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(54) Title: COMBINATION COMPRISING A PD-1 ANTAGONIST AND AN FGFR4 INHIBITOR

(57) Abstract: The present invention relates to the combination of an anti-PD-1 antibody molecule and an FGFR4 inhibitor and to the use of said combination in the treatment of cancer, in particular liver cancer.

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Combination comprising a PD-1 antagonist and an FGFR4 inhibitor**Sequence listing**

The instant application contains a Sequence Listing which has been submitted
electronically in ASCII format and is hereby incorporated by reference in its entirety. Said
ASCII copy, created on September 13, 2016, is named PAT057381_SL.txt and is 67,823
bytes in size.

Field of the invention

The present invention relates to a pharmaceutical combination comprising an anti-
PD1 antibody molecule and an FGFR4 inhibitor, in particular N-(5-cyano-4-((2-
methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-
dihydro-1,8-naphthyridine-1(2H)-carboxamide, to the use of said pharmaceutical
combination in the treatment of cancer, including liver cancer, and to methods of treatment
of cancer, including liver cancer, comprising administering said pharmaceutical combination.

Background

The ability of T cells to mediate an immune response against an antigen requires two
distinct signaling interactions (Viglietta, V. *et al.* (2007) *Neurotherapeutics* 4:666-675;
Korman, A. J. *et al.* (2007) *Adv. Immunol.* 90:297-339). First, an antigen that has been
arrayed on the surface of antigen-presenting cells (APC) is presented to an antigen-specific
naive CD4⁺ T cell. Such presentation delivers a signal via the T cell receptor (TCR) that
directs the T cell to initiate an immune response specific to the presented antigen. Second,
various co-stimulatory and inhibitory signals mediated through interactions between the APC
and distinct T cell surface molecules trigger the activation and proliferation of the T cells and
ultimately their inhibition.

The immune system is tightly controlled by a network of costimulatory and co-
inhibitory ligands and receptors. These molecules provide the second signal for T cell
activation and provide a balanced network of positive and negative signals to maximize
immune responses against infection, while limiting immunity to self (Wang, L. *et al.* (Epub
Mar. 7, 2011) *J. Exp. Med.* 208(3):577-92; Lepenies, B. *et al.* (2008) *Endocrine, Metabolic &
Immune Disorders--Drug Targets* 8:279-288). Examples of costimulatory signals include the
binding between the B7.1 (CD80) and B7.2 (CD86) ligands of the APC and the CD28 and
CTLA-4 receptors of the CD4⁺ T-lymphocyte (Sharpe, A. H. *et al.* (2002) *Nature Rev.
Immunol.* 2:116-126; Lindley, P. S. *et al.* (2009) *Immunol. Rev.* 229:307-321). Binding of
B7.1 or B7.2 to CD28 stimulates T cell activation, whereas binding of B7.1 or B7.2 to CTLA-
4 inhibits such activation (Dong, C. *et al.* (2003) *Immunolog. Res.* 28(1):39-48; Greenwald,

R. J. *et al.* (2005) *Ann. Rev. Immunol.* 23:515-548). CD28 is constitutively expressed on the surface of T cells (Gross, J., *et al.* (1992) *J. Immunol.* 149:380-388), whereas CTLA-4 expression is rapidly up-regulated following T-cell activation (Linsley, P. *et al.* (1996) *Immunity* 4:535-543).

5 Other ligands of the CD28 receptor include a group of related B7 molecules, also known as the "B7 Superfamily" (Coyle, A. J. *et al.* (2001) *Nature Immunol.* 2(3):203-209; Sharpe, A. H. *et al.* (2002) *Nature Rev. Immunol.* 2:116-126; Collins, M. *et al.* (2005) *Genome Biol.* 6:223.1-223.7; Korman, A. J. *et al.* (2007) *Adv. Immunol.* 90:297-339). Several members of the B7 Superfamily are known, including B7.1 (CD80), B7.2 (CD86), the
10 inducible co-stimulator ligand (ICOS-L), the programmed death-1 ligand (PD-L1; B7-H1), the programmed death-2 ligand (PD-L2; B7-DC), B7-H3, B7-H4 and B7-H6 (Collins, M. *et al.* (2005) *Genome Biol.* 6:223.1-223.7).

 The Programmed Death 1 (PD-1) protein is an inhibitory member of the extended CD28/CTLA-4 family of T cell regulators (Okazaki *et al.* (2002) *Curr Opin Immunol* 14:
15 391779-82; Bennett *et al.* (2003) *J. Immunol.* 170:711-8). Other members of the CD28 family include CD28, CTLA-4, ICOS and BTLA. PD-1 is suggested to exist as a monomer, lacking the unpaired cysteine residue characteristic of other CD28 family members. PD-1 is expressed on activated B cells, T cells, and monocytes.

 The PD-1 gene encodes a 55 kDa type I transmembrane protein (Agata *et al.* (1996)
20 *Int Immunol.* 8:765-72). Although structurally similar to CTLA-4, PD-1 lacks the MYPPY motif (SEQ ID NO: 236) that is important for B7-1 and B7-2 binding. Two ligands for PD-1 have been identified, PD-L1 (B7-H1) and PD-L2 (B7-DC), that have been shown to downregulate T cell activation upon binding to PD-1 (Freeman *et al.* (2000) *J. Exp. Med.* 192:1027-34; Carter *et al.* (2002) *Eur. J. Immunol.* 32:634-43). Both PD-L1 and PD-L2 are
25 B7 homologs that bind to PD-1, but do not bind to other CD28 family members. PD-L1 is abundant in a variety of human cancers (Dong *et al.* (2002) *Nat. Med.* 8:787-9).

 PD-1 is known as an immunoinhibitory protein that negatively regulates TCR signals (Ishida, Y. *et al.* (1992) *EMBO J.* 11:3887-3895; Blank, C. *et al.* (Epub 2006 Dec. 29) *Immunol. Immunother.* 56(5):739-745). The interaction between PD-1 and PD-L1 can act as
30 an immune checkpoint, which can lead to, e.g., a decrease in tumor infiltrating lymphocytes, a decrease in T-cell receptor mediated proliferation, and/or immune evasion by cancerous cells (Dong *et al.* (2003) *J. Mol. Med.* 81:281-7; Blank *et al.* (2005) *Cancer Immunol. Immunother.* 54:307-314; Konishi *et al.* (2004) *Clin. Cancer Res.* 10:5094-100). Immune suppression can be reversed by inhibiting the local interaction of PD-1 with PD-L1 or PD-L2;
35 the effect is additive when the interaction of PD-1 with PD-L2 is blocked as well (Iwai *et al.* (2002) *Proc. Nat'l. Acad. Sci. USA* 99:12293-7; Brown *et al.* (2003) *J. Immunol.* 170:1257-66).

Therapies involving anti-PD-1 antibodies have been described for instance in WO2015/112900. Combination therapies comprising an immunomodulator and a second therapeutic agent for the treatment of cancer have been described in WO2016040892 and
5 WO2016040880 .

Normal growth, as well as tissue repair and remodeling, require specific and delicate control of activating growth factors and their receptors. Fibroblast Growth Factors (FGFs) constitute a family of over twenty structurally related polypeptides that are developmentally regulated and expressed in a wide variety of tissues. FGFs stimulate proliferation, cell
10 migration and differentiation and play a major role in skeletal and limb development, wound healing, tissue repair, hematopoiesis, angiogenesis, and tumorigenesis (reviewed in Ornitz, Novartis Found Symp 232: 63-76; discussion 76-80, 272-82 (2001)).

The biological action of FGFs is mediated by specific cell surface receptors belonging to the Receptor Protein Tyrosine Kinase (RPTK) family of protein kinases. These proteins
15 consist of an extracellular ligand binding domain, a single transmembrane domain and an intracellular tyrosine kinase domain which undergoes phosphorylation upon binding of FGF. Four FGFRs have been identified to date: FGFR1 (also called Flg, fms-like gene, flt- 2, bFGFR, N-bFGFR or Cek1), FGFR2 (also called Bek-Bacterial Expressed Kinase, KGFR, Ksam, Ksam1 and Cek3), FGFR3 (also called Cek2) and FGFR4. All mature FGFRs share a
20 common structure consisting of an amino terminal signal peptide, three extracellular immunoglobulin-like domains (Ig domain I, Ig domain II, Ig domain III), with an acidic region between Ig domains (the "acidic box" domain), a transmembrane domain, and intracellular kinase domains (Ullrich and Schlessinger, Cell 61: 203,1990 ; Johnson and Williams (1992) Adv. Cancer Res. 60: 1-41). The distinct FGFR isoforms have different binding affinities for
25 the different FGF ligands.

Alterations in FGFRs have been associated with a number of human cancers including myeloma, breast, stomach, colon, bladder, pancreatic and hepatocellular carcinomas. Recently, it was reported that FGFR4 may play an important role in liver cancer in particular (PLoS One, 2012, volume 7, 36713). Other studies have also implicated FGFR4
30 or its ligand FGF19 in other cancer types including breast, glioblastoma, prostate, rhabdomyosarcoma, gastric, ovarian, lung, colon (Int. J. Cancer 1993; 54:378-382; Oncogene 2010; 29:1543-1552; Cancer Res 2010; 70:802-812; Cancer Res 2011; 71:4550-4561; Clin Cancer Res 2004; 10:6169-6178; Cancer Res 2013; 73:2551-2562; Clin Cancer Res 2012; 18:3780-3790; J. Clin. Invest. 2009; 119:3395-3407; Ann Surg Oncol
35 2010;17:3354-61; Cancer 2011; 117:5304-13; Clin Cancer Res 2013; 19:809-820; PNAS 2013; 110:12426-12431; Oncogene 2008; 27:85-97).

Hepatocellular carcinoma (HCC) is the seventh most common form of cancer worldwide and the third most common cause of cancer-related deaths. Potentially curative therapies, such as surgical resection, liver transplant or other local treatments, result in survival rates of between 50-70% at 5 years for patients with early stage HCC. However, despite advances in diagnostic techniques and increased surveillance, the majority of HCC cases present with advanced, inoperable tumors. Sorafenib is the only approved drug in HCC with marginal improvement in overall survival (OS) and poor tolerability.

There is thus a need to provide therapies for cancer, including therapies for HCC, which have improved safety profiles, improved toxicity profiles, improved efficacy compared to a standard of care, are well tolerated by patients, offer advantages to patients in terms of overall response rate, overall survival, time to progression, and/or even cure the disease. New therapies for cancer also could benefit such patients if they also provide tumor growth inhibition, decreased tumor volume, inhibition of cell proliferation, immunomodulatory activity, reduction in relapse time, apoptosis of cancer cells, increase in the time delay for the onset of exponential growth of tumor, reduction of required dosage, reduction of side effects, and/or reduction in resistance to treatment.

Given the importance of immune checkpoint pathways in regulating an immune response, the need also exists for developing novel combination therapies that modulate the activity of immunoinhibitory proteins, such as PD-1, thus leading to activation of the immune system. Such agents can be used, e.g., for cancer immunotherapy and treatment of other conditions, such as chronic infection. Recent clinical studies have highlighted the potential of targeting the PD-L1/PD-1 pathway in HCC. A pharmaceutical combination comprising a PD-1 antagonist and a second therapeutic agent may therefore be useful in treating a cancer, e.g. HCC.

Summary of the invention

The invention is expected to provide a solution at least to some of the needs outlined above by providing a pharmaceutical combination as defined herein.

A selective FGFR4 inhibitor may potentiate the effect of an immune checkpoint blocker such as an anti-PD-1 inhibitor. In particular, the combined inhibition of the FGFR4 signal with the selective FGFR4 inhibitor described herein, in particular, N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide, or a pharmaceutically acceptable salt thereof, and the inhibition of PD-1 with an anti-PD-1 antibody molecule described herein, in

particular the exemplary antibody molecule described herein, may be of particular benefit to subjects suffering from a cancer such as HCC, including advanced HCC. The combination of the invention may also have an acceptable and manageable overall toxicity profile.

5 Thus, in a first aspect, the invention relates to a pharmaceutical combination comprising an anti-PD-1 antibody molecule and N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in free form or in pharmaceutically acceptable salt form.

10 In another aspect, the invention relates to a pharmaceutical combination as defined herein for use as a medicament.

 In a further aspect, the invention relates to a pharmaceutical combination as defined herein for use in the treatment of cancer, in particular in the treatment of liver cancer.

15 In another aspect, the invention relates to a pharmaceutical combination comprising an FGFR4 inhibitor and anti-PD-1 antibody molecule for the treatment of liver cancer.

 In another aspect the invention relates to a method of treating cancer, in particular liver cancer, in a subject in need thereof, comprising administering to said subject simultaneously or sequentially N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in
20 free form or in pharmaceutically acceptable salt form and an anti-PD-1 antibody molecule.

 In another aspect, the invention relates to a method of treating liver cancer in a subject suffering from liver cancer comprising administering to said subject simultaneously or sequentially an FGFR4 inhibitor and an anti-PD-1 antibody molecule.

25 In a further aspect, the invention relates to a therapeutic regimen comprising the simultaneous or sequential administration of N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in free form or in pharmaceutically acceptable salt form and an anti-PD-1 antibody molecule. In a particular aspect, the therapeutic regimen is for the treatment of cancer, in particular liver cancer.

30 In another aspect, the invention relates to a kit comprising a pharmaceutical combination as defined herein with instructions for simultaneous or sequential administration of N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in free form or in pharmaceutically acceptable salt form and an anti-PD-1 antibody molecule.

35

Description

The present invention relates to a pharmaceutical combination comprising an anti-PD-1 antibody molecule and N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in free form or in pharmaceutically acceptable salt form.

In the present description, a "pharmaceutical combination" refers to a non-fixed combination.

The term "non-fixed combination" means that the active ingredients, e.g. an anti-PD-1 antibody molecule and N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in free form or in pharmaceutically acceptable salt form, are both administered to a patient or a subject in need thereof as separate entities either simultaneously or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the two active ingredients in the body of the patient or a subject in need thereof.

The skilled person will readily understand that when reference is made to a compound "in free form", the compound is present as the free acid or the free base, and not, e.g., as the salt.

As used herein, the term "treat", "treating" or "treatment" in connection to a disease or disorder refers in one embodiment, to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In yet another embodiment, "treat", "treating" or "treatment" refers to modulating the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both. In yet another embodiment, "treat", "treating" or "treatment" refers to preventing or delaying the onset or development or progression of the disease or disorder.

As used herein, the term "a therapeutically effective amount" when referring to the active ingredients present in the combination of the invention refers to the amounts of the active ingredients that, when administered to a subject either simultaneously or sequentially, will elicit a biological or medical response of a subject, for example, reduction or inhibition of an enzyme or a protein activity, or ameliorate symptoms, alleviate conditions, slow or delay disease progression.

In an embodiment, the term "a therapeutically effective amount" when referring to the active ingredients present in the combination of the invention refers to the amounts of the active ingredients that, when administered to a subject either simultaneously or sequentially are effective to provide at least one of the following benefits: improved safety profiles, improved toxicity profiles, improved efficacy, well tolerated by patients or subjects suffering from cancer, improved overall response rate, improved overall

survival, improved time to progression, tumor growth inhibition, decreased tumor volume, inhibition of cell proliferation, immunomodulatory activity, reduction in relapse time, apoptosis of cancer cells, increase in the time delay for the onset of exponential growth of tumor, reduction in resistance to treatment, synergistic effect leading to reduction of required
5 dosage and/or reduction of side effects leading to an enhancement of the long-term clinical effectiveness of the combination.

As used herein, the term "combination of the invention" or "combination of the present invention" refers to a combination comprising an anti-PD-1 antibody molecule and
10 an FGFR4 inhibitor, in particular N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide, in free form or in pharmaceutically acceptable salt form, as defined herein.

The preferred FGFR4 inhibitor in the combination of the invention is N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-
15 dihydro-1,8-naphthyridine-1(2H)-carboxamide, or a pharmaceutically acceptable salt thereof (e.g. the citrate salt). This compound is also known as FGF401 and is currently undergoing clinical trials involving HCC patients (see NCT02325739).

As used herein, the term "active ingredient" refers independently to each combination
20 partner, namely the anti-PD-1 antibody molecule and N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in free form or in pharmaceutically acceptable salt form (e.g. the citrate salt form).

As used herein "liver cancer" also refers to hepatocellular carcinoma (HCC).
25 As used herein, the term "FGFR4" refers to fibroblast growth factor receptor 4, also known as CD334, JTK2, or TKF.

As used herein, the term "FGFR4 inhibitor" is a compound which inhibits FGFR4. The FGFR4 inhibitor is preferably a selective FGFR4 inhibitor.

The term "about" generally means an acceptable degree of error for the quantity
30 measured given the nature or precision of the measurements. Exemplary degrees of error may be within 10%, or within 5% of a given value or range of values.

The combinations and methods of the present invention encompass polypeptides and nucleic acids having the sequences specified, or sequences substantially identical or similar thereto, e.g., sequences at least 85%, 90%, 95% identical or higher to the sequence
35 specified. In the context of an amino acid sequence, the term "substantially identical" is used herein to refer to a first amino acid that contains a sufficient or minimum number of amino acid residues that are i) identical to, or ii) conservative substitutions of aligned amino

acid residues in a second amino acid sequence such that the first and second amino acid sequences can have a common structural domain and/or common functional activity. For example, amino acid sequences that contain a common structural domain having at least about 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identity to a reference sequence, *e.g.*, a sequence provided herein.

In the context of nucleotide sequence, the term "substantially identical" is used herein to refer to a first nucleic acid sequence that contains a sufficient or minimum number of nucleotides that are identical to aligned nucleotides in a second nucleic acid sequence such that the first and second nucleotide sequences encode a polypeptide having common functional activity, or encode a common structural polypeptide domain or a common functional polypeptide activity. For example, nucleotide sequences having at least about 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identity to a reference sequence, *e.g.*, a sequence provided herein.

The term "functional variant" refers to polypeptides that have a substantially identical amino acid sequence to the naturally-occurring sequence, or are encoded by a substantially identical nucleotide sequence, and are capable of having one or more activities of the naturally-occurring sequence.

Calculations of homology or sequence identity between sequences (the terms are used interchangeably herein) are performed as follows.

To determine the percent identity of two amino acid sequences, or of two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in one or both of a first and a second amino acid or nucleic acid sequence for optimal alignment and non-homologous sequences can be disregarded for comparison purposes). In a preferred embodiment, the length of a reference sequence aligned for comparison purposes is at least 30%, preferably at least 40%, more preferably at least 50%, 60%, and even more preferably at least 70%, 80%, 90%, 100% of the length of the reference sequence. The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position (as used herein amino acid or nucleic acid "identity" is equivalent to amino acid or nucleic acid "homology").

The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences.

The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. In a preferred embodiment, the percent identity between two amino acid sequences is determined using

the Needleman and Wunsch ((1970) *J. Mol. Biol.* 48:444-453) algorithm which has been incorporated into the GAP program in the GCG software package (available at <http://www.gcg.com>), using either a Blossum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6. In yet another preferred embodiment, the percent identity between two nucleotide sequences is determined using the GAP program in the GCG software package (available at <http://www.gcg.com>), using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. A particularly preferred set of parameters (and the one that should be used unless otherwise specified) are a Blossum 62 scoring matrix with a gap penalty of 12, a gap extend penalty of 4, and a frameshift gap penalty of 5.

The percent identity between two amino acid or nucleotide sequences can be determined using the algorithm of E. Meyers and W. Miller ((1989) *CABIOS*, 4:11-17) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4.

The nucleic acid and protein sequences described herein can be used as a "query sequence" to perform a search against public databases to, for example, identify other family members or related sequences. Such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul, *et al.* (1990) *J. Mol. Biol.* 215:403-10. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to a nucleic acid (SEQ ID NO: 1) molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.*, (1997) *Nucleic Acids Res.* 25:3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (*e.g.*, XBLAST and NBLAST) can be used. See <http://www.ncbi.nlm.nih.gov>.

As used herein, the term "hybridizes under low stringency, medium stringency, high stringency, or very high stringency conditions" describes conditions for hybridization and washing. Guidance for performing hybridization reactions can be found in *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6, which is incorporated by reference. Aqueous and nonaqueous methods are described in that reference and either can be used. Specific hybridization conditions referred to herein are as follows: 1) low stringency hybridization conditions in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by two washes in 0.2X SSC, 0.1% SDS at least at 50°C (the temperature of the washes can be increased to 55°C for low stringency conditions); 2) medium stringency

hybridization conditions in 6X SSC at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 60°C; 3) high stringency hybridization conditions in 6X SSC at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 65°C; and preferably 4) very high stringency hybridization conditions are 0.5M sodium phosphate, 7% SDS at 65°C, followed by one or more washes at 0.2X SSC, 1% SDS at 65°C. Very high stringency conditions (4) are the preferred conditions and the ones that should be used unless otherwise specified.

It is understood that the anti-PD-1 antibody molecule used in the present invention may have additional conservative or non-essential amino acid substitutions, which do not have a substantial effect on their functions.

The term "amino acid" is intended to embrace all molecules, whether natural or synthetic, which include both an amino functionality and an acid functionality and capable of being included in a polymer of naturally-occurring amino acids. Exemplary amino acids include naturally-occurring amino acids; analogs, derivatives and congeners thereof; amino acid analogs having variant side chains; and all stereoisomers of any of any of the foregoing. As used herein the term "amino acid" includes both the D- or L- optical isomers and peptidomimetics.

A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine).

The terms "polypeptide", "peptide" and "protein" (if single chain) are used interchangeably herein to refer to polymers of amino acids of any length. The polymer may be linear or branched, it may comprise modified amino acids, and it may be interrupted by non-amino acids. The terms also encompass an amino acid polymer that has been modified; for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation, such as conjugation with a labeling component. The polypeptide can be isolated from natural sources, can be produced by recombinant techniques from a eukaryotic or prokaryotic host, or can be a product of synthetic procedures.

The terms "nucleic acid," "nucleic acid sequence," "nucleotide sequence," or "polynucleotide sequence," and "polynucleotide" are used interchangeably. They refer to a polymeric form of nucleotides of any length, either deoxyribonucleotides or ribonucleotides, or analogs thereof. The polynucleotide may be either single-stranded or double-stranded, and if single-stranded may be the coding strand or non-coding (antisense) strand. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and nucleotide analogs. The sequence of nucleotides may be interrupted by non-nucleotide components. A polynucleotide may be further modified after polymerization, such as by conjugation with a labeling component. The nucleic acid may be a recombinant polynucleotide, or a polynucleotide of genomic, cDNA, semisynthetic, or synthetic origin which either does not occur in nature or is linked to another polynucleotide in a nonnatural arrangement.

The term "isolated," as used herein, refers to material that is removed from its original or native environment (e.g., the natural environment if it is naturally occurring). For example, a naturally-occurring polynucleotide or polypeptide present in a living animal is not isolated, but the same polynucleotide or polypeptide, separated by human intervention from some or all of the co-existing materials in the natural system, is isolated. Such polynucleotides could be part of a vector and/or such polynucleotides or polypeptides could be part of a composition, and still be isolated in that such vector or composition is not part of the environment in which it is found in nature.

Various aspects of the invention are described in further detail below. Additional definitions are set out throughout the specification.

FGFR4 inhibitors

In an embodiment, the invention relates to a pharmaceutical combination comprising an anti-PD-1 antibody molecule and an FGFR4 inhibitor for use in the treatment of liver cancer.

The FGFR4 inhibitor used in the combination of the present invention is preferably a compound that inhibits FGFR4 selectively compared to FGFR1, FGFR2 and FGFR3. FGFR4 inhibitors may be small molecules or large molecules. Therapies involving FGFR4 blocking antibodies have been described for instance in the following patent applications WO2009/009173, WO2007/136893, WO2012/138975, WO2010/026291, WO2008/052798, WO2010/004204, WO2014/105849, WO2014/165287 and WO2016/023894. WO2014/144737, WO2014/145909, WO2014/011900, WO2015/057963, WO2015/057938, WO2015/030021, WO2015/107171, WO2015/059668, WO2016/064960, WO2016/134320, WO2016/134314, WO2016/134294 also describe low molecular weight FGFR4 inhibitors.

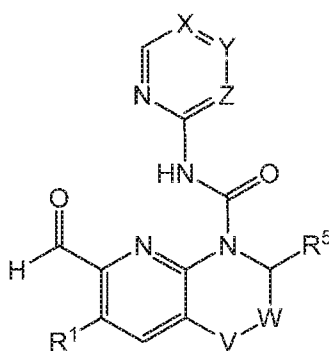
In an embodiment, the FGFR4 inhibitor used in the combination of the present invention is any of the FGFR4 inhibitors described in any of patent applications WO2009/009173, WO2007/136893, WO2012/138975, WO2010/026291, WO2008/052798, WO2010/004204, WO2014/105849, WO2014/165287, WO2016/023894, WO2014/144737, WO2014/145909, WO2014/011900, WO2015/057963, WO2015/057938, WO2015/030021, WO2015/107171, WO2015/059668, WO2016/064960, WO2016/134320, WO2016/134314, and WO2016/134294.

