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(71) Applicant: **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, 4056 Basel (CH).

(72) Inventors: **DOBSON, Jason Russell**; c/o Novartis Institutes for BioMedical Research, Inc., 250 Massachusetts Avenue, Cambridge, Massachusetts 02139 (US). **MOODY, Susan**; c/o Novartis Institutes for BioMedical Research, Inc., 250 Massachusetts Avenue, Cambridge, Massachusetts 02139 (US). **MCLAUGHLIN, Margaret Elise**; c/o Novartis Institutes for BioMedical Research, Inc., 250 Massachusetts Avenue, Cambridge, Massachusetts 02139 (US).

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(54) Title: DOSING SCHEDULE OF A WNT INHIBITOR AND AN ANTI-PD-1 ANTIBODY MOLECULE IN COMBINATION

(57) Abstract: The present disclosure relates to the field of pharmacy, particularly to a Wnt inhibitor and a PD-1 inhibitor for use in the treatment of cancer. Specifically, the disclosure relates to a pharmaceutical combination comprising a Wnt inhibitor, or a pharmaceutically acceptable salt thereof, and a PD-1 inhibitor, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, to a method for the treatment of cancer that involves administering the combination and to the use of the combination for the manufacture of a medicament for the treatment of cancer.

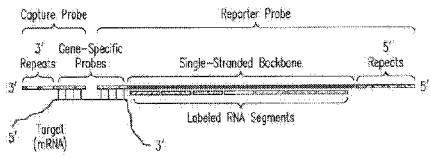


FIG.1A

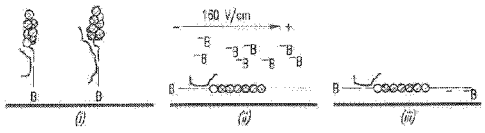


FIG.1B

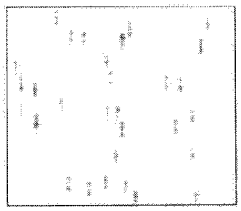


FIG.1C

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Dosing schedule of a Wnt inhibitor and an anti-PD-1 antibody molecule in combination

FIELD OF THE DISCLOSURE

The present disclosure relates to the field of pharmacy, particularly to a Wnt inhibitor and an anti-PD-1 antibody molecule for use in the treatment of cancer. Specifically, the disclosure relates to a pharmaceutical combination comprising a Wnt inhibitor, or a pharmaceutically acceptable salt thereof, and an anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer; to a method for the treatment of cancer that involves administering the combination; and to the use of the combination for the manufacture of a medicament for the treatment of cancer.

BACKGROUND OF THE DISCLOSURE

The Wnt (Wingless) family is a group of highly conserved secreted proteins that regulate cell-to-cell interactions during embryogenesis and is implicated in carcinogenesis, aging, and fibrosis. The Wnt gene was identified as an oncogene in murine mammary tumors 30 years ago and confirmed to be a key oncogenic pathway in many studies. The Wnt gene family encodes a large class of secreted proteins related to the Int1/Wnt1 proto-oncogene and Drosophila wingless ("Wg"), a Drosophila Wnt1 homologue (Cadigan *et al. Genes & Development* 1997, 11, 3286).

The Programmed Death 1 (PD-1) protein is an inhibitory member of the extended CD28/CTLA4 family of T-cell regulators (Okazaki *et al. Curr. Opin. Immunol.* 2002, 14, 391779; Bennett *et al. J. Immunol.* 2003, 170, 711). Ligands of the CD28 receptor include a group of related B7 molecules, also known as the "B7 Superfamily" (Coyle *et al. Nature Immunol.* 2001, 2(3), 203; Sharpe *et al. Nature Rev. Immunol.* 2002, 2, 116; Collins *et al. Genome Biol.* 2005, 6, 223.1; Korman *et al. Adv. Immunol.* 2007, 90, 297). Several members of the B7 Superfamily are known, including B7.1 (CD80), B7.2 (CD86), the 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 *et al. Genome Biol.* 2005, 6, 223.1). 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.

PD-L1 is abundant in a variety of human cancers (Dong *et al. Nat. Med.* 2002, 8, 787). PD-1 is known as an immune-inhibitory protein that negatively regulates TCR signals (Ishida *et al. EMBO J.* 1992, 11, 3887; Blank *et al. Immunol. Immunother.* 2006, 56(5), 739). The interaction between PD-1 and PD-L1 can act as 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. J. Mol. Med.* 2003, 81, 281; Blank *et al. Cancer Immunol. Immunother.* 2005, 54, 307; Konishi *et al. Clin. Cancer Res.* 2004, 10, 5094). Immune suppression can be reversed by inhibiting the local interaction of PD-1 with PD-L1 or PD-L2; the effect is additive when the interaction of PD-1 with PD-L2 is blocked as well (Iwai *et al. Proc. Nat. Acad. Sci.* USA 2002, 99:12293-7; Brown *et al. J. Immunol.* 2003, 170, 1257).

Several lines of evidence suggest that Wnt pathway signaling may be important in a variety of cancers. Mutations in components of the canonical Wnt pathway, such as APC and β-catenin, might play important roles in the pathogenesis of some malignancies. Recent molecular analysis of

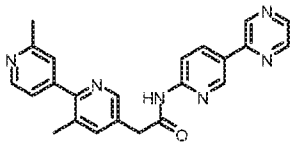
human metastatic melanoma samples revealed a correlation between activation of the WNT/b-catenin signaling pathway and the absence of a T-cell gene expression signature (Spranger *et al. Nature* 2015, 523, 231).

SUMMARY OF THE DISCLOSURE

Given the importance of immune checkpoint pathways in regulating an immune response in cancer therapy, the need exists to develop novel combination therapies that activate the immune system or overcome the resistance to immunotherapies.

The invention addresses this need by providing a pharmaceutical combination as defined herein.

The first aspect of the present disclosure is a pharmaceutical combination comprising a Wnt inhibitor of formula (i), 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide [Compound of Formula (I)], or a pharmaceutically acceptable salt thereof,



Formula (I)

and (ii) an anti-PD-1 antibody molecule or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, wherein (i) is administered daily on days 1 to 15 of each cycle for up to 4 cycles and (ii) is administered at least once per cycle.

Another aspect of the present disclosure provides the use of a wnt inhibitor of formula (i), 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof, in combination with an anti-PD-1 antibody molecule (ii), or a pharmaceutically acceptable salt, for the manufacture of a medicament for the treatment of cancer, wherein (i) and (ii) are administered as define herein, preferably wherein (i) is administered daily on days 1 to 15 of each cycle for up to 4 cycles and (ii) is administered at least once per cycle.

A yet another aspect of the present disclosure provides a method for the treatment of cancer, said method comprising administering an effective amount of the (i) and (ii) to a patient in need thereof, wherein (i) is administered daily on days 1 to 15 of each cycle for up to 4 cycles and (ii) is administered at least once per cycle.

BRIEF DESCRIPTION OF FIGURES

Figure 1 presents the NanoString measured gene expression of RNA samples isolated from tumor biopsies after 15 days exposure.

Figure 2 shows CD3 expression at screening and summary visits for the 9 paired subjects in this analysis.

Figure 3 shows one of the T-cell signatures selected for the study.

Figure 4 shows modulation of the Wnt pathway post treatment.

Figure 5 shows the chemokines signature associated with the recruitment of CD103+ dentritic cells.

Figure 6 shows the chemokines signature associated with the recruitment of CD8+ T-cells.

Figures 7A and 7B: shows the correlation between T-cell and Wnt signatures in the Cancer Genome Atlast (TCGA) for various types of cancer cells

Figure 8: illustrates the clinical study design.

DETAILED DESCRIPTION OF THE DISCLOSURE

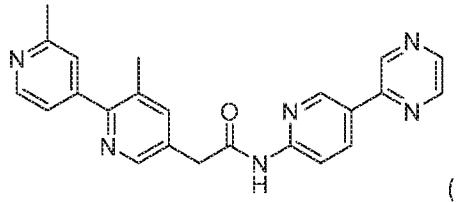
Recently, the secreted glycoproteins R-spondins 1-4 (RSPO1-4) have emerged as important activators of canonical Wnt signaling. RSPOs bind to leucine-rich repeat-containing G-protein-coupled receptors (LGR4-6) and the transmembrane E3 ubiquitin ligases RING finger 43/zinc and RING finger 3 (RNF43/ZNRF3), forming a ternary complex (Chen *et al. Genes Dev*; 2013, 27, 1345). RNF43/ZNRF3 antagonize Wnt signaling by promoting the turnover of Fz and LRP6 (Hao *et al. Nature* 2012, 485 (7397), 195-200; Koo *et al. Nature*, 2012, 488 (7413), 665). Binding of RSPO induces the endocytosis of RNF43/ZNRF3, thereby increasing levels of membrane-bound Fz and LRP6 and enhancing Wnt ligand-mediated signaling. In order to activate signaling within target cells, Wnt proteins must be properly secreted and transported across the extracellular space. Porcupine is a membrane-bound-O-acyltransferase (MBOAT) that adds palmitoyl groups to Wnt proteins (Takada *et al. Dev. Cell* 2006, 11, 791). Mutations in components of the canonical Wnt pathway such as APC and β-catenin play important roles in the pathogenesis of some malignancies and those genetic lesions affect upstream Wnt pathway regulation. The inhibition of the Wnt pathway signaling was recently associated with several drawbacks such as side effects and dose limiting toxicities. Such drawbacks were limiting the anti-tumor efficacy of Wnt inhibitors. Separately, activation of the Wnt pathway was linked to resistance to immunotherapy and offers a mechanism by which tumors can evade immune detection and decrease clinical benefit to check-point inhibitors (Spranger *et al. Nature* 2015, 523, 231). For example, the Wnt inhibitor of the present disclosure, namely 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide was tested and the levels of pLRP6 and AXIN2qPCR were analyzed in biopsies of skin and tumors. The levels of pLRP6 and AXIN2 were inhibited in post-treatment skin sample biopsies with 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof, indicating inhibition of the Wnt pathway. Unfortunately, in other studies 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof, alone as a single agent showed an increased cytotoxic gene signature and a lack of tumor efficacy. In addition, animal studies showed a decrease in trabeculae in rat studies; toxicities in gastrointestinal (GI) tract, bones and teeth in rat and dog models; and secondary effects affecting the bone marrow in rats and kidneys in dogs.

