a platinum-containing chemotherapy. Enfortumab vedotin is a conjugate of a Nectin-4 directed antibody and a microtubule inhibitor. In particular, enfortumab vedotin is a Nectin-4 directed antibody-drug conjugate comprised of a fully human anti-Nectin-4 IgG1 kappa monoclonal antibody (AGS-22C3) conjugated to monomethyl auristatin E, which is a small molecule microtubule disrupting agent. Conjugation takes place on cysteine residues that comprise the interchain disulfide bonds of the antibody. Enfortumab vedotin is also referred to as "enfortumab vedotin-ejfv" and "PADCEV."

Provided herein is a method of treating cancer in a patient, comprising administering to said patient:

(i) pemigatinib, having the structure:



Pemigatinib;

or a pharmaceutically acceptable salt thereof; and

(ii) enfortumab vedotin.

Provided herein is a method of treating cancer in a patient, comprising administering to said patient:

(i) pemigatinib, or a pharmaceutically acceptable salt thereof; and

(ii) enfortumab vedotin.

Provided herein is a method of treating cancer in a patient, comprising administering to said patient:

(i) pemigatinib; and

(ii) enfortumab vedotin.

In some embodiments, the cancer is bladder cancer.

In some embodiments, the cancer is a urogenital cancer (e.g., urogenital tumors).

In vivo studies demonstrated that the combination of pemigatnib and enfortumab vedotin had synergistic effects in the treatment of bladder cancer at certain dosages (Example C).

In some embodiments, pemigatinib, or a pharmaceutically acceptable salt thereof, and the enfortumab vedotin are administered to a patient simultaneously or sequentially. In some embodiments, pemigatinib, or a pharmaceutically acceptable salt thereof, and the enfortumab vedotin are administered to a patient simultaneously. In some embodiments, pemigatinib, or a pharmaceutically acceptable salt thereof, and the enfortumab vedotin are administered to a patient sequentially.

Pemigatinib and its pharmaceutically acceptable salts can be administered to a subject, e.g., a subject in need thereof, for example, a human subject, by a variety of methods. For many applications, the route of administration is oral. In some embodiments, pemigatinib, or a pharmaceutically acceptable salt thereof, is administered as a pharmaceutical composition.

In some embodiments, pemigatinib is administered orally. In some embodiments, pemigatinib is administered once daily.

In some embodiments, pemigatinib is administered in a daily dose of about 1 mg to about 50 mg. In some embodiments, pemigatinib is administered in a daily dose of about 1 mg to about 20 mg. In some embodiments, pemigatinib is administered in a daily dose of about 1 mg to about 15 mg. In some embodiments, pemigatinib is administered in a daily dose of about 1 mg to about 10 mg. In some embodiments, pemigatinib is administered in a daily dose of about 1 mg to about 5 mg. In some embodiments, pemigatinib is administered in a daily dose of about 5 mg to about 20 mg. In some embodiments, pemigatinib is administered in a daily dose of about 5 mg to about 10 mg. In some embodiments, pemigatinib is administered in a daily dose of about 10 mg to about 15 mg. In some embodiments, pemigatinib is administered in a daily dose of about 4.5 mg. In some

embodiments, pemigatinib is administered in a daily dose of about 9 mg. In some embodiments, pemigatinib is administered in a daily dose of about 13.5 mg.

In some embodiments, pemigatinib is administered in a daily dose of about 20 mg or less. In some embodiments, pemigatinib is administered in a daily dose of about 15 mg or less. In some embodiments, pemigatinib is administered in a daily dose of about 13.5 mg or less. In some embodiments, pemigatinib is administered in a daily dose of about 10 mg or less. In some embodiments, pemigatinib is administered in a daily dose of about 9 mg or less. In some embodiments, pemigatinib is administered in a daily dose of about 8 mg or less. In some embodiments, pemigatinib is administered in a daily dose of about 7 mg or less. In some embodiments, pemigatinib is administered in a daily dose of about 6 mg or less. In some embodiments, pemigatinib is administered in a daily dose of about 5 mg or less. In some embodiments, pemigatinib is administered in a daily dose of about 4 mg or less. In some embodiments, pemigatinib is administered in a daily dose of about 3 mg or less. In some embodiments, pemigatinib is administered in a daily dose of about 2 mg or less. In some embodiments, pemigatinib is administered in a daily dose of about 1 mg or less.

In some embodiments, pemigatinib is administered as a tablet. In some embodiments, the tablet comprises about 0.5 mg to about 10 mg of pemigatinib. In some embodiments, the tablet comprises about 0.5 mg to about 5 mg pemigatinib. In some embodiments, the tablet comprises about 2 mg, about 4.5 mg, about 9 mg, about 13.5 mg, or about 18 mg of pemigatinib. In some embodiments, the tablet comprises about 0.5 mg of pemigatinib. In some embodiments, the tablet comprises about 2 mg of pemigatinib. In some embodiments, the tablet comprises about 4.5 mg of pemigatinib. In some embodiments, the tablet comprises about 9 mg of pemigatinib. In some embodiments, the tablet comprises about 13.5 mg of pemigatinib. In some embodiments, the tablet comprises about 18 mg of pemigatinib.

In some embodiments, pemigatinib is administered once daily in a continuous dosing regimen. In some embodiments, pemigatinib is administered in a 21-day dosing regimen, wherein the 21-day dosing regimen comprises:

(a) a first period wherein pemigatinib is administered once daily for 14 days; and

(b) a second period wherein pemigatinib is not administered for 7 days.

In some embodiments, pemigatinib is administered in consecutive 21-day dosing regimens, wherein the 21-day dosing regimen comprises:

(a) a first period wherein pemigatinib is administered once daily for 14 days; and

(b) a second period wherein pemigatinib is not administered for 7 days.

In some embodiments, enfortumab vedotin is administered intravenously. In some embodiments, enfortumab vedotin is administered as an intravenous infusion in a dosage of about 0.5 mg/kg to about 5.0 mg/kg. In some embodiments, enfortumab vedotin is administered as an intravenous infusion in a dosage of about 0.5 mg/kg to about 2.0 mg/kg. In some embodiments, enfortumab vedotin is administered as an intravenous infusion in a dosage of about 0.5 mg/kg to about 1.5 mg/kg. In some embodiments, enfortumab vedotin is administered as an intravenous infusion in a dosage of about 0.5 mg/kg to about 1.25 mg/kg. In some embodiments, enfortumab vedotin is administered as an intravenous infusion in a dosage of about 1.0 mg/kg to about 5.0 mg/kg. In some embodiments, enfortumab vedotin is administered as an intravenous infusion in a dosage of about 1.0 mg/kg to about 2.0 mg/kg. In some embodiments, enfortumab vedotin is administered as an intravenous infusion in a dosage of about 1.0 mg/kg to about 1.5 mg/kg. In some embodiments, enfortumab vedotin is administered as an intravenous infusion up to a maximum of 125 mg for patients weighing 100 kg or more. In some embodiments, enfortumab vedotin is administered as an intravenous infusion up to a maximum of 100 mg for patients weighing 100 kg or more. In some embodiments, enfortumab vedotin is administered as an intravenous infusion up to a maximum of 75 mg for patients weighing 100 kg or more. In some embodiments, enfortumab vedotin is administered as an intravenous infusion in a dosage of about 1.25 mg/kg, up to a maximum of 125 mg for patients weighing 100 kg or more. In some embodiments, enfortumab vedotin is administered as an intravenous infusion in a dosage of about 1.25 mg/kg.

In some embodiments, enfortumab vedotin is administered once weekly in a continuous dosing regimen.

In some embodiments, In some embodiments, enfortumab vedotin is administered in a 28-day dosing regimen, wherein the 28-day dosing regimen comprises:

(a) a first period wherein enfortumab vedotin is administered once weekly for 21 days;

(b) a second period wherein enfortumab vedotin is not administered for 7 days.

In some embodiments, enfortumab vedotin is administered in a 28-day dosing regimen, wherein the 28-day dosing regimen comprises administering enfortumab vedotin on days 1, 8, and 15 of the 28-day period.

The methods disclosed herein are useful in the treatment of cancer. Example cancers include bladder cancer, breast cancer (e.g., hormone R positive, triple negative), cervical

cancer, colorectal cancer, cancer of the small intestine, colon cancer, rectal cancer, cancer of the anus, endometrial cancer, gastric cancer (e.g., gastrointestinal stromal tumors), head and neck cancer (e.g., cancers of the larynx, hypopharynx, nasopharynx, oropharynx, lips, and mouth, squamous head and neck cancers), kidney cancer (e.g., renal cell carcinoma, urothelial carcinoma, sarcoma, Wilms tumor), liver cancer (e.g., hepatocellular carcinoma, cholangiocellular carcinoma, liver angiosarcoma, hepatoblastoma), lung cancer (e.g., adenocarcinoma, small cell lung cancer and non-small cell lung carcinomas, parvicellular and non-parvicellular carcinoma, bronchial carcinoma, bronchial adenoma, pleuropulmonary blastoma), ovarian cancer, prostate cancer, testicular cancer, uterine cancer, vulvar cancer, esophageal cancer, gall bladder cancer, pancreatic cancer (e.g. exocrine pancreatic carcinoma), stomach cancer, thyroid cancer, parathyroid cancer, neuroendocrine cancer (e.g., pheochromocytoma, Merkel cell cancer, neuroendocrine carcinoma), skin cancer (e.g., squamous cell carcinoma, Kaposi sarcoma, Merkel cell skin cancer), and brain cancer (e.g., astrocytoma, medulloblastoma, ependymoma, neuro-ectodermal tumors, pineal tumors).

Further example cancers include hematopoietic malignancies such as leukemia or lymphoma, multiple myeloma, chronic lymphocytic lymphoma, adult T cell leukemia, B-cell lymphoma, cutaneous T-cell lymphoma, acute myelogenous leukemia, Hodgkin's or non-Hodgkin's lymphoma, myeloproliferative neoplasms (e.g., 8p11 myeloproliferative syndrome, polycythemia vera, essential thrombocythemia, and primary myelofibrosis), myelodysplastic syndrome, chronic eosinophilic leukemia, Waldenstrom's Macroglubulinemia, hairy cell lymphoma, chronic myelogenic lymphoma, acute lymphoblastic lymphoma, AIDS-related lymphomas, and Burkitt's lymphoma.

In certain embodiments, provided herein is a method of treating myeloid/lymphoid neoplasms in a patient in need thereof. In certain embodiments, the myeloid/lymphoid neoplasms are 8p11 myeloproliferative syndrome. As used herein, the term "8p11 myeloproliferative syndrome" (EMS) is meant to refer to myeloid/lymphoid neoplasms associated with eosinophilia and abnormalities of FGFR1 or myeloid/lymphoid neoplasms (MLN) with FGFR1 rearrangement. Eight P eleven myeloproliferative syndrome is reviewed in Jackson, Courtney C., et.al. *Human Pathology*, 2010, *41*, 461-476. In certain embodiments, the myeloid/lymphoid neoplasm exhibits an 8p11 translocation. In certain embodiments, the 8p11 translocation is associated with activation of FGFR1. In certain embodiments, the patient has failed at least one previous treatment for myeloid/lymphoid neoplasms (e.g., 8p11 myeloproliferative syndrome). In some embodiments, the previous treatment is surgery or radiation therapy. In some embodiments, the patient has a history of hepatitis. In some

embodiments, the hepatitis is chronic hepatitis B or hepatitis C. In some embodiments, the patient does not have a history of hepatitis.

In certain embodiments, the cancer is bladder cancer (e.g., urothelial carcinoma, squamous cell carcinoma, adenocarcinoma). In certain embodiments, the bladder cancer is the luminal papillary subtype of bladder cancer. In certain embodiments, the bladder cancer is characterized by an FGFR3 mutation, for example, an FGFR3 fusion. Examples of FGFR3 fusions include, but are not limited to, FGFR3-TACC3, FGFR3-BAIAP2L1, FGFR3-AES, FGFR3-ELAVL3, FGFR3-JAKMIP1, FGFR3-TNIP2, and FGFR3-WHSC1, as described in De Luca et al. *Int. J. Mol. Sci.* 2020, 21(8):6856 pp. 1-18.

In some embodiments, the cancer is a urogenital cancer (e.g., urogenital tumors). Urogenital cancers include, but are not limited to, bladder cancer, kidney cancer, testicular cancer, and prostate cancer. In some embodiments, the urogenital cancer is characterized by FGF/FGFR genetically altered tumors. In certain embodiments, the urogenital cancer is characterized by an FGFR3 mutation, for example, an FGFR3 fusion. Examples of FGFR3 fusions include, but are not limited to, FGFR3-TACC3, FGFR3-BAIAP2L1, FGFR3-AES, FGFR3-ELAVL3, FGFR3-JAKMIP1, FGFR3-TNIP2, and FGFR3-WHSC1, as described in De Luca et al. *Int. J. Mol. Sci.* 2020, 21(8):6856 pp. 1-18.

In certain embodiments, the cancer is glioblastoma or lung cancer, wherein the glioblastoma or lung cancer is characterized by an FGFR3 mutation, for example, an FGFR3 fusion. Examples of FGFR3 fusions include, but are not limited to, FGFR3-TACC3, FGFR3-BAIAP2L1, FGFR3-AES, FGFR3-ELAVL3, FGFR3-JAKMIP1, FGFR3-TNIP2, and FGFR3-WHSC1, as described in De Luca et al. *Int. J. Mol. Sci.* 2020, 21(8):6856 pp. 1-18.