In an embodiment, the FGFR4 inhibitor used in the combination of the present invention is any of the FGFR4 inhibitors described in WO2014/144737, WO2014/145909, WO2014/011900, WO2015/057963, WO2015/057938, WO2015/030021, WO2015/107171, WO2015/059668, WO2016/064960, WO2016/134320, WO2016/134314, WO2016/134294, in free form or in pharmaceutically acceptable salt form.

In an embodiment, the FGFR4 inhibitor used in the combination of the present invention is a compound as defined in WO2015/059668, in free form or in pharmaceutically acceptable salt form.

In an embodiment, the FGFR4 inhibitor used in the combination of the present invention is a compound of formula (I) in free form or in pharmaceutically acceptable salt form as described in patent application WO2015/059668.

Therefore, in one embodiment, the FGFR4 inhibitor used in the combination of the present invention is a compound of formula (I) in free form or in pharmaceutically acceptable salt form



(I)

wherein

V is selected from CH₂, O, CH(OH);

W is selected from CH₂, CH₂CH₂, bond;

X is C(R^X) or N;

Y is C(R^Y) or N;

Z is CH or N;

wherein when X is N, Y and Z are not N;

5 wherein when Y is N, X and Z are not N;

wherein when Z is N, X and Y are not N;

R^X is selected from hydrogen, halogen, haloC₁-C₃alkyl, cyano, C₁-C₆alkyl, hydroxyC₁-C₆alkyl;

10 R^Y is selected from hydrogen, halogen, C₁-C₃alkyl, C₁-C₆alkoxy, hydroxyC₁-C₃alkoxy, NR^{Y1}R^{Y2}, cyano, C₁-C₃alkoxyC₁-C₃alkoxy, C₁-C₃alkoxy-haloC₁-C₃alkoxy, di(C₁-C₃alkyl)aminoC₁-C₆alkoxy, O-(CH₂)₀₋₁-R^{Y3}, CR^{Y6}R^{Y7}, S-C₁-C₃alkyl, haloC₁-C₆alkoxy optionally substituted with hydroxy;

or

15 R^X and R^Y together with the ring to which they are attached form a bicyclic aromatic ring system optionally further comprising one or two heteroatoms selected from N, O, or S, which ring system is optionally substituted with C₁-C₃alkyl;

R^{Y1} is hydrogen and

20 R^{Y2} is selected from C₁-C₆alkyl; hydroxyC₁-C₆alkyl; haloC₁-C₆alkyl optionally substituted with hydroxy; C₁-C₄alkoxyC₁-C₆alkyl; haloC₁-C₃alkoxyC₁-C₆alkyl; (CH₂)₀₋₁-R^{Y4}; di(C₁-C₃alkyl)aminoC₁-C₆alkyl substituted with hydroxy; bicycloC₅-C₈alkyl optionally substituted with hydroxyC₁-C₃alkyl; phenyl substituted with S(O)₂-CH(CH₃)₂; C₂-C₃alkylsulfonic acid;

or

25 R^{Y1} and R^{Y2} together with the N atom to which they are attached form a saturated or unsaturated non-aromatic 6-membered heterocyclic ring which may contain an O atom, which ring may be substituted once or twice by R^{Y5};

R^{Y3} is selected from quinuclidinyl, a 4-, 5- or 6-membered saturated heterocyclic ring comprising at least one heteroatom selected from N, O or S, or a 5- or 6-membered aromatic heterocyclic ring, which saturated or aromatic heterocyclic ring is optionally substituted with C₁-C₃alkyl and/or oxo;

30 R^{Y4} is a 4-, 5- or 6-membered saturated heterocyclic ring comprising at least one heteroatom selected from N, O, or S, which ring is optionally substituted with C₁-C₃alkyl;

R^{Y5} is independently selected from C₁-C₃alkyl, hydroxy, di(C₁-C₃alkyl)aminoC₁-C₃alkyl, or

35 two R^{Y5} attached at the same carbon atom form together with the carbon atom to which they are attached a 5-membered saturated heterocyclic ring comprising at least one heteroatom selected from N, O or S, which ring is substituted once or more than once with C₁-C₃alkyl;

R^{Y6} and R^{Y7} together with the carbon atom to which they are attached form a 6-membered saturated or unsaturated non-aromatic heterocyclic ring comprising one heteroatom selected from N, O or S;

R^1 is selected from hydrogen; halogen; C_1 - C_3 alkyl; halo C_1 - C_3 alkyl; hydroxy C_1 - C_3 alkyl; C_3 - C_6 cycloalkyl; $CH_2NR^2R^3$; $CH(CH_3)NR^2R^3$; C_1 - C_3 alkoxy C_1 - C_3 alkyl; CH_2CO_2H ; $C(O)H$; C_1 - C_3 alkoxy; a 5- or 6-membered saturated heterocyclic or aromatic heterocyclic ring comprising at least one heteroatom selected from N, O or S, which ring is optionally substituted once or more than once with a group independently selected from C_1 - C_3 alkyl, halo C_1 - C_3 alkyl, oxetanyl or oxo;

R^2 is selected from C_1 - C_3 alkyl, di(C_1 - C_3 alkyl)amino C_1 - C_3 alkyl;

R^3 is selected from C_1 - C_3 alkyl, $C(O)C_1$ - C_3 alkyl, $C(O)-CH_2-OH$, $C(O)-CH_2-O-CH_3$, $C(O)-CH_2-N(CH_3)_2$, $S(O)_2CH_3$;

or

R^2 and R^3 together with the N atom to which they are attached form a saturated 5- or 6-membered ring optionally comprising one additional heteroatom selected from N, N-oxide, O or S, which ring may be substituted once or more than once with R^4 ;

R^4 is independently selected from C_1 - C_3 alkyl, di(C_1 - C_3 alkyl)amino, $C(O)CH_3$, hydroxy;

or

two R^4 attached at the same carbon atom form together with the carbon atom to which they are attached a 4-, 5- or 6-membered non-aromatic heterocyclic ring comprising at least one heteroatom selected from N, O or S;

or

two R^4 attached at the same ring atom form an oxo group;

R^5 is selected from hydrogen or C_1 - C_3 alkyl.

As used herein, the term " C_1 - C_6 alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to six carbon atoms, and which is attached to the rest of the molecule by a single bond. The term " C_1 - C_4 alkyl" is to be construed accordingly. The term " C_1 - C_3 alkyl" is to be construed accordingly. Examples of C_1 - C_6 alkyl include, but are not limited to, methyl, ethyl, *n*-propyl, 1-methylethyl (*iso*-propyl), *n*-butyl, *n*-pentyl and 1,1-dimethylethyl (*t*-butyl).

As used herein, the term "hydroxy C_1 - C_6 alkyl" refers to a radical of formula $-R_a-OH$, wherein R_a is C_1 - C_6 alkyl as defined above. Examples of hydroxy C_1 - C_6 alkyl include, but are not limited to, hydroxy-methyl, 2-hydroxy-ethyl, 2-hydroxy-propyl, 3-hydroxy-propyl and 5-hydroxy-pentyl.

As used herein, the term "C₃-C₆cycloalkyl" refers to saturated monocyclic hydrocarbon groups of 3-6 carbon atoms. Examples of C₃-C₆cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

As used herein, the term "C₁-C₆alkoxy" refers to a radical of the formula -OR_a where R_a is a C₁-C₆alkyl radical as generally defined above. The term "C₁-C₃alkoxy" is to be construed accordingly. Examples of C₁-C₆alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentoxy, and hexoxy.

As used herein, the term "C₁-C₄alkoxyC₁-C₆alkyl" refers to a radical of the formula -R_b-O-R_a where R_a is a C₁-C₄alkyl radical and R_b is a C₁-C₆alkyl radical as defined above. The term "C₁-C₃alkoxyC₁-C₆alkyl" is to be construed accordingly. The oxygen atom may be bonded to any carbon atom in either alkyl radical. Examples of C₁-C₄alkoxyC₁-C₆alkyl include, but are not limited to, methoxy-methyl, methoxy-ethyl, ethoxy-ethyl, 1-ethoxy-propyl and 2-methoxy-butyl.

"Halogen" or "halo" refers to bromo, chloro, fluoro or iodo.

As used herein, the term "halogenC₁-C₆alkyl" or "haloC₁-C₆alkyl" refers to C₁-C₆alkyl radical, as defined above, substituted by one or more halo radicals, as defined above. Examples of halogenC₁-C₆alkyl include, but are not limited to, trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, 3-bromo-2-fluoropropyl and 1-bromomethyl-2-bromoethyl.

As used herein, the term "haloC₁-C₃alkoxy" refers to C₁-C₃alkoxy as defined above, substituted by one or more halo radicals, as defined above. Examples of haloC₁-C₃alkoxy include, but are not limited to, trifluoromethoxy, difluoromethoxy, trifluoroethoxy.

As used herein, the term "hydroxyC₁-C₃alkoxy" refers to a C₁-C₃alkoxy radical as defined above, wherein one of the hydrogen atoms of the C₁-C₃alkoxy radical is replaced by OH. Examples of hydroxyC₁-C₃alkoxy include, but are not limited to, hydroxymethoxy, hydroxyethoxy.

As used herein, the term "C₁-C₃alkoxyC₁-C₃alkoxy" refers to a C₁-C₃alkoxy radical as defined above, wherein one of the hydrogen atoms of the C₁-C₃alkoxy radical is replaced by -O-C₁-C₃alkyl. Examples of C₁-C₃alkoxyC₁-C₃alkoxy include, but are not limited to, methoxymethoxy, ethoxymethoxy.

As used herein, the term "C₁-C₃alkoxy-haloC₁-C₃alkoxy" refers to a haloC₁-C₃alkoxy radical as defined above, wherein one of the hydrogen atoms of the haloC₁-C₃alkoxy radical is replaced by -O-C₁-C₃alkyl. Examples of C₁-C₃alkoxy-haloC₁-C₃alkoxy include, but are not limited to, methoxytrifluoropropoxy.

As used herein, the term "di(C₁-C₃alkyl)aminoC₁-C₆alkyl" refers to a radical of the formula -R_{a1}-N(R_{a2})-R_{a2} where R_{a1} is a C₁-C₆alkyl radical as defined above and each R_{a2} is a C₁-C₃alkyl radical, which may be the same or different, as defined above. The nitrogen atom

may be bonded to any carbon atom in any alkyl radical. As described herein, the "diC₁-C₃alkylaminoC₁-C₆alkyl" may be substituted with hydroxy.

As used herein, the term "di(C₁-C₃alkyl)aminoC₁-C₆alkoxy" refers to a radical of the formula -R_{a1}-N(R_{a2})-R_{a2} where R_{a1} is a C₁-C₆alkoxy radical as defined above and each R_{a2} is
5 a C₁-C₃alkyl radical, which may be the same or different, as defined above.

As used herein, the term "6-membered saturated heterocyclic ring comprising one heteroatom selected from N, O or S" includes piperidyl, tetrahydropyranyl and tetrahydrothiopyranyl.

As used herein, the term "6-membered unsaturated non-aromatic heterocyclic ring
10 comprising one heteroatom selected from N, O or S" includes, but is not limited to, tetrahydropyridinyl, dihydropyranyl, dihydrothiopyranyl.

As used herein, the term "a 4-, 5-, or 6-membered saturated heterocyclic ring comprising at least one heteroatom selected from N, O or S" includes as examples, but is not limited to, azetidiny, oxetanyl, pyrrolidyl, tetrahydrofuryl, tetrahydrothienyl, piperidyl,
15 piperazinyl, tetrahydropyranyl, morpholinyl.

As used herein, the term "5-membered saturated heterocyclic ring" includes as example, but is not limited to, pyrrolidine.

As used herein, the term "a saturated 5- or 6- membered ring optionally comprising one additional heteroatom selected from N, O or S" in relation to the embodiments where R² and R³ together with the N atom to which they are attached form said ring, includes as
20 examples, but is not limited to, pyrrolidine, oxazolidine, piperazine, morpholine, thiomorpholine rings.

As used herein, the term a "4-, 5- or 6-membered non-aromatic heterocyclic ring comprising at least one heteroatom selected from N, O or S" includes 4-, 5-, or 6-membered
25 saturated heterocyclic ring comprising at least one heteroatom selected from N, O or S as defined herein. It also includes 4-, 5-, or 6-membered unsaturated heterocyclic ring comprising at least one heteroatom selected from N, O or S.

As used herein, the term "bicyclic aromatic ring system optionally further comprising one or two heteroatoms selected from N, O or S" includes, but is not limited to,
30 imidazopyridine and isothiazolopyridine.

As used herein, the term "bicycloC₅-C₈alkyl" refers to bicyclic hydrocarbon groups comprising 5 to 8 carbon atoms including, but not limited to, bicyclo[2.1.1]hexyl, bicyclo[1.1.1]pentyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octyl.

As used herein, the term "optionally substituted" as used in the description of R^Y, R^X and R^Y together, R^{Y2}, R^{Y3}, R^{Y4} includes unsubstituted or substituted once or twice.
35

As used herein, the term "substituted" as used, for example in the description of R^{Y2}, two R^{Y5}, includes substituted once or twice, preferably once.

As used herein, the term "more than once" when referring to substituent R⁴, includes 2, 3, 4, 5, or 6 times. Preferably, it includes 2 or 3 times.

In an embodiment, the FGFR4 inhibitor used in the combination of the present invention is a compound in free form or in pharmaceutically acceptable salt form as described in the examples of patent application WO2015/059668.

Therefore, in an embodiment, the FGFR4 inhibitor used in the combination of the present invention is a compound in free form or in pharmaceutically acceptable salt form selected from the group consisting of:

- 10 7-formyl-*N*-(5-(trifluoromethyl)pyridin-2-yl)-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide;
- N*-(4,5-dichloropyridin-2-yl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide;
- N*-(5-cyanopyridin-2-yl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide;
- N*-(5-chloropyridin-2-yl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide;
- 15 7-formyl-*N*-(pyridin-2-yl)-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide;
- N*-(4,5-dimethylpyridin-2-yl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide;
- 7-formyl-*N*-(5-methylpyridin-2-yl)-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide;
- N*-(5-cyanopyrimidin-2-yl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide;
- 6-formyl-*N*-(5-methylpyridin-2-yl)-2*H*-pyrido[3,2-*b*][1,4]oxazine-4(3*H*)-carboxamide;
- 20 6-chloro-*N*-(5-cyanopyridin-2-yl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide;
- 7-formyl-*N*-(6-methoxypyrimidin-4-yl)-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide;
- N*-(5-cyanopyrazin-2-yl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide;
- N*-(5-cyano-4-methoxypyridin-2-yl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2*H*)-
- 25 carboxamide;
- 6-formyl-*N*-(5-(trifluoromethyl)pyridin-2-yl)-2*H*-pyrido[3,2-*b*][1,4]oxazine-4(3*H*)-carboxamide;
- 6-fluoro-7-formyl-*N*-(5-(trifluoromethyl)pyridin-2-yl)-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide;
- 30 *N*-(5-chloro-4-((2-(isopropylsulfonyl)phenyl)amino)pyrimidin-2-yl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide;
- N*-(4,5-dicyanopyridin-2-yl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide;
- 7-formyl-6-(hydroxymethyl)-*N*-(5-(trifluoromethyl)pyridin-2-yl)-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide;
- 35 *N*-(5-cyano-4-ethoxypyridin-2-yl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2*H*)-carboxamide;

- 7-formyl-6-methyl-*N*-(5-(trifluoromethyl)pyridin-2-yl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- N*-(5-cyanopyridin-2-yl)-7-formyl-6-methyl-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 5 7-formyl-*N*-(5-(1-hydroxypentyl)pyridin-2-yl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- N*-(5-cyano-4-(2-methoxyethoxy)pyridin-2-yl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- N*-(4-chloro-5-cyanopyridin-2-yl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 10 *N*-(5-cyano-4-morpholinopyridin-2-yl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- N*-(5-cyano-4-(4-hydroxy-4-methylpiperidin-1-yl)pyridin-2-yl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 15 *N*-(5-cyanopyridin-2-yl)-7-formyl-6-(hydroxymethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- N*-(5-cyano-4-(2-methyl-2,8-diazaspiro[4.5]decan-8-yl)pyridin-2-yl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- N*-(5-cyanopyridin-2-yl)-6-cyclopropyl-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 20 *N*-(5-cyano-4-(3,6-dihydro-2H-pyran-4-yl)pyridin-2-yl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- N*-(5-cyano-4-(tetrahydro-2H-pyran-4-yl)pyridin-2-yl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 25 *N*-(5-chloro-4-((tetrahydrofuran-3-yl)oxy)pyrimidin-2-yl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- N*-(5-cyano-4-isopropoxypyridin-2-yl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- N*-(5-cyano-4-((tetrahydrofuran-2-yl)methoxy)pyridin-2-yl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 30 *N*-(5-cyano-4-(oxetan-2-ylmethoxy)pyridin-2-yl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- N*-(5-cyano-4-((tetrahydro-2H-pyran-2-yl)methoxy)pyridin-2-yl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 35 *N*-(5-cyanopyridin-2-yl)-6-(difluoromethyl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;

- N*-(5-cyano-4-(2-(dimethylamino)ethoxy)pyridin-2-yl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- N*-(5-cyano-4-(2-methoxyethoxy)pyridin-2-yl)-7-formyl-6-(hydroxymethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 5 *N*-(5-cyano-4-((tetrahydrofuran-3-yl)oxy)pyridin-2-yl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- N*-(5-cyano-4-(4-hydroxy-4-methylpiperidin-1-yl)pyridin-2-yl)-7-formyl-6-(hydroxymethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 7-acetyl-*N*-(5-cyanopyridin-2-yl)-6-((dimethylamino)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 10 *N*-(5-cyano-4-((tetrahydrofuran-2-yl)methoxy)pyridin-2-yl)-7-formyl-6-(hydroxymethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- N*-(5-cyano-4-((tetrahydro-2H-pyran-2-yl)methoxy)pyridin-2-yl)-7-formyl-6-(hydroxymethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 15 *N*-(5-cyano-4-(2-methyl-2,8-diazaspiro[4.5]decan-8-yl)pyridin-2-yl)-7-formyl-6-(hydroxymethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- N*-(5-cyano-4-((1-methylpyrrolidin-3-yl)oxy)pyridin-2-yl)-7-formyl-6-(hydroxymethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- N*-(5-cyano-4-((1-methylpiperidin-4-yl)oxy)pyridin-2-yl)-7-formyl-6-(hydroxymethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 20 *N*-(5-cyano-4-((1-methoxypropan-2-yl)oxy)pyridin-2-yl)-7-formyl-6-(hydroxymethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- N*-(5-cyano-4-((tetrahydrofuran-3-yl)oxy)pyridin-2-yl)-7-formyl-6-(hydroxymethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 25 *N*-(5-cyano-4-((tetrahydrofuran-3-yl)oxy)pyridin-2-yl)-6-((dimethylamino)methyl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 2-(8-((5-cyanopyridin-2-yl)carbonyl)-2-formyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acetic acid;
- N*-(5-cyano-4-((tetrahydro-2H-pyran-4-yl)oxy)pyridin-2-yl)-7-formyl-6-(hydroxymethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 30 *N*-(5-cyano-4-((1-methylpyrrolidin-3-yl)oxy)pyridin-2-yl)-7-formyl-6-(hydroxymethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- N*-(5-cyano-4-(((tetrahydro-2H-pyran-3-yl)methyl)amino)pyridin-2-yl)-7-formyl-6-(hydroxymethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 35 *N*-(5-cyano-4-((tetrahydrofuran-3-yl)amino)pyridin-2-yl)-7-formyl-6-(hydroxymethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;

- N*-(5-cyano-4-((2-methoxypropyl)amino)pyridin-2-yl)-7-formyl-6-(hydroxymethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- N*-(5-chloro-4-((1-methoxypropan-2-yl)oxy)pyrimidin-2-yl)-7-formyl-6-(hydroxymethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 5 *N*-(4-(4-chloro-2-hydroxybutoxy)-5-cyanopyridin-2-yl)-7-formyl-6-(hydroxymethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- N*-(5-cyano-4-(2-methoxyethoxy)pyridin-2-yl)-7-formyl-6-(trifluoromethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 10 *N*-(5-cyano-4-(2-methoxyethoxy)pyridin-2-yl)-6-cyclopropyl-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- N*-(5-cyano-4-(2-methoxyethoxy)pyridin-2-yl)-6-(difluoromethyl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- N*-(5-cyano-4-(2-methoxyethoxy)pyridin-2-yl)-6-((dimethylamino)methyl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 15 *N*-(5-cyano-4-((3-(hydroxymethyl)bicyclo[2.2.1]heptan-2-yl)amino)pyridin-2-yl)-7-formyl-6-(hydroxymethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- N*-(5-cyano-4-((tetrahydro-2H-pyran-4-yl)amino)pyridin-2-yl)-7-formyl-6-(hydroxymethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- N*-(5-cyano-4-(2-methoxyethoxy)pyridin-2-yl)-7-formyl-6-(methoxymethyl)-3,4-dihydro-20 1,8-naphthyridine-1(2H)-carboxamide;
- N*-(5-cyanopyridin-2-yl)-7-formyl-6-((*N*-methylacetamido)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- N*-(5-chloro-4-((tetrahydrofuran-3-yl)oxy)pyrimidin-2-yl)-7-formyl-6-(hydroxymethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 25 *N*-(5-cyano-4-((tetrahydrofuran-3-yl)oxy)pyrimidin-2-yl)-7-formyl-6-(hydroxymethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 7-formyl-6-(hydroxymethyl)-*N*-(4-((tetrahydrofuran-3-yl)oxy)pyridin-2-yl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- N*-(5-chloro-4-((tetrahydrofuran-3-yl)oxy)pyridin-2-yl)-7-formyl-6-(hydroxymethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 30 *N*-(5-cyano-4-((1-methylpiperidin-3-yl)methoxy)pyridin-2-yl)-7-formyl-6-(hydroxymethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- N*-(5-cyano-4-((1-methylpyrrolidin-2-yl)methoxy)pyridin-2-yl)-7-formyl-6-(hydroxymethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 35 *N*-(5-cyano-4-((1-methylpiperidin-2-yl)methoxy)pyridin-2-yl)-7-formyl-6-(hydroxymethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;

- N*-(5-fluoropyridin-2-yl)-7-formyl-6-(hydroxymethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- N*-(5-cyano-4-(2-(dimethylamino)ethoxy)pyridin-2-yl)-6-form-¹³C-yl-2H-pyrido[3,2-b][1,4]oxazine-4(3H)-carboxamide;
- 5 *N*-(5-cyano-4-((1-methylpiperidin-4-yl)methoxy)pyridin-2-yl)-7-formyl-6-(hydroxymethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- N*-(5-cyanopyridin-2-yl)-7-formyl-4-hydroxy-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 10 *N*-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-(hydroxymethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- N*-(5-cyano-4-(2-((dimethylamino)methyl)morpholino)pyridin-2-yl)-7-formyl-6-(hydroxymethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- N*-(5-cyano-4-(quinuclidin-3-yloxy)pyridin-2-yl)-7-formyl-6-(hydroxymethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 15 *N*-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 7-formyl-6-(hydroxymethyl)-*N*-(4-((2-methoxyethyl)amino)-5-(trifluoromethyl)pyridin-2-yl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- N*-(5-cyano-4-(4-((dimethylamino)methyl)-4-hydroxypiperidin-1-yl)pyridin-2-yl)-7-formyl-6-(hydroxymethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 20 *N*-(5-cyano-4-((2-hydroxy-2-methylpropyl)amino)pyridin-2-yl)-7-formyl-6-(hydroxymethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- N*-(5-cyano-4-((3-(dimethylamino)-2-hydroxy-2-methylpropyl)amino)pyridin-2-yl)-7-formyl-6-(hydroxymethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 25 *N*-(5-cyano-4-((2-fluoroethyl)amino)pyridin-2-yl)-7-formyl-6-(hydroxymethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- N*-(5-cyano-4-(2,2,2-trifluoroethoxy)pyridin-2-yl)-7-formyl-6-(hydroxymethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- N*-(5-cyano-4-isopropoxy)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 30 *N*-(5-cyano-4-(isopropylamino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- N*-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((3-oxomorpholino)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 35 *N*-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((3-hydroxy-2-oxopyrrolidin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;