It has been discovered that treatment of patients with the Wnt inhibitor (i) alone resulted in changes in immune signatures in tumors and that 8-15 days of treatment with the single agent Wnt inhibitor (i) was sufficient to result in these changes. These findings led to conclude that intermittent dosing of a Wnt inhibitor (i) with an anti-PD-1 antibody molecule (ii), or a pharmaceutically acceptable salt thereof, can sensitize dendritic and T-cells and thus be sufficient to enhance the effects of PD-1 inhibition, while mitigating some of the toxicities of chronic Wnt administration, particularly to the bone.

The Wnt signaling pathway is required for development and survival of osteoblasts (involved in bone formation) and negatively regulates osteoclasts (involved in bone resorption). Linked to that, Wnt inhibitors were found to cause bone resorption and bone thinning. In a clinical study of the Wnt inhibitor, some patients experienced bone fractures, which may be related to the effects of the Wnt pathway inhibition on osteoblasts and osteoclasts. Therefore, administering the Wnt inhibitor (i), e.g. 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-N-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof, for a shorter period such as daily only on days 1 to 15 of up to 4 therapeutic cycles can reduce the risk of the Wnt inhibitor causing clinically relevant changes to

the bone. In addition, the short intermittent dosing of Wnt inhibitor was sufficient to result in upregulation of the activated dendritic cells signature. This is relevant because this subtype of dendritic cell is important for recruiting and activating T cells for an anti-tumoral response. Inhibition of the Wnt signaling in cancer treatment improves the response rate to PD-1 inhibition through release of inhibition of dendritic cells and T-cell activation. Overall, the combination of the Wnt inhibitor (i) and an anti-PD-1 antibody molecule, wherein Wnt inhibitor is administered only at the beginning of the treatment cycle for, e.g. 8 or 15 days, can show mutually coordinated effect of both compounds and offer better efficacy and much reduced safety profile compared to, for example, use of the Wnt inhibitor (i) alone.

According to the present disclosure, the Wnt inhibitor is a compound that targets, decreases or inhibits the activity of the Wnt signaling in a cell. For example, the Wnt inhibitor can also be a porcupine inhibitor. The Wnt inhibitor (i) is a compound disclosed in WO2010/101849. The Wnt inhibitor to be combined with the anti-PD-1 antibody molecule, or a pharmaceutical salt thereof, is 2-(2',3-dimethyl-2,4'-bipyridin-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof, of formula (I)



(I),

as disclosed in WO2010/101849 (compound 86, example 10).

Therefore the present disclosure provides a pharmaceutical combination comprising (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof, and (ii) an anti-PD-1 antibody molecule or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, wherein the compound of formula (i), namely 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof, is administered daily on days 1 to 15 of each cycle for up to 4 cycles and anti-PD-1 antibody molecule (ii) as described herein is administered at least once per cycle. The Wnt inhibitor can be administered for 4 cycles.

In the present disclosure the term "pharmaceutical combination" refers to a non-fixed combination. The term "non-fixed combination" means that the active ingredients, *e.g.* compound of formula (i), namely 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof and an anti-PD-1 antibody molecule , or a pharmaceutically acceptable salt form, are both administered to a patient as separate entities either simultaneously or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the two compounds in the body of the patient.

The terms "a combination" or "in combination with," it is not intended to imply that the therapy or the therapeutic agents must be administered at the same time and/or formulated for delivery together, although these methods of delivery are within the scope described herein. The therapeutic agents in the combination can be administered concurrently with, prior to, or subsequent to, one or more other additional therapies or therapeutic agents. The therapeutic agents or therapeutic protocol can be administered in any order. In general, each agent will be administered at a dose and/or on a time schedule determined for that agent. In will further be appreciated that the additional therapeutic agent utilized in this combination may be administered

together or separately in different compositions. In general, it is expected that additional therapeutic agents utilized in combination be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salts thereof, that can be used in combination with Wnt inhibitors of the present disclosure, is any anti-PD-1 antibody as disclosed herein. For example, the anti-PD-1 antibody molecule can comprise 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. The anti-PD1 antibody molecule is preferably selected from nivolumab (Opdivo), pembrolizumab (Keytruda), pidilizumab, PDR-001, or a pharmaceutical salt thereof. Most preferably the anti-PD-1 antibody molecule is PDR-001, or a pharmaceutical salt thereof. The anti-PD-1 antibody molecule designated as PDR-001 was described in PCT/CN2016/099494. More particularly the PDR-001 inhibitor, or a pharmaceutically acceptable salt thereof, comprises a heavy chain variable region (VH) comprising a HCDR1, a HCDR2 and a HCDR3 amino acid sequence of BAP049-Clone-E 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.

The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, of the present disclosure comprises, for example, 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.

The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, of the present disclosure comprises, for example, 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.

The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, of the present disclosure comprises, for example, 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.*, 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, or a pharmaceutically acceptable salt thereof, of the present disclosure includes, for example, a heavy chain constant region for an IgG4, *e.g.*, a human IgG4. The human IgG4 includes a substitution at position 228 according to EU numbering (*e.g.*, a Ser to Pro substitution). The anti-PD-1 antibody molecule includes a heavy chain constant region for an IgG1, *e.g.*, a human IgG1. The human IgG1 includes a substitution at position 297 according to EU numbering (*e.g.*, an Asn to Ala substitution). The human IgG1 may also include 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). The human IgG1 also 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). 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.

The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, according to the present disclosure includes, for example, a kappa light chain constant region, *e.g.*, a human kappa light chain constant region. 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.

The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, according to the present disclosure also includes, for example, 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. The human IgG4 includes a substitution at position 228 according to EU numbering (*e.g.*, a Ser to Pro substitution). 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. The human IgG1 may also include a substitution at position 297 according to EU numbering (*e.g.*, an Asn to Ala substitution). 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). 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).

The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, of the present disclosure also includes, for example, 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.

Theanti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, according to the present disclosure 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.

The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, according to the present disclosure includes, for example, 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. 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.

The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, according to the present disclosure includes, for example, 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.

The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, includes, for example, 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. 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.

The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, includes, for example, 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.

The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, includes, for example, 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. 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, or a pharmaceutically acceptable salt thereof, 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. The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, 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).

The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, according to the present disclosure includes, for example, 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.

The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, of the present disclosure includes, for example, 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). The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, may also include any CDR described herein. The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, 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. The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, according to the present disclosure, 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.

The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, of the present disclosure, 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 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.

The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, of the present invention, includes, for example, 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 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.

The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, according to the present disclosure, includes, for example, 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 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.

The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, of the present disclosure, includes all six CDRs according to Kabat *et al.* (*e.g.*, all six CDRs according to the Kabat 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. The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, according to the present disclosure, may include any CDR described herein.

The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, according to the present disclosure, includes, for example at least one, two, or three Chothia hypervariable loops (*e.g.*, at least one, two, or three hypervariable loops according to the Chothia 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.

The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, according to the present disclosure, includes, for example, at least one, two, or three Chothia hypervariable loops (*e.g.*, at least one, two, or three hypervariable loops according to the Chothia 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.

The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, according to the present disclosure, includes, for example, 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 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.

The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, according to the present disclosure, includes, for example, all six hypervariable loops (*e.g.*, all six hypervariable loops according to the Chothia 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. The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, according to the present disclosure may include any hypervariable loop described herein.

The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, according to the present disclosure, includes, for example, 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. J. Mol. Biol.* 1992, 227, 799; Tomlinson *et al. J. Mol. Biol.* 1992, 227:776-798 for descriptions of hypervariable loop canonical structures). These structures can be determined by inspection of the tables described in these references.

The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, according to the present disclosure, may also include, for example, a combination of CDRs or hypervariable loops defined according to the Kabat *et al.* and Chothia *et al.* as described herein in Table 1.