In certain embodiments, the liver cancer is cholangiocellular carcinoma (e.g., intrahepatic, hilar or perihilar, distal extrahepatic). As used herein, cholangiocellular carcinoma is the same as cholangiocarcinoma or bile duct cancer. In certain embodiments, the cholangiocarcinoma is advanced or metastatic cholangiocarcinoma. In certain embodiments, the cholangiocarcinoma is surgically unresectable. In certain embodiments, the cholangiocarcinoma is intrahepatic. In certain embodiments, the cholangiocarcinoma is extrahepatic. In certain embodiments, the cholangiocarcinoma exhibits FGFR2 tyrosine kinase fusions which define a unique molecular subtype as described in Arai, Yasuhito, et. al. *Hepatology*, 2014, *59*, 1427-1434. In some embodiments, the cholangiocarcinoma is characterized by FGF/FGFR genetically altered tumors. In some embodiments, the tumors exhibit FGFR2 fusions. The FGFR2 fusion can be a translocation, interstitial deletion, or a chromosomal inversion. In some embodiments, the FGFR2 fusion is an FGFR2 translocation.

The FGFR2 translocations can be selected from a group including, but not limited to, FGFR2-BICC1, FGFR2-AHCYL1, FGFR2-MACF1, FGFR2 intron 17 rearrangement. In some embodiments, the tumor exhibits FGF/FGFR alterations other than FGFR2 translocations. In some embodiments, the cholangiocarcinoma does not exhibit FGF/FGFR genetically altered tumors.

Other cancers treatable with the methods provided herein include tumors of the eye, glioblastoma, melanoma, rhabdosarcoma, lymphosarcoma, leiomyosarcoma, urothelial carcinoma (e.g., ureter, urethra, bladder, urachus), and osteosarcoma.

The methods of the present disclosure are also useful for the treatment of metastatic cancers, especially metastatic cancers that express PD-Ll.

In some embodiments, diseases and indications that are treatable using the methods of the present disclosure include, but are not limited to hematological cancers, head and neck cancers, sarcomas, lung cancers, gastrointestinal cancers, genitourinary tract cancers, liver cancers, bone cancers, nervous system cancers, gynecological cancers, and skin cancers.

Exemplary hematological cancers include lymphomas and leukemias such as acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), chronic myelogenous leukemia (CML), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), Non-Hodgkin lymphoma (including relapsed or refractory NHL), follicular lymphoma (FL), Hodgkin lymphoma, lymphoblastic lymphoma, myeloproliferative diseases (e.g., primary myelofibrosis (PMF), polycythemia vera (PV), essential thrombocytosis (ET)), myelodysplasia syndrome (MDS), T-cell acute lymphoblastic lymphoma (T-ALL), multiple myeloma, cutaneous T-cell lymphoma, peripheral T-cell lymphoma, Waldenstrom's Macroglubulinemia, hairy cell lymphoma, chronic myelogenic lymphoma and Burkitt's lymphoma.

Exemplary sarcomas include chondrosarcoma, Ewing’s sarcoma, osteosarcoma, rhabdomyosarcoma, angiosarcoma, fibrosarcoma, liposarcoma, myxoma, rhabdomyoma, rhabdosarcoma, fibroma, lipoma, harmatoma, and teratoma.

Exemplary lung cancers include non-small cell lung cancer (NSCLC), small cell lung cancer, bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, chondromatous hamartoma, and mesothelioma.

Exemplary gastrointestinal cancers include cancers of the esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma,

leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma), colorectal cancer, bile duct cancer (cholangiocarcinoma).

Exemplary genitourinary tract cancers include cancers of the kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], renal cell carcinoma), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma, urothelial carcinoma), prostate (adenocarcinoma, sarcoma), and testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma).

Exemplary liver cancers include hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, and hemangioma.

Exemplary bone cancers include, for example, osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma, and giant cell tumors

Exemplary nervous system cancers include cancers of the skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, meduoblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma, glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), and spinal cord (neurofibroma, meningioma, glioma, sarcoma), as well as neuroblastoma, Lhermitte-Duclos disease, neoplasm of the central nervous system (CNS), primary CNS lymphoma and spinal axis tumor.

Exemplary gynecological cancers include cancers of the uterus (endometrial carcinoma), cervix (cervical carcinoma, pre -tumor cervical dysplasia), ovaries (ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell

carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), and fallopian tubes (carcinoma).

Exemplary skin cancers include melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, Merkel cell skin cancer, moles dysplastic nevi, lipoma, angioma, dermatofibroma, and keloids.

Exemplary head and neck cancers include glioblastoma, melanoma, rhabdosarcoma, lymphosarcoma, osteosarcoma, squamous cell carcinomas, adenocarcinomas, oral cancer, laryngeal cancer, nasopharyngeal cancer, nasal and paranasal cancers, thyroid and parathyroid cancers.

In some embodiments, the present disclosure provides a method for treating hepatocellular carcinoma in a patient in need thereof. In some embodiments, the present disclosure provides a method for treating Rhabdomyosarcoma, esophageal cancer, breast cancer, or cancer of a head or neck, in a patient in need thereof.

The methods described herein involve the treatment of cancers, for example solid tumors.

In some embodiments, the solid tumor is selected from skin cancer, lung cancer, lymphoma, sarcoma, bladder cancer, cancer of the ureter, urethra, and urachus, gastric cancer, cervical cancer, liver cancer, breast cancer, renal cancer, squamous cell carcinoma, colorectal cancer, endometrial cancer, anal cancer, and a tumor with microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR) and/or DNA polymerase ε exonuclease domain mutation positive disease.

In some embodiments, the solid tumor is selected from cholangiocarcinoma, melanoma, non-small cell lung cancer, small cell lung cancer, Hodgkin's lymphoma, urothelial carcinomagastric cancer, hepatocellular carcinoma, Merkel cell carcinoma, triple-negative breast cancer, renal cell carcinoma, squamous cell carcinoma of the head and neck, and colorectal cancer.

In some embodiments, the solid tumor is selected from sarcomas, head and neck cancer, melanoma, and non-small cell lung cancer. In some embodiments, the solid tumor is sarcoma. In some embodiments, the solid tumor is head and neck cancer. In some embodiments, the solid tumor is melanoma. In some embodiments, the solid tumor is non-small cell lung cancer.

As used herein, the term "individual" or "patient," used interchangeably, refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

As used herein, the phrase “therapeutically effective amount” refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response that is being sought in a tissue, system, animal, individual or human by a researcher, veterinarian, medical doctor or other clinician.

As used herein, the term “treating” or “treatment” refers to one or more of (1) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology); and (2) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology) such as decreasing the severity of disease. In some embodiments, the term “treating” or “treatment” refers to inhibiting or ameliorating the disease.

As used herein, the term “coadministering” or “concomitant administering” refers to administering pemigatinib and one or more additional drugs (e.g., enfortumab vedotin) at or almost at the same time. For example, pemigatinib may be administered, e.g., on the same day, within a week, or within a month as the one or more additional drugs. In some embodiments, the one or more additional drugs is administered between administrations of pemigatinib.

As used herein, the term “therapy” refers to administration of a compound that is suitable for treating cancer. For example, therapy can refer to the administration of pemigatinib for treating cancer.

As used herein, and unless otherwise specified, the term "about", when used in connection with a numeric value or range of values, indicate that the value or range of values may deviate to an extent deemed reasonable by one of ordinary skill in the art. Specifically, the term "about", when used in this context, indicates that the numeric value or range of values may vary by 5%, 4%, 3%, 2%, 1%, 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2% or 0.1% of the recited value or range of values.

As used herein, the term “cell” is meant to refer to a cell that is *in vitro*, *ex vivo* or *in vivo*. In some embodiments, an *ex vivo* cell can be part of a tissue sample excised from an organism such as a mammal. In some embodiments, an *in vitro* cell can be a cell in a cell culture. In some embodiments, an *in vivo* cell is a cell living in an organism such as a mammal.

As used herein, the term "contacting" refers to the bringing together of indicated moieties in an *in vitro* system or an *in vivo* system. For example, "contacting" the FGFR enzyme with pemigatinib includes the administration of a compound described herein to an individual or patient, such as a human, having FGFR, as well as, for example, introducing pemigatinib into a sample containing a cellular or purified preparation containing the FGFR enzyme.

The phrase "pharmaceutically acceptable" is used herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, immunogenicity or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, the phrase "pharmaceutically acceptable carrier or excipient" refers to a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, solvent, or encapsulating material. Excipients or carriers are generally safe, non-toxic and neither biologically nor otherwise undesirable and include excipients or carriers that are acceptable for veterinary use as well as human pharmaceutical use. In one embodiment, each component is "pharmaceutically acceptable" as defined herein. See, e.g., *Remington: The Science and Practice of Pharmacy,* 21st *ed.;* Lippincott Williams & Wilkins: Philadelphia, Pa., 2005; *Handbook of Pharmaceutical Excipients, 6th ed.;* Rowe et al., Eds.; The Pharmaceutical Press and the American Pharmaceutical Association: 2009; *Handbook of Pharmaceutical Additives, 3rd ed.;* Ash and Ash Eds.; Gower Publishing Company: 2007; *Pharmaceutical Preformulation and Formulation, 2nd ed.;* Gibson Ed.; CRC Press LLC: Boca Raton, Fla., 2009.

In some embodiments, a pharmaceutically acceptable salt of pemigatinib is used in the methods and combination therapies described herein. Salt forms of pemigatinib are described in US Publication No. 2019/0337948.

Solid forms (e.g., crystalline forms) of pemigatinib can also be used in the methods and combination therapies described herein. Solid forms of pemigatinib, and methods of preparing solid forms of pemigatinib, are described in U.S. Publication No. 2020/0002338.

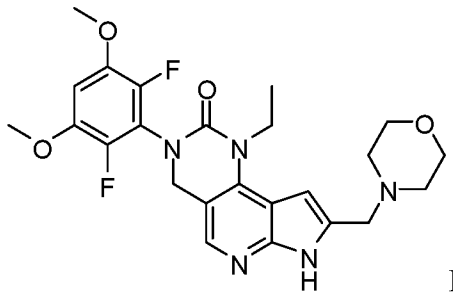
It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment (while the embodiments are intended to be combined as if written in multiply dependent form). Conversely, various features of the invention which are, for brevity,

described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

Combination Therapy with Additional Agents

Also provided herein is a method of treating cancer in a patient, comprising administering to said patient:

(i) pemigatinib, having the structure:



Pemigatinib;

or a pharmaceutically acceptable salt thereof;

(ii) enfortumab vedotin; and

(iii) one or more additional therapeutic agents.

Exemplary additional therapeutic agents are set forth below.

I. Cancer therapies

Cancer cell growth and survival can be impacted by dysfunction in multiple signaling pathways. Thus, it is useful to combine different enzyme/protein/receptor inhibitors, exhibiting different preferences in the targets which they modulate the activities of, to treat such conditions. Targeting more than one signaling pathway (or more than one biological molecule involved in a given signaling pathway) may reduce the likelihood of drug-resistance arising in a cell population, and/or reduce the toxicity of treatment.

One or more additional pharmaceutical agents such as, for example, chemotherapeutics, anti-inflammatory agents, steroids, immunosuppressants, immune-oncology agents, metabolic enzyme inhibitors, chemokine receptor inhibitors, and phosphatase inhibitors, as well as targeted therapies such as Bcr-Abl, Flt-3, EGFR, HER2, JAK, c-MET, VEGFR, PDGFR, c-Kit, IGF-1R, RAF, FAK, CDK2, and CDK4/6 kinase inhibitors such as, for example, those described in WO 2006/056399 can be used in combination with the treatment methods and regimens of the present disclosure for treatment of cancers and solid tumors. Other agents such as therapeutic antibodies can be used in combination with the treatment methods and regimens of the present disclosure for treatment

of cancers and solid tumors. The one or more additional pharmaceutical agents can be administered to a patient simultaneously or sequentially.

The treatment methods as disclosed herein can be used in combination with one or more other enzyme/protein/receptor inhibitors therapies for the treatment of diseases, such as cancer and other diseases or disorders described herein. For example, the treatment methods and regimens of the present disclosure can be combined with one or more inhibitors of the following kinases for the treatment of cancer: Akt1, Akt2, Akt3, BCL2, CDK2, CDK4/6, TGF-βR, PKA, PKG, PKC, CaM-kinase, phosphorylase kinase, MEKK, ERK, MAPK, mTOR, EGFR, HER2, HER3, HER4, INS-R, IDH2, IGF-1R, IR-R, PDGFαR, PDGFβR, PI3K (alpha, beta, gamma, delta, and multiple or selective), CSF1R, KIT, FLK-II, KDR/FLK-1, FLK-4, flt-1, FGFR1, FGFR2, FGFR3, FGFR4, c-Met, PARP, Ron, Sea, TRKA, TRKB, TRKC, TAM kinases (Axl, Mer, Tyro3), FLT3, VEGFR/Flt2, Flt4, EphA1, EphA2, EphA3, EphB2, EphB4, Tie2, Src, Fyn, Lck, Fgr, Btk, Fak, SYK, FRK, JAK, ABL, ALK and B-Raf. Non-limiting examples of inhibitors that can be combined with the treatment methods and regimens of the present disclosure for treatment of cancer include an FGFR inhibitor (FGFR1, FGFR2, FGFR3 or FGFR4, e.g., INCB62079), an EGFR inhibitor (also known as ErB-1 or HER-1; e.g. erlotinib, gefitinib, vandetanib, orsimertinib, cetuximab, necitumumab, or panitumumab), a VEGFR inhibitor or pathway blocker (e.g. bevacizumab, pazopanib, sunitinib, sorafenib, axitinib, regorafenib, ponatinib, cabozantinib, vandetanib, ramucirumab, lenvatinib, ziv-aflibercept), a PARP inhibitor (e.g. olaparib, rucaparib, veliparib or niraparib), a JAK inhibitor (JAK1 and/or JAK2, e.g., ruxolitinib, *baricitinib, itacitinib (INCB39110)*, an LSD1 inhibitor (e.g., INCB59872 and INCB60003), a TDO inhibitor, a PI3K-delta inhibitor (e.g., INCB50465 and INCB50797), a PI3K-gamma inhibitor such as PI3K-gamma selective inhibitor, a Pim inhibitor (e.g., INCB53914), a CSF1R inhibitor, a TAM receptor tyrosine kinases (Tyro-3, Axl, and Mer), an adenosine receptor antagonist (e.g., A2a/A2b receptor antagonist), an HPK1 inhibitor, a chemokine receptor inhibitor (e.g. CCR2 or CCR5 inhibitor), a SHP1/2 phosphatase inhibitor, a histone deacetylase inhibitor (HDAC) such as an HDAC8 inhibitor, an angiogenesis inhibitor, an interleukin receptor inhibitor, bromo and extra terminal family members inhibitors (for example, bromodomain inhibitors or BET inhibitors such as INCB54329 and INCB57643), c-MET inhibitors (*e.g.,* capmatinib), an anti-CD19 antibody (*e.g.,* tafasitamab), an ALK2 inhibitor (*e.g.,* INCB00928); or combinations thereof.