- N-(5-cyano-4-(2-methoxyethoxy)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
N-(5-cyano-4-ethylpyridin-2-yl)-6,7-diformyl-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 5 N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide hydrochloride;
N-(5-cyano-4-((1-methoxypropan-2-yl)oxy)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxooxazolidin-3-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((3-methyl-5-
- 10 oxomorpholino)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
6-((4-acetylpiperazin-1-yl)methyl)-N-(5-cyano-4-isopropoxypyridin-2-yl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-(1-(N-methylacetamido)ethyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 15 N-(5-cyano-4-isopropoxypyridin-2-yl)-7-formyl-6-((2-hydroxy-N-methylacetamido)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-6-((N-(2-(dimethylamino)ethyl)acetamido)methyl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 20 N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-6-((N-(2-(dimethylamino)ethyl)methylsulfonamido)methyl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
N-(5-cyano-4-isopropoxypyridin-2-yl)-6-((2-(dimethylamino)-N-methylacetamido)methyl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 25 N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((2-methoxy-N-methylacetamido)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((3-oxothiomorpholino)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-6-((1,1-dioxido-3-
- 30 oxothiomorpholino)methyl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
N-(5-cyano-4-(((4-methylmorpholin-2-yl)methyl)amino)pyridin-2-yl)-6-(difluoromethyl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
N-(5-cyano-4-((1,1,1-trifluoro-3-methoxypropan-2-yl)oxy)pyridin-2-yl)-6-(difluoromethyl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 35 N-(5-cyano-4-((2-(trifluoromethoxy)ethyl)amino)pyridin-2-yl)-7-formyl-6-((N-methylacetamido)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;

- 6-(2-oxa-5-azaspiro[3.4]octan-5-ylmethyl)-N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
N-(4-((2-(tert-butoxy)ethyl)amino)-5-cyanopyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
5 N-(5-cyano-4-((2-hydroxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
N-(5-cyano-4-(2-hydroxyethoxy)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
N-(5-cyanopyridin-2-yl)-2-formyl-7,8-dihydro-5H-pyrido[2,3-b]azepine-9(6H)-
10 carboxamide;
N-(5-cyano-4-(2-methoxyethoxy)pyridin-2-yl)-2-formyl-7,8-dihydro-5H-pyrido[2,3-b]azepine-9(6H)-carboxamide;
N-(5-cyano-4-((1-methoxypropan-2-yl)oxy)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
15 7-formyl-N-(1-isopropyl-1H-imidazo[4,5-c]pyridin-6-yl)-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
7-formyl-N-(1-isopropyl-1H-imidazo[4,5-c]pyridin-6-yl)-6-((2-oxopyrrolidin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
4-((8-((5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)carbonyl)-2-formyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)methyl)-1-methyl-3-oxopiperazine 1-oxide;
20 N-(5-cyano-4-((2-oxopiperidin-4-yl)methoxy)pyridin-2-yl)-7-formyl-6-((2-oxopyrrolidin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
N-(5-cyano-4-(2-methoxyethoxy)pyridin-2-yl)-7-formyl-2-methyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
25 N-(5-cyano-4-isopropoxy-pyridin-2-yl)-7-formyl-2-methyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-2-methyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((3-hydroxy-4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
30 N-(5-cyano-4-isopropoxy-pyridin-2-yl)-6-formyl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-1-carboxamide;
2-((5-cyano-2-(7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-1,2,3,4-tetrahydro-1,8-naphthyridine-1-carboxamido)pyridin-4-yl)amino)ethyl hydrogen sulfate;
35 N-(4-(bicyclo[1.1.1]pentan-1-ylamino)-5-cyanopyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;

- N-(5-cyano-4-(thiophen-2-ylmethoxy)pyridin-2-yl)-7-formyl-6-((N-methylacetamido)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
N-(5-cyano-4-(isopropylthio)pyridin-2-yl)-7-formyl-6-((N-methylacetamido)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 5 N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-6-((3,5-dimethylpiperazin-1-yl)methyl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((3,3,4-trimethyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
6-amino-N-(5-cyanopyridin-2-yl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2H)-
- 10 carboxamide;
N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-(tetrahydro-2H-pyran-4-yl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-6-(1,3-dimethyl-1H-pyrazol-4-yl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 15 N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-(2-methylthiazol-5-yl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-(thiophen-2-yl)-3,4-
- 20 dihydro-1,8-naphthyridine-1(2H)-carboxamide;
N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-(1H-imidazol-1-yl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-(pyridin-3-yl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 25 N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-(1-methyl-1H-pyrazol-5-yl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-(3-methyl-1H-1,2,4-triazol-1-yl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-(3-methyl-2-oxopyrrolidin-1-yl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 30 N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-(3-oxomorpholino)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-(2-oxooxazolidin-3-yl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;
- 35 N-(5-cyano-4-isopropoxypyridin-2-yl)-7-formyl-6-(tetrahydrofuran-3-yl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;

N-(5-cyano-4-isopropoxypyridin-2-yl)-7-formyl-6-(piperidin-4-yl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide;

N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-(1-(oxetan-3-yl)piperidin-4-yl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide; and

5 N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-6-(1-(2,2-difluoroethyl)piperidin-4-yl)-7-formyl-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide.

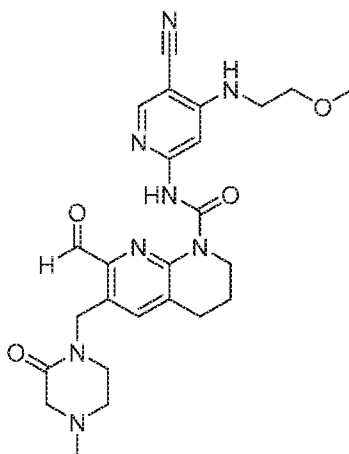
Patent application WO2015/059668 describes how to make the compounds of formula (I) and the specific compounds described above.

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In an embodiment of the invention, the preferred FGFR4 inhibitor used in the combination of the present invention is N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in free form or in pharmaceutically acceptable salt form.

15 This compound is also known by the code name FGF401. A preferred salt of the preferred FGFR4 inhibitor is the citrate salt .

N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide is described specifically in example 83 of patent application WO2015/059668, which WO2015/059668 is
20 hereby incorporated by reference in its entirety, and has the following structure:



In an embodiment of the invention, the FGFR4 inhibitor used in the combination of the present invention is N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in free
25 form.

In an embodiment of the invention, the FGFR4 inhibitor used in the combination of the present invention is N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in citric acid salt form.

5

Antibody Molecules to PD-1

The present invention relates to a pharmaceutical combination comprising an anti-PD-1 antibody molecule and N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in free form or in pharmaceutically acceptable salt form.

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In one embodiment, the anti-PD-1 antibody molecule used in the combination of the present invention is one described in WO2015/112900, entitled "Antibody Molecules to PD-1 and Uses Thereof," which is hereby incorporated by reference in its entirety. In one embodiment, the anti-PD-1 antibody molecule comprises at least one antigen-binding region, e.g., a variable region or an antigen-binding fragment thereof, from an antibody described herein, e.g., an antibody chosen from any of BAP049-Clone-B or BAP049-Clone-E; or as described in Table 1, or encoded by the nucleotide sequence in Table 1; or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences.

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In yet another embodiment, the anti-PD-1 antibody molecule comprises at least one, two, three or four variable regions from an antibody described herein, e.g., an antibody chosen from any of BAP049-Clone-B or BAP049-Clone-E; or as described in Table 1, or encoded by the nucleotide sequence in Table 1; or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences.

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In yet another embodiment, the anti-PD-1 antibody molecule comprises at least one or two heavy chain variable regions from an antibody described herein, e.g., an antibody chosen from any of BAP049-Clone-B or BAP049-Clone-E; or as described in Table 1, or encoded by the nucleotide sequence in Table 1; or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences.

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In yet another embodiment, the anti-PD-1 antibody molecule comprises at least one or two light chain variable regions from an antibody described herein, e.g., an antibody chosen from any of BAP049-Clone-B or BAP049-Clone-E; or as described in Table 1, or encoded by the nucleotide sequence in Table 1; or a sequence substantially identical (e.g.,

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at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences.

In yet another embodiment, the anti-PD-1 antibody molecule includes a heavy chain constant region for an IgG4, *e.g.*, a human IgG4. In one embodiment, the human IgG4 includes a substitution at position 228 according to EU numbering (*e.g.*, a Ser to Pro substitution). In still another embodiment, the anti-PD-1 antibody molecule includes a heavy chain constant region for an IgG1, *e.g.*, a human IgG1. In one embodiment, the human IgG1 includes a substitution at position 297 according to EU numbering (*e.g.*, an Asn to Ala substitution). In one embodiment, the human IgG1 includes a substitution at position 265 according to EU numbering, a substitution at position 329 according to EU numbering, or both (*e.g.*, an Asp to Ala substitution at position 265 and/or a Pro to Ala substitution at position 329). In one embodiment, the human IgG1 includes a substitution at position 234 according to EU numbering, a substitution at position 235 according to EU numbering, or both (*e.g.*, a Leu to Ala substitution at position 234 and/or a Leu to Ala substitution at position 235). In one embodiment, the heavy chain constant region comprises an amino sequence set forth in Table 3, or a sequence substantially identical (*e.g.*, at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) thereto.

In yet another embodiment, the anti-PD-1 antibody molecule includes a kappa light chain constant region, *e.g.*, a human kappa light chain constant region. In one embodiment, the light chain constant region comprises an amino sequence set forth in Table 3, or a sequence substantially identical (*e.g.*, at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) thereto.

In another embodiment, the anti-PD-1 antibody molecule includes a heavy chain constant region for an IgG4, *e.g.*, a human IgG4, and a kappa light chain constant region, *e.g.*, a human kappa light chain constant region, *e.g.*, a heavy and light chain constant region comprising an amino sequence set forth in Table 3, or a sequence substantially identical (*e.g.*, at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) thereto. In one embodiment, the human IgG4 includes a substitution at position 228 according to EU numbering (*e.g.*, a Ser to Pro substitution). In yet another embodiment, the anti-PD-1 antibody molecule includes a heavy chain constant region for an IgG1, *e.g.*, a human IgG1, and a kappa light chain constant region, *e.g.*, a human kappa light chain constant region, *e.g.*, a heavy and light chain constant region comprising an amino sequence set forth in Table 3, or a sequence substantially identical (*e.g.*, at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) thereto. In one embodiment, the human IgG1 includes a substitution at position 297 according to EU numbering (*e.g.*, an Asn to Ala substitution). In one embodiment, the human IgG1 includes a substitution at position 265 according to EU numbering, a substitution at position 329 according to EU numbering,

or both (e.g., an Asp to Ala substitution at position 265 and/or a Pro to Ala substitution at position 329). In one embodiment, the human IgG1 includes a substitution at position 234 according to EU numbering, a substitution at position 235 according to EU numbering, or both (e.g., a Leu to Ala substitution at position 234 and/or a Leu to Ala substitution at position 235).

In another embodiment, the anti-PD-1 antibody molecule includes a heavy chain variable domain and a constant region, a light chain variable domain and a constant region, or both, comprising the amino acid sequence of BAP049-Clone-B or BAP049-Clone-E; or as described in Table 1, or encoded by the nucleotide sequence in Table 1; or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences. The anti-PD-1 antibody molecule, optionally, comprises a leader sequence from a heavy chain, a light chain, or both, as shown in Table 4; or a sequence substantially identical thereto.

In yet another embodiment, the anti-PD-1 antibody molecule includes at least one, two, or three complementarity determining regions (CDRs) from a heavy chain variable region of an antibody described herein, e.g., an antibody chosen from any of BAP049-Clone-B or BAP049-Clone-E; or as described in Table 1, or encoded by the nucleotide sequence in Table 1; or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences.

In yet another embodiment, the anti-PD-1 antibody molecule includes at least one, two, or three CDRs (or collectively all of the CDRs) from a heavy chain variable region comprising an amino acid sequence shown in Table 1, or encoded by a nucleotide sequence shown in Table 1. In one embodiment, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five, six or more changes, e.g., amino acid substitutions or deletions, relative to the amino acid sequence shown in Table 1, or encoded by a nucleotide sequence shown in Table 1.

In yet another embodiment, the anti-PD-1 antibody molecule includes at least one, two, or three CDRs from a light chain variable region of an antibody described herein, e.g., an antibody chosen from any of BAP049-Clone-B or BAP049-Clone-E; or as described in Table 1, or encoded by the nucleotide sequence in Table 1; or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequence.

In yet another embodiment, the anti-PD-1 antibody molecule includes at least one, two, or three CDRs (or collectively all of the CDRs) from a light chain variable region comprising an amino acid sequence shown in Table 1, or encoded by a nucleotide sequence shown in Table 1. In one embodiment, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five, six or more changes, e.g., amino acid substitutions or

deletions, relative to the amino acid sequence shown in Table 1, or encoded by a nucleotide sequence shown in Table 1. In certain embodiments, the anti-PD-1 antibody molecule includes a substitution in a light chain CDR, e.g., one or more substitutions in a CDR1, CDR2 and/or CDR3 of the light chain. In one embodiment, the anti-PD-1 antibody molecule includes a substitution in the light chain CDR3 at position 102 of the light variable region, e.g., a substitution of a cysteine to tyrosine, or a cysteine to serine residue, at position 102 of the light variable region according to Table 1 (e.g., SEQ ID NO: 54 or 70 for a modified sequence).

In another embodiment, the anti-PD-1 antibody molecule includes at least one, two, three, four, five or six CDRs (or collectively all of the CDRs) from a heavy and light chain variable region comprising an amino acid sequence shown in Table 1, or encoded by a nucleotide sequence shown in Table 1. In one embodiment, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five, six or more changes, e.g., amino acid substitutions or deletions, relative to the amino acid sequence shown in Table 1, or encoded by a nucleotide sequence shown in Table 1.

In one embodiment, the anti-PD-1 antibody molecule includes all six CDRs from an antibody described herein, e.g., an antibody chosen from any of BAP049-Clone-B or BAP049-Clone-E; or as described in Table 1, or encoded by the nucleotide sequence in Table 1, or closely related CDRs, e.g., CDRs which are identical or which have at least one amino acid alteration, but not more than two, three or four alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions). In one embodiment, the anti-PD-1 antibody molecule may include any CDR described herein. In certain embodiments, the anti-PD-1 antibody molecule includes a substitution in a light chain CDR, e.g., one or more substitutions in a CDR1, CDR2 and/or CDR3 of the light chain. In one embodiment, the anti-PD-1 antibody molecule includes a substitution in the light chain CDR3 at position 102 of the light variable region, e.g., a substitution of a cysteine to tyrosine, or a cysteine to serine residue, at position 102 of the light variable region according to Table 1.

In another embodiment, the anti-PD-1 antibody molecule includes at least one, two, or three CDRs according to Kabat *et al.* (e.g., at least one, two, or three CDRs according to the Kabat *et al.* definition as set out in Table 1) from a heavy chain variable region of an antibody described herein, e.g., an antibody chosen from any of BAP049-Clone-B or BAP049-Clone-E; or as described in Table 1, or encoded by the nucleotide sequence in Table 1; or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) relative to one, two, or three CDRs according to Kabat *et al.* shown in Table 1.

In another embodiment, the anti-PD-1 antibody molecule includes at least one, two, or three CDRs according to Kabat *et al.* (e.g., at least one, two, or three CDRs according to the Kabat *et al.* definition as set out in Table 1) from a light chain variable region of an antibody described herein, e.g., an antibody chosen from any of BAP049-Clone-B or BAP049-Clone-E; or as described in Table 1, or encoded by the nucleotide sequence in Table 1; or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) relative to one, two, or three CDRs according to Kabat *et al.* shown in Table 1.

In yet another embodiment, the anti-PD-1 antibody molecule includes at least one, two, three, four, five, or six CDRs according to Kabat *et al.* (e.g., at least one, two, three, four, five, or six CDRs according to the Kabat *et al.* definition as set out in Table 1) from the heavy and light chain variable regions of an antibody described herein, e.g., an antibody chosen from any of BAP049-Clone-B or BAP049-Clone-E; or as described in Table 1, or encoded by the nucleotide sequence in Table 1; or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) relative to one, two, three, four, five, or six CDRs according to Kabat *et al.* shown in Table 1.

In yet another embodiment, the anti-PD-1 antibody molecule includes all six CDRs according to Kabat *et al.* (e.g., all six CDRs according to the Kabat *et al.* definition as set out in Table 1) from the heavy and light chain variable regions of an antibody described herein, e.g., an antibody chosen from any of BAP049-Clone-B or BAP049-Clone-E; or as described in Table 1, or encoded by the nucleotide sequence in Table 1; or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) relative to all six CDRs according to Kabat *et al.* shown in Table 1. In one embodiment, the anti-PD-1 antibody molecule may include any CDR described herein.

In another embodiment, the anti-PD-1 antibody molecule includes at least one, two, or three Chothia hypervariable loops (e.g., at least one, two, or three hypervariable loops according to the Chothia *et al.* definition as set out in Table 1) from a heavy chain variable region of an antibody described herein, e.g., an antibody chosen from any of BAP049-Clone-B or BAP049-Clone-E; or as described in Table 1, or encoded by the nucleotide sequence in

Table 1; or at least the amino acids from those hypervariable loops that contact PD-1; or which have at least one amino acid alteration, but not more than two, three or four alterations (*e.g.*, substitutions, deletions, or insertions, *e.g.*, conservative substitutions) relative to one, two, or three hypervariable loops according to Chothia *et al.* shown in Table 1.

In another embodiment, the anti-PD-1 antibody molecule includes at least one, two, or three Chothia hypervariable loops (*e.g.*, at least one, two, or three hypervariable loops according to the Chothia *et al.* definition as set out in Table 1) of a light chain variable region of an antibody described herein, *e.g.*, an antibody chosen from any of BAP049-Clone-B or BAP049-Clone-E; or as described in Table 1, or encoded by the nucleotide sequence in Table 1; or at least the amino acids from those hypervariable loops that contact PD-1; or which have at least one amino acid alteration, but not more than two, three or four alterations (*e.g.*, substitutions, deletions, or insertions, *e.g.*, conservative substitutions) relative to one, two, or three hypervariable loops according to Chothia *et al.* shown in Table 1.

In yet another embodiment, the anti-PD-1 antibody molecule includes at least one, two, three, four, five, or six hypervariable loops (*e.g.*, at least one, two, three, four, five, or six hypervariable loops according to the Chothia *et al.* definition as set out in Table 1) from the heavy and light chain variable regions of an antibody described herein, *e.g.*, an antibody chosen from any of BAP049-Clone-B or BAP049-Clone-E; or as described in Table 1, or encoded by the nucleotide sequence in Table 1; or at least the amino acids from those hypervariable loops that contact PD-1; or which have at least one amino acid alteration, but not more than two, three or four alterations (*e.g.*, substitutions, deletions, or insertions, *e.g.*, conservative substitutions) relative to one, two, three, four, five or six hypervariable loops according to Chothia *et al.* shown in Table 1.

In one embodiment, the anti-PD-1 antibody molecule includes all six hypervariable loops (*e.g.*, all six hypervariable loops according to the Chothia *et al.* definition as set out in Table 1) of an antibody described herein, *e.g.*, an antibody chosen from any of BAP049-Clone-B or BAP049-Clone-E, or closely related hypervariable loops, *e.g.*, hypervariable loops which are identical or which have at least one amino acid alteration, but not more than two, three or four alterations (*e.g.*, substitutions, deletions, or insertions, *e.g.*, conservative substitutions); or which have at least one amino acid alteration, but not more than two, three or four alterations (*e.g.*, substitutions, deletions, or insertions, *e.g.*, conservative substitutions) relative to all six hypervariable loops according to Chothia *et al.* shown in Table 1. In one embodiment, the anti-PD-1 antibody molecule may include any hypervariable loop described herein.

In still another embodiment, the anti-PD-1 antibody molecule includes at least one, two, or three hypervariable loops that have the same canonical structures as the corresponding hypervariable loop of an antibody described herein, e.g., an antibody chosen from any of BAP049-Clone-B or BAP049-Clone-E, e.g., the same canonical structures as at least loop 1 and/or loop 2 of the heavy and/or light chain variable domains of an antibody described herein. See, e.g., Chothia *et al.*, (1992) *J. Mol. Biol.* 227:799-817; Tomlinson *et al.*, (1992) *J. Mol. Biol.* 227:776-798 for descriptions of hypervariable loop canonical structures. These structures can be determined by inspection of the tables described in these references.

In certain embodiments, the anti-PD-1 antibody molecule includes a combination of CDRs or hypervariable loops defined according to the Kabat *et al.* and Chothia *et al.* as described herein in table 1.

In one embodiment, the anti-PD-1 antibody molecule includes at least one, two or three CDRs or hypervariable loops from a heavy chain variable region of an antibody described herein, e.g., an antibody chosen from any of BAP049-Clone-B or BAP049-Clone-E, according to the Kabat *et al.* and Chothia *et al.* definition (e.g., at least one, two, or three CDRs or hypervariable loops according to the Kabat *et al.* and Chothia *et al.* definition as set out in Table 1); or encoded by the nucleotide sequence in Table 1; or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) relative to one, two, or three CDRs or hypervariable loops according to Kabat and/or Chothia shown in Table 1.

For example, the anti-PD-1 antibody molecule can include VH CDR1 according to Kabat *et al.* or VH hypervariable loop 1 according to Chothia *et al.*, or a combination thereof, e.g., as shown in Table 1. In one embodiment, the combination of Kabat and Chothia CDR of VH CDR1 comprises the amino acid sequence GYTFTTYWMH (SEQ ID NO: 224), or an amino acid sequence substantially identical thereto (e.g., having at least one amino acid alteration, but not more than two, three or four alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions)). The anti-PD-1 antibody molecule can further include, e.g., VH CDRs 2-3 according to Kabat *et al.* and VL CDRs 1-3 according to Kabat *et al.*, e.g., as shown in Table 1. Accordingly, in some embodiments, framework regions (FW) are defined based on a combination of CDRs defined according to Kabat *et al.* and hypervariable loops defined according to Chothia *et al.* For example, the anti-PD-1 antibody molecule can include VH FW1 defined based on VH hypervariable loop 1 according to Chothia *et al.* and VH FW2 defined based on VH CDRs 1-2 according to Kabat *et al.*, e.g., as shown in Table 1. The anti-PD-1 antibody molecule can further include, e.g., VH FWs 3-4

defined based on VH CDRs 2-3 according to Kabat *et al.* and VL FWs 1-4 defined based on VL CDRs 1-3 according to Kabat *et al.*

In one embodiment, the anti-PD-1 antibody molecule includes at least one, two or three CDRs from a light chain variable region of an antibody described herein, *e.g.*, an antibody chosen from any of BAP049-Clone-B or BAP049-Clone-E, according to the Kabat *et al.* and Chothia *et al.* definition (*e.g.*, at least one, two, or three CDRs according to the Kabat *et al.* and Chothia *et al.* definition as set out in Table 1).

In one embodiment, the anti-PD-1 antibody molecule includes

(a) a heavy chain variable region (VH) comprising a HCDR1 amino acid sequence of SEQ ID NO: 4, a HCDR2 amino acid sequence of SEQ ID NO: 5, and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a light chain variable region (VL) comprising a LCDR1 amino acid sequence of SEQ ID NO: 13, a LCDR2 amino acid sequence of SEQ ID NO: 14, and a LCDR3 amino acid sequence of SEQ ID NO: 33;

(b) a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 1; a HCDR2 amino acid sequence of SEQ ID NO: 2; and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 10, a LCDR2 amino acid sequence of SEQ ID NO: 11, and a LCDR3 amino acid sequence of SEQ ID NO: 32;

(c) a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 224, a HCDR2 amino acid sequence of SEQ ID NO: 5, and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 13, a LCDR2 amino acid sequence of SEQ ID NO: 14, and a LCDR3 amino acid sequence of SEQ ID NO: 33; or

(d) a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 224; a HCDR2 amino acid sequence of SEQ ID NO: 2; and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 10, a LCDR2 amino acid sequence of SEQ ID NO: 11, and a LCDR3 amino acid sequence of SEQ ID NO: 32.

In one embodiment, the anti-PD-1 antibody molecule includes:

(a) a heavy chain variable region (VH) comprising a HCDR1 amino acid sequence of SEQ ID NO: 4, a HCDR2 amino acid sequence of SEQ ID NO: 5, and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a light chain variable region (VL) comprising a LCDR1 amino acid sequence of SEQ ID NO: 13, a LCDR2 amino acid sequence of SEQ ID NO: 14, and a LCDR3 amino acid sequence of SEQ ID NO: 33;

(b) a VH comprising a HCDR1 amino acid sequence chosen from SEQ ID NO: 1; a HCDR2 amino acid sequence of SEQ ID NO: 2; and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 10, a LCDR2

amino acid sequence of SEQ ID NO: 11, and a LCDR3 amino acid sequence of SEQ ID NO: 32;

(c) a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 224, a HCDR2 amino acid sequence of SEQ ID NO: 5, and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 13, a LCDR2 amino acid sequence of SEQ ID NO: 14, and a LCDR3 amino acid sequence of SEQ ID NO: 33; or

(d) a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 224; a HCDR2 amino acid sequence of SEQ ID NO: 2; and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 10, a LCDR2 amino acid sequence of SEQ ID NO: 11, and a LCDR3 amino acid sequence of SEQ ID NO: 32.

In another embodiment, the anti-PD-1 antibody molecule comprises (i) a heavy chain variable region (VH) comprising a HCDR1 amino acid sequence chosen from SEQ ID NO: 1, SEQ ID NO: 4, or SEQ ID NO: 224; a HCDR2 amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 5; and a HCDR3 amino acid sequence of SEQ ID NO: 3; and (ii) a light chain variable region (VL) comprising a LCDR1 amino acid sequence of SEQ ID NO: 10 or SEQ ID NO: 13, a LCDR2 amino acid sequence of SEQ ID NO: 11 or SEQ ID NO: 14, and a LCDR3 amino acid sequence of SEQ ID NO: 32 or SEQ ID NO: 33.