The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, according to the present disclosure, includes, for example, 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 and Chothia definition (*e.g.*, at least one, two, or three CDRs or hypervariable loops according to the Kabat and Chothia 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, or a pharmaceutically acceptable salt thereof, according to the present disclosure, 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. 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, the 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.*

The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, according to the present disclosure, 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 and Chothia definitions (*e.g.*, at least one, two, or three CDRs according to the Kabat and Chothia definitions as set out in Table 1).

The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, according to the present disclosure, includes:

(a) a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence of SEQ ID NO: 4, a VHCDR2 amino acid sequence of SEQ ID NO: 5, and a VHCDR3 amino acid sequence of SEQ ID NO: 3;

and a light chain variable region (VL) comprising a VLCDR1 amino acid sequence of SEQ ID NO: 13, a VLCDR2 amino acid sequence of SEQ ID NO: 14, and a VLCDR3 amino acid sequence of SEQ ID NO: 33;

(b) a VH comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 1; a VHCDR2 amino acid sequence of SEQ ID NO: 2; and a VHCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 10, a VLCDR2 amino acid sequence of SEQ ID NO: 11, and a VLCDR3 amino acid sequence of SEQ ID NO: 32;

(c) a VH comprising a VHCDR1 amino acid sequence of SEQ ID NO: 224, a VHCDR2 amino acid sequence of SEQ ID NO: 5, and a VHCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 13, a VLCDR2 amino acid sequence of SEQ ID NO: 14, and a VLCDR3 amino acid sequence of SEQ ID NO: 33; or

(d) a VH comprising a VHCDR1 amino acid sequence of SEQ ID NO: 224; a VHCDR2 amino acid sequence of SEQ ID NO: 2; and a VHCDR3 amino acid sequence of SEQ ID NO: 3; and a VL comprising a VLCDR1 amino acid sequence of SEQ ID NO: 10, a VLCDR2 amino acid sequence of SEQ ID NO: 11, and a VLCDR3 amino acid sequence of SEQ ID NO: 32.

The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, according to the present disclosure, comprises a heavy chain variable region (VH) comprising a VHCDR1 amino acid sequence chosen from SEQ ID NO: 1, SEQ ID NO: 4, or SEQ ID NO: 224; a VHCDR2 amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 5; and a VHCDR3 amino acid sequence of SEQ ID NO: 3; and a light chain variable region (VL) comprising a VLCDR1 amino acid sequence of SEQ ID NO: 10 or SEQ ID NO: 13, a VLCDR2 amino acid sequence of SEQ ID NO: 11 or SEQ ID NO: 14, and a VLCDR3 amino acid sequence of SEQ ID NO: 32 or SEQ ID NO: 33.

The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, according to the present disclosure, can comprise, for example, 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.

The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, according to the present disclosure, can comprise, for example, 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.

The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, according to the present disclosure, 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.

The anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, according to the present disclosure, 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.

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

The term "antibody molecule" refers to a protein, *e.g.*, an immunoglobulin chain or fragment thereof, comprising at least one immunoglobulin variable domain sequence. The term "antibody molecule" includes, for example, a monoclonal antibody (including a full length antibody

which has an immunoglobulin Fc region). An antibody molecule comprises a full length antibody, or a full length immunoglobulin chain, or an antigen binding or functional fragment of a full length antibody, or a full length immunoglobulin chain. An antibody molecule can also be a multi-specific antibody molecule, *e.g.*, it comprises a plurality of immunoglobulin variable domain sequences, wherein a first immunoglobulin variable domain sequence of the plurality has binding specificity for a first epitope and a second immunoglobulin variable domain sequence of the plurality has binding specificity for a second epitope.

The term "Pharmaceutically acceptable salts" can be formed, for example, as acid addition salts, preferably with organic or inorganic acids. Suitable inorganic acids are, for example, halogen acids, such as hydrochloric acid. Suitable organic acids are, *e.g.*, carboxylic acids or sulfonic acids, such as fumaric acid or methanesulfonic acid. For isolation or purification purposes it is also possible to use pharmaceutically unacceptable salts, for example picrates or perchlorates. For therapeutic use, only pharmaceutically acceptable salts or free compounds are employed (where applicable in the form of pharmaceutical preparations), and these are therefore preferred. Any reference to the free compound herein is to be understood as referring also to the corresponding salt, as appropriate and expedient. The salts of the inhibitors, as described herein, are preferably pharmaceutically acceptable salts; suitable counter-ions forming pharmaceutically acceptable salts are known in the field.

The term "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The term "inhibition" or "inhibitor" includes a reduction in a certain parameter, *e.g.*, an activity, of a given molecule, *e.g.*, an immune checkpoint inhibitor, such as the anti-PD-1 antibody molecule. For example, inhibition of an activity, *e.g.*, a PD-1 or PD-L1 activity, of at least 5%, 10%, 20%, 30%, 40% or more is included by this term. Thus, inhibition need not be 100%.

The term "cancer" refers to a disease characterized by the rapid and uncontrolled growth of aberrant cell proliferation. Cancer cells can spread locally or through the bloodstream and lymphatic system to other parts of the body. Examples of various cancers are, but are not limited to, leukemia, prostate cancer, renal cancer, liver cancer, brain cancer, lymphoma, ovarian cancer, lung cancer, cervical cancer, skin cancer, breast cancer, head and neck squamous cell carcinoma (HNSCC), pancreatic cancer, gastrointestinal cancer, colorectal cancer, triple-negative breast cancer (TNBC), squamous cell cancer of the lung, squamous cell cancer of the esophagus, squamous cell cancer of the cervix, or melanoma. According to the disclosure the particularly amenable disease conditions to be treated with the aforementioned combination are triple-negative breast cancer (TNBC), pancreatic cancer, squamous cell cancer of the lung, squamous cell cancer of the esophagus, squamous cell cancer of the cervix, or melanoma.

The terms "tumor" and "cancer" are used interchangeably herein, *e.g.*, both terms encompass solid and liquid, *e.g.*, diffuse or circulating tumors. In one embodiment, the term "cancer" or "tumor" includes malignant cancers and tumors, as well as advanced cancers and tumors.

The term "treatment" comprises, for example, the therapeutic administration of the combination of a Wnt inhibitor, or a pharmaceutically acceptable salt thereof, and an anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, as described herein to a warm-blooded animal, in particular a human being, in need of such treatment with the aim to cure the

disease or to have an effect on disease regression or on the delay of progression of a disease. The terms "treat", "treating" or "treatment" of any disease or disorder refers to ameliorating the disease or disorder (*e.g.* slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof), to preventing or delaying the onset or development or progression of the disease or disorder.

A Wnt inhibitor, (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-N-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof can be administered daily on days 1 to 15 of each cycle or on days 1 to 8 of each cycle. The Wnt inhibitor, (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-N-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide can be administered up to 4 cycles. The Wnt inhibitor (i) can be administered during 4 cycles. It can also be administered in the first cycle only. Preferably, the Wnt inhibitor (i) is administered during days 1 to 15 of each cycle for up to 4 cycles. Most preferably, the Wnt inhibitor (i) is administered daily on days 1 to 8 of each cycle for up to 4 cycles. The present invention also provides that (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof, is administered during the first cycle only. The present invention also provides that (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof, is administered during four cycles only. The Wnt inhibitor as disclosed herein can be administered once daily or twice daily with a 12-hour gap between two consecutive doses. The combination partner (ii) an anti-PD-1 antibody molecule can continue to be administered for more cycles as long as it is clinically meaningful. In one embodiment, the (ii) anti-PD-1 antibody molecule is administered for up to 4 cycles or for 4 cycles.

The combination partners, as disclosed herein, are administered on the same day or on different days of a cycle. The term "cycle" refers to a specific period of time expressed in days or months that is repeated on a regular schedule. The cycle as disclosed herein is more preferably expressed in days. For example, the cycle can be, but is not limited to, 28 days, 30 days, 60 days, 90 days. Most preferably, the "cycle" as referred to in the present disclosure is 28 days long. Such cycle can be repeated several time (*e.g.* 2 times, 3 times, 4 times, 5 times, etc...), each cycle being the same length and can be repeated as long as it is clinically meaningful, *i.e.* the tumor growth is at least reduced, or controlled, or the tumor shrinks, and the adverse events are tolerable. While one of the combination partners, e.g. the Wnt inhibitor, is administered for up to 4 cycles, the other combination partner can continue to be administered for more cycles. The treatment by administering (i) of the present disclosure is most preferably repeated for up to 4 cycles, particularly 4 cycles. Even though the Wnt inhibitor can be administered for up to 4 cycles, it is contemplated herein that after a period of time - for example, when the compound has been completely eliminated from the body and the Wnt inhibitor that has been administered for up to 4 cycled cease to bring any positive effects, either alone or via enhancement of the effects caused by the anti-PD-1 antibody molecule, the Wnt inhibitor can again be administered for another row of up to 4 cycles. The period between the first row of up to 4 cycles (including only 1 cycle or only 4 cycles) and the second or later row of up to 4 cycles has to be long enough to prevent any accumulation of effects brought by inhibition of Wnt pathway, such as reduction of bone density.