In some embodiments, the treatment methods described herein are combined with administration of a PI3Kδ inhibitor. In some embodiments, the treatment methods described herein are combined with administration of a JAK inhibitor. In some embodiments, the treatment methods described herein are combined with administration of a JAK1 or JAK2 inhibitor (e.g., baricitinib or ruxolitinib). In some embodiments, the treatment methods described herein are combined with administration of a JAK1 inhibitor. In some embodiments, the treatment methods described herein are combined with administration of a JAK1 inhibitor, which is selective over JAK2.

Example antibodies that can be administered in combination therapy include, but are not limited to, trastuzumab (*e.g.*, anti-HER2), ranibizumab (*e.g.*, anti-VEGF-A), bevacizumab (AVASTIN™, *e.g.*, anti-VEGF), panitumumab (*e.g.*, anti-EGFR), cetuximab (*e.g.*, anti-EGFR), rituxan (*e.g.*, anti-CD20), and antibodies directed to c-MET.

One or more of the following agents may be administered to a patient in combination with the treatment methods of the present disclosure and are presented as a non-limiting list: a cytostatic agent, cisplatin, doxorubicin, taxotere, taxol, etoposide, irinotecan, camptostar, topotecan, paclitaxel, docetaxel, epothilones, tamoxifen, 5-fluorouracil, methoxtrexate, temozolomide, cyclophosphamide, SCH 66336, R115777, L778,123, BMS 214662, IRESSA™(gefitinib), TARCEVA™ (erlotinib), antibodies to EGFR, intron, ara-C, adriamycin, cytoxan, gemcitabine, uracil mustard, chlormethine, ifosfamide, melphalan, chlorambucil, pipobroman, triethylenemelamine, triethylenethiophosphoramine, busulfan, carmustine, lomustine, streptozocin, dacarbazine, floxuridine, cytarabine, 6-mercaptopurine, 6-thioguanine, fludarabine phosphate, oxaliplatin, leucovirin, ELOXATIN™ (oxaliplatin), pentostatine, vinblastine, vincristine, vindesine, bleomycin, dactinomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, mithramycin, deoxycoformycin, mitomycin-C, L-asparaginase, teniposide 17.alpha.-ethinylestradiol, diethylstilbestrol, testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, testolactone, megestrolacetate, methylprednisolone, methyltestosterone, prednisolone, triamcinolone, chlorotrianisene, hydroxyprogesterone, aminoglutethimide, estramustine, medroxyprogesteroneacetate, leuprolide, flutamide, toremifene, goserelin, carboplatin, hydroxyurea, amsacrine, procarbazine, mitotane, mitoxantrone, levamisole, navelbene, anastrazole, letrazole, capecitabine, reloxafine, droloxafine, hexamethylmelamine, avastin, HERCEPTIN™ (trastuzumab), BEXXAR™ (tositumomab), VELCADE™ (bortezomib), ZEVALIN™ (ibritumomab tiuxetan), TRISENOX™ (arsenic trioxide), XELODA™ (capecitabine), vinorelbine, porfimer, ERBITUX™ (cetuximab), thiotepa, altretamine, melphalan,

trastuzumab, lerozole, fulvestrant, exemestane, ifosfomide, rituximab, C225 (cetuximab), Campath (alemtuzumab), clofarabine, cladribine, aphidicolon, rituxan, sunitinib, dasatinib, tezacitabine, Sml1, fludarabine, pentostatin, triapine, didox, trimidox, amidox, 3-AP, and MDL-101,731.

The treatment methods and regimens of the present disclosure can further be used in combination with other methods of treating cancers, for example by chemotherapy, irradiation therapy, tumor-targeted therapy, adjuvant therapy, immunotherapy or surgery. Examples of immunotherapy include cytokine treatment (e.g., interferons, GM-CSF, G-CSF, IL-2), CRS-207 immunotherapy, cancer vaccine, monoclonal antibody, bispecific or multi-specific antibody, antibody drug conjugate, adoptive T cell transfer, Toll receptor agonists, RIG-I agonists, oncolytic virotherapy and immunomodulating small molecules, including thalidomide or JAK1/2 inhibitor, PI3Kδ inhibitor and the like. The compounds can be administered in combination with one or more anti-cancer drugs, such as a chemotherapeutic agent. Examples of chemotherapeutics include any of: abarelix, aldesleukin, alemtuzumab, alitretinoin, allopurinol, altretamine, anastrozole, arsenic trioxide, asparaginase, azacitidine, bevacizumab, bexarotene, baricitinib, bleomycin, bortezomib, busulfan intravenous, busulfan oral, calusterone, capecitabine, carboplatin, carmustine, cetuximab, chlorambucil, cisplatin, cladribine, clofarabine, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, dalteparin sodium, dasatinib, daunorubicin, decitabine, denileukin, denileukin diftitox, dexrazoxane, docetaxel, doxorubicin, dromostanolone propionate, eculizumab, epacadostat, epirubicin, erlotinib, estramustine, etoposide phosphate, etoposide, exemestane, fentanyl citrate, filgrastim, floxuridine, fludarabine, fluorouracil, fulvestrant, gefitinib, gemcitabine, gemtuzumab ozogamicin, goserelin acetate, histrelin acetate, ibritumomab tiuxetan, idarubicin, ifosfamide, imatinib mesylate, interferon alfa 2a, irinotecan, lapatinib ditosylate, lenalidomide, letrozole, leucovorin, leuprolide acetate, levamisole, lomustine, meclorethamine, megestrol acetate, melphalan, mercaptopurine, methotrexate, methoxsalen, mitomycin C, mitotane, mitoxantrone, nandrolone phenpropionate, nelarabine, nofetumomab, oxaliplatin, paclitaxel, pamidronate, panitumumab, pegaspargase, pegfilgrastim, pemetrexed disodium, pentostatin, pipobroman, plicamycin, procarbazine, quinacrine, rasburicase, rituximab, ruxolitinib, sorafenib, streptozocin, sunitinib, sunitinib maleate, tamoxifen, temozolomide, teniposide, testolactone, thalidomide, thioguanine, thiotepa, topotecan, toremifene, tositumomab, trastuzumab, tretinoin, uracil mustard, valrubicin, vinblastine, vincristine, vinorelbine, vorinostat, and zoledronate.

Additional examples of chemotherapeutics include proteosome inhibitors (*e.g.*, bortezomib), thalidomide, revlimid, and DNA-damaging agents such as melphalan, doxorubicin, cyclophosphamide, vincristine, etoposide, carmustine, and the like.

Example steroids include corticosteroids such as dexamethasone or prednisone.

Example Bcr-Abl inhibitors include imatinib mesylate (GLEEVAC™), nilotinib, dasatinib, bosutinib, and ponatinib, and pharmaceutically acceptable salts. Other example suitable Bcr-Abl inhibitors include the compounds, and pharmaceutically acceptable salts thereof, of the genera and species disclosed in U.S. Pat. No. 5,521,184, WO 04/005281, and U.S. Ser. No. 60/578,491.

Example suitable Flt-3 inhibitors include midostaurin, lestaurtinib, linifanib, sunitinib, sunitinib, maleate, sorafenib, quizartinib, crenolanib, pacritinib, tandutinib, PLX3397 and ASP2215, and their pharmaceutically acceptable salts. Other example suitable Flt-3 inhibitors include compounds, and their pharmaceutically acceptable salts, as disclosed in WO 03/037347, WO 03/099771, and WO 04/046120.

Example suitable RAF inhibitors include dabrafenib, sorafenib, and vemurafenib, and their pharmaceutically acceptable salts. Other example suitable RAF inhibitors include compounds, and their pharmaceutically acceptable salts, as disclosed in WO 00/09495 and WO 05/028444.

Example suitable FAK inhibitors include VS-4718, VS-5095, VS-6062, VS-6063, BI853520, and GSK2256098,and their pharmaceutically acceptable salts. Other example suitable FAK inhibitors include compounds, and their pharmaceutically acceptable salts, as disclosed in WO 04/080980, WO 04/056786, WO 03/024967, WO 01/064655, WO 00/053595, and WO 01/014402.

Example suitable CDK4/6 inhibitors include palbociclib, ribociclib, trilaciclib, lerociclib, and abemaciclib, and their pharmaceutically acceptable salts. Other example suitable CDK4/6 inhibitors include compounds, and their pharmaceutically acceptable salts, as disclosed in WO 09/085185, WO 12/129344, WO 11/101409, WO 03/062236, WO 10/075074, and WO 12/061156.

The treatment methods and regimens of the present disclosure can further be used in combination with one or more other kinase inhibitors including imatinib, particularly for treating patients resistant to imatinib or other kinase inhibitors.

In some embodiments, the treatment methods of the disclosure can be used in combination with a chemotherapeutic in the treatment of cancer, and may improve the treatment response as compared to the response to the chemotherapeutic agent alone, without

exacerbation of its toxic effects. In some embodiments, the treatment methods of the disclosure can be used in combination with a chemotherapeutic provided herein. For example, additional pharmaceutical agents used in the treatment of multiple myeloma, can include, without limitation, melphalan, melphalan plus prednisone [MP], doxorubicin, dexamethasone, and Velcade (bortezomib). Further additional agents used in the treatment of multiple myeloma include Bcr-Abl, Flt-3, RAF and FAK kinase inhibitors. In some embodiments, the agent is an alkylating agent, a proteasome inhibitor, a corticosteroid, or an immunomodulatory agent. Examples of an alkylating agent include cyclophosphamide (CY), melphalan (MEL), and bendamustine. In some embodiments, the proteasome inhibitor is carfilzomib. In some embodiments, the corticosteroid is dexamethasone (DEX). In some embodiments, the immunomodulatory agent is lenalidomide (LEN) or pomalidomide (POM). Additive or synergistic effects are desirable outcomes of combining treatment methods of the present disclosure with an additional agent.

The treatment methods of the disclosure can be combined with an antibody that binds to human PD-1 or human PD-L1, or antigen-binding fragment thereof.

In some embodiments, a corticosteroid such as dexamethasone is administered to a patient in combination with the treatment methods of the disclosure where the dexamethasone is administered intermittently as opposed to continuously.

The treatment methods described herein can be combined with another immunogenic agent, such as cancerous cells, purified tumor antigens (including recombinant proteins, peptides, and carbohydrate molecules), cells, and cells transfected with genes encoding immune stimulating cytokines. Non-limiting examples of tumor vaccines that can be used include peptides of melanoma antigens, such as peptides of gp100, MAGE antigens, Trp-2, MARTI and/or tyrosinase, or tumor cells transfected to express the cytokine GM-CSF.

The treatment methods described herein can be used in combination with a vaccination protocol for the treatment of cancer. In some embodiments, the tumor cells are transduced to express GM-CSF. In some embodiments, tumor vaccines include the proteins from viruses implicated in human cancers such as Human Papilloma Viruses (HPV), Hepatitis Viruses (HBV and HCV) and Kaposi's Herpes Sarcoma Virus (KHSV). In some embodiments, the treatment methods and regimens of the present disclosure can be used in combination with tumor specific antigen such as heat shock proteins isolated from tumor tissue itself. In some embodiments, the treatment methods described herein can be combined with dendritic cells immunization to activate potent anti-tumor responses.

The treatment methods and regimens of the present disclosure can be used in combination with bispecific macrocyclic peptides that target Fe alpha or Fe gamma receptor-expressing effectors cells to tumor cells. The treatment methods and regimens of the present disclosure can also be combined with macrocyclic peptides that activate host immune responsiveness.

In some further embodiments, the treatment methods of the disclosure are combined with administration of other therapeutic agents to a patient prior to, during, and/or after a bone marrow transplant or stem cell transplant. The treatment methods and regimens of the present disclosure can be used in combination with bone marrow transplant for the treatment of a variety of tumors of hematopoietic origin.

When more than one pharmaceutical agents is administered to a patient, as discussed in any of the above embodiments, they can be administered simultaneously, separately, sequentially, or in combination (*e.g.*, for more than two agents).

Methods for the safe and effective administration of most of these chemotherapeutic agents are known to those skilled in the art. In addition, their administration is described in the standard literature. For example, the administration of many of the chemotherapeutic agents is described in the "Physicians' Desk Reference" (PDR, e.g., 1996 edition, Medical Economics Company, Montvale, NJ), the disclosure of which is incorporated herein by reference as if set forth in its entirety.