In another embodiment, the anti-PD-1 antibody molecule comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 38 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 70.

In another embodiment, the anti-PD-1 antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 91 and a light chain comprising the amino acid sequence of SEQ ID NO: 72.

In one embodiment, the anti-PD-1 antibody molecule comprises a heavy chain variable region (VH) comprising a HCDR1, a HCDR2 and a HCDR3 amino acid sequence of BAP049-Clone-B or BAP049-Clone-E as described in Table 1 and a light chain variable region (VL) comprising a LCDR1, a LCDR2 and a LCDR3 amino acid sequence of BAP049-Clone-B or BAP049-Clone-E as described in Table 1.

In one embodiment, the anti-PD-1 antibody molecule comprises a heavy chain variable region (VH) comprising a HCDR1, a HCDR2 and a HCDR3 amino acid sequence of BAP049-Clone-E as described in Table 1 and a light chain variable region (VL) comprising a

LCDR1, a LCDR2 and a LCDR3 amino acid sequence of BAP049-Clone-E as described in Table 1.

In one embodiment, the anti-PD-1 antibody molecule is selected from Nivolumab
5 (Opdivo), Pembrolizumab (Keytruda) and Pidilizumab.

A preferred anti-PD-1 antibody molecule of the present combination is a molecule designated PDR001, also referred to herein as Antibody Molecule A.

PDR001 is described in USSN 14/604,415, entitled "Antibody Molecules to PD-1 and Uses
10 Thereof," and WO/2015/112900, Based on preliminary data, PDR001 is well tolerated, with a safety profile similar to those of other marketed anti-PD-1 antibodies. The combination of the present invention is therefore also expected to be well tolerated.

Thus, in one embodiment, the combination of the invention comprises an anti-PD-1
15 antibody molecule designated PDR001 and comprising a heavy chain variable region (VH) comprising a HCDR1, a HCDR2 and a HCDR3 amino acid sequence of BAP049-Clone-E as described in Table 1 and a light chain variable region (VL) comprising a LCDR1, a LCDR2 and a LCDR3 amino acid sequence of BAP049-Clone-E as described in Table 1 and N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in free form or in
20 pharmaceutically acceptable salt form.

A preferred pharmaceutical combination is a pharmaceutical combination comprising an anti-PD-1 antibody molecule designated PDR001 and FGF401, or a pharmaceutically
25 acceptable salt thereof.

Thus, in an embodiment, the invention relates to a pharmaceutical combination comprising an anti-PD-1 antibody molecule designated PDR001 and comprising a heavy chain variable region (VH) comprising a HCDR1, a HCDR2 and a HCDR3 amino acid
30 sequence of BAP049-Clone-E as described in Table 1 and a light chain variable region (VL) comprising a LCDR1, a LCDR2 and a LCDR3 amino acid sequence of BAP049-Clone-E as described in Table 1 and N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in citric acid salt form.

Uses of the Combination

The combinations of the invention are believed to result in one or more of: an increase in antigen presentation, an increase in effector cell function (e.g., one or more of T cell proliferation, IFN- γ secretion or cytolytic function), inhibition of regulatory T cell function, an effect on the activity of multiple cell types, such as regulatory T cell, effector T cells and NK cells), an increase in tumor infiltrating lymphocytes, an increase in T-cell receptor mediated proliferation, and a decrease in immune evasion by cancerous cells. In one embodiment, the use of anti-PD-1 antibody molecule in the combination of the invention inhibits, reduces or neutralizes one or more activities of PD-1, resulting in blockade or reduction of an immune checkpoint. Thus, the combination of the invention can be used to treat disorders where enhancing an immune response in a subject is desired. In ongoing clinical trials, administering N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide, e.g. in citric acid salt form, to a patient with liver cancer resulted in confirmed tumor shrinkage of 70%. Thus, the combination of the invention may also be used to treat cancers such as liver cancer.

Accordingly, in another aspect, a method of modulating an immune response in a subject is provided. The method comprises administering to the subject in need thereof a combination of the invention (e.g., a combination comprising a therapeutically effective amount of an anti-PD-1 antibody molecule with a therapeutically effective amount of N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in free form or in pharmaceutically acceptable salt form), such that the immune response in the subject is modulated. In one embodiment, the anti-PD-1 antibody molecule enhances, stimulates or increases the immune response in the subject.

As described herein, the subject or patient is a human (e.g., a patient having a disorder described herein). In one embodiment, the subject is in need of enhancing an immune response. In one embodiment, the subject has a disorder described herein, e.g., a cancer, in particular liver cancer. In certain embodiments, the subject is, or is at risk of being, immunocompromised. For example, the subject is undergoing or has undergone a chemotherapeutic treatment and/or radiation therapy. Alternatively, or in combination, the subject is, or is at risk of being, immunocompromised as a result of an infection.

Alternatively, or in combination with any and all embodiments of the invention comprising administering to a subject or administration, it is recognized that the administering or administration is to a subject in need thereof, and that such subject includes each subject stated in the foregoing paragraph; for example, a subject having cancer. For

example, the embodiments of the invention include one or more methods of treating cancer comprising administering to a subject in need thereof a pharmaceutical combination comprising an anti-PD-1 antibody molecule and N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in free form or in pharmaceutically acceptable salt form.

In one aspect, a method of treating (e.g., one or more of reducing, inhibiting, or delaying progression) a cancer or a tumor in a subject is provided. The method comprises administering to the subject a combination of the invention (e.g., a combination comprising a therapeutically effective amount of an anti-PD-1 antibody molecule and N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in free form or in pharmaceutically acceptable salt form).

Thus there is provided a method of treating cancer in a subject comprising administering to said subject simultaneously or sequentially N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in free form or in pharmaceutically acceptable salt form and an anti-PD-1 antibody molecule, wherein the anti-PD-1 antibody molecule comprises:

(a) a heavy chain variable region (VH) comprising a HCDR1 amino acid sequence of SEQ ID NO: 4, a HCDR2 amino acid sequence of SEQ ID NO: 5, and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a light chain variable region (VL) comprising a LCDR1 amino acid sequence of SEQ ID NO: 13, a LCDR2 amino acid sequence of SEQ ID NO: 14, and a LCDR3 amino acid sequence of SEQ ID NO: 33;

(b) a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 1; a HCDR2 amino acid sequence of SEQ ID NO: 2; and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 10, a LCDR2 amino acid sequence of SEQ ID NO: 11, and a LCDR3 amino acid sequence of SEQ ID NO: 32;

(c) a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 224, a HCDR2 amino acid sequence of SEQ ID NO: 5, and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 13, a LCDR2 amino acid sequence of SEQ ID NO: 14, and a LCDR3 amino acid sequence of SEQ ID NO: 33;

(d) a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 224 a HCDR2 amino acid sequence of SEQ ID NO: 2; and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 10, a LCDR2

amino acid sequence of SEQ ID NO: 11, and a LCDR3 amino acid sequence of SEQ ID NO: 32;

(e) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 38 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 70; or

(f) a heavy chain comprising the amino acid sequence of SEQ ID NO: 91 and a light chain comprising the amino acid sequence of SEQ ID NO: 72.

There is also provided a method of treating cancer in a subject comprising administering to said subject simultaneously or sequentially N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in free form or in pharmaceutically acceptable salt form and an anti-PD-1 antibody molecule, wherein the anti-PD-1 antibody molecule comprises:

(a) a heavy chain variable region (VH) comprising a HCDR1 amino acid sequence of SEQ ID NO: 4, a HCDR2 amino acid sequence of SEQ ID NO: 5, and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a light chain variable region (VL) comprising a LCDR1 amino acid sequence of SEQ ID NO: 13, a LCDR2 amino acid sequence of SEQ ID NO: 14, and a LCDR3 amino acid sequence of SEQ ID NO: 33;

(b) a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 1; a HCDR2 amino acid sequence of SEQ ID NO: 2; and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 10, a LCDR2 amino acid sequence of SEQ ID NO: 11, and a LCDR3 amino acid sequence of SEQ ID NO: 32;

(c) a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 224, a HCDR2 amino acid sequence of SEQ ID NO: 5, and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 13, a LCDR2 amino acid sequence of SEQ ID NO: 14, and a LCDR3 amino acid sequence of SEQ ID NO: 33;

(d) a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 224; a HCDR2 amino acid sequence of SEQ ID NO: 2; and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 10, a LCDR2 amino acid sequence of SEQ ID NO: 11, and a LCDR3 amino acid sequence of SEQ ID NO: 32;

(e) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 38 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 70; or

(f) a heavy chain comprising the amino acid sequence of SEQ ID NO: 91 and a light chain comprising the amino acid sequence of SEQ ID NO: 72.

In certain embodiments, the cancer treated with the combination, includes but is not limited to lung cancer, melanoma, renal cancer, liver cancer, breast cancer, colorectal cancer, thyroid cancer, cholangiocarcinoma, glioblastoma, prostate cancer, rhabdomyosarcoma, gastric cancer, or ovarian cancer.

In one preferred embodiment, the cancer is liver cancer.

In one embodiment, the treatment is a first-line or a second-line treatment. In one embodiment, the treatment is a second-line treatment. In another embodiment, the treatment is a first-line treatment.

As used herein, the term "second-line treatment" refers to a treatment that is given when an initial treatment (first-line treatment) does not work or no longer works. The pharmaceutical combination may be particularly useful in treating hepatocellular carcinoma (HCC), e.g. advanced HCC. The pharmaceutical combination may be useful for subjects suffering from HCC, including advanced HCC, who have received prior treatment with sorafenib and progressed during or after discontinuation of sorafenib treatment. Subjects suffering from HCC, including advanced HCC, who are intolerant to sorafenib treatment may also benefit from the administration of the pharmaceutical combination.

The hepatocellular carcinoma (HCC) to be treated by a pharmaceutical combination of the invention may be optionally characterized by positive FGFR4 and KLB expression. In one embodiment, the HCC to be treated may be characterized by positive FGFR4 and FGF19 expression or by positive FGFR4 and KLB expression.

In one embodiment, the HCC to be treated is characterized by positive FGF19 expression. Thus there is provided a pharmaceutical combination described herein for use in the treatment of FGF19+ HCC, including for use in the treatment of FGF19+ advanced HCC.

The biomarkers FGFR4, KLB and FGF19 can be assayed using any method known in the art such as reverse Transcriptase PCR (RT-PCR), see, e.g. WO/2016/054483, published on 7th April 2016.

In an embodiment of the invention, the combination of the invention provides at least one of the following benefits:

improved safety profiles, improved toxicity profiles, improved efficacy, well tolerated by subjects suffering from cancer, improved overall response rate, improved overall survival, improved time to progression, tumor growth inhibition, decreased tumor volume, inhibition of

cell proliferation, immunomodulatory activity, reduction in relapse time, apoptosis of cancer cells, increase in the time delay for the onset of exponential growth of tumor, reduction in resistance to treatment, synergistic effect leading to reduction of required dosage and/or reduction of side effects leading to an enhancement of the long-term clinical effectiveness of the combination.

Each active ingredient of the combination of the invention may be administered by different routes. For instance, the anti-PD-1 antibody molecule is typically administered to the subject systemically (e.g. subcutaneously, intravenously, intramuscularly or intraperitoneally). N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in free form or in pharmaceutically acceptable form is preferably administered to the subject orally.

Thus, in another aspect, the anti-PD-1 antibody molecule used in the pharmaceutical combination of the invention is formulated together with a pharmaceutically acceptable carrier. As used herein, the term "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, surfactants, antioxidants, preservatives (e.g., antibacterial agents, antifungal agents), isotonic agents, absorption delaying agents, salts, preservatives, drug stabilizers, binders, excipients, disintegration agents, lubricants, sweetening agents, flavoring agents, dyes, and the like and combinations thereof, as would be known to those skilled in the art (see, for example, Remington The Science and Practice of Pharmacy, 22nd Ed. Pharmaceutical Press, 2013, pp. 1049-1070). Except insofar as any conventional carrier is incompatible with the active ingredient, its use in the therapeutic or pharmaceutical compositions is contemplated.

The carrier can be suitable for intravenous, intramuscular, subcutaneous, parenteral, spinal or epidermal administration (e.g. by injection or infusion).

The anti-PD-1 antibody molecule used in the present invention may, thus, be in a variety of forms. These include, for example, liquid or semi-solid dosage forms, such as liquid solutions (e.g., injectable and infusible solutions), dispersions or suspensions. The preferred form depends on the intended mode of administration and therapeutic application. Typical preferred compositions are in the form of injectable or infusible solutions. The preferred mode of administration is parenteral (e.g., intravenous, subcutaneous, intraperitoneal, intramuscular). In a preferred embodiment, the anti-PD-1 antibody molecule disclosed herein is administered by intravenous infusion or injection. In another preferred embodiment, the anti-PD-1 antibody molecule disclosed herein is administered by intramuscular or subcutaneous injection.

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion.

Therapeutic compositions typically should be sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, microemulsion, dispersion, liposome, or other ordered structure suitable to high antibody concentration. Sterile injectable solutions can be prepared by incorporating the active compound (*i.e.*, the anti-PD-1 antibody molecule) in the required amount in an appropriate solvent with one or a combination of further carriers, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other carriers. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. The proper fluidity of a solution can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prolonged absorption of injectable compositions can be brought about by including in the composition an agent that delays absorption, for example, monostearate salts and gelatin.

An anti-PD-1 antibody molecule described herein can be formulated into a formulation (*e.g.*, a dosage form) for administration (*e.g.*, intravenous administration) to a subject.

In certain embodiments, the formulation is a drug substance formulation. In other embodiments, the formulation is a lyophilized formulation, *e.g.*, lyophilized from a drug substance formulation. In other embodiments, the formulation is a reconstituted formulation, *e.g.*, reconstituted from a lyophilized formulation. In other embodiments, the formulation is a liquid formulation.

In some embodiments, the formulation (*e.g.*, drug substance formulation) comprises the anti-PD-1 antibody molecule and a buffering agent.

In some embodiments, the formulation (*e.g.*, drug substance formulation) comprises an anti-PD-1 antibody molecule present at a concentration of 10 to 50 mg/mL, *e.g.*, 15 to 50

mg/mL, 20 to 45 mg/mL, 25 to 40 mg/mL, 30 to 35 mg/mL, 25 to 35 mg/mL, 30 to 40 mg/mL, *e.g.*, 15 mg/mL, 20 mg/mL, 25 mg/mL, 30 mg/mL, 33.3 mg/mL, 35 mg/mL, 40 mg/mL, 45 mg/mL, or 50 mg/mL. In certain embodiments, the anti-PD-1 antibody molecule is present at a concentration of 30 to 35 mg/mL, *e.g.*, 33.3 mg/mL.

5 In some embodiments, the formulation (*e.g.*, drug substance formulation) comprises a buffering agent comprising histidine (*e.g.*, a histidine buffer). In certain embodiments, the buffering agent (*e.g.*, histidine buffer) is present at a concentration of 1 mM to 20 mM, *e.g.*, 2 mM to 15 mM, 3 mM to 10 mM, 4 mM to 9 mM, 5 mM to 8 mM, or 6 mM to 7 mM, *e.g.*, 1 mM, 2 mM, 3 mM, 4 mM, 5 mM, 6 mM, 6.7 mM, 7 mM, 8 mM, 9 mM, 10 mM, 11 mM, 12
10 mM, 13 mM, 14 mM, 15 mM, 16 mM, 17 mM, 18 mM, 19 mM, or 20 mM. In some embodiments, the buffering agent (*e.g.*, histidine buffer) is present at a concentration of 6 mM to 7 mM, *e.g.*, 6.7 mM. In other embodiments, the buffering agent (*e.g.*, a histidine buffer) has a pH of 4 to 7, *e.g.*, 5 to 6, *e.g.*, 5, 5.5 or 6. In some embodiments, the buffering agent (*e.g.*, histidine buffer) has a pH of 5 to 6, *e.g.*, 5.5. In certain embodiments, the buffering
15 agent comprises histidine at a concentration of 6 mM to 7 mM (*e.g.*, 6.7 mM) and has a pH of 5 to 6 (*e.g.*, 5.5). In some embodiments, the formulation (*e.g.*, drug substance formulation) comprises an anti-PD-1 antibody molecule present at a concentration of 30 to 35 mg/mL, *e.g.*, 33.3 mg/mL; and a buffering agent that comprises histidine at a concentration of 6 mM to 7 mM (*e.g.*, 6.7 mM) and has a pH of 5 to 6 (*e.g.*, 5.5).

20 In some embodiments, the formulation (*e.g.*, drug substance formulation) further comprises a carbohydrate. In certain embodiments, the carbohydrate is sucrose. In some embodiments, the carbohydrate (*e.g.*, sucrose) is present at a concentration of 50 mM to 150 mM, *e.g.*, 25 mM to 150 mM, 50 mM to 100 mM, 60 mM to 90 mM, 70 mM to 80 mM, or 70 mM to 75 mM, *e.g.*, 25 mM, 50 mM, 60 mM, 70 mM, 73.3 mM, 80 mM, 90 mM, 100 mM,
25 or 150 mM. In some embodiments, the formulation comprises a carbohydrate or sucrose present at a concentration of 70 mM to 75 mM, *e.g.*, 73.3 mM.

In some embodiments, the formulation (*e.g.*, drug substance formulation) comprises an anti-PD-1 antibody molecule present at a concentration of 30 to 35 mg/mL, *e.g.*, 33.3 mg/mL; a buffering agent that comprises histidine at a concentration of 6 mM to 7 mM (*e.g.*,
30 6.7 mM) and has a pH of 5 to 6 (*e.g.*, 5.5); and a carbohydrate or sucrose present at a concentration of 70 mM to 75 mM, *e.g.*, 73.3 mM.

In some embodiments, the formulation (*e.g.*, drug substance formulation) further comprises a surfactant. In certain embodiments, the surfactant is polysorbate 20. In some
35 embodiments, the surfactant or polysorbate 20 is present at a concentration of 0.005 % to 0.025% (w/w), *e.g.*, 0.0075% to 0.02% or 0.01 % to 0.015% (w/w), *e.g.*, 0.005%, 0.0075%, 0.01%, 0.013%, 0.015%, or 0.02% (w/w). In some embodiments, the formulation comprises

a surfactant or polysorbate 20 present at a concentration of 0.01% to 0.015%, e.g., 0.013% (w/w).

In some embodiments, the formulation (e.g., drug substance formulation) comprises an anti-PD-1 antibody molecule present at a concentration of 30 to 35 mg/mL, e.g., 33.3 mg/mL; a buffering agent that comprises histidine at a concentration of 6 mM to 7 mM (e.g., 6.7 mM) and has a pH of 5 to 6 (e.g., 5.5); and a surfactant or polysorbate 20 present at a concentration of 0.01% to 0.015%, e.g., 0.013% (w/w).

In some embodiments, the formulation (e.g., drug substance formulation) comprises an anti-PD-1 antibody molecule present at a concentration of 30 to 35 mg/mL, e.g., 33.3 mg/mL; a buffering agent that comprises histidine at a concentration of 6 mM to 7 mM (e.g., 6.7 mM) and has a pH of 5 to 6 (e.g., 5.5); a carbohydrate or sucrose present at a concentration of 70 mM to 75 mM, e.g., 73.3 mM; and a surfactant or polysorbate 20 present at a concentration of 0.01% to 0.015%, e.g., 0.013% (w/w).

In some embodiments, the formulation (e.g., drug substance formulation) comprises an anti-PD-1 antibody molecule present at a concentration of 33.3 mg/mL; a buffering agent that comprises histidine at a concentration of 6.7 mM and has a pH of 5.5; sucrose present at a concentration of 73.3 mM; and polysorbate 20 present at a concentration of 0.013% (w/w).

In some embodiments, the formulation is a lyophilized formulation. In certain embodiments, the lyophilized formulation is lyophilized from a drug substance formulation described herein. For example, 2 to 5 mL, e.g., 3 to 4 mL, e.g., 3.6 mL, of the drug substance formulation described herein can be filled per container (e.g., vial) and lyophilized.

In some embodiments, the lyophilized formulation is reconstituted with 0.5 mL to 2 mL, e.g., 1 mL, of water or buffer for injection. In certain embodiments, the lyophilized formulation is reconstituted with 1 mL of water for injection, e.g., at a clinical site.

In some embodiments, the formulation (e.g., reconstituted formulation) comprises the PD-1 inhibitor (e.g., the anti-PD-1 antibody molecule) and a buffering agent.

In some embodiments, the formulation (e.g., reconstituted formulation) comprises an anti-PD-1 antibody molecule present at a concentration of 20 mg/mL to 200 mg/mL, e.g., 50 mg/mL to 150 mg/mL, 80 mg/mL to 120 mg/mL, or 90 mg/mL to 110 mg/mL, e.g., 50 mg/mL, 60 mg/mL, 70 mg/mL, 80 mg/mL, 90 mg/mL, 100 mg/mL, 110 mg/mL, 120 mg/mL, 130 mg/mL, 140 mg/mL, 150 mg/mL, 160 mg/mL, 170 mg/mL, 180 mg/mL, 190 mg/mL, or 200 mg/mL. In certain embodiments, the PD-1 inhibitor (e.g., the anti-PD-1 antibody molecule) is present at a concentration of 80 to 120 mg/mL, e.g., 100 mg/mL.

In some embodiments, the formulation (e.g., reconstituted formulation) comprises a buffering agent comprising histidine (e.g., a histidine buffer). In certain embodiments, the

buffering agent (e.g., histine buffer) is present at a concentration of 5 mM to 100 mM, e.g., 10 mM to 50 mM, 15 mM to 25 mM, e.g., 5 mM, 10 mM, 20 mM, 30 mM, 40 mM, 50 mM, 60 mM, 70 mM, 80 mM, 90 mM, or 100 mM. In some embodiments, the buffering agent (e.g., histine buffer) is present at a concentration of 15 mM to 25 mM, e.g., 20 mM. In other
5 embodiments, the buffering agent (e.g., a histidine buffer) has a pH of 4 to 7, e.g., 5 to 6, e.g., 5, 5.5 or 6. In some embodiments, the buffering agent (e.g., histidine buffer) has a pH of 5 to 6, e.g., 5.5. In certain embodiments, the buffering agent comprises histidine at a concentration of 15 mM to 25 mM (e.g., 20 mM) and has a pH of 5 to 6 (e.g., 5.5).

In some embodiments, the formulation (e.g., reconstituted formulation) comprises an
10 anti-PD-1 antibody molecule present at a concentration of 80 to 120 mg/mL, e.g., 100 mg/mL; and a buffering agent that comprises histidine at a concentration of 6 mM to 7 mM (e.g., 6.7 mM) and has a pH of 5 to 6 (e.g., 5.5).

In some embodiments, the formulation (e.g., reconstituted formulation) further comprises a carbohydrate. In certain embodiments, the carbohydrate is sucrose. In some
15 embodiments, the carbohydrate (e.g., sucrose) is present at a concentration of 100 mM to 500 mM, e.g., 150 mM to 400 mM, 175 mM to 300 mM, or 200 mM to 250 mM, e.g., 150 mM, 160 mM, 170 mM, 180 mM, 190 mM, 200 mM, 210 mM, 220 mM, 230 mM, 240 mM, 250 mM, 260 mM, 270 mM, 280 mM, 290 mM, or 300 mM. In some embodiments, the formulation comprises a carbohydrate or sucrose present at a concentration of 200 mM to
20 250 mM, e.g., 220 mM.

In some embodiments, the formulation (e.g., reconstituted formulation) comprises an anti-PD-1 antibody molecule present at a concentration of 80 to 120 mg/mL, e.g., 100 mg/mL; and a buffering agent that comprises histidine at a concentration of 6 mM to 7 mM (e.g., 6.7 mM) and has a pH of 5 to 6 (e.g., 5.5); and a carbohydrate or sucrose present at a
25 concentration of 200 mM to 250 mM, e.g., 220 mM.

In some embodiments, the formulation (e.g., reconstituted formulation) further comprises a surfactant. In certain embodiments, the surfactant is polysorbate 20. In some
embodiments, the surfactant or polysorbate 20 is present at a concentration of 0.01 % to 0.1% (w/w), e.g., 0.02% to 0.08%, 0.025% to 0.06% or 0.03 % to 0.05% (w/w), e.g., 0.01%,
30 0.025%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, or 0.1% (w/w). In some embodiments, the formulation comprises a surfactant or polysorbate 20 present at a concentration of 0.03% to 0.05%, e.g., 0.04% (w/w).

In some embodiments, the formulation (e.g., reconstituted formulation) comprises an
35 anti-PD-1 antibody molecule present at a concentration of 80 to 120 mg/mL, e.g., 100 mg/mL; and a buffering agent that comprises histidine at a concentration of 6 mM to 7 mM (e.g., 6.7 mM) and has a pH of 5 to 6 (e.g., 5.5); and a surfactant or polysorbate 20 present at a concentration of 0.03% to 0.05%, e.g., 0.04% (w/w).