The Wnt inhibitor (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof, can be administered orally or intravenously, most preferably orally, at a daily dose of 2.5 mg/day, 5 mg/day, 7.5 mg/day, 10 mg/day, 20 mg/day, 40 mg/day, 80 mg/day, 120 mg/day, or 180 mg/day. Preferably, the daily dose is 2.5 mg/day, 5 mg/day, or 10 mg/day. Most preferably, the daily dose is 10 mg/day.

According to the present disclosure (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof, can be administered orally, for example, in a pharmaceutical composition together with an inert diluent or carrier.

In accordance with the present disclosure the anti-PD-1 antibody molecule (ii), or a pharmaceutically acceptable salt thereof, selected from nivolumab (Opdivo), pembrolizumab (Keytruda), pidilizumab, PDR-001, or a pharmaceutical salt thereof, can be used in the treatment of cancer, and is administered every two weeks or every four weeks in a cycle. Most preferably the anti-PD-1 antibody molecule PDR-001 (ii), or a pharmaceutically acceptable salt thereof, as described herein, used in the treatment of cancer. Most preferably PDR-001 (ii) is administered every four weeks. PDR-001 is administered by injection (*e.g.* subcutaneously or intravenously) at a dose of 300-400 mg/day. Preferably, the anti-PD-1 antibody molecule PDR-001, or a pharmaceutically acceptable salt thereof, is administered intravenously in a single dose of 300 to 400 mg/day. Most preferably, the anti-PD-1 antibody molecule PDR-001 (ii), or a pharmaceutically acceptable salt thereof, is administered in a single dose of 400 mg/day. Most preferably, the anti-PD-1 antibody molecule PDR-001, or a pharmaceutically acceptable salt thereof, is administered at a dose of 400 mg/day every four weeks. The dose can be administered in a single bolus or in several divided doses.

Specifically, the dosing schedule can vary from 2.5 mg/day, 5 mg/day or 10 mg/day of Wnt inhibitor of formula (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof (on days 1-15 or on days 1-8 of the first cycle only or 4 cycles only or of every cycle for up to 4 cycles) and from 300 mg/day to 400 mg/day of anti-PD-1 antibody molecule (ii), or a pharmaceutically acceptable salt thereof, every two or four weeks. For example, according to the present disclosure, 2.5 mg/day of (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof, is administered on days 1-8 or on days 1-15 and anti-PD-1 antibody molecule (ii), or a pharmaceutically acceptable salt thereof, is administered once every 4 weeks for 4 cycles or up to 4 cycles at a dose of 400 mg/day. Another example, according to the present disclosure, consists of administering 5 mg/day of (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof, on days 1-8 or on days 1-15 and administering anti-PD-1 antibody molecule (ii), or a pharmaceutically acceptable salt thereof, once every 4 weeks for 4 cycles or up to 4 cycles at a dose of 400 mg/day. Yet another example, according to the present disclosure, provides the administration of 10 mg/day of (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof on days 1-8 or on days 1-15 and anti-PD-1 antibody molecule (ii), or a pharmaceutically acceptable salt thereof, is administered once every 4 weeks for 4 cycles or up to 4 cycles at a dose of 400 mg/day.

Another example, according to the present disclosure, provides the administration of 2.5 mg/day of (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof, only during cycle 1 and the administration of anti-PD-1 antibody molecule (ii), or a pharmaceutically acceptable salt thereof, every 4 weeks, at a dose of 400 mg/day. Another example, according to the present disclosure, provides administering 5 mg/day of (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof, during cycle 1 only and administering an anti-PD-1 antibody molecule (ii), or a pharmaceutically acceptable salt thereof, every 4 weeks, at a dose of 400 mg/day. Yet another example, according to the present disclosure, provides the administration of 10 mg/day of (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a

pharmaceutically acceptable salt thereof only during cycle 1 and the administration of anti-PD-1 antibody molecule (ii), or a pharmaceutically acceptable salt thereof, every 4 weeks, at a dose of 400 mg/day.

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 300 to 400 mg/day. For intravenous injection or 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., antibody or antibody portion) in the required amount in an appropriate solvent with one or a combination of ingredients 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 ingredients. 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.

It would be understood that the route and/or mode of administration will vary depending upon the desired results. For example, 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 (*e.g.*, Sustained and Controlled Release Drug Delivery Systems, J. R. Robinson, ed., Marcel Dekker, Inc., New York, 1978).

Equally, (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof, in combination with anti-PD-1 antibody molecule (ii), or a pharmaceutically acceptable salt, can be used for the manufacture of a medicament for the treatment of cancer.

By the same token, the present disclosure also provides a method for the treatment of cancer, comprising administering an effective amount of the combination partners (*e.g.* (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof and anti-PD-1 antibody molecule (ii), or a pharmaceutically acceptable salt thereof) to a patient in need thereof.

The term "patient" or "subject" refers to a warm-blooded animal. In a most preferred embodiment, the subject or patient is human. It may be a human who has been diagnosed and is in the need of treatment for a disease or disorder, as disclosed herein.

When used for the manufacture of a medicament for the treatment of cancer or in a method of treating a cancer in a patient in need thereof, (i) and (ii) can be used in doses and dosing schedules as explained above.

Most preferably the combination comprises the Wnt inhibitor (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof, and anti-PD-1 antibody moleculePDR-001(ii) , or a pharmaceutically acceptable salt thereof. Both combination partners (i) and (ii) can be administered according to the doing schedule as described herein. For example (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof, can be administered daily on days 1 to 15 or on days 1 to 8 of each cycle for up to 4 cycles, for example for 4 cycles or only during the first cycle. The PDR-001 (ii), or a pharmaceutically acceptable salt thereof, is administered at least once per cycle. For example, (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof is administered in this specific combination at a dose of 2.5 mg/day, 5 mg/day, 7.5 mg/day, 10 mg/day, 20 mg/day, 40 mg/day, 80 mg/day, 120 mg/day, 180 mg/day. Preferably the dose is 2.5 mg/day, 5 mg/day, or 10 mg/day. Most preferably the dose is 10 mg/day. PDR-001 inhibitor (ii), or a pharmaceutically acceptable salt thereof, is administered in a single dose of 300-400 mg/day, most preferably a dose of 400 mg/day.

By the same token, the present disclosure also provides a method for the treatment of cancer, comprising administering an effective amount of the combination partners (*e.g.* (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof and anti-PD-1 antibody molecule (ii), or a pharmaceutically acceptable salt thereof) to a patient in need thereof.

The combination partners (i) and (ii), as described herein, can be synergistically active, while causing less side effects caused by the Wnt signaling pathway inhibition such as reduced bone density.

The term "effective amount" or "therapeutically effective amount" of the combination partners of the present disclosure, refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result. A therapeutically effective amount of the combination partners may vary according to factors such as the disease state, age, sex, and weight of the individual. A therapeutically effective amount is also one in which any toxic or detrimental effects of the combination, as described herein, is outweighed by the therapeutically beneficial effects. A "therapeutically effective dosage" preferably inhibits a measurable parameter, *e.g.*, tumor growth rate by at least about 20%, more preferably by at least about 40%, even more preferably by at least about 60%, and still more preferably by at least about 80% relative to untreated subjects.

EXAMPLES

Example 1:

NanoString measures gene expression for a selected panel of up to about 1000 genes. This is executed using uniquely barcoded probes that hybridize directly to target RNAs (ribonucleic acids). The RNA-probe hybrids are then run out on a gel to linearize the barcodes. These barcodes are then counted and then normalized using an internally developed pipeline.

Tumor biopsies were performed at screening and between days 8 and 28 on treatment with the Wnt inhibitor of formula (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide. Tumors were fixed in formalin and embedded in paraffin (FFPE) or directly placed in RNA Later. These samples were transferred to Genoptix where RNA was isolated for real time qPCR

analyses of the pharmacodynamics (PD) marker AXIN2. Remnant RNA was transferred to the assay research laboratory (ARL) where gene expression was profiled using (2016) NanoString pan-cancer immune profiling panel as well as a custom design panel of immune-related genes. Gene expression was normalized using methods recommended by NanoString, with the exception that samples were normalized within specific indications (e.g. melanoma or pancreatic cancer samples were normalized separately) and housekeeping genes were selected using the geNorm stability metric [PMID: 12184808]. Certain genes overlapped between both panels, which we used to assess variability and other quality control parameters. QC metrics imposed by the NanoString normalization procedure and manual review of hematoxylin and eosin (H&E) stained adjacent core biopsies narrowed down the cohort to 11 paired samples. A further two samples were removed, as they were found to be outliers in principle component analyses leaving 9 paired samples for the analysis cohort. The count data described herein was normalized according to the methods recommended by NanoString with one exception, namely that the samples were normalized within the specific indications as described herein and approximately 40 housekeeping genes (defined on the NanoString website for their commercially available cancer immune panel, 2016) were used for biological normalization across samples.