II. Immune-checkpoint therapies

The treatment methods described herein can be used in combination with one or more immune checkpoint inhibitors for the treatment of diseases, such as cancer or infections. Exemplary immune checkpoint inhibitors include inhibitors against immune checkpoint molecules such as CBL-B, CD20, CD28, CD40, CD70, CD122, CD96, CD73, CD47, CDK2, GITR, CSF1R, JAK, PI3K delta, PI3K gamma, TAM, arginase, HPK1, CD137 (also known as 4-1BB), ICOS, A2AR, B7-H3, B7-H4, BTLA, CTLA-4, LAG3, TIM3, TLR (TLR7/8), TIGIT, CD112R, VISTA, PD-1, PD-L1 and PD-L2. In some embodiments, the immune checkpoint molecule is a stimulatory checkpoint molecule selected from CD27, CD28, CD40, ICOS, OX40, GITR and CD137. In some embodiments, the immune checkpoint molecule is an inhibitory checkpoint molecule selected from A2AR, B7-H3, B7-H4, BTLA, CTLA-4, IDO, KIR, LAG3, PD-1, TIM3, TIGIT, and VISTA. In some embodiments, the compounds provided herein can be used in combination with one or more agents selected from KIR

inhibitors, TIGIT inhibitors, LAIR1 inhibitors, CD160 inhibitors, 2B4 inhibitors and TGFR beta inhibitors.

In some embodiments, the treatment methods provided herein can be used in combination with one or more agonists of immune checkpoint molecules, e.g., OX40, CD27, GITR, and CD137 (also known as 4-1BB).

In some embodiments, the inhibitor of an immune checkpoint molecule is anti-PD1 antibody, anti-PD-L1 antibody, or anti-CTLA-4 antibody.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of PD-1 or PD-L1, e.g., an anti-PD-1 or anti-PD-L1 monoclonal antibody. In some embodiments, the anti-PD-1 or anti-PD-L1 antibody is nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab, cemiplimab, atezolizumab, avelumab, tislelizumab, spartalizumab (PDR001), cetrelimab (JNJ-63723283), toripalimab (JS001), camrelizumab (SHR-1210), sintilimab (IBI308), AB122 (GLS-010), AMP-224, AMP-514/MEDI-0680, BMS936559, JTX-4014, BGB-108, SHR-1210, MEDI4736, FAZ053, BCD-100, KN035, CS1001, BAT1306, LZM009, AK105, HLX10, SHR-1316, CBT-502 (TQB2450), A167 (KL-A167), STI-A101 (ZKAB001), CK-301, BGB-A333, MSB-2311, HLX20, TSR-042, or LY3300054. In some embodiments, the inhibitor of PD-1 or PD-L1 is one disclosed in U.S. Pat. Nos. 7,488,802, 7,943,743, 8,008,449, 8,168,757, 8,217, 149, or 10,308,644; U.S. Publ. Nos. 2017/0145025, 2017/0174671, 2017/0174679, 2017/0320875, 2017/0342060, 2017/0362253, 2018/0016260, 2018/0057486, 2018/0177784, 2018/0177870, 2018/0179179, 2018/0179201, 2018/0179202, 2018/0273519, 2019/0040082, 2019/0062345, 2019/0071439, 2019/0127467, 2019/0144439, 2019/0202824, 2019/0225601, 2019/0300524, or 2019/0345170; or PCT Pub. Nos. WO 03042402, WO 2008156712, WO 2010089411, WO 2010036959, WO 2011066342, WO 2011159877, WO 2011082400, or WO 2011161699, which are each incorporated herein by reference in their entirety. In some embodiments, the inhibitor of PD-L1 is INCB086550.

In some embodiments, the antibody is an anti-PD-1 antibody, e.g., an anti-PD-1 monoclonal antibody. In some embodiments, the anti-PD-1 antibody is nivolumab, retifanlimab pembrolizumab, cemiplimab, spartalizumab, camrelizumab, cetrelimab, toripalimab, sintilimab, AB122, AMP-224, JTX-4014, BGB-108, BCD-100, BAT1306, LZM009, AK105, HLX10, or TSR-042. In some embodiments, the anti-PD-1 antibody is nivolumab, pembrolizumab, cemiplimab, spartalizumab, camrelizumab, cetrelimab, toripalimab, or sintilimab. In some embodiments, the anti-PD-1 antibody is pembrolizumab. In some embodiments, the anti-PD-1 antibody is nivolumab. In some embodiments, the anti-

PD-1 monoclonal antibody is retifanlimab. In some embodiments, the anti-PD-1 antibody is cemiplimab. In some embodiments, the anti-PD-1 antibody is spartalizumab. In some embodiments, the anti-PD-1 antibody is camrelizumab. In some embodiments, the anti-PD-1 antibody is cetrelimab. In some embodiments, the anti-PD-1 antibody is toripalimab. In some embodiments, the anti-PD-1 antibody is sintilimab. In some embodiments, the anti-PD-1 antibody is AB122. In some embodiments, the anti-PD-1 antibody is AMP-224. In some embodiments, the anti-PD-1 antibody is JTX-4014. In some embodiments, the anti-PD-1 antibody is BGB-108. In some embodiments, the anti-PD-1 antibody is BCD-100. In some embodiments, the anti-PD-1 antibody is BAT1306. In some embodiments, the anti-PD-1 antibody is LZM009. In some embodiments, the anti-PD-1 antibody is AK105. In some embodiments, the anti-PD-1 antibody is HLX10. In some embodiments, the anti-PD-1 antibody is TSR-042. In some embodiments, the anti-PD-1 monoclonal antibody is nivolumab or pembrolizumab. In some embodiments, the anti-PD1 antibody is SHR-1210. Other anti-cancer agent(s) include antibody therapeutics such as 4-1BB (*e.g.*, urelumab, utomilumab). In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of PD-L1, e.g., an anti-PD-L1 monoclonal antibody. In some embodiments, the anti-PD-L1 monoclonal antibody is atezolizumab, avelumab, durvalumab, tislelizumab, BMS-935559, MEDI4736, atezolizumab (MPDL3280A;also known as RG7446), avelumab (MSB0010718C), FAZ053, KN035, CS1001, SHR-1316, CBT-502, A167, STI-A101, CK-301, BGB-A333, MSB-2311, HLX20, or LY3300054. In some embodiments, the anti-PD-L1 antibody is atezolizumab, avelumab, durvalumab, or tislelizumab. In some embodiments, the anti-PD-L1 antibody is atezolizumab. In some embodiments, the anti-PD-L1 antibody is avelumab. In some embodiments, the anti-PD-L1 antibody is durvalumab. In some embodiments, the anti-PD-L1 antibody is tislelizumab. In some embodiments, the anti-PD-L1 antibody is BMS-935559. In some embodiments, the anti-PD-L1 antibody is MEDI4736. In some embodiments, the anti-PD-L1 antibody is FAZ053. In some embodiments, the anti-PD-L1 antibody is KN035. In some embodiments, the anti-PD-L1 antibody is CS1001. In some embodiments, the anti-PD-L1 antibody is SHR-1316. In some embodiments, the anti-PD-L1 antibody is CBT-502. In some embodiments, the anti-PD-L1 antibody is A167. In some embodiments, the anti-PD-L1 antibody is STI-A101. In some embodiments, the anti-PD-L1 antibody is CK-301. In some embodiments, the anti-PD-L1 antibody is BGB-A333. In some embodiments, the anti-PD-L1 antibody is MSB-2311. In some embodiments, the anti-PD-L1 antibody is HLX20. In some embodiments, the anti-PD-L1 antibody is LY3300054.

In some embodiments, the inhibitor of an immune checkpoint molecule is a small molecule that binds to PD-L1, or a pharmaceutically acceptable salt thereof. In some embodiments, the inhibitor of an immune checkpoint molecule is a small molecule that binds to and internalizes PD-L1, or a pharmaceutically acceptable salt thereof. In some embodiments, the inhibitor of an immune checkpoint molecule is a compound selected from those in US 2018/0179201, US 2018/0179197, US 2018/0179179, US 2018/0179202, US 2018/0177784, US 2018/0177870, US Ser. No. 16/369,654 (filed Mar. 29, 2019), and US Ser. No. 62/688,164, or a pharmaceutically acceptable salt thereof, each of which is incorporated herein by reference in its entirety.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of KIR, TIGIT, LAIR1, CD160, 2B4 and TGFR beta.

In some embodiments, the inhibitor is MCLA-145.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of CTLA-4, e.g., an anti-CTLA-4 antibody. In some embodiments, the anti-CTLA-4 antibody is ipilimumab, tremelimumab, AGEN1884, or CP-675,206.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of LAG3, e.g., an anti-LAG3 antibody. In some embodiments, the anti-LAG3 antibody is BMS-986016, LAG525, INCAGN2385, or eftilagimod alpha (IMP321).

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of CD73. In some embodiments, the inhibitor of CD73 is oleclumab.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of TIGIT. In some embodiments, the inhibitor of TIGIT is OMP-31M32.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of VISTA. In some embodiments, the inhibitor of VISTA is JNJ-61610588 or CA-170.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of B7-H3. In some embodiments, the inhibitor of B7-H3 is enoblituzumab, MGD009, or 8H9.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of KIR. In some embodiments, the inhibitor of KIR is lirilumab or IPH4102.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of A2aR. In some embodiments, the inhibitor of A2aR is CPI-444.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of TGF-beta. In some embodiments, the inhibitor of TGF-beta is trabedersen, galusertinib, or M7824.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of PI3K-gamma. In some embodiments, the inhibitor of PI3K-gamma is IPI-549.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of CD47. In some embodiments, the inhibitor of CD47 is Hu5F9-G4 or TTI-621.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of CD73. In some embodiments, the inhibitor of CD73 is MEDI9447.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of CD70. In some embodiments, the inhibitor of CD70 is cusatuzumab or BMS-936561.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of TIM3, e.g., an anti-TIM3 antibody. In some embodiments, the anti-TIM3 antibody is INCAGN2390, MBG453, or TSR-022.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of CD20, e.g., an anti-CD20 antibody. In some embodiments, the anti-CD20 antibody is obinutuzumab or rituximab.

In some embodiments, the agonist of an immune checkpoint molecule is an agonist of OX40, CD27, CD28, GITR, ICOS, CD40, TLR7/8, and CD137 (also known as 4-1BB).

In some embodiments, the agonist of CD137 is urelumab. In some embodiments, the agonist of CD137 is utomilumab.

In some embodiments, the agonist of an immune checkpoint molecule is an inhibitor of GITR. In some embodiments, the agonist of GITR is TRX518, MK-4166, INCAGN1876, MK-1248, AMG228, BMS-986156, GWN323, MEDI1873, or MEDI6469.In some embodiments, the agonist of an immune checkpoint molecule is an agonist of OX40, e.g., OX40 agonist antibody or OX40L fusion protein. In some embodiments, the anti-OX40 antibody is INCAGN01949, MEDI0562 (tavolimab), MOXR-0916, PF-04518600, GSK3174998, BMS-986178, or 9B12. In some embodiments, the OX40L fusion protein is MEDI6383.

In some embodiments, the agonist of an immune checkpoint molecule is an agonist of CD40. In some embodiments, the agonist of CD40 is CP-870893, ADC-1013, CDX-1140, SEA-CD40, RO7009789, JNJ-64457107, APX-005M, or Chi Lob 7/4.

In some embodiments, the agonist of an immune checkpoint molecule is an agonist of ICOS. In some embodiments, the agonist of ICOS is GSK-3359609, JTX-2011, or MEDI-570.

In some embodiments, the agonist of an immune checkpoint molecule is an agonist of CD28. In some embodiments, the agonist of CD28 is theralizumab.

In some embodiments, the agonist of an immune checkpoint molecule is an agonist of CD27. In some embodiments, the agonist of CD27 is varlilumab.

In some embodiments, the agonist of an immune checkpoint molecule is an agonist of TLR7/8. In some embodiments, the agonist of TLR7/8 is MEDI9197.

The compounds of the present disclosure can be used in combination with bispecific antibodies. In some embodiments, one of the domains of the bispecific antibody targets PD-1, PD-L1, CTLA-4, GITR, OX40, TIM3, LAG3, CD137, ICOS, CD3 or TGFβ receptor. In some embodiments, the bispecific antibody binds to PD-1 and PD-L1. In some embodiments, the bispecific antibody that binds to PD-1 and PD-L1 is MCLA-136. In some embodiments, the bispecific antibody binds to PD-L1 and CTLA-4. In some embodiments, the bispecific antibody that binds to PD-L1 and CTLA-4 is AK104.

In some embodiments, the compounds of the disclosure can be used in combination with one or more metabolic enzyme inhibitors. In some embodiments, the metabolic enzyme inhibitor is an inhibitor of IDO1, TDO, or arginase. Examples of IDO1 inhibitors include epacadostat, NLG919, BMS-986205, PF-06840003, IOM2983, RG-70099 and LY338196. Inhibitors of arginase inhibitors include INCB1158.

As provided throughout, the additional compounds, inhibitors, agents, etc. can be combined with the present compound in a single or continuous dosage form, or they can be administered simultaneously or sequentially as separate dosage forms.