In some embodiments, the formulation (*e.g.*, reconstituted formulation) comprises an anti-PD-1 antibody molecule present at a concentration of 80 to 120 mg/mL, *e.g.*, 100 mg/mL; and a buffering agent that comprises histidine at a concentration of 6 mM to 7 mM (*e.g.*, 6.7 mM) and has a pH of 5 to 6 (*e.g.*, 5.5); a carbohydrate or sucrose present at a concentration of 200 mM to 250 mM, *e.g.*, 220 mM; and a surfactant or polysorbate 20 present at a concentration of 0.03% to 0.05%, *e.g.*, 0.04% (w/w).

In some embodiments, the formulation (*e.g.*, reconstituted formulation) comprises an anti-PD-1 antibody molecule present at a concentration of 100 mg/mL; and a buffering agent that comprises histidine at a concentration of 6.7 mM and has a pH of 5.5; sucrose present at a concentration of 220 mM; and polysorbate 20 present at a concentration of 0.04% (w/w). In some embodiments, the formulation is reconstituted such that an extractable volume of at least 1 mL (*e.g.*, at least 1.5 mL, 2 mL, 2.5 mL, or 3 mL) of the reconstituted formulation can be withdrawn from the container (*e.g.*, vial) containing the reconstituted formulation. In certain embodiments, the formulation is reconstituted and/or extracted from the container (*e.g.*, vial) at a clinical site. In certain embodiments, the formulation (*e.g.*, reconstituted formulation) is injected to an infusion bag, *e.g.*, within 1 hour (*e.g.*, within 45 minutes, 30 minutes, or 15 minutes) before the infusion starts to the patient or the subject in need thereof.

In certain embodiments, the formulation is a liquid formulation. In some embodiments, the liquid formulation is prepared by diluting a drug substance formulation comprising the anti-PD-1 antibody molecule described herein. For example, a drug substance formulation can be diluted, *e.g.*, 10 to 30 mg/mL (*e.g.*, 25 mg/mL), *e.g.*, with a solution comprising one or more excipients (*e.g.*, concentrated excipients). In some embodiments, the solution comprises one, two, or all of histidine, sucrose, or polysorbate 20. In certain embodiments, the solution comprises the same excipient(s) as the drug substance formulation.

In some embodiments, the formulation (*e.g.*, liquid formulation) comprises an anti-PD-1 antibody molecule present at a concentration of 5 mg/mL to 50 mg/mL, *e.g.*, 10 mg/mL to 40 mg/mL, 15 mg/mL to 35 mg/mL, or 20 mg/mL to 30 mg/mL, *e.g.*, 5 mg/mL, 10 mg/mL, 15 mg/mL, 20 mg/mL, 25 mg/mL, 30 mg/mL, 35 mg/mL, 40 mg/mL, 45 mg/mL, or 50 mg/mL. In certain embodiments, the PD-1 inhibitor (*e.g.*, the anti-PD-1 antibody molecule) is present at a concentration of 20 to 30 mg/mL, *e.g.*, 25 mg/mL.

In some embodiments, the formulation (*e.g.*, liquid formulation) comprises a buffering agent comprising histidine (*e.g.*, a histidine buffer). In certain embodiments, the buffering agent (*e.g.*, histidine buffer) is present at a concentration of 5 mM to 100 mM, *e.g.*, 10 mM to 50 mM, 15 mM to 25 mM, *e.g.*, 5 mM, 10 mM, 20 mM, 30 mM, 40 mM, 50 mM, 60 mM, 70

mM, 80 mM, 90 mM, or 100 mM. In some embodiments, the buffering agent (e.g., histine buffer) is present at a concentration of 15 mM to 25 mM, e.g., 20 mM. In other embodiments, the buffering agent (e.g., a histidine buffer) has a pH of 4 to 7, e.g., 5 to 6, e.g., 5, 5.5 or 6. In some embodiments, the buffering agent (e.g., histidine buffer) has a pH of 5 to 6, e.g., 5.5. In certain embodiments, the buffering agent comprises histidine at a concentration of 15 mM to 25 mM (e.g., 20 mM) and has a pH of 5 to 6 (e.g., 5.5).

In some embodiments, the formulation (e.g., liquid formulation) comprises an anti-PD-1 antibody molecule present at a concentration of 20 to 30 mg/mL, e.g., 25 mg/mL; and a buffering agent that comprises histidine at a concentration of 6 mM to 7 mM (e.g., 6.7 mM) and has a pH of 5 to 6 (e.g., 5.5).

In some embodiments, the formulation (e.g., liquid formulation) further comprises a carbohydrate. In certain embodiments, the carbohydrate is sucrose. In some embodiments, the carbohydrate (e.g., sucrose) is present at a concentration of 100 mM to 500 mM, e.g., 150 mM to 400 mM, 175 mM to 300 mM, or 200 mM to 250 mM, e.g., 150 mM, 160 mM, 170 mM, 180 mM, 190 mM, 200 mM, 210 mM, 220 mM, 230 mM, 240 mM, 250 mM, 260 mM, 270 mM, 280 mM, 290 mM, or 300 mM. In some embodiments, the formulation comprises a carbohydrate or sucrose present at a concentration of 200 mM to 250 mM, e.g., 220 mM.

In some embodiments, the formulation (e.g., liquid formulation) comprises an anti-PD-1 antibody molecule present at a concentration of 20 to 30 mg/mL, e.g., 25 mg/mL; and a buffering agent that comprises histidine at a concentration of 6 mM to 7 mM (e.g., 6.7 mM) and has a pH of 5 to 6 (e.g., 5.5); and a carbohydrate or sucrose present at a concentration of 200 mM to 250 mM, e.g., 220 mM.

In some embodiments, the formulation (e.g., liquid formulation) further comprises a surfactant. In certain embodiments, the surfactant is polysorbate 20. In some embodiments, the surfactant or polysorbate 20 is present at a concentration of 0.01 % to 0.1% (w/w), e.g., 0.02% to 0.08%, 0.025% to 0.06% or 0.03 % to 0.05% (w/w), e.g., 0.01%, 0.025%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, or 0.1% (w/w). In some embodiments, the formulation comprises a surfactant or polysorbate 20 present at a concentration of 0.03% to 0.05%, e.g., 0.04% (w/w).

In some embodiments, the formulation (e.g., liquid formulation) comprises an anti-PD-1 antibody molecule present at a concentration of 20 to 30 mg/mL, e.g., 25 mg/mL; and a buffering agent that comprises histidine at a concentration of 6 mM to 7 mM (e.g., 6.7 mM) and has a pH of 5 to 6 (e.g., 5.5); and a surfactant or polysorbate 20 present at a concentration of 0.03% to 0.05%, e.g., 0.04% (w/w).

In some embodiments, the formulation (e.g., liquid d formulation) comprises an anti-PD-1 antibody molecule present at a concentration of 20 to 30 mg/mL, e.g., 25 mg/mL; and a buffering agent that comprises histidine at a concentration of 6 mM to 7 mM (e.g., 6.7 mM)

and has a pH of 5 to 6 (*e.g.*, 5.5); a carbohydrate or sucrose present at a concentration of 200 mM to 250 mM, *e.g.*, 220 mM; and a surfactant or polysorbate 20 present at a concentration of 0.03% to 0.05%, *e.g.*, 0.04% (w/w).

5 In some embodiments, the formulation (*e.g.*, liquid formulation) comprises an anti-PD-1 antibody molecule present at a concentration of 25 mg/mL; and a buffering agent that comprises histidine at a concentration of 6.7 mM and has a pH of 5.5; sucrose present at a concentration of 220 mM; and polysorbate 20 present at a concentration of 0.04% (w/w).

10 In certain embodiments, 1 mL to 10 mL (*e.g.*, 2 mL to 8 mL, 3 mL to 7 mL, or 4 mL to 5 mL, *e.g.*, 3 mL, 4 mL, 4.3 mL, 4.5 mL, 5 mL, or 6 mL) of the liquid formulation is filled per container (*e.g.*, vial). In other embodiments, the liquid formulation is filled into a container (*e.g.*, vial) such that an extractable volume of at least 2 mL (*e.g.*, at least 3 mL, at least 4 mL, or at least 5 mL) of the liquid formulation can be withdrawn per container (*e.g.*, vial). In certain embodiments, the liquid formulation is diluted from the drug substance formulation and/or extracted from the container (*e.g.*, vial) at a clinical site. In certain embodiments, the
15 formulation (*e.g.*, liquid formulation) is injected to an infusion bag, *e.g.*, within 1 hour (*e.g.*, within 45 minutes, 30 minutes, or 15 minutes) before the infusion starts to the patient or the subject in need thereof.

The container used for any of the formulations described herein can include, *e.g.*, a vial, and optionally, a stopper, a cap, or both. In certain embodiments, the vial is a glass
20 vial, *e.g.*, a 6R white glass vial. In other embodiments, the stopper is a rubber stopper, *e.g.*, a grey rubber stopper. In other embodiments, the cap is a flip-off cap, *e.g.*, an aluminum flip-off cap. In some embodiments, the container comprises a 6R white glass vial, a grey rubber stopper, and an aluminum flip-off cap. In some embodiments, the container (*e.g.*, vial) is for a single-use container. In certain embodiments, 50 mg to 150 mg, *e.g.*, 80 mg to 120 mg, 90
25 mg to 110 mg, 100 mg to 120 mg, 100 mg to 110 mg, 110 mg to 120 mg, or 110 mg to 130 mg, of the PD-1 inhibitor (*e.g.*, the anti-PD-1 antibody molecule), is present in the container (*e.g.*, vial). Other exemplary buffering agents that can be used in the formulation described herein include, but are not limited to, an arginine buffer, a citrate buffer, or a phosphate buffer. Other exemplary carbohydrates that can be used in the formulation described herein
30 include, but are not limited to, trehalose, mannitol, sorbitol, or a combination thereof. The formulation described herein may also contain a tonicity agent, *e.g.*, sodium chloride, and/or a stabilizing agent, *e.g.*, an amino acid (*e.g.*, glycine, arginine, methionine, or a combination thereof).

35 The antibody molecules can be administered by a variety of methods known in the art, although for many therapeutic applications, the preferred route/mode of administration is intravenous injection or infusion. For example, the antibody molecules can be administered

by intravenous infusion at a rate of more than 20 mg/min, e.g., 20-40 mg/min, and typically greater than or equal to 40 mg/min to reach a dose of about 35 to 440 mg/m², typically about 70 to 310 mg/m², and more typically, about 110 to 130 mg/m². In embodiments, the antibody molecules can be administered by intravenous infusion at a rate of less than 10mg/min; preferably less than or equal to 5 mg/min to reach a dose of about 1 to 100 mg/m², preferably about 5 to 50 mg/m², about 7 to 25 mg/m² and more preferably, about 10 mg/m². As will be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results. In certain embodiments, the active compound may be prepared with a carrier that will protect the compound against rapid release, such as a controlled release formulation, including implants, transdermal patches, and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Many methods for the preparation of such formulations are patented or generally known to those skilled in the art. See, e.g., *Sustained and Controlled Release Drug Delivery Systems*, J. R. Robinson, ed., Marcel Dekker, Inc., New York, 1978.

N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in free form or in pharmaceutically acceptable salt form is preferably formulated for oral administration. In addition, N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in citric acid salt form can be made up in a solid form (including without limitation capsules, tablets, pills, granules, powders). The pharmaceutical compositions can be subjected to conventional pharmaceutical operations such as sterilization and/or can contain conventional inert diluents, lubricating agents, or buffering agents, as well as adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers and buffers, etc.

Typically, N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in citric acid salt form is in the form of tablets or gelatin capsules comprising N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in citric acid salt form together with one or more of:

- a) diluents, e.g., lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine;
- b) lubricants, e.g., silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also
- c) binders, e.g., magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone; if desired

d) disintegrants, e.g., starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and

e) absorbents, colorants, flavors and sweeteners.

Tablets may be either film coated or enteric coated according to methods known in the art.

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Suitable compositions for oral administration include an effective amount of N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in citric acid salt form in the form of tablets, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs. Compositions comprising N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide or a pharmaceutically acceptable salt thereof intended for oral use are prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions can contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets may contain N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in citric acid salt form in admixture with nontoxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients are, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example, starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets are uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed.

Formulations for oral use can be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

In an embodiment, the pharmaceutical combination of the invention comprises N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in citric acid salt form in the form of a tablet.

In another embodiment, the pharmaceutical combination of the invention comprises N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in citric acid salt form in the

form of a capsule comprising N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in citric acid salt form only.

In another embodiment, the pharmaceutical combination of the invention comprises
5 N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in citric acid salt form in the form of a capsule comprising N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in citric acid salt form and a glidant.

10 Glidants are typically used to promote powder flow by reducing interparticle friction and cohesion. Examples include colloidal silicon dioxide (fumed silica), talc and magnesium carbonate.

In a preferred embodiment, the pharmaceutical composition comprising N-(5-cyano-
15 4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide or a pharmaceutically acceptable salt thereof includes a glidant, and preferably, the glidant is colloidal silicon dioxide (sold under the trade name aerosil).

20 Dosages of the active ingredients and therapeutic regimens of the combination of the invention can be determined by a skilled artisan. In certain embodiments, the anti-PD-1 antibody molecule is administered to the subject in need thereof by injection (e.g., subcutaneously or intravenously) at a dose of about 1 to 30 mg/kg, e.g., about 5 to 25 mg/kg, about 10 to 20 mg/kg, about 1 to 5 mg/kg, or about 3 mg/kg. The dosing schedule
25 can vary from e.g., once a week to once every 2, 3, or 4 weeks. In one embodiment, the anti-PD-1 antibody molecule is administered at a dose from about 10 to 20 mg/kg every other week.

In some embodiments, the anti-PD-1 antibody molecule is administered by injection
30 (e.g., subcutaneously or intravenously) at a dose (e.g., a flat dose) of about 200 mg to 500 mg, e.g., about 250 mg to 450 mg, about 300 mg to 400 mg, about 250 mg to 350 mg, about 350 mg to 450 mg. The dosing schedule (e.g., flat dosing schedule) can vary from e.g., once a week to once every 2, 3, 4, 5, or 6 weeks. In one embodiment, the anti-PD-1 antibody molecule, e.g., the exemplary antibody molecule, is administered at a dose from about 300
35 mg to 400 mg once every three weeks or once every four weeks.

In an embodiment of the invention, the anti-PD-1 antibody molecule is administered at a dose of 300mg once every three weeks.

In an embodiment of the invention, the anti-PD-1 antibody molecule is administered at a dose of 400mg once every four weeks.

In one embodiment, the anti-PD-1 antibody molecule is administered at a dose from about 300 mg once every four weeks.

- 5 In one embodiment, the anti-PD-1 antibody molecule is administered at a dose from about 400 mg once every three weeks.

In one embodiment, the anti-PD-1 antibody molecule is administered via i.v. infusion over 30 minutes (up to 2 hours, if clinically indicated) once every 3 weeks.

- 10 In one embodiment, the anti-PD-1 antibody molecule is administered via i.v. infusion over 30 minutes (up to 2 hours, if clinically indicated) once every 4 weeks.

- In one embodiment, a method of treating (e.g., one or more of reducing, inhibiting, or delaying progression) a cancer or a tumor in a subject is provided. The method comprises administering, in combination with an FGFR4 inhibitor (e.g. N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in citric acid salt form), to the subject an anti-PD-1 antibody molecule, e.g., the preferred anti-PD-1 antibody molecule described herein, at a dose of about 300 mg to 400 mg once every three weeks or once every four weeks. In certain embodiments, the preferred anti-PD-1 antibody molecule is administered at a dose of about 300 mg once every three weeks. In other embodiments, the preferred anti-PD-1 antibody molecule is administered at a dose of about 400 mg once every four weeks.
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- In another aspect, the invention features a method of reducing an activity (e.g., growth, survival, or viability, or all), of a hyperproliferative (e.g., a cancer) cell. The method includes contacting the cell with an anti-PD-1 antibody molecule, e.g., an anti-PD-1 antibody molecule described herein. The method can be performed in a subject, e.g., as part of a therapeutic regimen in combination with an FGFR4 inhibitor, e.g., at a dose of about 300 mg to 400 mg of an anti-PD-1 antibody molecule once every three weeks or once every four weeks.
- 25
30

- The dose or dosage of the FGFR4 inhibitor as described herein refers to the amount of the free base. For example, if the dosage quoted is 80 mg, and a pharmaceutically acceptable salt of the FGFR4 inhibitor is used, such as the citrate salt thereof, the dose of 80mg corresponds to the amount of free base of the FGFR4 inhibitor, namely N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide.
- 35

The FGFR4 inhibitor of the combination of the present invention, i.e. N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide may be administered at a total daily dose of about 25-200 mg, or about 50-150 mg (e.g., once per day). The total daily dose of N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide (e.g. in citric acid salt form) which is administered may be 50 mg, 80 mg, 100 mg, 120 mg or 150 mg. In particular N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide may be administered at a dose of 80 mg daily or 120 mg daily.

The dose of the FGFR4 inhibitor may be administered once daily, or twice daily, or three times daily, or four times daily; preferably once or twice daily, more preferably once daily.

N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide, e.g. in citric acid salt form, may in particular be administered at a dose of 50 mg once daily, 80 mg once daily, 100 mg once daily, 120 mg once daily or 150 mg once daily. In particular N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide may be administered at a dose of 80 mg daily or 120 mg daily.

In an embodiment, N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide, e.g. in citric acid salt form, is administered at a dose of 80mg daily, e.g. once daily. The dose of 80mg corresponds to the amount of free base of N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide.

In another embodiment, N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide, e.g. in citric acid salt form, is administered at a dose of 120 mg daily, e.g. once daily. The dose of 120 mg corresponds to the amount of free base of N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide. In a preferred embodiment, N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in citric acid salt form is administered orally.

PDR001 (Antibody Molecule A) may be administered at a dose of 300mg once every three weeks and N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide may be
5 administered at a daily dose of 50 mg, 80 mg, 100 mg, 120 mg or 200 mg. The FGFR4 inhibitor may be administered once or twice daily.

In another embodiment, PDR001 (Antibody Molecule A) may be administered at a dose of 400mg once every four weeks and N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-
10 carboxamide may be administered at a daily dose of 50 mg, 80 mg, 100 mg, 120 mg or 200 mg. The FGFR4 inhibitor may be administered once or twice daily.

In an embodiment, N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide, e.g. in
15 citric acid salt form, is administered prior to the anti-PD-1 antibody molecule. In an embodiment, the administration of the anti-PD-1 antibody molecule designated PDR001 comprising a heavy chain variable region (VH) comprising a HCDR1, a HCDR2 and a HCDR3 amino acid sequence of BAP049-Clone-E as described in Table 1 and a light chain
20 variable region (VL) comprising a LCDR1, a LCDR2 and a LCDR3 amino acid sequence of BAP049-Clone-E as described in Table 1 is at least 1 hour after the administration of N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide, e.g. in citric acid salt form.

25 In an embodiment, the invention relates to a pharmaceutical combination comprising an anti-PD-1 antibody molecule and N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in free form or in pharmaceutically acceptable salt form, preferably in citric acid salt form, wherein the anti-PD-1 antibody molecule comprises:

30 (a) a heavy chain variable region (VH) comprising a HCDR1 amino acid sequence of SEQ ID NO: 4, a HCDR2 amino acid sequence of SEQ ID NO: 5, and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a light chain variable region (VL) comprising a LCDR1 amino acid sequence of SEQ ID NO: 13, a LCDR2 amino acid sequence of SEQ ID NO: 14, and a LCDR3 amino acid sequence of SEQ ID NO: 33;

35 (b) a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 1; a HCDR2 amino acid sequence of SEQ ID NO: 2; and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 10, a LCDR2

amino acid sequence of SEQ ID NO: 11, and a LCDR3 amino acid sequence of SEQ ID NO: 32;

5 (c) a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 224, a HCDR2 amino acid sequence of SEQ ID NO: 5, and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 13, a LCDR2 amino acid sequence of SEQ ID NO: 14, and a LCDR3 amino acid sequence of SEQ ID NO: 33;

10 (d) a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 224; a HCDR2 amino acid sequence of SEQ ID NO: 2; and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 10, a LCDR2 amino acid sequence of SEQ ID NO: 11, and a LCDR3 amino acid sequence of SEQ ID NO: 32;

15 (e) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 38 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 70; or

(f) a heavy chain comprising the amino acid sequence of SEQ ID NO: 91 and a light chain comprising the amino acid sequence of SEQ ID NO: 72;

20 for use in a therapeutic regimen, wherein N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide is administered at a dose of 80mg to 120 mg daily and the anti-PD-1 antibody molecule is administered at a dose of 300mg once every three weeks.

25 In an embodiment, the invention relates to a pharmaceutical combination comprising an anti-PD-1 antibody molecule and N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in free form or in pharmaceutically acceptable salt form, preferably in citric acid salt form, wherein the anti-PD-1 antibody molecule comprises:

30 (a) a heavy chain variable region (VH) comprising a HCDR1 amino acid sequence of SEQ ID NO: 4, a HCDR2 amino acid sequence of SEQ ID NO: 5, and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a light chain variable region (VL) comprising a LCDR1 amino acid sequence of SEQ ID NO: 13, a LCDR2 amino acid sequence of SEQ ID NO: 14, and a LCDR3 amino acid sequence of SEQ ID NO: 33;

35 (b) a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 1; a HCDR2 amino acid sequence of SEQ ID NO: 2; and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 10, a LCDR2 amino acid sequence of SEQ ID NO: 11, and a LCDR3 amino acid sequence of SEQ ID NO: 32;

(c) a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 224, a HCDR2 amino acid sequence of SEQ ID NO: 5, and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 13, a LCDR2 amino acid sequence of SEQ ID NO: 14, and a LCDR3 amino acid sequence of SEQ ID NO: 33;

(d) a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 224; a HCDR2 amino acid sequence of SEQ ID NO: 2; and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 10, a LCDR2 amino acid sequence of SEQ ID NO: 11, and a LCDR3 amino acid sequence of SEQ ID NO: 32;

(e) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 38 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 70; or

(f) a heavy chain comprising the amino acid sequence of SEQ ID NO: 91 and a light chain comprising the amino acid sequence of SEQ ID NO: 72; for use in a therapeutic regimen, wherein N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide is administered at a dose of 80mg to 120 mg daily and the anti-PD-1 antibody molecule is administered at a dose of 300mg once every three weeks.

In one embodiment, the invention provides a kit comprising a pharmaceutical combination comprising an anti-PD-1 antibody molecule, wherein the anti-PD-1 antibody molecule comprises:

(a) a heavy chain variable region (VH) comprising a HCDR1 amino acid sequence of SEQ ID NO: 4, a HCDR2 amino acid sequence of SEQ ID NO: 5, and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a light chain variable region (VL) comprising a LCDR1 amino acid sequence of SEQ ID NO: 13, a LCDR2 amino acid sequence of SEQ ID NO: 14, and a LCDR3 amino acid sequence of SEQ ID NO: 33;

(b) a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 1; a HCDR2 amino acid sequence of SEQ ID NO: 2; and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 10, a LCDR2 amino acid sequence of SEQ ID NO: 11, and a LCDR3 amino acid sequence of SEQ ID NO: 32;

(c) a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 224, a HCDR2 amino acid sequence of SEQ ID NO: 5, and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 13, a LCDR2

amino acid sequence of SEQ ID NO: 14, and a LCDR3 amino acid sequence of SEQ ID NO: 33;

(d) a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 224; a HCDR2 amino acid sequence of SEQ ID NO: 2; and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 10, a LCDR2 amino acid sequence of SEQ ID NO: 11, and a LCDR3 amino acid sequence of SEQ ID NO: 32;

(e) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 38 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 70; or

(f) a heavy chain comprising the amino acid sequence of SEQ ID NO: 91 and a light chain comprising the amino acid sequence of SEQ ID NO: 72;

and N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in free form or in pharmaceutically acceptable salt form, with instructions for simultaneous or sequential administration of the anti-PD-1 antibody molecule and N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide.

In one embodiment, the invention provides a kit comprising a pharmaceutical combination comprising an anti-PD-1 antibody molecule designated PDR001 comprising a heavy chain variable region (VH) comprising a HCDR1, a HCDR2 and a HCDR3 amino acid sequence of BAP049-Clone-E as described in Table 1 and a light chain variable region (VL) comprising a LCDR1, a LCDR2 and a LCDR3 amino acid sequence of BAP049-Clone-E as described in Table 1 and N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in free form or in pharmaceutically acceptable salt form, with instructions for simultaneous or sequential administration of PDR001 and N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide.

In one embodiment, the kit comprises two separate pharmaceutical compositions, one of which contains N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in citric acid salt form and one of which contains the anti-PD-1 antibody molecule. In one embodiment, the kit comprises means for separately retaining said compositions, such as a

container, divided bottle, or divided foil packet. An example of such a kit is a blister pack, as typically used for the packaging of tablets, capsules and the like.

The kit of the invention may be used for administering different dosage forms, for administering the separate compositions at different dosage intervals. To assist compliance,
5 the kit of the invention typically comprises directions for administration.