Gene signatures were used before to probe the data for phenotypic changes in the tumor-immune microenvironment. It has been previously shown that in genetically engineered mice with activated WNT signaling the dendritic cells and T-cells in the tumor microenvironment are inhibited; however, it has not been shown that this effect is reversible. Therefore, our objective was to use gene expression analyses in samples from the patients treated with the Wnt inhibitor to determine the extent to which the inhibitory effects of WNT signaling in the tumor on the proximal immune cells can be reversed by pharmacological inhibition of the WNT pathway.

To understand whether the Compound of Formula (I) has effects on the tumor immune microenvironment, we looked at the relationships between immune gene expression and the PD marker AXIN2. By using this marker, we can understand the extent to which the WNT pathway has been inhibited in a given tumor. Instead of focusing on individual genes, we used the geometric average expression of sets of genes (gene signatures) that describe a particular pathway or cellular function. One gene signature is a chemokine signature that is associated with recruitment of CD8+ T-cells [PMID: 19293190] and other signature is associated with activated CD103+ dendritic cells [PMID: 25970248]. Not every subject presented with a strong inhibition of the WNT pathway as evidenced by the fold-changes observed in AXIN2 expression. Interestingly, there appears to be fairly linear relationship between AXIN2 inhibition and increased expression of the chemokine signature as well as the dendritic cell signature (see below). We observed that pharmacological inhibition of the WNT pathway resulted in concomitant stimulation of the surrounding dendritic cell population. These dendritic cells, when stimulated, function to recruit T-cells to the tumor. Importantly, this observation was made after 15 days of exposure to the Wnt inhibitor, which supported that intermittent dosing of the Compound of Formula (I) could be combined with a checkpoint inhibitor to stimulate an anti-tumor immune response in the context of tumors that previously had lacked immune infiltrate.

Gene signatures allowed us to observe a strong correlation across many samples in a given indication as well as biological relatedness even with a small sample size. The samples of the Wnt inhibitor treated patients had T-cell signatures expressed and this across patients and treatment conditions such as different dose levels (Figure 2). Figure 2 depicts the strong correlation between

CD3 expression at screening and the T-cells levels present in summary visits for the 9 paired subjects in this analysis.

One of the gene signatures used within our study was the T-cell signature as shown in Figure 3.

Modulation on the Wnt pathway with the Wnt inhibitor of formula (i) was considered along with the way such Wnt inhibitor, namely (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide affected the tumor-immune microenvironment (Figure 4). Changes in AXIN2 expression, which were measured by using the same exact RNA samples, were used as a measure of how Wnt inhibitor (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide affected the WNT pathway. The changes in AXIN2 expression were fitted by linear model to immune signature changes.

Each graph in Figure 4, depicts as follows: the Y-axis depicts the change in a given immune signature after exposure to Wnt inhibitor (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide and the X-axis provides the change in AXIN2. Both are in log2 scale. A positive value indicates an increase in the average expression of the genes in a given signature or in AXIN2. First, a weak relationship between a type I interferon signature and AXIN2 inhibition was observed. Second, a relationship between interferon gamma (or type II interferon) and AXIN2 inhibition was observed. Interferon gamma is typically expressed by CD8+ T-cells. Finally, a modest inverse relationship between AXIN2 inhibition and mast cell and T-regulation (T-reg) signatures was observed. Both of these cell types have been observed to be immuno-suppressive in the tumor-immune microenvironment. Interestingly, there appears to be fairly linear relationships between AXIN2 inhibition and increased expression of the chemokine signature (Figure 6) as well as the dendritic cell signature (Figure 5). This is the first observation that pharmacological inhibition of the WNT pathway results in concomitant stimulation of the surrounding dendritic cell population.

Then some of the specific genes that were identified to be modulated in CD103+ dendritic cells in response to increased WNT signaling (Spranger *et al,. Nature* 2015, 523, 231) were used to create a specific signature of sorts and model this against AXIN2 inhibition (Figure 5). In Figure 5, each point represents a pair of samples from one patient. Plotted on the X-axis is the log2 fold-change in AXIN2 expression in the tumor from screening to on-treatment. Plotted on the Y-axis is the log2 fold-change in expression of the dendritic cell signature in the tumor from screening to on-treatment. The genes included in the dendritic signature are: BATF3, ITGAE, IRF8, CCR5, CCL3, CCL4, CXCL1. The trend line is a linear estimate made by regression of the data points using a robust linear model. The numbers next to each point represent the number of days between the start of treatment and the on-treatment biopsy. According to the Spranger *et al* (*Nature* 2015, 523, 231) the genes that are Wnt-responsive are BATF3, ITGAE, IRF8, CCR5, CCL3, CCL4, CXCL1. Here, similar to some of the other signatures, a positive relationship between AXIN2 inhibition and increased expression of genes associated with activation of CD103+ dendritic cells were observed. This is relevant because this subtype of dendritic cell is important for licensing and activating T cells for an anti-tumoral response.

These data suggest that the Wnt inhibitor (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof, is affecting the tumor-immune microenvironment by increasing immune cell infiltrates and alleviating the inhibition of CD103+ dendritic cells. These cells are important for activation and recruitment of cytotoxic T cells that drive the anti-tumor immune response. This supports adding an anti PD-1 antibody molecule

(also referred to as PD-1 inhibitor), which alleviates the inhibition of T cells, to synergize with the effect of a Wnt inhibitor on the dendritic cells.

Another gene signature that was discovered to be strongly correlated with the recruitment of CD8+ T cells into the tumor was also investigated. This gene signature is made up primarily of chemokines and has some overlap with the Spranger *et al* (*Nature* 2015, 523, 231) dendritic cell signature mentioned above. These chemokines have been shown to recruit CD8+ T cells in a dose-dependent manner. The chemokines that correlate with the CD8+ T-cell recruitment are CCL2, CCL3, CCL4, CCL 5, CXCL9 and CXCL10. When we measured in patient samples the average expression of the genes in this chemokine signature and compared them to AXIN2 inhibition, again we observed a linear relationship between the extent to which the WNT pathway was inhibited and the expression of this gene signature (Figure 6). In Figure 6, each point represents a pair of samples from one patient. Plotted on the X-axis is the log2 fold-change in AXIN2 expression in the tumor from screening to on-treatment. Plotted on the Y-axis is the log2 fold-change in expression of the chemokine signature in the tumor from screening to on-treatment. The genes included in the chemokine signature are: CCL2, CCL3, CCL4, CCL5, CXCL9, and CXCL10. The trend line is a linear estimate made by regression of the data points using a robust linear model. The numbers next to each point represent the number of days between the start of treatment and the on-treatment biopsy. As shown in Figure 6, the dendritic cells, when stimulated, function to recruit T-cells to the tumor. Importantly, this observation was made after about 15 days of exposure to WNT inhibitor (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof, which suggests that intermittent dosing of WNT inhibitor (i) can be combined with a checkpoint inhibitor to stimulate an anti-tumor immune response in the context of tumors that previously lacked immune infiltrate.

It was found that the inverse correlation between a T-cell and a Wnt/CTNNB1 signature in the Cancer Genome Atlas (TCGA) was consistent across squamous cell cancers, irrespective of the tissue of origin of the cancer cell (Sanger et al., 2015). The inverse correlation was also strong in basal-like breast cancers, which is the gene-expression based subtype most closely associated with TNBC (Bertucci et al., 2008). Figure 7 illustrates the correlation in several different types of cancer cells. The Wnt1 signature consists of the six CTNNB1 targets: EFNB3, APC2, HNF1A, TCF12, and VEGFA.

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	EVQLVQSGAEVKKPGESLRISCKGSGYTFT TYWMHWVRQATGQGLEWMGNIYPGTGGS NFDEKFKNRVTITADKSTSTAYMELSSLRSE DTAVYYCTRWTTGTGAYWGQGTTVTVSS
SEQ ID NO: 95	DNA VH	GAGGTGCAGCTGGTGCAGTCAGGCGCCG AAGTGAAGAAGCCCGGCGAGTCACTGAG AATTAGCTGTAAAGGTTCAGGCTACACCT TCACTACCTACTGGATGCACTGGGTCCGC CAGGCTACCGGTCAAGGCCTCGAGTGGA TGGGTAATATCTACCCCGGCACCGGCGG CTCTAACTTCGACGAGAAGTTTAAGAATA GAGTGACTATCACCGCCGATAAGTCTACT AGCACCGCCTATATGGAACTGTCTAGCCT GAGATCAGAGGACACCGCCGTCTACTACT GCACTAGGTGGACTACCGGCACAGGCGC CTACTGGGGTCAAGGCACTACCGTGACC GTGTCTAGC
SEQ ID NO: 91	HC	EVQLVQSGAEVKKPGESLRISCKGSGYTFT TYWMHWVRQATGQGLEWMGNIYPGTGGS NFDEKFKNRVTITADKSTSTAYMELSSLRSE DTAVYYCTRWTTGTGAYWGQGTTVTVSSA STKGPSVFPLAPCSRSTSESTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSSLGTKTYTCNVDHKPSN TKVDKRVESKYGPPCPPCPAPEFLGGPSVF LFPPKPKDTLMISRTPEVTCVVVDVSQEDP EVQFNWYVDGVEVHNAKTKPREEQFNSTY RVVSVLTVLHQDWLNGKEYKCKVSNKGLP SSIEKTISKAKGQPREPQVYTLPPSQEEMTK NQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSRLTVDKSRWQEG NVFSCSVMHEALHNHYTQKSLSLSLG
SEQ ID NO: 96	DNA HC	GAGGTGCAGCTGGTGCAGTCAGGCGCCG AAGTGAAGAAGCCCGGCGAGTCACTGAG AATTAGCTGTAAAGGTTCAGGCTACACCT TCACTACCTACTGGATGCACTGGGTCCGC CAGGCTACCGGTCAAGGCCTCGAGTGGA TGGGTAATATCTACCCCGGCACCGGCGG CTCTAACTTCGACGAGAAGTTTAAGAATA GAGTGACTATCACCGCCGATAAGTCTACT AGCACCGCCTATATGGAACTGTCTAGCCT GAGATCAGAGGACACCGCCGTCTACTACT GCACTAGGTGGACTACCGGCACAGGCGC CTACTGGGGTCAAGGCACTACCGTGACC GTGTCTAGCGCTAGCACTAAGGGCCCGT CCGTGTTCCCCCTGGCACCTTGTAGCCG