Pharmaceutical Formulations and Dosage Forms

When employed as pharmaceuticals, pemigatinib as described herein can be administered in the form of pharmaceutical compositions which refers to a combination of pemigatinib as described herein, and at least one pharmaceutically acceptable carrier. These compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes, depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including ophthalmic and to mucous membranes including intranasal, vaginal and rectal delivery), pulmonary (*e.g.*, by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal, intranasal, epidermal and transdermal), ocular, oral or parenteral. Methods for ocular delivery can include topical administration (eye drops), subconjunctival, periocular or intravitreal injection or introduction by balloon catheter or ophthalmic inserts surgically placed in the conjunctival sac. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal, or intramuscular injection or infusion; or intracranial, e.g., intrathecal or

intraventricular, administration. Parenteral administration can be in the form of a single bolus dose, or may be, for example, by a continuous perfusion pump. Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable.

This disclosure also includes pharmaceutical compositions which contain, as the active ingredient, pemigatinib in combination with one or more pharmaceutically acceptable carriers. In making the compositions described herein, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, for example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10 % by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, the active compound can be milled to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it can be milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size can be adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions described herein can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The compositions can be formulated in a unit dosage form, each dosage containing from about 4 to about 5 mg, or about 4.5 mg, of the active ingredient. In some embodiments, the unit dosage form contains about 9 mg of the active ingredient. In some embodiments, the

unity dosage form contains about 13.5 mg of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

The active compound can be effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It will be understood, however, that the amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid pre-formulation composition containing a homogeneous mixture of pemigatinib. When referring to these pre-formulation compositions as homogeneous, the active ingredient is typically dispersed evenly throughout the composition so that the composition can be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid pre-formulation is then subdivided into unit dosage forms of the type described above containing from, for example, 0.1 to about 500 mg of the active ingredient of the present disclosure.

In some embodiments, pemigatinib is administered orally. In some embodiments, pemigatinib is administered once daily. In some embodiments, pemigatinib is administered in a daily dose of about 5 mg to about 20 mg. In some embodiments, pemigatinib is administered in a daily dose of about 10 mg to about 15 mg. In some embodiments, pemigatinib is administered in a daily dose of about 13.5 mg. In some embodiments, pemigatinib is administered as a tablet. In some embodiments, the tablet comprises about 0.5 mg to about 10 mg of pemigatinib. In some embodiments, the tablet comprises about 0.5 mg to about 5 mg pemigatinib. In some embodiments, the tablet comprises about 2 mg, about 4.5 mg, about 9 mg, about 13.5 mg, or about 18 mg of pemigatinib. In some embodiments, the tablet comprises about 0.5 mg of pemigatinib. In some embodiments, the tablet comprises about 2 mg of pemigatinib. In some embodiments, the tablet comprises about 4.5 mg of pemigatinib. In some embodiments, the tablet comprises about 9 mg of pemigatinib. In some embodiments, the tablet comprises about 13.5 mg of pemigatinib. In some embodiments, the tablet comprises about 18 mg of pemigatinib.

The tablets or pills of the present disclosure can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

The liquid forms in which the pemigatinib, or compositions as described herein can be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described supra. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in can be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device can be attached to a face masks tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions can be administered orally or nasally from devices which deliver the formulation in an appropriate manner.

The amount of compound or composition administered to a patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, and the like. In therapeutic applications, compositions can be administered to a patient already suffering from a disease in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. Effective doses will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the disease, the age, weight and general condition of the patient, and the like.

The compositions administered to a patient can be in the form of pharmaceutical compositions described above. These compositions can be sterilized by conventional sterilization techniques, or may be sterile filtered. Aqueous solutions can be packaged for use

as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

The therapeutic dosage of pemigatinib can vary according to, for example, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of pemigatinib in a pharmaceutical composition can vary depending upon a number of factors including dosage, chemical characteristics (e.g., hydrophobicity), and the route of administration. For example, pemigatinib can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral administration. Some typical dose ranges are from about 1 μg/kg to about 1 g/kg of body weight per day. In some embodiments, the dose range is from about 0.01 mg/kg to about 100 mg/kg of body weight per day. The dosage is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, formulation of the excipient, and its route of administration. Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

Pemigatinib can also be formulated in combination with one or more additional active ingredients which can include any pharmaceutical agent such as anti-viral agents, vaccines, antibodies, immune enhancers, immune suppressants, anti-inflammatory agents and the like.

Enfortumab vedotin as described herein can be administered in the form of pharmaceutical compositions and at least one pharmaceutically acceptable excipient. These compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes, depending upon whether local or systemic treatment is desired and upon the area to be treated. The pharmaceutical compositions may be in a variety of forms. These include, for example, liquid, semi-solid and solid dosage forms, such as liquid solutions (e.g., injectable and infusible solutions), dispersions or suspensions, tablets, pills, powders, liposomes and suppositories. The preferred form can depend on the intended mode of administration and therapeutic application. Typically compositions for the agents described herein are in the form of injectable or infusible solutions.

Enfortumab vedotin can be administered by a variety of methods. For many applications, the route of administration is one of: intravenous injection or infusion (IV), subcutaneous injection (SC), intraperitoneally (IP), or intramuscular injection. It is also possible to use intra-articular delivery. Other modes of parenteral administration can also be used. Examples of such modes include: intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, transtracheal, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, and epidural and intrasternal injection.

Labeled Compound

Another aspect of the present disclosure relates to labeled pemigatinib (radio-labeled, fluorescent-labeled, isotopically-labeled, etc.) that would be useful not only in imaging techniques but also in assays, both *in vitro* and *in vivo*.

The present disclosure further includes isotopically-labeled pemigatinib. An "isotopically" or "radio-labeled" compound is pemigatinib, where one or more atoms are replaced or substituted by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature (i.e., naturally occurring). Suitable radionuclides that may be incorporated in compounds of the present disclosure include but are not limited to ^{2}H (also written as D for deuterium), ^{3}H (also written as T for tritium), ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{18}F, ^{35}S, ^{36}Cl, ^{82}Br, ^{75}Br, ^{76}Br, ^{77}Br, ^{123}I, ^{124}I, ^{125}I and ^{131}I. For example, one or more hydrogen atoms in a compound of the present disclosure can be replaced by deuterium atoms can be optionally substituted with deuterium atoms.

One or more constituent atoms of pemigatinib can be replaced or substituted with isotopes of the atoms in natural or non-natural abundance. In some embodiments, pemigatinib includes at least one deuterium atom. For example, one or more hydrogen atoms in a compound presented herein can be replaced or substituted by deuterium. In some embodiments, the compound includes two or more deuterium atoms. In some embodiments, the compound includes 1-2, 1-3, 1-4, 1-5, or 1-6 deuterium atoms. In some embodiments, all of the hydrogen atoms in a compound can be replaced or substituted by deuterium atoms.

Synthetic methods for including isotopes into organic compounds are known in the art (Deuterium Labeling in Organic Chemistry by Alan F. Thomas (New York, N.Y., Appleton-Century-Crofts, 1971; The Renaissance of H/D Exchange by Jens Atzrodt, Volker Derdau, Thorsten Fey and Jochen Zimmermann, Angew. Chem. Int. Ed. 2007, 7744-7765; The Organic Chemistry of Isotopic Labelling by James R. Hanson, Royal Society of Chemistry,

2011). Isotopically labeled compounds can be used in various studies such as NMR spectroscopy, metabolism experiments, and/or assays.

Substitution with heavier isotopes, such as deuterium, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances. (see *e.g.*, A. Kerekes et al. *J. Med. Chem.* 2011, 54, 201-210; R. Xu et al. *J. Label Compd. Radiopharm.* 2015, 58, 308-312). In particular, substitution at one or more metabolism sites may afford one or more of the therapeutic advantages.

It is understood that a "radio-labeled" or "labeled compound" is a compound that has incorporated at least one radionuclide. In some embodiments, the radionuclide is selected from the group consisting of ^{3}H and ^{14}C. In some embodiments, the radionuclide is selected from the group consisting of ^{11}C, ^{18}F, ^{75}Br, ^{76}Br, and ^{77}Br.

Kits

The present disclosure also includes pharmaceutical kits useful, *e.g.*, in the treatment of cancer, which include one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of pemigatinib, or any of the embodiments thereof. Such kits can further include one or more of various conventional pharmaceutical kit components, such as, *e.g.*, containers with one or more pharmaceutically acceptable carriers, additional containers, *etc.*, as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, can also be included in the kit.

EXAMPLES

The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of non-critical parameters which can be changed or modified to yield essentially the same results.

Example A. RT112/84 and UM-UC-14 in vitro Proliferation Assay

The effect of combining pemigatinib plus enfortumab vedotin (EV) (Padcev, Refdrug Inc.) on proliferation was assessed in vitro in both RT112/84 and UM-UC-14 bladder cancer

cell lines. Briefly, RT112/84 and UM-UC-14 cells were plated at 1000 cells/well overnight on 96 well plates. Pemigatinib (dose response curve from 1 to 100 nM) was added to wells alone or in combination with either 300, 100 or 10 ng/mL of EV. Viability was determined after 5 days of treatment by Cell Titer glo (Promega) on a PHERAStar (BMG LABTECH) plate reader. The data shows that treatment of RT112/84 cells with pemigatinib in combination with intermediate and high dose EV results in decreased proliferation at low doses of pemigatinib. By contrast, treatment of UM-UC-14 with pemigatinib in combination with EV results in only modest effect at high EV concentration.

FIG. 1A is a graph depicting the effects on cell proliferation on RT112/84 bladder cancer cell lines treated with different concentrations of pemigatinib ranging from 1 to 100 nM alone or in combination with either 300, 100 or 10 ng/mL of EV.

FIG. 1B is a graph depicting the effects on cell proliferation on UM-UC-14 bladder cancer cell lines treated with different concentrations of pemigatinib ranging from 1 to 100 nM alone or in combination with either 300, 100 or 10 ng/mL of EV.

Example B. Effect of Pemigatinib on Nectin-4 Levels

RT112/84 in vitro Nectin-4 Receptor density

The effect of combining pemigatinib plus enfortumab vedotin ("EV") (Padcev, Refdrug Inc.) on Nectin-4 receptor density was assessed in vitro in the RT112/84 bladder cancer cell line. Briefly, RT112/84 cells were treated with either 100 nM pemigatinib, 100 nM EV, or the combination of both. The receptor density of Nectin-4 was then assessed by flow cytometry upon a LSRFortessa X-20 instrument (BD Biosciences) with Quantibrite phycoerythrin (PE) beads (BD Biosciences Cat No 340495) using an anti-Nectin-4 PE conjugated antibody (RnD Systems Cat No FAB2659) at different time points after treatment (FIG. 2A). The data shows that treatment of RT112/84 cells with 100nM EV either alone or in combination with 100 nM pemigatinib results in a decrease of receptor density associated with target internalization. By contrast, treatment of RT112/84 cells with 100 nM pemigatinib did not induce changes in Nectin-4 receptor density associated with target internalization.

FIG. 2A is a graph depicting the Nectin-4 receptor density in RT112/84 cell treated with (i) 100 nM of pemigatinib, (ii) 100 nM of EV, or (iii) 100 nM of pemigatinib and 100 nM of EV.

RT112/84 in vivo Nectin-4 Receptor density

The effect of combining pemigatinib plus EV (Padcev, Refdrug Inc.) on Nectin-4 receptor density was also assessed in vivo in the RT112/84 bladder cancer xenograft model (FIG. 2B) in 6 to 8 weeks old NSG mice (Jackson laboratories). Pemigatinib was suspended in 5% N,N-dimethyl acetamide (DMAC) + 50 mM Citrate buffer in 0.5% methyl cellulose for oral administration and EV was suspended in saline for intravenous administration. Briefly, the left flanks of the mice were shaved the day prior to subcutaneous inoculation with $2x10^6$ RT112/84 suspended in matrigel (Corning Life Sciences, Tewksbury, Mass). On day 16, mice were dosed with (i) vehicle; (ii) 0.3 mg/kg of pemigatinib; (iii) 1 mg/kg of pemigatinib; (iv) 3 mg/kg of EV; (v) 0.3 mg/kg of pemigatinib and 3 mg/kg of EV; or (vi) 1 mg/kg of pemigatinib and 3 mg/kg of EV, and tumors were collected 4 h post dose. Tumors were then processed to single cell suspensions and the receptor density of Nectin-4 was then assessed by flow cytometry upon a LSRFortessa X-20 instrument (BD Biosciences with Quantibrite phycoerythrin (PE) beads (BD Biosciences Cat No 340495) using an anti-Nectin-4 PE conjugated antibody (RnD Systems, Cat No FAB2659). The data shows that treatment of RT112/84 tumor bearing mice with EV either alone or in combination with pemigatinib results in decrease of receptor density associated with target internalization. By contrast, treatment of RT112/84 tumor bearing mice with pemigatinib did not induce changes in Nectin-4 receptor density associated with target internalization.

FIG. 2B is a graph depicting the Nectin-4 receptor density in tumor cells obtained from RT112/84 tumor bearing mice that were administered (i) vehicle, (ii) 0.3 mg/kg of pemigatinib, (iii) 1 mg/kg of pemigatinib, (iv) 3 mg/kg of EV, (v) 0.3 mg/kg of pemigatinib and 3 mg/kg of EV, or (vi) 1 mg/kg of pemigatinib and 3 mg/kg of EV.