In the combination of the invention, both active ingredients be manufactured and/or formulated by the same or different manufacturers. Moreover, the active ingredients of the combination of the invention may be brought together into a combination therapy: (i) prior to
10 release of the combination product to physicians (*e.g.* in the case of a kit comprising the combination of the invention); (ii) by the physician themselves (or under the guidance of the physician) shortly before administration; (iii) in the subjects in need thereof themselves, *e.g.* during sequential administration of the active ingredients.

The following Examples illustrate the invention described above; they are not, however, intended to limit the scope of the invention in any way.

Examples

Example 1

5 Example 1: Characterization of Humanized Anti-PD-1 Antibody

Binding affinity and specificity

The Generation of humanized BAP049-Clone-B and BAP049-Clone E and characterization thereof is described in PCT application PCT/US2015/012754, which was published on 30th July 2015, as WO/2015/112900.

- 10 Murine anti-PD-1 monoclonal antibody BAP049 was humanized. The sequences and test samples of sixteen humanized BAP049 clones with unique variable region sequences were obtained. These clones were further analyzed for their biological functions (e.g., antigen binding and ligand blocking), structural features, and transcient expression in CHO cells.

Binding affinity and specificity

- 15 The binding of an exemplary humanized anti-PD-1 antibody on human PD-1 protein was measured using Biacore method. The results are: $K_a = 2.78 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$; $K_d = 2.13 \times 10^{-4} \text{ s}^{-1}$; $K_D = 0.0827 \pm 0.005505 \text{ nM}$.

Humanization Technology and Process

- Humanization of BAP049 was performed using a combinatorial library of human
20 germline variable region frameworks (FWs). The technology entails transferring the murine CDRs in frame to a library of human variable regions (VRs) that had been constructed by randomly combining human germ line FW1, FW2 and FW3 sequences. Only one FW4 sequence was used, which is WGQGTTVTVSS (SEQ ID NO: 67) for the heavy chain (HC) (Kabat human HC subgroup I) and FGQGTVKVEIK (SEQ ID NO: 208) for the light chain
25 (LC) (Kabat human κ subgroup I). The library of VR sequences was fused to human constant region (CR) sequences, human IgG4(S228P) of HC and human κ CR of LC, and the resulting library of whole IgG was expressed in CHO cells for screening. Screening was performed with tissue culture supernatants measuring binding avidity on antigen-expressing cells in a whole cell ELISA format or on FACS.

- 30 The humanization process was performed in a stepwise manner starting with the construction and expression of the appropriate chimeric mAb (murine VR, IgG4(S228P), human κ), which can serve as a comparator for the screening of the humanized clones. The constant region amino acid sequences for human IgG4(S228P) heavy chain and human kappa light chain are shown in Table 3.

- 35 Humanization of the VR of LC and HC were performed in two independent steps. The library of humanized LC (huLC) was paired with the chimeric HC (murine VR, IgG4(S228P)) and the resulting "half-humanized" mAbs were screened for binding activity by

ELISA. The huLC of clones with adequate binding activity ($\geq$ binding of chimeric mAb) were selected. Analogously, the library of humanized HC (huHC) was paired with the chimeric LC (murine VR, human κ) and screened for binding activity by ELISA. The huHC of clones with appropriate binding activity ($\geq$ binding of chimeric mAb) were selected.

5 The variable regions of the selected huLC and huHC were then sequenced to identify the huLC and huHC with unique sequences (some clones from the initial selection process may share the same LC or HC). The unique huLC and huHC were then randomly combined to form a small library of humanized mAbs (humAbs), which was expressed in CHO cells and screened on antigen- expressing cells in an ELISA and FACS format. Clones with
10 binding activities that were equal or better than the binding of the chimeric comparator mAb are the final product of the humanization process.

Construction of Chimeric Antibody

 Three variants of the chimeric antibody were prepared that either had a Cys, Tyr or
15 Ser residue at position 102 of the LC sequence. The three chimeric antibodies, *i.e.*, BAP049-chi (Cys), BAP049-chi (Tyr), and BAP049-chi (Ser) (also known as BAP049-chi, BAP049-chi-Y, and BAP049-chi-S, respectively), were expressed in CHO cells and tested for their ability to compete with labeled murine antibody for binding to PD-1 expressing Jurkat cells. The three variants were indistinguishable in the competition experiment. The
20 results show that the three chimeric mAbs (Cys, Tyr, Ser) compete equally well with the binding of the labeled murine mAb BAP049. The slight difference between the chimeric mAb curves and the murine mAb curve is probably due to the different methods used for determining mAb concentrations. The concentration of the murine mAb was determined by OD280 measurement, whereas the chimeric mAb concentrations in supernatants were
25 determined with an ELISA using an IgG4 standard. The germline residue Tyr was selected for humanized antibodies.

Humanized Antibody Clones

 The process of humanization yielded sixteen clones with binding affinities comparable to that of the chimeric antibody. In addition to binding data, for each clone, the
30 VR sequences were provided along with a sample of the mAb. The samples had been prepared by transient transfections of CHO cells and were concentrated tissue culture supernatants. The antibody concentrations in the solutions had been determined by an IgG4-specific ELISA.

 The sixteen unique clones are combinations of four unique HC sequences and nine
35 unique LC sequences. For the HC FW regions, the HC sequences are combinations of one of two different VHFW1, one of three different VHFW2, and one of two different VHFW3 sequences. For the LC FW regions, the LC sequences are combinations of one of five

different VLFW1, one of three different VLFW2, and one of four different VLFW3 sequences. The amino acid and nucleotide sequences of the heavy and light chain variable domains for the humanized BAP049 clones B and E are shown in Table 1. The amino acid and nucleotide sequences of the heavy and light chain CDRs of the humanized BAP049 clones are also shown in Table 1.

Analysis of Humanized Clones

Analysis of binding activity and binding specificity

The binding activity and specificity was measured in a competition binding assay using a constant concentration of Alexa 488-labeled murine mAb, serial dilutions of the test mAbs, and PD-1-expressing 300.19 cells. Incubations with the mAb mixtures having different concentration ratios of test mAb to labeled mAb was at 4 °C for 30 min. Bound labeled murine mAb was then quantified using a FACS machine. The experiment was performed twice. Within the accuracy of the experiment, all humanized clones show similar activity for competing with binding of labeled murine mAb. The activity is also comparable to the activity of the parent murine mAb and chimeric mAb. MAb were ranked relative to each other. For example, it can be a weaker competitor if in both experiments the curve of a certain clone is to the right of the chimeric mAb curve or it can be a better competitor if the curve of a certain clone is to the left of the chimeric mAb curve.

Selection of humanized clones

Selected clones including clones B and E were further tested for their ability to block the binding of PD-L1 and PD-L2 to PD-1 and for enhancing T cell activity *in vitro* assays with human PBMC.

Blocking of ligand binding

Murine anti-PD-1 mAb blocks the binding of the natural ligands PD-L1 and PD-L2 to PD-1 expressed on cells at low concentrations. Whether the humanized clones had preserved the blocking capacity of the parent murine mAb was tested in comparative experiments with murine and chimeric antibodies.

The blocking capacity of the mAbs was evaluated in a competition binding assay using a constant concentration of PD-L1-hulgG1 Fc fusion protein or PD-L2-hulgG1 Fc fusion protein, serial dilutions of the mAbs to be tested, and PD-1-expressing 300.19 cells. Incubation was at 4 °C for 30 min. Bound ligand fusion proteins were detected with PE-conjugated F(ab')₂ fragment of goat anti-human IgG which doesn't recognize IgG4 mAbs (Southern Biotech 2043-09), and flow cytometry. Within the accuracy of the experiments, the humanized clones, chimeric antibody and murine parent mAb demonstrated comparable blocking activity for both the PD-L1 and PD-L2 ligands.

Expression of Humanized Anti-PD-1 Antibody, BAP049

Five humanized clones were selected for evaluation of expression in Chinese Hamster Ovary (CHO) cells.

Single gene vectors (SGVs) were constructed using Lonza's GS Xceed vectors (IgG4proΔk for heavy chain and Kappa for light chain). The SGVs were amplified and transiently co-transfected into CHOK1SV GS-KO cells for expression at a volume of 2.8 L.

Expression cultures were harvested Day 6 post-transfection and clarified by centrifugation and sterile filtration. The clarified cell culture supernatant was purified using one-step Protein A chromatography. Product quality analysis in the form of SE-HPLC, SDS-PAGE, IEF, and LAL was carried out using purified material at a concentration of 1 mg/ml including an antibody as a control sample.

Vector Construction

The sequences of the light and heavy chain variable domain encoding regions were synthesised by GeneArt AG. Light chain variable domain encoding regions were sub-cloned into pXC-Kappa and heavy chain variable domain encoding regions into pXC-IgG4pro ΔK vectors respectively using the N-terminal restriction site Hind III and the C-terminal restriction sites BsiWI (light chain) and Apal (heavy chain). Positive clones were screened by PCR amplification (primers 1053: GCTGACAGACTAACAGACTGTTCC (SEQ ID NO: 226) and 1072: CAAATGTGGTATGGCTGA (SEQ ID NO: 227)) and verified by restriction digest (using a double digest of EcoRI-HF and HindIII-HF) and nucleotide sequencing of the gene of interest.

DNA Amplification

A single bacterial colony was picked into 15 ml Luria Bertani (LB) medium (LB Broth, Sigma-Aldrich, L7275) containing 50 µg/ml ampicillin and incubated at 37 °C overnight with shaking at 220 rpm. The resulting starter culture was used to inoculate 1 L Luria Bertani (LB) medium containing 50 µg/ml ampicillin and incubated at 37 °C overnight with shaking at 220 rpm. Vector DNA was isolated using the QIAGEN Plasmid Plus Gigaprep system (QIAGEN, 12991). In all instances, DNA concentration was measured using a Nanodrop 1000 spectrophotometer (Thermo-Scientific) and adjusted to 1 mg/ml with EB buffer (10 mM Tris-Cl, pH 8.5). DNA quality for the single gene vectors was assessed by measuring the absorbance ratio A260/A280. This was found to be between 1.88 and 1.90.

Culture of CHOK1SV GS-KO Cells

CHOK1SV GS-KO cells were cultured in CD-CHO media (Invitrogen, 10743-029) supplemented with 6 mM glutamine (Invitrogen, 25030-123). Cells were incubated in a

shaking incubator at 36.5 °C, 5% CO₂, 85% humidity, 140 rpm. Cells were routinely sub-cultured every 3-4 days, seeding at 2×10^5 cells/ml and were propagated in order to have sufficient cells available for transfection. Cells were discarded by passage 20.

5 Transient Transfections of CHOK1SV GS-KO Cells

Transient transfections were performed using CHOK1SV GS-KO cells which had been in culture a minimum two weeks. Cells were sub-cultured 24 h prior to transfection and cell viability was >99% at the time of transfection.

10 All transfections were carried out via electroporation using a Gene Pulse MXCell (Bio-Rad), a plate based system for electroporation. For each transfection, viable cells were resuspended in pre-warmed media to 2.86×10^7 cells/ml. 80 µg DNA (1:1 ratio of heavy and light chain SGVs) and 700 µl cell suspension were aliquotted into each cuvette/well. Cells were electroporated at 300 V, 1300 µF. Transfected cells were transferred to pre-warmed media in Erlenmeyer flasks and the cuvette/wells rinsed twice with pre-warmed media which
15 was also transferred to the flasks. Transfected cell cultures were incubated in a shaking incubator at 36.5 °C, 5% CO₂, 85% humidity, 140 rpm for 6 days. Cell viability and viable cell concentrations were measured at the time of harvest using a Cedex HiRes automated cell counter (Roche).

20 Protein A Affinity Chromatography

Cell culture supernatant was harvested and clarified by centrifugation at 2000 rpm for 10 min, then filtered through a 0.22 µm PES membrane filter. Clarified supernatant was purified using a pre-packed 5 ml HiTrap MabSelect SuRE column (GE Healthcare, 11-0034-94) on an AKTA purifier (10 ml/min). The column was equilibrated with 50 mM sodium
25 phosphate, 125 mM sodium chloride, pH 7.0 (equilibration buffer) for 5 column volumes (CVs). After sample loading, the column was washed with 2 CVs of equilibration buffer followed by 3 CVs of 50 mM sodium phosphate, 1 M sodium chloride pH 7.0 and a repeat wash of 2 CVs of equilibration buffer. The Product was then eluted with 10 mM sodium formate, pH 3.5 over 5 CVs. Protein containing, eluted fractions were immediately pH
30 adjusted to pH 7.2 and filtered through a 0.2 µm filter.

A single protein-containing peak was observed during the elution phase. This peak was shown to contain the mAb, when analyzed by SE-HPLC and SDS-PAGE. Recovered protein yield is shown in Table 5. The clones expressed transiently in a range from 32.4 to 43.0 mg/L.

35

Table 5. Summary of yield, titre, monomer content and endotoxin levels

Product	Yield* (mg)	Titre* (mg/L)	Monomer Content (%)	Endotoxin levels (EU/mg)
Clone A	107.5	38.38	93.94	0.04
Clone B	93.8	33.50	95.28	0.63
Clone C	90.7	32.38	97.83	0.04
Clone D	108.9	38.88	96.53	0.35
Clone E	120.4	43.00	97.73	0.14
*Post Protein A purification				

SE-HPLC Analysis

5 Samples of Protein A purified antibodies were analyzed in duplicate by SE-HPLC on an Agilent 1200 series HPLC system, using a Zorbax GF-250 4 µm 9.4 mm ID x 250 mm column (Agilent). Aliquots of sample at a concentration of 1 mg/ml were filtered through a 0.2 µm filter prior to injection. 80 µl aliquots were injected respectively and run at 1 ml/min for 15 minutes. Soluble aggregate levels were analysed using Chemstation (Agilent) software.

10 Chromatography profiles with retention time showing the percentage of the overall detected peak areas were obtained for the tested antibodies and a control IgG4 antibody. The products show a single protein peak at approximately 8.65 to 8.72 min comparable to the human IgG4 antibody control (about 8.64 min) and consistent with a monomeric antibody. Small amounts (up to about 4-5%) of higher molecular weight impurities, 15 consistent with soluble aggregates, were detected at retention times between about 7.43 and 8.08 min.

SDS-PAGE Analysis

20 Reduced samples were prepared for analysis by mixing with NuPage 4x LDS sample buffer (Invitrogen, NP0007) and NuPage 10x sample reducing agent (Invitrogen, NP0009), and incubated at 70 °C, 10 min. For non-reduced samples, the reducing agent and heat incubation were omitted. Samples were electrophoresed on 1.5 mm NuPage 4-12% Bis-Tris Novex pre-cast gels (Invitrogen, NP0335PK2) with NuPage MES SDS running buffer under denaturing conditions. 10 µl aliquots of SeeBlue Plus 2 pre-stained molecular weight 25 standard (Invitrogen, LC5925) and a control IgG4 antibody at 1 mg/ml were included on the gel. 1 µl of each sample at 1 mg/ml were loaded onto the gel. Once electrophoresed, gels were stained with InstantBlue (TripleRed, ISB01L) for 30 min at room temperature. Images of the stained gels were analysed on a BioSpectrum Imaging System (UVP).

The analysis confirmed the presence of the antibody products and good levels of purity. Under non-reducing conditions, a predominant protein band close to 98 kDa was observed comparable with the control IgG4 antibody. The control IgG4 antibody and one tested clone display an additional fainter band corresponding to a heavy plus light chain half-antibody at approximately 70 kDa under non-reducing conditions. This is expected for the control antibody. Two bands were observed under reducing conditions consistent with the size of heavy (close to the position of the 49 kDa marker) and light chains (close to the position of the 28 kDa marker) and comparable with the bands found for the control IgG4 antibody.

Iso-electric Focussing (IEF) Analysis

Non-reduced samples of Protein A purified antibody were electrophoresed as described below.

5 µg of Protein A purified samples were electrophoresed on a 1.0 mm Novex pH 3-10 gradient gel (Invitrogen, EC66552BOX) using manufacturers recommended running conditions. A 10 µl aliquot of IEF pH 3 – 10 markers (Invitrogen, 39212-01) was included on the gel. Once electrophoresed, gels were fixed with 10% TCA solution for 30 min and then stained with InstantBlue (TripleRed, ISB01L) over night at room temperature. Images of the stained gels were analysed on a BioSpectrum Imaging System (UVP).

The tested clones show charge isoforms between pH 7.4 and 8.0 markers. The detected charge isoforms are slightly more basic than the theoretically calculated pIs for these antibodies which were predicted to be between 6.99 and 7.56. The general shift to more basic charge isoforms suggests the presence of post-translational modifications such as glycosylation on the molecules. Clone C and Clone E show comparable charge isoforms, which is also consistent with the theoretically calculated pI being the same for both (6.99). The control IgG4 antibody behaved as expected.

Table 6. Charge isoforms as detected by Novex IEF analysis

Product	pI of predominant charge isoform*	Acidic charge isoforms*	Basic charge isoforms*
Clone A	7.6	2x; 7.5 to 7.55	7.7
Clone B	7.75	2x; 7.5 to 7.6	7.8
Clone C	7.5	2x; 7.4 to 7.5	7.55
Clone D	8.0	7.9	8.1
Clone E	7.5	2x; 7.4 to 7.5	7.55
*pI readings are estimated from the staining positions correlated against the IEF 3-10			

marker.

Characterization of Humanized Anti-PD-1 Antibodies

Binding affinity and specificity

The binding of exemplary humanized anti-PD-1 antibodies including Clone B and
5 Clone E as shown in Table 1 on human PD-1 protein was measured using Biacore method.
The results are: $K_a = 2.78 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$; $K_d = 2.13 \times 10^{-4} \text{ s}^{-1}$; $K_D = 0.0827 \pm 0.005505 \text{ nM}$.

The binding of the same humanized anti-PD-1 antibody on human PD-1-expressing
300.19 cells was measured using FACS analysis. The result shows that the anti-PD-1
antibody (human IgG4) binds with high affinity to human PD-1 compared to a human IgG4
10 isotype control.

The exemplary humanized anti-PD-1 antibody was found to exhibit high affinity to
cynomolgus PD-1 protein and cynomolgus PD-1-expressing 300.19 cells. As measured by
Biacore method, the anti-PD-1 antibody binds to cynomolgus PD-1 with a K_D of 0.093 ± 0.015
nM. The binding affinity to cynomolgus PD-1 is comparable to its binding affinity to human
15 PD-1.

Additional binding analyses show that the exemplary humanized anti-PD-1 antibody
is not cross-reactive with mouse PD-1 or cross-reactive with parental cell line.

Blocking of interactions between PD-1 and its ligands

The ability of the exemplary humanized anti-PD-1 antibody to block the interactions
20 between PD-1 and both of its known ligands, PD-L1 and PD-L2 was examined. The results
show that the anti-PD-1 antibody blocked the binding of PD-L1 and PD-L2 on human PD-1-
expressing 300.19 cells compared to human IgG4 isotype control and no antibody control.
The anti-PD-1 antibody blocked PD-L1 binding on the 300.19 cells with an IC_{50} of
 $0.94 \pm 0.15 \text{ nM}$. The same antibody blocked PD-L2 binding on the 300.19 cells with an IC_{50}
25 of $1.3 \pm 0.25 \text{ nM}$.

Cellular activity

The ability of the exemplary humanized anti-PD-1 antibody to enhance the
Staphylococcal enterotoxin B (SEB)-stimulated expression of IL-2 was tested in human
whole blood *ex vivo* assay. Diluted human whole blood was incubated with the anti-PD-1
30 antibody in the presence or absence of SEB at 37°C for 48 hours prior to IL-2
measurement. The result shows that the anti-PD-1 antibody increased SEB-stimulated IL-2
expression by 2.28 ± 0.32 fold compared to a human IgG4 isotype control (25 µg/ml SEB;
n=5 donors).

Example 2: A phase Ib/II, multicenter, open-label study of oral FGF401 in combination with an anti-PD-1 antibody molecule ("Antibody Molecule A", detailed below) in adult patients with hepatocellular carcinoma (HCC).

- 5 For this study, the investigational drugs are FGF401 and Antibody Molecule A, an anti-PD-1 receptor recombinant humanized monoclonal antibody, designated PDR001.

Antibody Molecule A:

- 10 The exemplary antibody molecule, Antibody A, (BAP049-Clone-E) tested in this study is a humanized anti-programmed death-1 (PD-1) IgG4 monoclonal antibody (mAb) that blocks binding of programmed cell death ligand-1 (PD-L1) and programmed cell death ligand-2 (PD-L2) to PD-1. It binds to PD-1 with high affinity and inhibits its biological activity. The amino acid sequences of this antibody molecule are described in **Table 1** herein. Results from pre-clinical toxicology studies have shown that it has a favorable safety profile.
- 15 Its pharmacodynamic activity has also been demonstrated in vivo.

Antibody Molecule A is in the form of lyophilisate in vial for i.v. infusion. The starting dose is 300 mg, and it is administered every 3 weeks (Q3W).

- 20 Antibody Molecule A is administered via i.v. infusion over 30 minutes (up to 2 hours, if clinically indicated) once every 3 weeks. The next scheduled dose may be delayed by up to 7 days to recover from previous AEs (adverse events). If the next dose cannot be administered within the above mentioned 7-days delay, then the assessments should be shifted accordingly.

25 *FGF401*

- FGF401 corresponds to N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide. FGF401 may be used in citric acid salt form. FGF401 may be given in the form of capsules. The starting dose is 80mg of FGF401 (amount of free base) and it is administered once
- 30 daily. FGF401 may also be administered at a total daily dose of 50 mg, 80 mg, 100 mg, 120 mg or 150 mg. Preferred dosages include 50 mg, 80 mg and 120 mg.

Objective of the trial:

Main objective:

Primary objective

- Phase I: To estimate the MTD (maximum tolerated dose) and/or RP2D (recommended

phase II dose) of FGF401 in combination with PDR001 Phase II: To investigate the anti-tumor activity of FGF401 in combination with PDR001
Secondary objective - To characterize the safety and tolerability of FGF401 in combination with PDR001 in advanced HCC - To further investigate the anti-tumor activity of FGF401 in combination with PDR001

PRINCIPAL INCLUSION CRITERIA

Key Inclusion criteria	a. Diagnosis of advanced HCC (hepatocellular carcinoma) according to the AASLD (American Association for the Study of Liver Diseases) Guidelines b. HCC stage C according to the BCLC (Barcelona-Clinic Liver Cancer) staging classification c. Prior systemic treatment with sorafenib for advanced HCC with documented disease progression during or after discontinuation of sorafenib treatment, or intolerance to sorafenib treatment. Specifically, this can be defined as: - Documented radiological confirmation (radiology scans or report) of disease progression during or after sorafenib treatment. [For France only: patients must have received at least 8 weeks of prior sorafenib treatment.] - Intolerance to sorafenib (at any dose and/or duration) is defined as documented sorafenib-related Grade 3 or 4 adverse events that led to sorafenib discontinuation. - Patients for whom sorafenib is contraindicated as national full prescribing information. d. Current cirrhotic status of Child-Pugh class A (5-6 points), with no encephalopathy and/or ascites. Child-Pugh status must be calculated based on clinical findings and laboratory results during the Screening period.
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Key Exclusion	1. History of severe hypersensitivity to study treatment ingredients
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criteria	or other monoclonal antibodies and/or their excipients or which in the opinion of the investigator may pose an increased risk of serious infusion reaction. 2. Impaired cardiac function or clinically significant cardiac disease, including any of the following: • Clinically significant and/or uncontrolled heart disease such as congestive heart failure requiring treatment (NYHA Grade ≥ 2), uncontrolled hypertension or clinically significant arrhythmia • QTcF > 470 msec on screening ECG or congenital long QT syndrome • Acute myocardial infarction or unstable angina pectoris < 3 months prior to study entry 3. HIV infection 4. Active HBV or HCV infection tested during screening. Patients whose disease is controlled under antiviral therapy should not be excluded. The adequately controlled hepatitis is defined as: • patients with positive HBV-DNA and/or positive HbsAg results, must be on antiviral therapy (according to institutions guideline), as prophylaxis at least 1 week prior to start of study treatment • having undetectable level of serum HCV RNA level prior to enrollment. 5. Active, known or suspected autoimmune disease. Patients with vitiligo, type I diabetes, residual hypothyroidism only requiring hormone replacement, psoriasis not requiring systemic treatment or conditions not expected to recur in the absence of an external trigger should not be excluded. 6. Prior anti-PD-1/PD-L1 treatment 7. Systemic chronic steroid therapy or any immunosuppressive therapy (≥ 10mg/day prednisone or equivalent). Topical, inhaled, nasal and ophthalmic steroids are allowed. 8. Use of any live vaccines against infectious diseases within 4 weeks of initiation of study treatment. 9. Use of hematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF, M-CSF), thrombopoietin mimetics or erythroid
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	stimulating agents ≤ 2 weeks prior to start of study treatment. If erythroid stimulating agents were initiated more than 2 weeks prior to the first dose of study treatment and the patient is on a stable dose, they can be maintained. 10. Patients with a history of drug-induced pneumonitis or current pneumonitis.
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END POINTS:

Objective	Endpoint
Primary	
Phase I part To estimate the MTD and/or RP2D of FGF401 in combination with PDR001	Incidence rate and characteristics of DLT (dose limiting toxicities) during the first two cycles of FGF401 co-administration with PDR001
Phase II part To investigate the anti-tumor activity of FGF401 in combination with PDR001	FGF401 in combination with PDR001 ORR (overall response rate) based on local assessment per RECIST v1.1
Secondary (Phase I and II part)	
To characterize the safety and tolerability of FGF401 in combination with PDR001	Safety: Incidence and severity of AEs and SAEs, including changes in laboratory values, vital signs and ECGs Tolerability: Dose interruptions and reductions
To further investigate the anti-tumor activity of FGF401 in combination with PDR001	Phase I part BOR (best overall response), ORR (overall response rate), DCR (disease control rate), TTP (time to tumor progression) and OS (overall survival), based on local assessment per RECIST v1.1 Phase II part FGF401 in combination with PDR001 TTP (time to tumor progression), PFS (progression free survival), OS (overall survival), BOR (best overall response) and DCR (disease control rate)

Endpoints may also be determined by using Guidelines for immune-related Response

5 Criteria (irRC).

Table 1. Amino acid and nucleotide sequences for humanized antibody molecules. The antibody molecules include BAP049-Clone-B and BAP049-Clone-E. The amino acid and nucleotide sequences of the heavy and light chain CDRs, the heavy and light chain variable regions, and the heavy and light chains are shown.