		GAGCACTAGCGAATCCACCGCTGCCCTC GGCTGCCTGGTCAAGGATTACTTCCCGG AGCCCGTGACCGTGTCCTGGAACAGCGG AGCCCTGACCTCCGGAGTGCACACCTTC CCCGCTGTGCTGCAGAGCTCCGGGCTGT ACTCGCTGTCGTCGGTGGTCACGGTGCC TTCATCTAGCCTGGGTACCAAGACCTACA CTTGCAACGTGGACCACAAGCCTTCCAAC ACTAAGGTGGACAAGCGCGTCGAATCGA AGTACGGCCCACCGTGCCCGCCTTGTCC CGCGCCGGAGTTCCTCGGCGGTCCCTCG GTCTTTCTGTTCCCACCGAAGCCCAAGGA CACTTTGATGATTTCCCGCACCCCTGAAG TGACATGCGTGGTCGTGGACGTGTCACA GGAAGATCCGGAGGTGCAGTTCAATTGG TACGTGGATGGCGTCGAGGTGCACAACG CCAAAACCAAGCCGAGGGAGGAGCAGTT CAACTCCACTTACCGCGTCGTGTCCGTGC TGACGGTGCTGCATCAGGACTGGCTGAA CGGGAAGGAGTACAAGTGCAAAGTGTCC AACAAGGGACTTCCTAGCTCAATCGAAAA GACCATCTCGAAAGCCAAGGGACAGCCC CGGGAACCCCAAGTGTATACCCTGCCAC CGAGCCAGGAAGAAATGACTAAGAACCAA GTCTCATTGACTTGCCTTGTGAAGGGCTT CTACCCATCGGATATCGCCGTGGAATGG GAGTCCAACGGCCAGCCGGAAAACAACT ACAAGACCACCCCTCCGGTGCTGGACTC AGACGGATCCTTCTTCCTCTACTCGCGGC TGACCGTGGATAAGAGCAGATGGCAGGA GGGAAATGTGTTCAGCTGTTCTGTGATGC ATGAAGCCCTGCACAACCACTACACTCAG AAGTCCCTGTCCCTCTCCCTGGGA
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	EIVLTQSPATLSLSPGERATLSCKSSQSLLD SGNQKNFLTWYQQKPGKAPKLLIYWASTR ESGVPSRFSGSGSGTDFTFTISSLQPEDIAT YYCQNDYSYPYTFGQGTKVEIK

SEQ ID NO: 97	DNA VL	GAGATCGTCCTGACTCAGTCACCCGCTAC CCTGAGCCTGAGCCCTGGCGAGCGGGCT ACACTGAGCTGTAAATCTAGTCAGTCACT GCTGGATAGCGGTAATCAGAAGAACTTCC TGACCTGGTATCAGCAGAAGCCCGGTAAA GCCCCTAAGCTGCTGATCTACTGGGCCTC TACTAGAGAATCAGGCGTGCCCTCTAGGT TTAGCGGTAGCGGTAGTGGCACCGACTT CACCTTCACTATCTCTAGCCTGCAGCCCG AGGATATCGCTACCTACTACTGTCAGAAC GACTATAGCTACCCCTACACCTTCGGTCA AGGCACTAAGGTCGAGATTAAG
SEQ ID NO: 56	LC	EIVLTQSPATLSLSPGERATLSCKSSQSLLD SGNQKNFLTWYQQKPGKAPKLLIYWASTR ESGVPSRFSGSGSGTDFTFTISSLQPEDIAT YYCQNDYSYPYTFGQGTKVEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAKV QWKVDNALQSGNSQESVTEQDSKDSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGEC
SEQ ID NO: 98	DNA LC	GAGATCGTCCTGACTCAGTCACCCGCTAC CCTGAGCCTGAGCCCTGGCGAGCGGGCT ACACTGAGCTGTAAATCTAGTCAGTCACT GCTGGATAGCGGTAATCAGAAGAACTTCC TGACCTGGTATCAGCAGAAGCCCGGTAAA GCCCCTAAGCTGCTGATCTACTGGGCCTC TACTAGAGAATCAGGCGTGCCCTCTAGGT TTAGCGGTAGCGGTAGTGGCACCGACTT CACCTTCACTATCTCTAGCCTGCAGCCCG AGGATATCGCTACCTACTACTGTCAGAAC GACTATAGCTACCCCTACACCTTCGGTCA AGGCACTAAGGTCGAGATTAAGCGTACG GTGGCCGCTCCCAGCGTGTTCATCTTCCC CCCCAGCGACGAGCAGCTGAAGAGCGGC ACCGCCAGCGTGGTGTGCCTGCTGAACA ACTTCTACCCCCGGGAGGCCAAGGTGCA GTGGAAGGTGGACAACGCCCTGCAGAGC GGCAACAGCCAGGAGAGCGTCACCGAGC AGGACAGCAAGGACTCCACCTACAGCCT GAGCAGCACCCTGACCCTGAGCAAGGCC GACTACGAGAAGCATAAGGTGTACGCCT GCGAGGTGACCCACCAGGGCCTGTCCAG CCCCGTGACCAAGAGCTTCAACAGGGGC GAGTGC
SEQ ID NO: 92	DNA HC	GAAGTGCAGCTGGTGCAGTCTGGCGCCG AAGTGAAGAAGCCTGGCGAGTCCCTGCG GATCTCCTGCAAGGGCTCTGGCTACACCT TCACCACCTACTGGATGCACTGGGTGCG ACAGGCTACCGGCCAGGGCCTGGAATGG ATGGGCAACATCTATCCTGGCACCGGCG