RT112/84 in vivo pERK inhibition

The effect of combining pemigatinib plus EV (Padcev, Refdrug Inc.) on pERK inhibition was assessed in vivo in the RT112/84 bladder cancer xenograft model (FIG. 3) in 6 to 8 weeks old NSG mice (Jackson laboratories). Pemigatinib was suspended in 5% N,N-dimethyl acetamide (DMAC) + 50 mM Citrate buffer in 0.5% methyl cellulose for oral administration and EV was suspended in saline for intravenous administration. Briefly, the left flanks of the mice were shaved the day prior to subcutaneous inoculation with $2x10^6$ RT112/84 suspended in matrigel (Corning Life Sciences, Tewksbury, Mass). On day 16, mice were dosed with (i) vehicle; (ii) 1 mg/kg of pemigatinib; (iii) 3 mg/kg of EV; or (iv) 1 mg/kg of pemigatinib and 3 mg/kg of EV, and tumors were collected 4 h post dose. Tumors were then processed and levels of phospho ERK were assessed on tumor lysates by MSD

(Mesoscale). The data shows that treatment of RT112/84 tumor bearing mice with pemigatinib either alone or in combination with EV results in decrease phosphorylation of ERK. By contrast, treatment of RT112/84 tumor bearing mice with EV alone did not induce changes ERK phosphorylation levels when compared to vehicle treated tumors.

FIG. 3 is a graph depicting the phosphorylation of ERK in tumor cells obtained from RT112/84 tumor bearing mice that were administered (i) vehicle, (ii) 1 mg/kg of pemigatinib, (iii) 3 mg/kg of EV, or (iv) 1 mg/kg of pemigatinib and 3 mg/kg of EV.

Example C. Combinational effect of pemigatinib with Enfortumab vedotin results in increased tumor growth control in vivo

RT112/84 xenograft model

The in vivo effect of combining pemigatinib plus EV (Padcev, Refdrug Inc.) was assessed in the RT112/84 bladder cancer (85061106, Sigma/ECACC, UK) xenograft model (FIG. 4) in 6 to 8 weeks old NSG mice (Jackson laboratories). Pemigatinib was suspended in 5% N,N-dimethyl acetamide (DMAC) + 50 mM Citrate buffer in 0.5% methyl cellulose for oral administration and EV was suspended in saline for intravenous administration. Briefly, the left flank of the mice were shaved the day prior to subcutaneous inoculation with $2x10^6$ RT112/84 suspended in matrigel (Corning Life Sciences, Tewksbury, Mass). On day 7, tumor dimensions were measured by Vernier calipers, and volume estimated by the formula Volume = [L (long dimension) x W2 (short dimension)]/2. Mice were randomized into 6 groups of 10 mice of approximate mean volume (~200mm^3). Tumors were measured 3 times per week for the duration of the study. Starting day 7, mice were dosed with (i) vehicle; (ii) 0.3 mg/kg of pemigatinib; (iii) 1 mg/kg of pemigatinib; (iv) 3 mg/kg of EV; (v) 0.3 mg/kg of pemigatinib and 3 mg/kg of EV; or (vi) 1 mg/kg of pemigatinib and 3 mg/kg of EV. Pemigatinib was administered orally once daily (QD) for 10 days, while EV was dosed every 4 days (for a total of 2 doses). The data shows that all the treatments, with the exemption of pemigatinib 0.3 mg/kg, had a therapeutic effect in delaying tumor growth when compared to the control vehicle group. Bliss independence (fraction unaffected) analysis of the data suggested the combination of 0.3 mg/kg pemigatinib with 3 mg/kg EV results in a synergistic effect in tumor growth delay when compared to their respective controls.

FIG. 4 is a graph depicting the tumor volume of RT112/84 tumor bearing mice administered (i) vehicle, (ii) 0.3 mg/kg of pemigatinib, (iii) 1 mg/kg of pemigatinib, (iv) 3 mg/kg of EV, (v) 0.3 mg/kg of pemigatinib and 3 mg/kg of EV, or (vi) 1 mg/kg of pemigatinib and 3 mg/kg of EV.

In a separate experiment, mice were randomized on day 7 into 9 groups of 10 mice of approximate mean volume (~200mm^3). Tumors were measured 3 times a week for the duration of the efficacy study (day 21). Starting day 7, mice were dosed with (i) vehicle; (ii) 0.3 mg/kg of pemigatinib; (iii) 1 mg/kg of pemigatinib; (iv) 3 mg/kg of EV; (v) 10 mg/kg of EV; (vi) 0.3 mg/kg of pemigatinib and 3 mg/kg of EV; (vii) 0.3 mg/kg of pemigatinib and 10 mg/kg of EV; (viii) 1 mg/kg of pemigatinib and 3 mg/kg of EV; or (ix) 1 mg/kg of pemigatinib and 10 mg/kg of EV. Pemigatinib was administered orally QD for 10 days, while EV was dosed every 4 days (for a total of 2 doses). The data show that high dose of EV can achieve greater tumor growth inhibition independent of pemigatinib combinations and to similar levels as the low dose 3 mg/kg EV combined with high dose 1 mg/kg pemigatinib. In addition, mice were observed to determine overall survival (FIG. 6). The data shows that high dose EV in combination with high dose pemigatinib results in a better overall survival in these mice compared to controls or single arm treatments.

FIG. 5 is a graph depicting the tumor volume of RT112/84 tumor bearing mice administered (i) vehicle, (ii) 0.3 mg/kg of pemigatinib, (iii) 1 mg/kg of pemigatinib, (iv) 3 mg/kg of EV; (v) 10 mg/kg of EV, (vi) 0.3 mg/kg of pemigatinib and 3 mg/kg of EV, (vii) 0.3 mg/kg of pemigatinib and 10 mg/kg of EV, (viii) 1 mg/kg of pemigatinib and 3 mg/kg of EV, or (ix) 1 mg/kg of pemigatinib and 10 mg/kg of EV.

FIG. 6A is a Kaplan-Meier graph depicting the overall survival of RT112/84 tumor bearing mice administered (i) vehicle, (ii) 0.3 mg/kg of pemigatinib, (iii) 1 mg/kg of pemigatinib, (iv) 3 mg/kg of EV; (v) 10 mg/kg of EV, (vi) 0.3 mg/kg of pemigatinib and 3 mg/kg of EV, (vii) 0.3 mg/kg of pemigatinib and 10 mg/kg of EV, (viii) 1 mg/kg of pemigatinib and 3 mg/kg of EV, or (ix) 1 mg/kg of pemigatinib and 10 mg/kg of EV.

FIG. 6B is a Kaplan-Meier graph depicting the overall survival of RT112/84 tumor bearing mice administered (i) vehicle, (ii) 0.3 mg/kg of pemigatinib, (iii) 1 mg/kg of pemigatinib, (iv) 3 mg/kg of EV; (v) 10 mg/kg of EV, (vi) 0.3 mg/kg of pemigatinib and 3 mg/kg of EV, (vii) 0.3 mg/kg of pemigatinib and 10 mg/kg of EV, (viii) 1 mg/kg of pemigatinib and 3 mg/kg of EV, or (ix) 1 mg/kg of pemigatinib and 10 mg/kg of EV, for a period of 100 days after inoculation.

UM-UC-14 xenograft model

The in vivo effect of combining pemigatinib plus EV was also assessed in another cancer xenograft model UM-UC-14 (08090509, Sigma/ECACC, UK) in NSG mice (FIG. 7).

Pemigatinib was suspended in 5% DMAC + 50 mM Citrate buffer in 0.5% methyl cellulose for oral administration and EV was suspended in 1x PBS for intravenous administration. Briefly, the left flanks of the mice were shaved the day prior to subcutaneous inoculation with $5x10^6$ UM-UC-14 suspended in matrigel (Corning Life Sciences, Tewksbury, Mass). On day 5, tumor dimensions were measured by Vernier calipers, and volume estimated by the formula Volume = [L (long dimension) x W2 (short dimension)]/2. Mice were randomized into 6 groups of 10 mice of approximate mean volume (~$100mm^3$). Tumors were measured 3 times per week for the duration of the study. Starting day 5, mice were dosed with (i) vehicle; (ii) 0.3 mg/kg of pemigatinib; (iii) 1 mg/kg of pemigatinib; (iv) 3 mg/kg of EV; (v) 0.3 mg/kg of pemigatinib and 3 mg/kg of EV; or (vi) 1 mg/kg of pemigatinib and 3 mg/kg of EV. Pemigatinib was administered orally QD for 10 days, while EV was dosed every 4 days (for a total of 2 doses). The data shows that only pemigatinib 1 mg/kg treatment had a therapeutic effect in delaying tumor growth as single agent when compared to the control vehicle group, while both combinations of pemigatinib 0.3 mg/kg and 1 mg/kg with EV 3 mg/kg had significant therapeutic effect in delaying tumor growth. Bliss independence (fraction unaffected) analysis of the data suggested the combination of 0.3 mg/kg pemigatinib with 3 mg/kg EV results in a synergistic effect in tumor growth delay when compared to their respective controls.

FIG. 7 is a graph depicting the tumor volume of UM-UC-14 tumor bearing mice administered (i) vehicle, (ii) 0.3 mg/kg of pemigatinib, (iii) 1 mg/kg of pemigatinib, (iv) 3 mg/kg of EV, (v) 0.3 mg/kg of pemigatinib and 3 mg/kg of EV, or (vi) 1 mg/kg of pemigatinib and 3 mg/kg of EV.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. Each reference, including all patent, patent applications, and publications, cited in the present application is incorporated herein by reference in its entirety.

WHAT IS CLAIMED IS:

1. A method of treating cancer in a patient, comprising administering to said patient:
   (i) pemigatinib, or a pharmaceutically acceptable salt thereof; and
   (ii) enfortumab vedotin.

2. The method of claim 1, wherein pemigatinib and enfortumab vedotin are administered simultaneously.

3. The method of claim 1, wherein pemigatinib and enfortumab vedotin are administered sequentially.

4. The method of any one of claims 1-3, wherein pemigatinib is administered orally.

5. The method of any one of claims 1-4, wherein pemigatinib is administered in a daily dose of about 1 mg to about 20 mg.

6. The method of any one of claims 1-4, wherein pemigatinib is administered in a daily dose of about 13.5 mg.

7. The method of any one of claims 1-4, wherein pemigatinib is administered in a daily dose of about 9 mg.

8. The method of any one of claims 1-7, wherein enfortumab vedotin is administered intravenously.

9. The method of any one of claims 1-8 wherein enfortumab vedotin is administered as an intravenous infusion in a dosage of about 0.5 mg/kg to about 2.0 mg/kg.

10. The method of any one of claims 1-8, wherein enfortumab vedotin is administered as an intravenous infusion in a dosage of about 1.25 mg/kg.

11. The method of any one of claims 1-10, further comprising administering one or more additional therapeutic agents.

12. The method of claim 11, comprising administering one additional therapeutic agent.

13. The method of claim 12, wherein the additional therapeutic agent in an inhibitor of PD-1 or PD-L1.

14. The method of any one of claims 1-13, wherein the cancer is bladder cancer.

15. The method of any one of claims 1-13, wherein the cancer is selected from hepatocellular cancer, bladder cancer, breast cancer, cervical cancer, colorectal cancer, endometrial cancer, anal cancer, Merkel cell carcinoma, gastric cancer, head and neck cancer, kidney cancer, liver cancer, lung cancer, ovarian cancer, prostate cancer, esophageal cancer, gall bladder cancer, pancreatic cancer, thyroid cancer, skin cancer, leukemia, multiple myeloma, chronic lymphocytic lymphoma, adult T cell leukemia, B-cell lymphoma, acute myelogenous leukemia, Hodgkin's or non-Hodgkin's lymphoma, Waldenstrom's Macroglubulinemia, hairy cell lymphoma, Burkett's lymphoma, glioblastoma, melanoma, rhabdosarcoma, and adenocarcinoma.

16. The method of any one of claims 1-13, wherein the cancer is selected from sarcoma, head and neck cancer, melanoma, and non-small cell lung cancer.

17. The method of any one of claims 1-13, wherein the cancer is cholangiocarcinoma.

18. The method of any one of claims 1-13, wherein the cancer is myeloid/lymphoid neoplasms.

19. The method of claim 18, wherein the myeloid/lymphoid neoplasm is 8p11 myeloproliferative syndrome.

20. The method of any one of claims 1-13, wherein the cancer is a urogenital cancer.

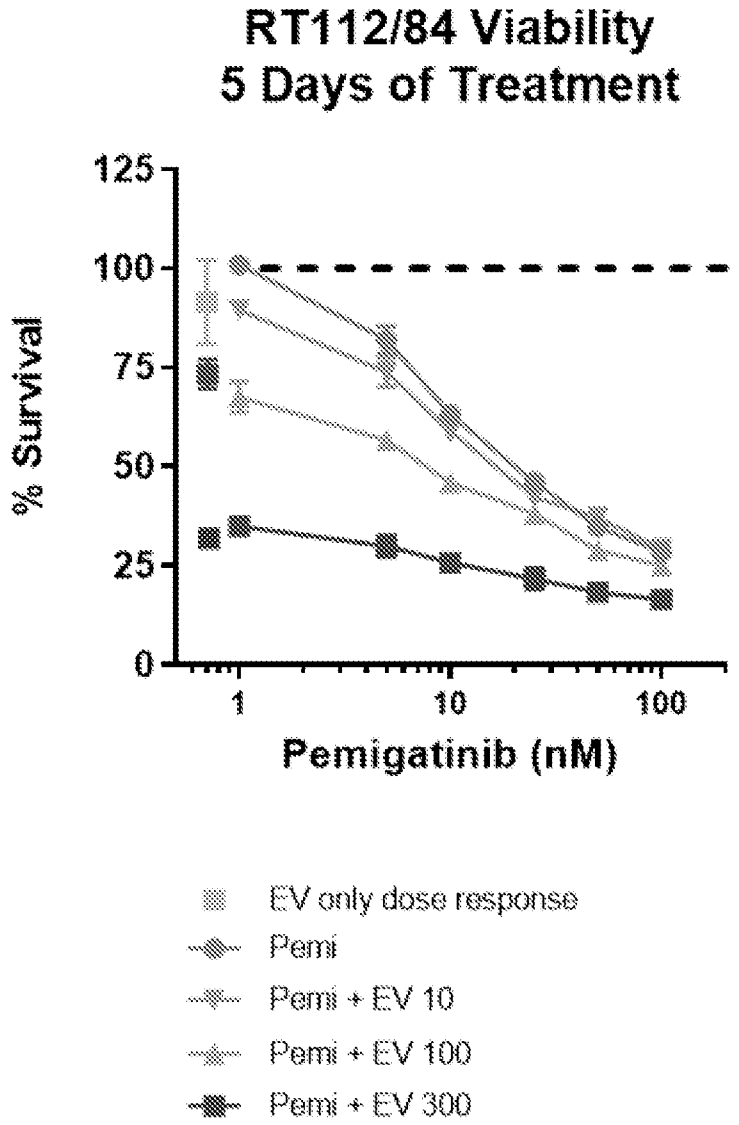

RT112/84 Viability
5 Days of Treatment
% Survival
125
100
75
50
25
0
1
10
100
Pemigatinib (nM)
EV only dose response
Pemi
Pemi + EV 10
Pemi + EV 100
Pemi + EV 300