BAP049-Clone-B HC		
SEQ ID NO: 1 (Kabat)	HCDR1	TYWMH
SEQ ID NO: 2 (Kabat)	HCDR2	NIYPGTGGSNFDEKFKN
SEQ ID NO: 3 (Kabat)	HCDR3	WTTGTGAY
SEQ ID NO: 4 (Chothia)	HCDR1	GYTFTTY
SEQ ID NO: 5 (Chothia)	HCDR2	YPGTGG
SEQ ID NO: 3 (Chothia)	HCDR3	WTTGTGAY
SEQ ID NO: 38	VH	EVQLVQSGAEVKKPGESLRISCKGSGY TFTTYWMHWWRQATGQGLEWMGNIYP GTGGSNFDEKFKNRVTITADKSTSTAY MELSSLRSED TAVYYCTR WTTGTGAY WGQGT TVTVSS
SEQ ID NO: 95	DNA VH	GAGGTGCAGCTGGTGCAGTCAGGCG CCGAAGTGAAGAAGCCCGGCGAGTC ACTGAGAATTAGCTGTAAAGGTTTCAG GCTACACCTTCACTACCTACTGGATG CACTGGGTCCGCCAGGCTACCGGTC AAGGCCTCGAGTGGATGGGTAATATC TACCCCGGCACCGGCGGCTCTAACTT CGACGAGAAGTTTAAGAATAGAGTGA CTATCACCGCCGATAAGTCTACTAGC ACCGCCTATATGGAAGTGTCTAGCCT GAGATCAGAGGACACCGCCGTCTACT ACTGCACTAGGTGGACTACCGGCACA GGCGCCTACTGGGGTCAAGGCACTA CCGTGACCGTGTCTAGC
SEQ ID NO: 91	HC	EVQLVQSGAEVKKPGESLRISCKGSGY TFTTYWMHWWRQATGQGLEWMGNIYP GTGGSNFDEKFKNRVTITADKSTSTAY MELSSLRSED TAVYYCTR WTTGTGAY WGQGT TVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNS

		GALTSGVHTFPAVLQSSGLYSLSSVVTV PSSSLGTKTYTCNVDHKPSNTKVDKRV ESKYGPPCPPCPAPEFLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSQEDPE VQFNWYVDGVEVHNAKTKPREEQFNS TYRVSVLTVLHQDWLNGKEYKCKVSN KGLPSSIEKTISKAKGQPREPQVYTLPP SQEEMTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTTPVLDSDGSFFLY SRLTVDKSRWQEGNVFSCSVMHEALH NHYTQKSLSLSLG
SEQ ID NO: 96	DNA HC	GAGGTGCAGCTGGTGCAGTCAGGCG CCGAAGTGAAGAAGCCCGGCGAGTC ACTGAGAATTAGCTGTAAAGGTTTCAG GCTACACCTTCACTACCTACTGGATG CACTGGGTCCGCCAGGCTACCGGTC AAGGCCTCGAGTGGATGGGTAATATC TACCCCGGCACCGGCGGCTCTAACTT CGACGAGAAGTTTAAGAATAGAGTGA CTATCACCGCCGATAAGTCTACTAGC ACCGCCTATATGGAAGTGTCTAGCCT GAGATCAGAGGACACCGCCGTCTACT ACTGCACTAGGTGGACTACCGGCACA GGCGCCTACTGGGGTCAAGGCACTA CCGTGACCGTGTCTAGCGCTAGCACT AAGGGCCCGTCCGTGTTCCCCCTGG CACCTTGTAGCCGGAGCACTAGCGAA TCCACCGCTGCCCTCGGCTGCCTGGT CAAGGATTACTTCCCGGAGCCCGTGA CCGTGTCCTGGAACAGCGGAGCCCT GACCTCCGGAGTGACACACCTTCCCCG CTGTGCTGCAGAGCTCCGGGCTGTAC TCGCTGTCGTCCGTGGTCACGGTGCC TTCATCTAGCCTGGGTACCAAGACCT ACACTTGCAACGTGGACCACAAGCCT TCCAACACTAAGGTGGACAAGCGCGT

		CGAATCGAAGTACGGCCCACCGTGCC CGCCTTGTCCCGCGCCGGAGTTCCTC GGCGGTCCCTCGGTCTTTCTGTTCCC ACCGAAGCCCAAGGACACTTTGATGA TTTCCCGCACCCCTGAAGTGACATGC GTGGTCGTGGACGTGTCACAGGAAGA TCCGGAGGTGCAGTTCAATTGGTACG TGGATGGCGTCGAGGTGCACAACGC CAAAACCAAGCCGAGGGAGGAGCAG TTCAACTCCACTTACCGCGTCGTGTC CGTGCTGACGGTGCTGCATCAGGACT GGCTGAACGGGAAGGAGTACAAGTG CAAAGTGTCCAACAAGGGACTTCCTA GCTCAATCGAAAAGACCATCTCGAAA GCCAAGGGACAGCCCCGGGAACCCC AAGTGTATACCCTGCCACCGAGCCAG GAAGAAATGACTAAGAACCAAGTCTC ATTGACTTGCCTTGTGAAGGGCTTCTA CCCATCGGATATCGCCGTGGAATGGG AGTCCAACGGCCAGCCGGAAAAACAAC TACAAGACCACCCCTCCGGTGCTGGA CTCAGACGGATCCTTCTTCTCTACTC GCGGCTGACCGTGGATAAGAGCAGAT GGCAGGAGGGAAATGTGTTCACTGT TCTGTGATGCATGAAGCCCTGCACAA CCACTACACTCAGAAGTCCCTGTCCC TCTCCCTGGGA
BAP049-Clone-B LC		
SEQ ID NO: 10 (Kabat)	LCDR1	KSSQSLLDSGNQKNFLT
SEQ ID NO: 11 (Kabat)	LCDR2	WASTRES
SEQ ID NO: 32 (Kabat)	LCDR3	QNDYSYPYT
SEQ ID NO: 13 (Chothia)	LCDR1	SQSLLDSGNQKNF
SEQ ID NO: 14 (Chothia)	LCDR2	WAS
SEQ ID NO: 33 (Chothia)	LCDR3	DYSYPY
SEQ ID NO: 54	VL	EIVLTQSPATLSLSPGERATLSCKSSQS LLDSGNQKNFLTWYQQKPGKAPKLLIY

		WASTRESGVPSRFSGSGSGTDFTFTIS SLQPEDIATYYCQNDYSYPYTFGQGTK VEIK
SEQ ID NO: 97	DNA VL	GAGATCGTCCTGACTCAGTCACCCGC TACCCTGAGCCTGAGCCCTGGCGAG CGGGCTACACTGAGCTGTAAATCTAG TCAGTCACTGCTGGATAGCGGTAATC AGAAGAACTTCCTGACCTGGTATCAG CAGAAGCCCGGTAAAGCCCCTAAGCT GCTGATCTACTGGGCCTCTACTAGAG AATCAGGCGTGCCCTCTAGGTTTAGC GGTAGCGGTAGTGGCACCGACTTCAC CTTCACTATCTCTAGCCTGCAGCCCG AGGATATCGCTACCTACTACTGTCAG AACGACTATAGCTACCCCTACACCTTC GGTCAAGGCACTAAGGTCGAGATTAA G
SEQ ID NO: 56	LC	EIMLTQSPATLSLSPGERATLSCKSSQS LLDSGNQKNFLTWYQQKPGKAPKLLIY WASTRESGVPSRFSGSGSGTDFTFTIS SLQPEDIATYYCQNDYSYPYTFGQGTK VEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSG NSQESVTEQDSKDYSLSTLTLSKA DYEKHKVYACEVTHQGLSSPVTKSFNR GEC
SEQ ID NO: 98	DNA LC	GAGATCGTCCTGACTCAGTCACCCGC TACCCTGAGCCTGAGCCCTGGCGAG CGGGCTACACTGAGCTGTAAATCTAG TCAGTCACTGCTGGATAGCGGTAATC AGAAGAACTTCCTGACCTGGTATCAG CAGAAGCCCGGTAAAGCCCCTAAGCT GCTGATCTACTGGGCCTCTACTAGAG AATCAGGCGTGCCCTCTAGGTTTAGC GGTAGCGGTAGTGGCACCGACTTCAC CTTCACTATCTCTAGCCTGCAGCCCG

		AGGATATCGCTACCTACTACTGTCAG AACGACTATAGCTACCCCTACACCTTC GGTCAAGGCACTAAGGTGCGAGATTAA GCGTACGGTGGCCGCTCCCAGCGTG TTCATCTTCCCCCCCAGCGACGAGCA GCTGAAGAGCGGCACCGCCAGCGTG GTGTGCCTGCTGAACAACCTTCTACCC CCGGGAGGCCAAGGTGCAGTGGAAG GTGGACAACGCCCTGCAGAGCGGCA ACAGCCAGGAGAGCGTCACCGAGCA GGACAGCAAGGACTCCACCTACAGCC TGAGCAGCACCCCTGACCCTGAGCAAG GCCGACTACGAGAAGCATAAAGGTGTA CGCCTGCGAGGTGACCCACCAGGGC CTGTCCAGCCCCGTGACCAAGAGCTT CAACAGGGGGCGAGTGC
SEQ ID NO: 92	DNA HC	GAAGTGCAGCTGGTGCACTCTGGCG CCGAAGTGAAGAAGCCTGGCGAGTC CCTGCGGATCTCCTGCAAGGGCTCTG GCTACACCTTCACCACCTACTGGATG CACTGGGTGCGACAGGCTACCGGCC AGGGCCTGGAATGGATGGGCAACATC TATCCTGGCACCGGCGGCTCCAACCTT CGACGAGAAGTTCAAGAACAGAGTGA CCATCACCGCCGACAAGTCCACCTCC ACCGCCTACATGGAAGTGTCTCCCT GAGATCCGAGGACACCGCCGTGTACT ACTGCACCCGGTGGACAACCGGCAC AGGCGCTTATTGGGGCCAGGGCACC ACAGTGACCGTGTCTCTGCTTCTAC CAAGGGGGCCCAGCGTGTTCCCCCTG GCCCCCTGCTCCAGAAGCACCGAGCG AGAGCACAGCCGCCCTGGGCTGCCT GGTGAAGGACTACTTCCCCGAGCCCG TGACCGTGTCTTGGAACAGCGGAGC CCTGACCAGCGGCGTGCACACCTTCC

		CCGCCGTGCTGCAGAGCAGCGGCCT GTACAGCCTGAGCAGCGTGGTGACC GTGCCCAGCAGCAGCCTGGGCACCA AGACCTACACCTGTAACGTGGACCAC AAGCCCAGCAACACCAAGGTGGACAA GAGGGTGGAGAGCAAGTACGGCCCA CCCTGCCCCCCTGCCAGCCCCCG AGTTCCTGGGCGGACCCAGCGTGTTT CTGTTCCCCCCTAAGCCCAAGGACAC CCTGATGATCAGCAGAACCCCCGAGG TGACCTGTGTGGTGGTGGACGTGTCC CAGGAGGACCCCGAGGTCCAGTTCAA CTGGTACGTGGACGGCGTGGAGGTG CACAACGCCAAGACCAAGCCCAGAGA GGAGCAGTTTAACAGCACCTACCGGG TGGTGTCCGTGCTGACCGTGCTGCAC CAGGACTGGCTGAACGGCAAAGAGTA CAAGTGTAAGGTCTCCAACAAGGGCC TGCCAAGCAGCATCGAAAAGACCATC AGCAAGGCCAAGGGCCAGCCTAGAG AGCCCCAGGTCTACACCCTGCCACCC AGCCAAGAGGAGATGACCAAGAACCA GGTGTCCCTGACCTGTCTGGTGAAGG GCTTCTACCCAAGCGACATCGCCGTG GAGTGGGAGAGCAACGGCCAGCCCG AGAACAACTACAAGACCACCCCCCA GTGCTGGACAGCGACGGCAGCTTCTT CCTGTACAGCAGGCTGACCGTGGACA AGTCCAGATGGCAGGAGGGCAACGT CTTTAGCTGCTCCGTGATGCACGAGG CCCTGCACAACCACTACACCCAGAAG AGCCTGAGCCTGTCCCTGGGC
BAP049-Clone-E HC		
SEQ ID NO: 1 (Kabat)	HCDR1	TYWMH
SEQ ID NO: 2 (Kabat)	HCDR2	NIYPGTGGSNFDEKFKN
SEQ ID NO: 3 (Kabat)	HCDR3	WTTGTGAY

SEQ ID NO: 4 (Chothia)	HCDR1	GYTFTTY
SEQ ID NO: 5 (Chothia)	HCDR2	YPGTGG
SEQ ID NO: 3 (Chothia)	HCDR3	WTTGTGAY
SEQ ID NO: 38	VH	EVQLVQSGAEVKKPGESLRISCKGSGY TFTTYWMHWRQATGQGLEWMGNIYP GTGGSNFDEKFKNRVTITADKSTSTAY MELSSLRSEDTAVYYCTRWTGTGAY WGQGTTTVTVSS
SEQ ID NO: 95	DNA VH	GAGGTGCAGCTGGTGCAGTCAGGCG CCGAAGTGAAGAAGCCCGGCGAGTC ACTGAGAATTAGCTGTAAAGGTTTCAG GCTACACCTTCACTACCTACTGGATG CACTGGGTCCGCCAGGCTACCGGTC AAGGCCTCGAGTGGATGGGTAATATC TACCCCGGCACCGGCGGCTCTAACTT CGACGAGAAGTTTAAGAATAGAGTGA CTATCACCGCCGATAAGTCTACTAGC ACCGCCTATATGGAAGTGTCTAGCCT GAGATCAGAGGACACCGCCGTCTACT ACTGCACTAGGTGGACTACCGGCACA GGCGCCTACTGGGGTCAAGGCACTA CCGTGACCGTGTCTAGC
SEQ ID NO: 91	HC	EVQLVQSGAEVKKPGESLRISCKGSGY TFTTYWMHWRQATGQGLEWMGNIYP GTGGSNFDEKFKNRVTITADKSTSTAY MELSSLRSEDTAVYYCTRWTGTGAY WGQGTTTVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNS GALTSGVHTFPAVLQSSGLYSLSSVTV PSSSLGKTYTCNVDHKPSNTKVDKRV ESKYGPPCPPCPAPEFLGGPSVFLFPP KPKDTLMISRTPEVTCVVVDVSQEDPE VQFNWYVDGVEVHNAKTKPREEQFNS TYRVVSVLTVLHQDWLNGKEYKCKVSN KGLPSSIEKTISKAKGQPREPQVYTLPP SQEEMTKNQVSLTCLVKGFYPSDIAVE

		WESNGQPENNYKTPPVLDSDGSFFLY SRLTVDKSRWQEGNVFSCSVMHEALH NHYTQKSLSLSLG
SEQ ID NO: 96	DNA HC	GAGGTGCAGCTGGTGCAGTCAGGCG CCGAAGTGAAGAAGCCCGGCGAGTC ACTGAGAATTAGCTGTAAAGGTTTCAG GCTACACCTTCACTACCTACTGGATG CACTGGGTCCGCCAGGCTACCGGTC AAGGCCTCGAGTGGATGGGTAATATC TACCCCGGCACCGGCGGCTCTAACTT CGACGAGAAGTTTAAGAATAGAGTGA CTATCACCGCCGATAAGTCTACTAGC ACCGCCTATATGGAAGTGTCTAGCCT GAGATCAGAGGACACCGCCGTCTACT ACTGCACTAGGTGGACTACCGGCACA GGCGCCTACTGGGGTCAAGGCACTA CCGTGACCGTGTCTAGCGCTAGCACT AAGGGCCCGTCCGTGTTCCCCCTGG CACCTTGTAGCCGGAGCACTAGCGAA TCCACCGCTGCCCTCGGCTGCCTGGT CAAGGATTACTTCCCGGAGCCCGTGA CCGTGTCCTGGAACAGCGGAGCCCT GACCTCCGGAGTGACACCTTCCCCG CTGTGCTGCAGAGCTCCGGGCTGTAC TCGCTGTCGTCGGTGGTCACGGTGCC TTCATCTAGCCTGGGTACCAAGACCT ACACTTGCAACGTGGACCACAAGCCT TCCAACACTAAGGTGGACAAGCGCGT CGAATCGAAGTACGGCCACCGTGCC CGCCTTGTCCCGCGCCGGAGTTCCTC GGCGGTCCCTCGGTCTTCTGTTCCC ACCGAAGCCCAAGGACACTTTGATGA TTTCCCGCACCCCTGAAGTGACATGC GTGGTCGTGGACGTGTCACAGGAAGA TCCGGAGGTGCAGTTCAATTGGTACG TGGATGGCGTCGAGGTGCACAACGC

		CAAAACCAAGCCGAGGGAGGAGCAG TTCAACTCCACTTACCGCGTCGTGTC CGTGCTGACGGTGCTGCATCAGGACT GGCTGAACGGGAAGGAGTACAAGTG CAAAGTGTCCAACAAGGGACTTCCTA GCTCAATCGAAAAGACCATCTCGAAA GCCAAGGGACAGCCCCGGGAACCCC AAGTGTATACCCTGCCACCGAGCCAG GAAGAAATGACTAAGAACCAAGTCTC ATTGACTTGCCTTGTGAAGGGCTTCTA CCCATCGGATATCGCCGTGGAATGGG AGTCCAACGGCCAGCCGGAAAAACAAC TACAAGACCACCCCTCCGGTGCTGGA CTCAGACGGATCCTTCTTCTCTACTC GCGGCTGACCGTGGATAAGAGCAGAT GGCAGGAGGGAAATGTGTTTCAGCTGT TCTGTGATGCATGAAGCCCTGCACAA CCACTACACTCAGAAGTCCCTGTCCC TCTCCCTGGGA
BAP049-Clone-E LC		
SEQ ID NO: 10 (Kabat)	LCDR1	KSSQSLLDSGNQKNFLT
SEQ ID NO: 11 (Kabat)	LCDR2	WASTRES
SEQ ID NO: 32 (Kabat)	LCDR3	QNDYSYPYT
SEQ ID NO: 13 (Chothia)	LCDR1	SQSLLDSGNQKNF
SEQ ID NO: 14 (Chothia)	LCDR2	WAS
SEQ ID NO: 33 (Chothia)	LCDR3	DYSYPY
SEQ ID NO: 70	VL	EIVLTQSPATLSLSPGERATLSCKSSQS LLDSGNQKNFLTWYQQKPGQAPRLLIY WASTRESGVPSRFSGSGSGTDFTFTIS SLEAEDAATYYCQNDYSYPYTFGQGK VEIK
SEQ ID NO: 106	DNA VL	GAGATCGTCCTGACTCAGTCACCCGC TACCCTGAGCCTGAGCCCTGGCGAG CGGGCTACACTGAGCTGTAAATCTAG TCAGTCACTGCTGGATAGCGGTAATC AGAAGAAGTTCCTGACCTGGTATCAG

		CAGAAGCCCGGTCAAGCCCCTAGACT GCTGATCTACTGGGCCTCTACTAGAG AATCAGGCGTGCCCTCTAGGTTTAGC GGTAGCGGTAGTGGCACCGACTTCAC CTTCACTATCTCTAGCCTGGAAGCCG AGGACGCCGCTACCTACTACTGTCAG AACGACTATAGCTACCCCTACACCTTC GGTCAAGGCACTAAGGTGCGAGATTAA G
SEQ ID NO: 72	LC	EIVLTQSPATLSLSPGERATLSCKSSQS LLDSGNQKNFLTWYQQKPGQAPRLIY WASTRESGVPSRFSGSGSGTDFTFTIS SLEAEDAATYYCQNDYSYPYTFGQGTK VEIKRTVAAPSVFIFPPSDEQLKSGTAS VVCLLNNFYPREAKVQWKVDNALQSG NSQESVTEQDSKDYSLSTLTLSKA DYEKHKVYACEVTHQGLSSPVTKSFNR GEC
SEQ ID NO: 107	DNA LC	GAGATCGTCCTGACTCAGTCACCCGC TACCCTGAGCCTGAGCCCTGGCGAG CGGGCTACACTGAGCTGTAAATCTAG TCAGTCACTGCTGGATAGCGGTAATC AGAAGAACTTCCTGACCTGGTATCAG CAGAAGCCCGGTCAAGCCCCTAGACT GCTGATCTACTGGGCCTCTACTAGAG AATCAGGCGTGCCCTCTAGGTTTAGC GGTAGCGGTAGTGGCACCGACTTCAC CTTCACTATCTCTAGCCTGGAAGCCG AGGACGCCGCTACCTACTACTGTCAG AACGACTATAGCTACCCCTACACCTTC GGTCAAGGCACTAAGGTGCGAGATTAA GCGTACGGTGGCCGCTCCCAGCGTG TTCATCTTCCCCCCCAGCGACGAGCA GCTGAAGAGCGGCACCGCCAGCGTG GTGTGCCTGCTGAACAATTCTACCC CCGGGAGGCCAAGGTGCGAGTGAAG

		GTGGACAACGCCCTGCAGAGCGGCA ACAGCCAGGAGAGCGTCACCGAGCA GGACAGCAAGGACTCCACCTACAGCC TGAGCAGCACCCTGACCCTGAGCAAG GCCGACTACGAGAAGCATAAGGTGTA CGCCTGCGAGGTGACCCACCAGGGC CTGTCCAGCCCCGTGACCAAGAGCTT CAACAGGGGCGAGTGC
BAP049-Clone-B HC		
SEQ ID NO: 133 (Kabat)	HCDR1	ACCTACTGGATGCAC
SEQ ID NO: 134 (Kabat)	HCDR2	AATATCTACCCCGGCACCGGCGGCTC
SEQ ID NO: 135 (Kabat)	HCDR3	TGGACTACCGGCACAGGCGCCTAC
SEQ ID NO: 136 (Chothia)	HCDR1	GGCTACACCTTCACTACCTAC
SEQ ID NO: 137 (Chothia)	HCDR2	TACCCCGGCACCGGCGGC
SEQ ID NO: 135 (Chothia)	HCDR3	TGGACTACCGGCACAGGCGCCTAC
BAP049-Clone-B LC		
SEQ ID NO: 138 (Kabat)	LCDR1	AAATCTAGTCAGTCACTGCTGGATAG CGGTAATCAGAAGAACTTCTGACC
SEQ ID NO: 139 (Kabat)	LCDR2	TGGGCCTCTACTAGAGAATCA
SEQ ID NO: 140 (Kabat)	LCDR3	CAGAACGACTATAGCTACCCCTACAC C
SEQ ID NO: 141 (Chothia)	LCDR1	AGTCAGTCACTGCTGGATAGCGGTAA TCAGAAGAACTTC
SEQ ID NO: 142 (Chothia)	LCDR2	TGGGCCTCT
SEQ ID NO: 143 (Chothia)	LCDR3	GACTATAGCTACCCCTAC
BAP049-Clone-E HC		
SEQ ID NO: 133 (Kabat)	HCDR1	ACCTACTGGATGCAC
SEQ ID NO: 134 (Kabat)	HCDR2	AATATCTACCCCGGCACCGGCGGCTC
SEQ ID NO: 135 (Kabat)	HCDR3	TGGACTACCGGCACAGGCGCCTAC
SEQ ID NO: 136 (Chothia)	HCDR1	GGCTACACCTTCACTACCTAC
SEQ ID NO: 137 (Chothia)	HCDR2	TACCCCGGCACCGGCGGC
SEQ ID NO: 135 (Chothia)	HCDR3	TGGACTACCGGCACAGGCGCCTAC
BAP049-Clone-E LC		