		GCTCCAACTTCGACGAGAAGTTCAAGAAC AGAGTGACCATCACCGCCGACAAGTCCA CCTCCACCGCCTACATGGAACTGTCCTCC CTGAGATCCGAGGACACCGCCGTGTACT ACTGCACCCGGTGGACAACCGGCACAGG CGCTTATTGGGGCCAGGGCACCACAGTG ACCGTGTCCTCTGCTTCTACCAAGGGGCC CAGCGTGTTCCCCCTGGCCCCCTGCTCC AGAAGCACCAGCGAGAGCACAGCCGCCC TGGGCTGCCTGGTGAAGGACTACTTCCC CGAGCCCGTGACCGTGTCCTGGAACAGC GGAGCCCTGACCAGCGGCGTGCACACCT TCCCCGCCGTGCTGCAGAGCAGCGGCCT GTACAGCCTGAGCAGCGTGGTGACCGTG CCCAGCAGCAGCCTGGGCACCAAGACCT ACACCTGTAACGTGGACCACAAGCCCAG CAACACCAAGGTGGACAAGAGGGTGGAG AGCAAGTACGGCCCACCCTGCCCCCCCT GCCCAGCCCCCGAGTTCCTGGGCGGACC CAGCGTGTTCCTGTTCCCCCCCAAGCCCA AGGACACCCTGATGATCAGCAGAACCCC CGAGGTGACCTGTGTGGTGGTGGACGTG TCCCAGGAGGACCCCGAGGTCCAGTTCA ACTGGTACGTGGACGGCGTGGAGGTGCA CAACGCCAAGACCAAGCCCAGAGAGGAG CAGTTTAACAGCACCTACCGGGTGGTGTC CGTGCTGACCGTGCTGCACCAGGACTGG CTGAACGGCAAAGAGTACAAGTGTAAGGT CTCCAACAAGGGCCTGCCAAGCAGCATC GAAAAGACCATCAGCAAGGCCAAGGGCC AGCCTAGAGAGCCCCAGGTCTACACCCT GCCACCCAGCCAAGAGGAGATGACCAAG AACCAGGTGTCCCTGACCTGTCTGGTGAA GGGCTTCTACCCAAGCGACATCGCCGTG GAGTGGGAGAGCAACGGCCAGCCCGAGA ACAACTACAAGACCACCCCCCCAGTGCTG GACAGCGACGGCAGCTTCTTCCTGTACA GCAGGCTGACCGTGGACAAGTCCAGATG GCAGGAGGGCAACGTCTTTAGCTGCTCC GTGATGCACGAGGCCCTGCACAACCACT ACACCCAGAAGAGCCTGAGCCTGTCCCT GGGC
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	EIVLTQSPATLSLSPGERATLSCKSSQSLLD SGNQKNFLTWYQQKPGQAPRLLIYWASTR ESGVPSRFSGSGSGTDFTFTISSLEAEDAA TYYCQNDYSYPYTFGQGTKVEIK
SEQ ID NO: 106	DNA VL	GAGATCGTCCTGACTCAGTCACCCGCTAC CCTGAGCCTGAGCCCTGGCGAGCGGGCT ACACTGAGCTGTAAATCTAGTCAGTCACT GCTGGATAGCGGTAATCAGAAGAACTTCC TGACCTGGTATCAGCAGAAGCCCGGTCA AGCCCCTAGACTGCTGATCTACTGGGCCT CTACTAGAGAATCAGGCGTGCCCTCTAGG TTTAGCGGTAGCGGTAGTGGCACCGACTT CACCTTCACTATCTCTAGCCTGGAAGCCG AGGACGCCGCTACCTACTACTGTCAGAAC GACTATAGCTACCCCTACACCTTCGGTCA AGGCACTAAGGTCGAGATTAAG
SEQ ID NO: 72	LC	EIVLTQSPATLSLSPGERATLSCKSSQSLLD SGNQKNFLTWYQQKPGQAPRLLIYWASTR ESGVPSRFSGSGSGTDFTFTISSLEAEDAA TYYCQNDYSYPYTFGQGTKVEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYS LSSTLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGEC
SEQ ID NO: 107	DNA LC	GAGATCGTCCTGACTCAGTCACCCGCTAC CCTGAGCCTGAGCCCTGGCGAGCGGGCT ACACTGAGCTGTAAATCTAGTCAGTCACT GCTGGATAGCGGTAATCAGAAGAACTTCC TGACCTGGTATCAGCAGAAGCCCGGTCA AGCCCCTAGACTGCTGATCTACTGGGCCT CTACTAGAGAATCAGGCGTGCCCTCTAGG TTTAGCGGTAGCGGTAGTGGCACCGACTT CACCTTCACTATCTCTAGCCTGGAAGCCG AGGACGCCGCTACCTACTACTGTCAGAAC GACTATAGCTACCCCTACACCTTCGGTCA AGGCACTAAGGTCGAGATTAAGCGTACG GTGGCCGCTCCCAGCGTGTTCATCTTCCC CCCCAGCGACGAGCAGCTGAAGAGCGGC ACCGCCAGCGTGGTGTGCCTGCTGAACA ACTTCTACCCCCGGGAGGCCAAGGTGCA GTGGAAGGTGGACAACGCCCTGCAGAGC GGCAACAGCCAGGAGAGCGTCACCGAGC AGGACAGCAAGGACTCCACCTACAGCCT GAGCAGCACCCTGACCCTGAGCAAGGCC GACTACGAGAAGCATAAGGTGTACGCCT GCGAGGTGACCCACCAGGGCCTGTCCAG

		CCCCGTGACCAAGAGCTTCAACAGGGGC GAGTGC
BAP049-Clone-B HC		
SEQ ID NO: 133 (Kabat)	HCDR1	ACCTACTGGATGCAC
SEQ ID NO: 134 (Kabat)	HCDR2	AATATCTACCCCGGCACCGGCGGCTCTAA CTTCGACGAGAAGTTTAAGAAT
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	AAATCTAGTCAGTCACTGCTGGATAGCGG TAATCAGAAGAACTTCCTGACC
SEQ ID NO: 139 (Kabat)	LCDR2	TGGGCCTCTACTAGAGAATCA
SEQ ID NO: 140 (Kabat)	LCDR3	CAGAACGACTATAGCTACCCCTACACC
SEQ ID NO: 141 (Chothia)	LCDR1	AGTCAGTCACTGCTGGATAGCGGTAATCA GAAGAACTTC
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	AATATCTACCCCGGCACCGGCGGCTCTAA CTTCGACGAGAAGTTTAAGAAT
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	AAATCTAGTCAGTCACTGCTGGATAGCGG TAATCAGAAGAACTTCCTGACC
SEQ ID NO: 139 (Kabat)	LCDR2	TGGGCCTCTACTAGAGAATCA

SEQ ID NO: 140 (Kabat)	LCDR3	CAGAACGACTATAGCTACCCCTACACC
SEQ ID NO: 141 (Chothia)	LCDR1	AGTCAGTCACTGCTGGATAGCGGTAATCA GAAGAACTTC
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)	EVQLVQSGAEVKKPGESLRISCKGS (SEQ ID NO: 147)	GAAGTGCAGCTGGTGCAGTCTGGAGCAGA GGTGAAAAAGCCCGGGGAGTCTCTGAGGAT CTCCTGTAAGGGTTCT (SEQ ID NO: 148) GAAGTGCAGCTGGTGCAGTCTGGCGCCGA AGTGAAGAAGCCTGGCGAGTCCCTGCGGAT CTCCTGCAAGGGCTCT (SEQ ID NO: 149) GAGGTGCAGCTGGTGCAGTCAGGCGCCGA AGTGAAGAAGCCCGGCGAGTCACTGAGAAT TAGCTGTAAAGGTTCA (SEQ ID NO: 150)
VHFW1 (type b)	QVQLVQSGAEVKKPGASVKVSCKA S (SEQ ID NO: 151)	CAGGTTCAGCTGGTGCAGTCTGGAGCTGAG GTGAAGAAGCCTGGGGCCTCAGTGAAGGTC TCCTGCAAGGCTTCT (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) TGGATCCGGCAGTCCCCCTCTAGGGGCCTG GAATGGCTGGGC (SEQ ID NO: 159)
VHFW2 (type c)	WVRQAPGQGLEWMG (SEQ ID NO: 160)	TGGGTGCGACAGGCCCCTGGACAAGGGCT TGAGTGGATGGGT (SEQ ID NO: 161)
VHFW3 (type a)	RVTITADKSTSTAYMELSSLRSEDTA VYYCTR (SEQ ID NO: 162)	AGAGTCACGATTACCGCGGACAAATCCACG AGCACAGCCTACATGGAGCTGAGCAGCCTG AGATCTGAGGACACGGCCGTGTATTACTGT ACAAGA (SEQ ID NO: 163)

		AGAGTGACCATCACCGCCGACAAGTCCACC TCCACCGCCTACATGGAACTGTCCTCCCTG AGATCCGAGGACACCGCCGTGTACTACTGC ACCCGG (SEQ ID NO: 164) AGAGTGACTATCACCGCCGATAAGTCTACTA GCACCGCCTATATGGAACTGTCTAGCCTGA GATCAGAGGACACCGCCGTCTACTACTGCA CTAGG (SEQ ID NO: 165)
VHFW3 (type b)	RFTISRDNSKNTLYLQMNSLRAEDT AVYYCTR (SEQ ID NO: 166)	AGATTCACCATCTCCAGAGACAATTCCAAGA ACACGCTGTATCTTCAAATGAACAGCCTGAG AGCCGAGGACACGGCCGTGTATTACTGTAC AAGA (SEQ ID NO: 167) AGGTTCACCATCTCCCGGGACAACTCCAAG AACACCCTGTACCTGCAGATGAACTCCCTG CGGGCCGAGGACACCGCCGTGTACTACTGT ACCAGA (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)	GAAATTGTGCTGACTCAGTCTCCAGACTTTC AGTCTGTGACTCCAAAGGAGAAAGTCACCA TCACCTGC (SEQ ID NO: 175) GAGATCGTGCTGACCCAGTCCCCCGACTTC CAGTCCGTGACCCCCAAAGAAAAAGTGACC ATCACATGC (SEQ ID NO: 176)
VLFW1 (type b)	EIVLTQSPATLSLSPGERATLSC (SEQ ID NO: 177)	GAAATTGTGTTGACACAGTCTCCAGCCACC CTGTCTTTGTCTCCAGGGGAAAGAGCCACC CTCTCCTGC (SEQ ID NO: 178) GAGATCGTGCTGACCCAGTCCCCTGCCACC CTGTCACTGTCTCCAGGCGAGAGAGCTACC CTGTCCTGC (SEQ ID NO: 179) GAGATCGTCCTGACTCAGTCACCCGCTACC CTGAGCCTGAGCCCTGGCGAGCGGGCTAC ACTGAGCTGT (SEQ ID NO: 180)
VLFW1 (type c)	DIVMTQTPLSLPVTPGEPASISC (SEQ ID NO: 181)	GATATTGTGATGACCCAGACTCCACTCTCCC TGCCCGTCACCCCTGGAGAGCCGGCCTCC