FIG. 1A

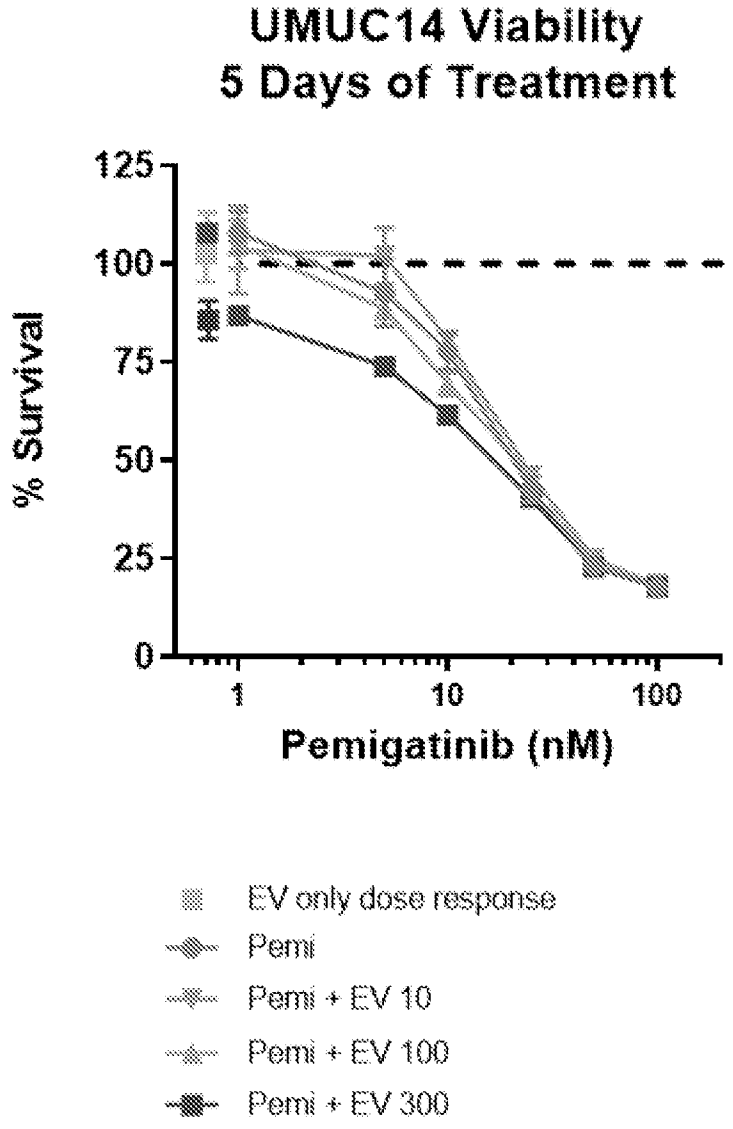

UMUC14 Viability
5 Days of Treatment
% Survival
125
100
75
50
25
0
1
10
100
Pemigatinib (nM)
EV only dose response
Pemi
Pemi + EV 10
Pemi + EV 100
Pemi + EV 300

FIG. 1B

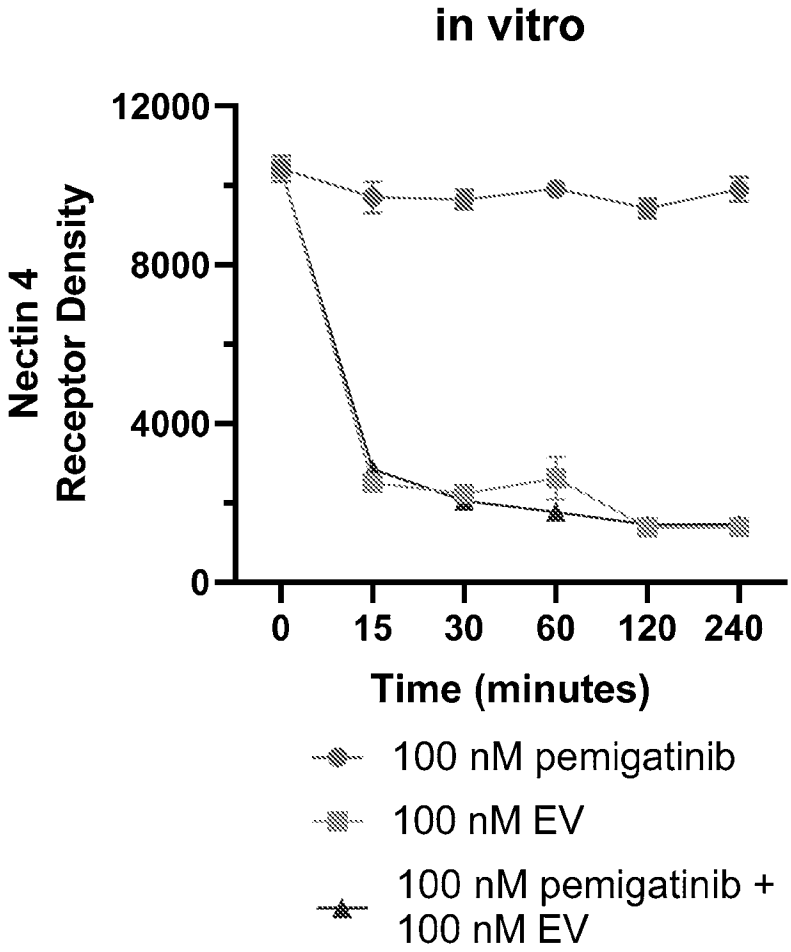

in vitro
12000
8000
4000
0
Nectin 4
Receptor Density
0
15
30
60
120
240
Time (minutes)
100 nM pemigatinib
100 nM EV
100 nM pemigatinib +
100 nM EV

FIG. 2A

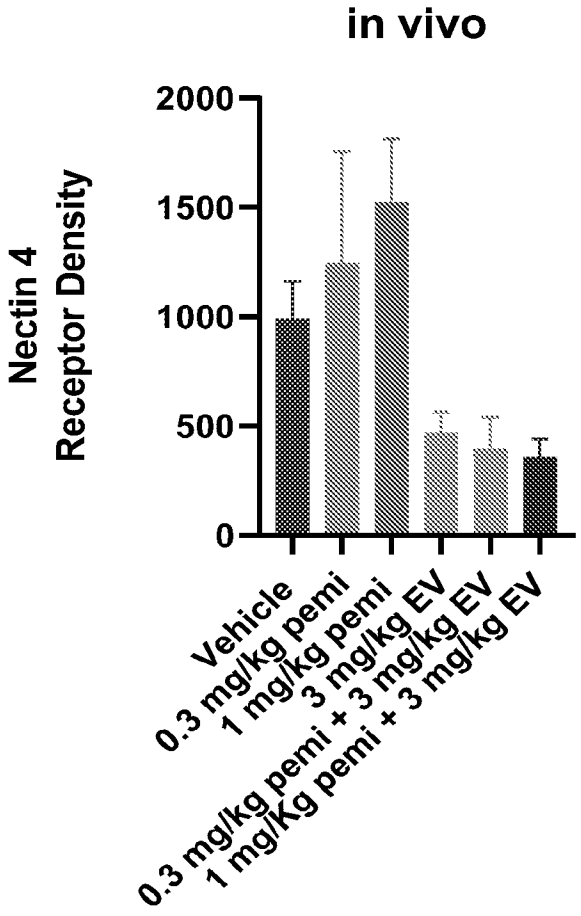

in vivo
Nectin 4
Receptor Density
2000
1500
1000
500
0
Vehicle
0.3 mg/kg pemi
1 mg/kg pemi
3 mg/kg EV
0.3 mg/kg pemi + 3 mg/kg EV
1 mg/Kg pemi + 3 mg/kg EV

FIG. 2B

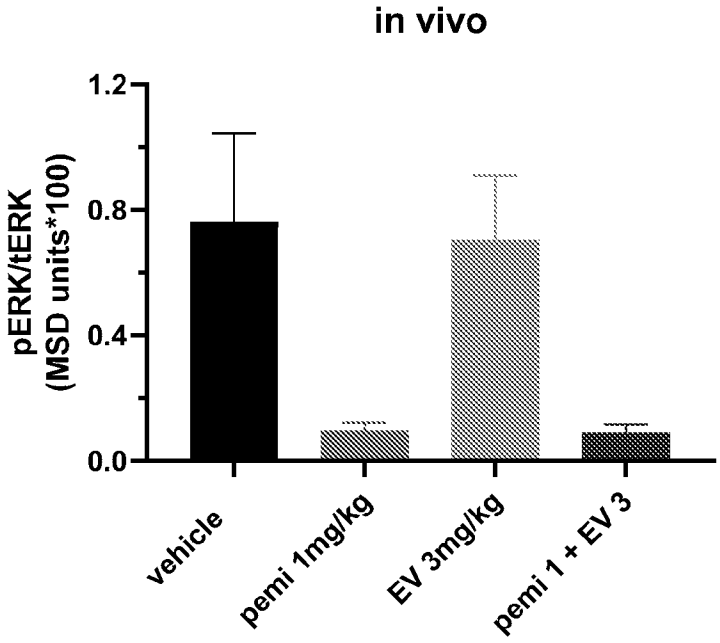

in vivo
pERK/tERK
(MSD units*100)
1.2
0.8
0.4
0.0
vehicle
pemi 1mg/kg
EV 3mg/kg
pemi 1 + EV 3

FIG. 3

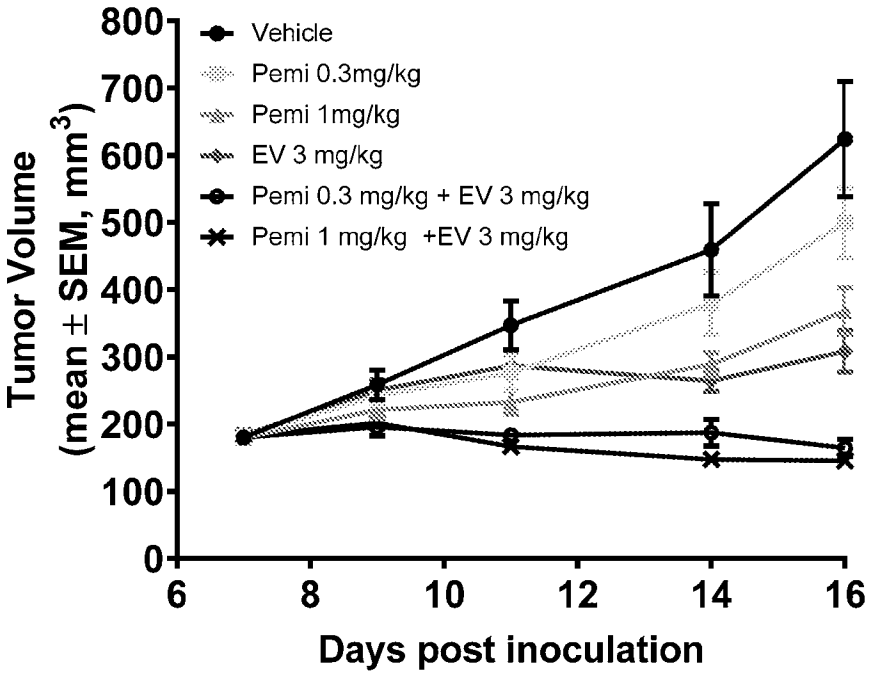

Vehicle
Pemi 0.3mg/kg
Pemi 1mg/kg
EV 3 mg/kg
Pemi 0.3 mg/kg + EV 3 mg/kg
Pemi 1 mg/kg +EV 3 mg/kg
Tumor Volume (mean ± SEM, mm3)
800
700
600
500
400
300
200
100
0
6
8
10
12
14
16
Days post inoculation