SEQ ID NO: 138 (Kabat)	LCDR1	AAATCTAGTCAGTCACTGCTGGATAG CGGTAATCAGAAGAACTTCCTGACC
SEQ ID NO: 139 (Kabat)	LCDR2	TGGGCCTCTACTAGAGAATCA
SEQ ID NO: 140 (Kabat)	LCDR3	CAGAACGACTATAGCTACCCCTACAC C
SEQ ID NO: 141 (Chothia)	LCDR1	AGTCAGTCACTGCTGGATAGCGGTAA TCAGAAGAACTTC
SEQ ID NO: 142 (Chothia)	LCDR2	TGGGCCTCT
SEQ ID NO: 143 (Chothia)	LCDR3	GACTATAGCTACCCCTAC

Table 2. Amino acid and nucleotide sequences of the heavy and light chain framework regions for humanized mAbs BAP049-Clone-B and BAP049-Clone-E

	Amino Acid Sequence	Nucleotide Sequence
VHFW1 (type a)	EVQLVQSGAEVKKPGESLRISCK GS (SEQ ID NO: 147)	GAAGTGCAGCTGGTGCAGTCTGGAGCAGA GGTGAAAAAGCCCGGGGAGTCTCTGAGGA TCTCCTGTAAGGGTTCT (SEQ ID NO: 148) GAAGTGCAGCTGGTGCAGTCTGGCGCCGA AGTGAAGAAGCCTGGCGAGTCCCTGCGGA TCTCCTGCAAGGGCTCT (SEQ ID NO: 149) GAGGTGCAGCTGGTGCAGTCAGGCGCCGA AGTGAAGAAGCCCGGGCGAGTCACTGAGAA TTAGCTGTAAAGGTTCA (SEQ ID NO: 150)
VHFW1 (type b)	QVQLVQSGAEVKKPGASVKVSC KAS (SEQ ID NO: 151)	CAGGTTCACTGGTGCAGTCTGGAGCTGA GGTGAAGAAGCCTGGGGCCTCAGTGAAGG TCTCCTGCAAGGCTTCT (SEQ ID NO: 152)
VHFW2 (type a)	WVRQATGQGLEWMG (SEQ ID NO: 153)	TGGGTGCGACAGGCCACTGGACAAGGGCT TGAGTGGATGGGT (SEQ ID NO: 154) TGGGTGCGACAGGCTACCGGCCAGGGCCT GGAATGGATGGGC (SEQ ID NO: 155) TGGGTCCGCCAGGCTACCGGTCAAGGCCT

		CGAGTGGATGGGT (SEQ ID NO: 156)
VHFW2 (type b)	WIRQSPSRGLEWLG (SEQ ID NO: 157)	TGGATCAGGCAGTCCCCATCGAGAGGCCTT GAGTGGCTGGGT (SEQ ID NO: 158) TGGATCCGGCAGTCCCCCTCTAGGGGCCT GGAATGGCTGGGC (SEQ ID NO: 159)
VHFW2 (type c)	WVRQAPGQGLEWMG (SEQ ID NO: 160)	TGGGTGCGACAGGCCCCCTGGACAAGGGCT TGAGTGGATGGGT (SEQ ID NO: 161)
VHFW3 (type a)	RVTITADKSTSTAYMELSSLRSE DTAVYYCTR (SEQ ID NO: 162)	AGAGTCACGATTACCGCGGACAAATCCACG AGCACAGCCTACATGGAGCTGAGCAGCCT GAGATCTGAGGACACGGCCGTGTATTACTG TACAAGA (SEQ ID NO: 163) AGAGTGACCATCACCGCCGACAAGTCCACC TCCACCGCCTACATGGAAGTGTCTCCCTG AGATCCGAGGACACCGCCGTGTACTACTGC ACCCGG (SEQ ID NO: 164) AGAGTGAATATCACCGCCGATAAGTCTACT AGCACCGCCTATATGGAAGTGTCTAGCCTG AGATCAGAGGACACCGCCGTCTACTACTGC ACTAGG (SEQ ID NO: 165)
VHFW3 (type b)	RFTISRDNKNTLYLQMNSLRAE DTAVYYCTR (SEQ ID NO: 166)	AGATTCACCATCTCCAGAGACAATTCCAAG AACACGCTGTATCTTCAAATGAACAGCCTG AGAGCCGAGGACACGGCCGTGTATTACTGT ACAAGA (SEQ ID NO: 167) AGGTTACCATCTCCCGGGACAAGTCCAAG AACACCCTGTACCTGCAGATGAACTCCCTG CGGGCCGAGGACACCGCCGTGTACTACTG TACCAGA (SEQ ID NO: 168)
VHFW4	WGQGTTVTVSS (SEQ ID NO: 169)	TGGGGCCAGGGCACCACCGTGACCGTGTC CTCC (SEQ ID NO: 170)

		TGGGGCCAGGGCACCACAGTGACCGTGTC CTCT (SEQ ID NO: 171) TGGGGTCAAGGCACTACCGTGACCGTGTCT AGC (SEQ ID NO: 172) TGGGGCCAGGGCACAACAGTGACCGTGTC CTCC (SEQ ID NO: 173)
VLFW1 (type a)	EIVLTQSPDFQSVTPKEKVTITC (SEQ ID NO: 174)	GAAATTGTGCTGACTCAGTCTCCAGACTTT CAGTCTGTGACTCCAAAGGAGAAAGTCACC ATCACCTGC (SEQ ID NO: 175) GAGATCGTGCTGACCCAGTCCCCGACTTC CAGTCCGTGACCCCCAAAGAAAAGTGACC ATCACATGC (SEQ ID NO: 176)
VLFW1 (type b)	EIVLTQSPATLSLSPGERATLSC (SEQ ID NO: 177)	GAAATTGTGTTGACACAGTCTCCAGCCACC CTGTCTTTGTCTCCAGGGGAAAGAGCCACC CTCTCCTGC (SEQ ID NO: 178) GAGATCGTGCTGACCCAGTCCCCTGCCAC CCTGTCACTGTCTCCAGGCGAGAGAGCTAC CCTGTCCTGC (SEQ ID NO: 179) GAGATCGTCCTGACTCAGTCACCCGCTACC CTGAGCCTGAGCCCTGGCGAGCGGGCTAC ACTGAGCTGT (SEQ ID NO: 180)
VLFW1 (type c)	DIVMTQTPLSLPVTGPGEPAISIC (SEQ ID NO: 181)	GATATTGTGATGACCCAGACTCCACTCTCC CTGCCCCGTACCCCTGGAGAGCCGGCCTC CATCTCCTGC (SEQ ID NO: 182)
VLFW1 (type d)	DVVMTQSPLSLPVTLGQPASISC (SEQ ID NO: 183)	GATGTTGTGATGACTCAGTCTCCACTCTCC CTGCCCCGTACCCCTTGACAGCCGGCCTC

		CATCTCCTGC (SEQ ID NO: 184)
VLFW1 (type e)	DIQMTQSPSSLSASVGDRVITC (SEQ ID NO: 185)	GACATCCAGATGACCCAGTCTCCATCCTCC CTGTCTGCATCTGTAGGAGACAGAGTCACC ATCACTTGC (SEQ ID NO: 186)
VLFW2 (type a)	WYQQKPGQAPRLIY (SEQ ID NO: 187)	TGGTACCAGCAGAAACCTGGCCAGGCTCC CAGGCTCCTCATCTAT (SEQ ID NO: 188) TGGTATCAGCAGAAGCCCGGCCAGGCCCC CAGACTGCTGATCTAC (SEQ ID NO: 189) TGGTATCAGCAGAAGCCCGGTCAAGCCCCT AGACTGCTGATCTAC (SEQ ID NO: 190)
VLFW2 (type b)	WYQQKPGKAPKLLIY (SEQ ID NO: 191)	TGGTATCAGCAGAAACCAGGGAAAGCTCCT AAGCTCCTGATCTAT (SEQ ID NO: 192) TGGTATCAGCAGAAGCCCGGTAAAGCCCCT AAGCTGCTGATCTAC (SEQ ID NO: 193)
VLFW2 (type c)	WYLQKPGQSPQLLIY (SEQ ID NO: 194)	TGGTACCTGCAGAAGCCAGGGCAGTCTCC ACAGCTCCTGATCTAT (SEQ ID NO: 195)
VLFW3 (type a)	GVPSRFSGSGSGTDFFTISSLE AEDAATYYC (SEQ ID NO: 196)	GGGGTCCCCTCGAGGTTCAGTGGCAGTGG ATCTGGGACAGATTTACCTTTACCATCAGT AGCCTGGAAGCTGAAGATGCTGCAACATAT TACTGT (SEQ ID NO: 197) GGCGTGCCCTCTAGATTCTCCGGCTCCGG CTCTGGCACCGACTTTACCTTCACCATCTC CAGCCTGGAAGCCGAGGACGCCGCCACCT ACTACTGC (SEQ ID NO: 198) GGCGTGCCCTCTAGGTTTAGCGGTAGCGG TAGTGGCACCGACTTCACCTTCACTATCTCT AGCCTGGAAGCCGAGGACGCCGCTACCTA

		CTACTGT (SEQ ID NO: 199)
VLFW3 (type b)	GIPPRFSGSGYGTDFTLTINNIES EDAAYYFC (SEQ ID NO: 200)	GGGATCCACCTCGATTTCAGTGGCAGCGG GTATGGAACAGATTTTACCCTCACAATTAAT AACATAGAATCTGAGGATGCTGCATATTACT TCTGT (SEQ ID NO: 201)
VLFW3 (type c)	GVPSRFSGSGSGTEFTLTISLQ PDDFATYYC (SEQ ID NO: 202)	GGGGTCCCATCAAGGTTTCAGCGGCAGTGG ATCTGGGACAGAATTCACTCTCACCATCAG CAGCCTGCAGCCTGATGATTTTGCAACTTA TTACTGT (SEQ ID NO: 203) GGCGTGCCCTCTAGATTCTCCGGCTCCGG CTCTGGCACCGAGTTTACCCTGACCATCTC CAGCCTGCAGCCCGACGACTTCGCCACCT ACTACTGC (SEQ ID NO: 204)
VLFW3 (type d)	GVPSRFSGSGSGTDFTFTISLQ PEDIATYYC (SEQ ID NO: 205)	GGGGTCCCATCAAGGTTTCAGTGGAAGTGG ATCTGGGACAGATTTTACTTTTACCATCAGC AGCCTGCAGCCTGAAGATATTGCAACATAT TACTGT (SEQ ID NO: 206) GGCGTGCCCTCTAGGTTTAGCGGTAGCGG TAGTGGCACCGACTTCACCTTCACTATCTCT AGCCTGCAGCCCGAGGATATCGCTACCTAC TACTGT (SEQ ID NO: 207)
VLFW4	FGQGTKVEIK (SEQ ID NO: 208)	TTCGGCCAAGGGACCAAGGTGGAAATCAAA (SEQ ID NO: 209) TTCGGCCAGGGCACCAAGGTGGAAATCAA G (SEQ ID NO: 210) TTCGGTCAAGGCACTAAGGTGCGAGATTAAG (SEQ ID NO: 211)

Table 3. Constant region amino acid sequences of human IgG heavy chains and human kappa light chain

HC	IgG4 (S228P) mutant constant region amino acid sequence (EU Numbering) ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTKT YTCNVDHKPS NTKVDKRVES KYGPPCPPCP APEFLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSQED PEVQFNWYVD GVEVHNAKTK PREEQFNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKGLPS SIEKTISKAK GQPREPQVYT LPPSQEEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTPPVLDSDGSFFLYSRL TVDKSRWQEG NVFSCSV MHEALHNHYTQKSLSLSPGK (SEQ ID NO: 212)
LC	Human kappa constant region amino acid sequence RTVAAPSVFI FPPSDEQLKS GTASVCLLN NFYPREAKVQ WKVDNALQSG NSQESVTEQD SKDSTYSLSS TLTLKADYE KHKVYACEVT HQGLSSPVTK SFNRGEC (SEQ ID NO: 213)
HC	IgG4 (S228P) mutant constant region amino acid sequence lacking C-terminal lysine (K) (EU Numbering) ASTKGPSVFP LAPCSRSTSE STAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTKT YTCNVDHKPS NTKVDKRVES KYGPPCPPCP APEFLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSQED PEVQFNWYVD GVEVHNAKTK PREEQFNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKGLPS SIEKTISKAK GQPREPQVYT LPPSQEEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTPPVLDSDGSFFLYSRL TVDKSRWQEG NVFSCSV MHEALHNHYTQKSLSLSPG (SEQ ID NO: 214)
HC	IgG1 wild type ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCDKHTTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTPEVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN STYRVVSVLT VLNQDNLNGK EYKCKVSNKA LPAIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLTCL LVKGFYPSDI AVEWESNGQP ENNYKTPPVLDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYTQKSLSLSPGK (SEQ ID NO: 215)
HC	IgG1 (N297A) mutant constant region amino acid sequence (EU Numbering)

	ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMIS RTP EVTCVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYA STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTPPV LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 216)
HC	IgG1 (D265A, P329A) mutant constant region amino acid sequence (EU Numbering) ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMIS RTP EVTCVWVAVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LAAPIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTPPV LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 217)
HC	IgG1 (L234A, L235A) mutant constant region amino acid sequence (EU Numbering) ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPEAAGG PSVFLFPPKP KDTLMIS RTP EVTCVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTPPV LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (SEQ ID NO: 218)

Table 4. Amino acid sequences of the heavy and light chain leader sequences for humanized mAbs BAP049-Clone-B and BAP049-Clone-E

BAP049-Clone-B	HC	MAWWWTLPFLMAAAQSVQA (SEQ ID NO: 221)
	LC	MSVLTQVLALLLLWLTGTRC (SEQ ID NO: 222)
BAP049-Clone-E	HC	MAWWWTLPFLMAAAQSVQA (SEQ ID NO: 221)

	LC	MSVLTQVLALLLWLTGTRC (SEQ ID NO: 222)

Claims

1. A pharmaceutical combination comprising an anti-PD-1 antibody molecule and N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in free form or in pharmaceutically acceptable salt form.
2. A pharmaceutical combination according to claim 1, wherein the anti-PD-1 antibody molecule is an isolated antibody molecule capable of binding to a human Programmed Death-1 (PD-1) comprising a heavy chain variable region (VH) comprising a HCDR1, a HCDR2 and a HCDR3 amino acid sequence of BAP049-Clone-B or BAP049-Clone-E as described in Table 1 and a light chain variable region (VL) comprising a LCDR1, a LCDR2 and a LCDR3 amino acid sequence of BAP049-Clone-B or BAP049-Clone-E as described in Table 1.
3. A pharmaceutical combination according to claim 1, wherein the anti-PD-1 antibody molecule comprises:
- (a) a heavy chain variable region (VH) comprising a HCDR1 amino acid sequence of SEQ ID NO: 4, a HCDR2 amino acid sequence of SEQ ID NO: 5, and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a light chain variable region (VL) comprising a LCDR1 amino acid sequence of SEQ ID NO: 13, a LCDR2 amino acid sequence of SEQ ID NO: 14, and a LCDR3 amino acid sequence of SEQ ID NO: 33;
- (b) a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 1; a HCDR2 amino acid sequence of SEQ ID NO: 2; and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 10, a LCDR2 amino acid sequence of SEQ ID NO: 11, and a LCDR3 amino acid sequence of SEQ ID NO: 32;
- (c) a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 224, a HCDR2 amino acid sequence of SEQ ID NO: 5, and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 13, a LCDR2 amino acid sequence of SEQ ID NO: 14, and a LCDR3 amino acid sequence of SEQ ID NO: 33; or
- (d) a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 224; a HCDR2 amino acid sequence of SEQ ID NO: 2; and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 10, a LCDR2 amino acid sequence of SEQ ID NO: 11, and a LCDR3 amino acid sequence of SEQ ID NO: 32.

4. A pharmaceutical combination according to claim 1 or 2 or 3, wherein the anti-PD-1 antibody molecule comprises a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 38 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 70.
5. A pharmaceutical combination according to any one of claims 1 to 4, wherein the anti-PD-1 antibody molecule comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 91 and a light chain comprising the amino acid sequence of SEQ ID NO: 72.
6. The pharmaceutical combination according to any one of claims 1 to 5 for use as a medicament.
7. A pharmaceutical combination according to any one of claims 1 to 5 for use in the treatment of cancer.
8. A pharmaceutical combination according to any one of claims 1 to 5 for use in the treatment of liver cancer (HCC).
9. A pharmaceutical combination according to any one of claims 1 to 5 for use according to claim 8 wherein the HCC is characterized by positive FGFR4 and KLB expression.
10. A pharmaceutical combination according to any one of claims 1 to 5 for use according to claim 8 or 9 wherein the HCC has progressed during or after discontinuation of sorafenib treatment or wherein the patient suffering from the HCC is intolerant to sorafenib treatment.
11. A pharmaceutical combination comprising an FGFR4 inhibitor and an anti-PD-1 antibody molecule for use in the treatment of liver cancer.
12. A method of treating cancer in a subject in need thereof comprising administering to said subject simultaneously or sequentially N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in free form or in pharmaceutically acceptable salt form and an anti-PD-1 antibody molecule, wherein the anti-PD-1 antibody molecule comprises:

(a) a heavy chain variable region (VH) comprising a HCDR1 amino acid sequence of SEQ ID NO: 4, a HCDR2 amino acid sequence of SEQ ID NO: 5, and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a light chain variable region (VL) comprising a LCDR1 amino acid sequence of SEQ ID NO: 13, a LCDR2 amino acid sequence of SEQ ID NO: 14, and a LCDR3 amino acid sequence of SEQ ID NO: 33;

(b) a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 1; a HCDR2 amino acid sequence of SEQ ID NO: 2; and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 10, a LCDR2 amino acid sequence of SEQ ID NO: 11, and a LCDR3 amino acid sequence of SEQ ID NO: 32;

(c) a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 224, a HCDR2 amino acid sequence of SEQ ID NO: 5, and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 13, a LCDR2 amino acid sequence of SEQ ID NO: 14, and a LCDR3 amino acid sequence of SEQ ID NO: 33;

(d) a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 224; a HCDR2 amino acid sequence of SEQ ID NO: 2; and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 10, a LCDR2 amino acid sequence of SEQ ID NO: 11, and a LCDR3 amino acid sequence of SEQ ID NO: 32;

(e) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 38 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 70; or

(f) a heavy chain comprising the amino acid sequence of SEQ ID NO: 91 and a light chain comprising the amino acid sequence of SEQ ID NO: 72.

13. A method according to claim 9, wherein the cancer is liver cancer.

14. A therapeutic regimen comprising the simultaneous or sequential administration of N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in free form or in pharmaceutically acceptable salt form and an anti-PD-1 antibody molecule, wherein the anti-PD-1 antibody molecule comprises:

(a) a heavy chain variable region (VH) comprising a HCDR1 amino acid sequence of SEQ ID NO: 4, a HCDR2 amino acid sequence of SEQ ID NO: 5, and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a light chain variable region (VL) comprising a

LCDR1 amino acid sequence of SEQ ID NO: 13, a LCDR2 amino acid sequence of SEQ ID NO: 14, and a LCDR3 amino acid sequence of SEQ ID NO: 33;

5 (b) a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 1; a HCDR2 amino acid sequence of SEQ ID NO: 2; and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 10, a LCDR2 amino acid sequence of SEQ ID NO: 11, and a LCDR3 amino acid sequence of SEQ ID NO: 32;

10 (c) a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 224, a HCDR2 amino acid sequence of SEQ ID NO: 5, and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 13, a LCDR2 amino acid sequence of SEQ ID NO: 14, and a LCDR3 amino acid sequence of SEQ ID NO: 33;

15 (d) a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 224; a HCDR2 amino acid sequence of SEQ ID NO: 2; and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 10, a LCDR2 amino acid sequence of SEQ ID NO: 11, and a LCDR3 amino acid sequence of SEQ ID NO: 32;

20 (e) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 38 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 70; or

(f) a heavy chain comprising the amino acid sequence of SEQ ID NO: 91 and a light chain comprising the amino acid sequence of SEQ ID NO: 72.

25 15. A therapeutic regimen according to claim 14, wherein the anti-PD-1 antibody molecule is administered at a dose of about 300 mg once every three weeks.

16. A therapeutic regimen according to claim 14, wherein the anti-PD-1 antibody molecule is administered at a dose of about 400 mg once every four weeks.

30 17. A therapeutic regimen according to any one of claims 14 to 16 wherein N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide is administered at a dose of about 80 to 120 mg daily.

35 18. The therapeutic regimen of claim 17 wherein N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide is administered at a dose of about 80 mg daily.

19. A therapeutic regimen according to any one of claims 14 to 18 for the treatment of liver cancer.
- 5 20. Use of a pharmaceutical combination according to any one of claims 1 to 5 for the preparation of a medicament for the treatment of liver cancer.
21. A kit comprising a pharmaceutical combination according to any one of claims 1 to 5 with instructions for simultaneous or sequential administration of N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide in free form or in pharmaceutically acceptable salt form and the anti-PD-1 antibody molecule.
- 10 22. A pharmaceutical combination comprising N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide, or a pharmaceutically acceptable salt thereof, and an anti-PD-1 antibody molecule, wherein the anti-PD-1 antibody molecule comprises:
- 15 (a) a heavy chain variable region (VH) comprising a HCDR1 amino acid sequence of SEQ ID NO: 4, a HCDR2 amino acid sequence of SEQ ID NO: 5, and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a light chain variable region (VL) comprising a LCDR1 amino acid sequence of SEQ ID NO: 13, a LCDR2 amino acid sequence of SEQ ID NO: 14, and a LCDR3 amino acid sequence of SEQ ID NO: 33;
- 20 (b) a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 1; a HCDR2 amino acid sequence of SEQ ID NO: 2; and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 10, a LCDR2 amino acid sequence of SEQ ID NO: 11, and a LCDR3 amino acid sequence of SEQ ID NO: 32;
- 25 (c) a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 224, a HCDR2 amino acid sequence of SEQ ID NO: 5, and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 13, a LCDR2 amino acid sequence of SEQ ID NO: 14, and a LCDR3 amino acid sequence of SEQ ID NO: 33;
- 30 (d) a VH comprising a HCDR1 amino acid sequence of SEQ ID NO: 224; a HCDR2 amino acid sequence of SEQ ID NO: 2; and a HCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a LCDR1 amino acid sequence of SEQ ID NO: 10, a LCDR2
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amino acid sequence of SEQ ID NO: 11, and a LCDR3 amino acid sequence of SEQ ID NO: 32;

(e) a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 38 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 70; or

(f) a heavy chain comprising the amino acid sequence of SEQ ID NO: 91 and a light chain comprising the amino acid sequence of SEQ ID NO: 72,

for use in treating HCC, wherein the anti-PD-1 antibody molecule is administered in a dose of about 300 mg to 400 mg once every three weeks or once every four weeks.

23. A pharmaceutical combination for use according to claim 22, wherein the anti-PD-1 antibody molecule is administered at a dose of about 300 mg once every three weeks.

24. A pharmaceutical combination for use according to claim 22, wherein the anti-PD-1 antibody molecule is administered at a dose of about 400 mg once every four weeks.

25. A pharmaceutical combination for use according to any one of claims 22 to 24 wherein N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide is administered at a dose of about 50 to 150 mg daily.

26. A pharmaceutical combination for use according to claim 25 wherein N-(5-cyano-4-((2-methoxyethyl)amino)pyridin-2-yl)-7-formyl-6-((4-methyl-2-oxopiperazin-1-yl)methyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxamide is administered at a dose of about 80 mg daily or 120 mg daily.

INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K39/395 A61K31/00 C07K16/28 A61P35/00
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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)

A61K C07K

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)

EP0-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	YE et al: "Combination of the FGFR4 inhibitor PD173074 and 5-fluorouracil reduces proliferation and promotes apoptosis in gastric cancer", 11 October 2013 (2013-10-11), XP055426546, Retrieved from the Internet: URL:https://www.spandidos-publications.com/or/30/6/2777 [retrieved on 2017-11-20] last paragraph before the paragraph "Material and Methods" ----- -/--	1-26



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MASARU KATOH: "FGFR inhibitors: Effects on cancer cells, tumor microenvironment and whole-body homeostasis (Review)", INTERNATIONAL JOURNAL OF MOLECULAR MEDICINE, 31 May 2016 (2016-05-31), XP055340831, GR ISSN: 1107-3756, DOI: 10.3892/ijmm.2016.2620	11
Y	last paragraph before the last paragraph of the article	1-10, 12-26
X	----- US 2015/210769 A1 (FREEMAN GORDON JAMES [US] ET AL) 30 July 2015 (2015-07-30)	11
Y	paragraph [0654]	1-10, 12-26
Y	----- Castanon Alvarez: "Looking into the "Garden of the Hesperides": new drugs for hepatocellular carcinoma.", , 23 January 2015 (2015-01-23), XP055426521, Retrieved from the Internet: URL:http://www.ncbi.nlm.nih.gov/pubmed/25614940 [retrieved on 2017-11-20] paragraph "Immunotherapy" and paragraph "FGFR4" -----	1-10, 12-26

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Information on patent family members

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