FIG. 4

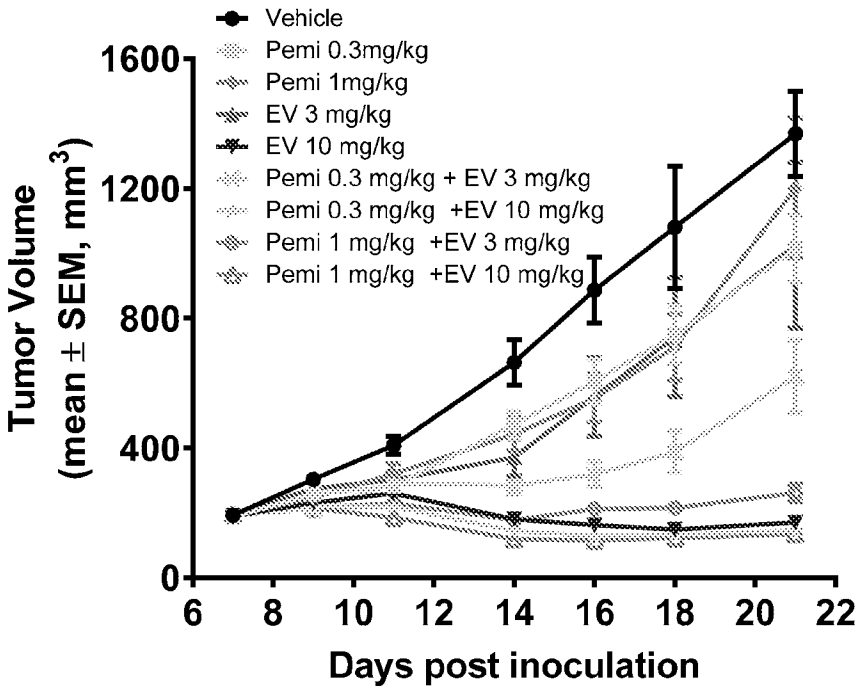

Vehicle
Pemi 0.3mg/kg
Pemi 1mg/kg
EV 3 mg/kg
EV 10 mg/kg
Pemi 0.3 mg/kg + EV 3 mg/kg
Pemi 0.3 mg/kg +EV 10 mg/kg
Pemi 1 mg/kg +EV 3 mg/kg
Pemi 1 mg/kg +EV 10 mg/kg
Tumor Volume (mean ± SEM, mm3)
1600
1200
800
400
0
6
8
10
12
14
16
18
20
22
Days post inoculation

FIG. 5

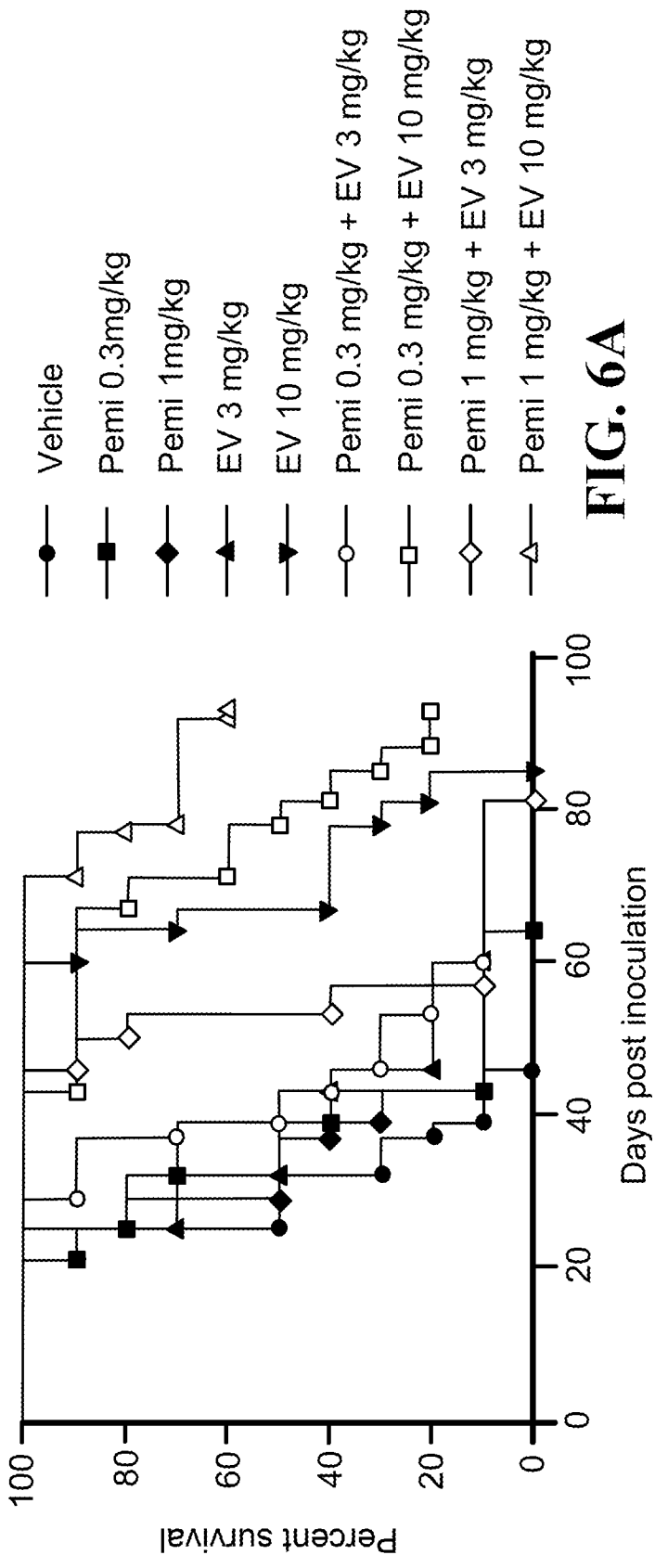

Vehicle
Pemi 0.3mg/kg
Pemi 1mg/kg
EV 3 mg/kg
EV 10 mg/kg
Pemi 0.3 mg/kg + EV 3 mg/kg
Pemi 0.3 mg/kg + EV 10 mg/kg
Pemi 1 mg/kg + EV 3 mg/kg
Pemi 1 mg/kg + EV 10 mg/kg
Percent survival
0
20
40
60
80
100
Days post inoculation
0
20
40
60
80
100

FIG. 6A

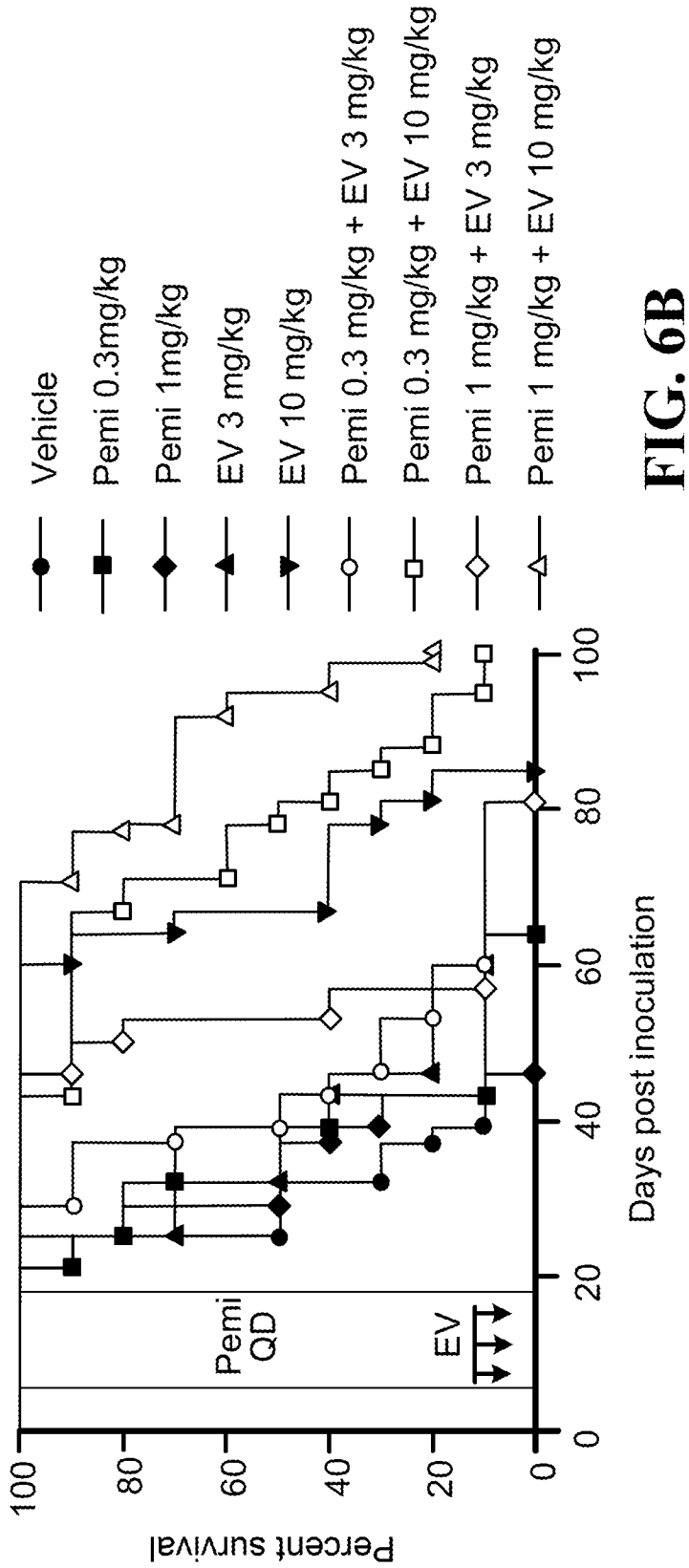

Vehicle
Pemi 0.3mg/kg
Pemi 1mg/kg
EV 3 mg/kg
EV 10 mg/kg
Pemi 0.3 mg/kg + EV 3 mg/kg
Pemi 0.3 mg/kg + EV 10 mg/kg
Pemi 1 mg/kg + EV 3 mg/kg
Pemi 1 mg/kg + EV 10 mg/kg
Percent survival
100
80
60
40
20
0
Pemi QD
EV
0
20
40
60
80
100
Days post inoculation

FIG. 6B

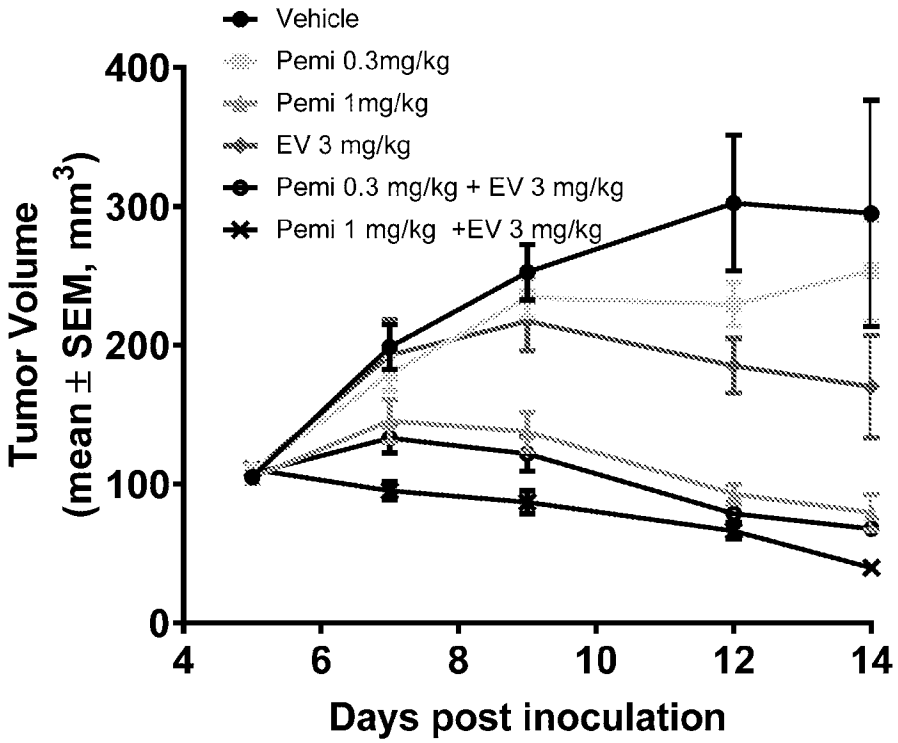

Vehicle
Pemi 0.3mg/kg
Pemi 1mg/kg
EV 3 mg/kg
Pemi 0.3 mg/kg + EV 3 mg/kg
Pemi 1 mg/kg +EV 3 mg/kg
Tumor Volume
(mean ± SEM, mm3)
400
300
200
100
0
4
6
8
10
12
14
Days post inoculation

FIG. 7

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2022/024210

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/28 A61K31/5375 A61K39/395 A61K47/68 A61P35/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TAMALUNAS ALEXANDER ET AL: "Systemtherapie des Harnblasenkarzinoms", DER UROLOGE, vol. 60, no. 2, 4 January 2021 (2021-01-04), pages 247-258, XP037371309, ISSN: 0340-2592, DOI: 10.1007/S00120-020-01420-5 Page 254, end of section entitled 'Erdafitinib', and section on 'Enfortumab Vedotin'	1-20
X	WO 2020/081898 A1 (UNIV JOHNS HOPKINS [US]) 23 April 2020 (2020-04-23) page 10, line 25 - line 27	1-20

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[x] Further documents are listed in the continuation of Box C.

[x] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 June 2022	28/06/2022

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sitch, David

1

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2022/024210

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	Hess Et Al: "Abstract P245: Synergistic effect of combination of pemigatinib with enfortumab vedotin (EV) in human bladder cancer models", Molecular Cancer Therapeutics ¦ American Association for Cancer Research.2021, 20 (12 Supplement): P245, 1 October 2021 (2021-10-01), XP55932549, Retrieved from the Internet: URL:https://aacrjournals.org/mct/article/20/12_Supplement/P245/676032/Abstract-P245-Synergistic-effect-of-combination-of [retrieved on 2022-06-17] the whole document -----	1-20

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2022/024210

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2020081898 A1	23-04-2020	US 2021355547 A1	18-11-2021
		WO 2020081898 A1	23-04-2020