		ATCTCCTGC (SEQ ID NO: 182)
VLFW1 (type d)	DVVMTQSPLSLPVTLGQPASISC (SEQ ID NO: 183)	GATGTTGTGATGACTCAGTCTCCACTCTCCC TGCCCGTCACCCTTGGACAGCCGGCCTCCA TCTCCTGC (SEQ ID NO: 184)
VLFW1 (type e)	DIQMTQSPSSLSASVGDRVTITC (SEQ ID NO: 185)	GACATCCAGATGACCCAGTCTCCATCCTCC CTGTCTGCATCTGTAGGAGACAGAGTCACC ATCACTTGC (SEQ ID NO: 186)
VLFW2 (type a)	WYQQKPGQAPRLLIY (SEQ ID NO: 187)	TGGTACCAGCAGAAACCTGGCCAGGCTCCC AGGCTCCTCATCTAT (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)	TGGTACCTGCAGAAGCCAGGGCAGTCTCCA CAGCTCCTGATCTAT (SEQ ID NO: 195)
VLFW3 (type a)	GVPSRFSGSGSGTDFTFTISSLEAE DAATYYC (SEQ ID NO: 196)	GGGGTCCCCTCGAGGTTCAGTGGCAGTGG ATCTGGGACAGATTTCACCTTTACCATCAGT AGCCTGGAAGCTGAAGATGCTGCAACATAT TACTGT (SEQ ID NO: 197) GGCGTGCCCTCTAGATTCTCCGGCTCCGGC TCTGGCACCGACTTTACCTTCACCATCTCCA GCCTGGAAGCCGAGGACGCCGCCACCTAC TACTGC (SEQ ID NO: 198) GGCGTGCCCTCTAGGTTTAGCGGTAGCGGT AGTGGCACCGACTTCACCTTCACTATCTCTA GCCTGGAAGCCGAGGACGCCGCTACCTACT ACTGT (SEQ ID NO: 199)
VLFW3 (type b)	GIPPRFSGSGYGTDFTLTINNIESED AAYYFC (SEQ ID NO: 200)	GGGATCCCACCTCGATTCAGTGGCAGCGG GTATGGAACAGATTTTACCCTCACAATTAAT AACATAGAATCTGAGGATGCTGCATATTACT TCTGT (SEQ ID NO: 201)
VLFW3 (type c)	GVPSRFSGSGSGTEFTLTISSLQPD DFATYYC (SEQ ID NO: 202)	GGGGTCCCATCAAGGTTCAGCGGCAGTGG ATCTGGGACAGAATTCACTCTCACCATCAGC AGCCTGCAGCCTGATGATTTTGCAACTTATT ACTGT (SEQ ID NO: 203) GGCGTGCCCTCTAGATTCTCCGGCTCCGGC TCTGGCACCGAGTTTACCCTGACCATCTCC

		AGCCTGCAGCCCGACGACTTCGCCACCTAC TACTGC (SEQ ID NO: 204)
VLFW3 (type d)	GVPSRFSGSGSGTDFTFTISSLQPE DIATYYC (SEQ ID NO: 205)	GGGGTCCCATCAAGGTTCAGTGGAAGTGGA TCTGGGACAGATTTTACTTTCACCATCAGCA GCCTGCAGCCTGAAGATATTGCAACATATTA CTGT (SEQ ID NO: 206) GGCGTGCCCTCTAGGTTTAGCGGTAGCGGT AGTGGCACCGACTTCACCTTCACTATCTCTA GCCTGCAGCCCGAGGATATCGCTACCTACT ACTGT (SEQ ID NO: 207)
VLFW4	FGQGTKVEIK (SEQ ID NO: 208)	TTCGGCCAAGGGACCAAGGTGGAAATCAAA (SEQ ID NO: 209) TTCGGCCAGGGCACCAAGGTGGAAATCAAG (SEQ ID NO: 210) TTCGGTCAAGGCACTAAGGTCGAGATTAAG (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 YKTTPPVLDS DGSFFLYSRL TVDKSRWQEG NVFSCSVMHE ALHNHYTQKS LSLSLGK (SEQ ID NO: 212)
LC	**Human kappa constant region amino acid sequence** RTVAAPSVFI FPPSDEQLKS GTASVVCLLN NFYPREAKVQ WKVDNALQSG NSQESVTEQD SKDSTYSLSS TLTLSKADYE KHKVYACEVT HQGLSSPVTK SFNRGEC (SEQ ID NO: 213)
HC	**IgG4 (S228P) mutant constant region amino acid sequence lacing 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 YKTTPPVLDS DGSFFLYSRL TVDKSRWQEG NVFSCSVMHE ALHNHYTQKS LSLSLG (SEQ ID NO: 214)
HC	**IgG1 wild type** ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN

	STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK (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 KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYA STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV 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 KDTLMISRTP EVTCVVVAVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LAPIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV 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 KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV 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	MAWVWTLPFLMAAAQSVQA (SEQ ID NO: 221)
	LC	MSVLTQVLALLLLWLTGTRC (SEQ ID NO: 222)
BAP049-Clone-E	HC	MAWVWTLPFLMAAAQSVQA (SEQ ID NO: 221)
	LC	MSVLTQVLALLLLWLTGTRC (SEQ ID NO: 222)

Example 2: Clinical Study Summary

The following clinical study will be used to confirm the rationale, findings, and conclusions of Example 1. The safety and efficacy expected from Example 1 will also be further evaluated.

A Phase I, open-label, dose escalation study of oral LGK974 and PDR001 in patients with malignancies dependent on Wnt Ligands	
Purpose and rationale	The purpose of this study is to assess the recommended dose of the Compound of Formula (I) in combination with PDR001 that can be safely administered to patients with selected solid malignancies for whom no

	effective standard treatment is available.
Primary Objective	To determine the MTD and/or recommended dose for the Compound of Formula (I) in combination with PDR001 when administered to patients with malignancies dependent on Wnt ligands as specified in the inclusion criteria.
Secondary Objectives	To characterize the safety and tolerability of the Compound of Formula (I) in combination with PDR001. To evaluate the PK of the Compound of Formula (I) in combination with PDR001 To assess the anti-tumor activity of the Compound of Formula (I) in combination with PDR001.
Study design	This is a multi-center, open-label phase 1 study. The initial dose of the Compound of Formula (I) and PDR001 in combination will be 2.5 mg QD days 1- 8 day in cycle 1 only and 400 mg Q4W, respectively. The PDR001 dose of 400mg Q4W is the RP2D determined within the CPDR001X2101 clinical study. The Compound of Formula (I) will be started at 2.5 mg QD, the -1 dose from which target inhibition is observed in the single agent portion of the study. Other schedules of the Compound of Formula (I) dosing may be explored (i.e. Cycle 1-4 LGK974 QD dosing on day 1 through day 8 each cycle; the Compound of Formula (I) QD dosing on day 1-15 Cycle 1 only; or Cycle 1-4 LGK974 QD dosing on day 1 through 15 each cycle), depending on safety, PK, PD, and efficacy data. Dose escalation will continue until the MTD and/or RDE is reached. For the dose escalation part, a Bayesian logistic regression model (BLRM) with overdose control (EWOC) principle will be employed for dose level selection and determination of the MTD and/or RDE. The expansion part of the study will be initiated at the determination of the RDE and will be carried out with one regimen. The goal of the expansion part is to better characterize the safety and tolerability, PK/PD relationship as well as to explore the anti-tumor activity of the combination. Approximately 40 patients across the 4 disease areas will be treated in the dose expansion part of the study. Toxicity will be evaluated according to CTCAE version 4.03 to evaluate the safety and tolerability of the Compound of Formula (I) as a single agent and in combination with PDR001. Disease response will be assessed using RECIST v1.1 within the single agent portion and RECIST v1.1 and irRC in the combination portion. Patients will be treated until disease progression or unacceptable toxicity occurs, or withdrawal of consent after which all patients will have a study evaluation completion (SEC) safety follow-up for adverse events (AEs) and serious adverse events (SAEs) for 30 days after the last dose of the Compound of Formula (I) within the single agent portion, and 150 days after last dose of PDR001 or 30 days after last dose of the Compound of Formula (I), whichever is latest within the combination portion.
Population	Adult and adolescent patients with advanced cancer and who have progressed despite standard therapy or for whom no effective standard therapy exists with a histologically confirmed diagnosis of: the Compound of Formula (I)in combination with PDR001:

	• pancreatic adenocarcinoma • triple negative breast cancer (TNBC), • melanoma • head and neck squamous cell cancer • squamous cell cancer of the lung • squamous cell cancer of the esophagus • squamous cell cancer of the cervix
Inclusion criteria	Patients eligible for inclusion in this study have to meet **all** of the following criteria: 1. Diagnosis of locally advanced or metastatic cancer that has progressed despite standard therapy or for which no effective standard therapy exists and histological confirmation of one of the following diseases indicated below: • the Compound of Formula (I) with PDR001: **Dose escalation:** patients with the following cancers that were previously treated with anti-PD-1 therapy and whose best response on that therapy was progressive disease (i.e., primary refractory): melanoma, lung SCC, HNSCC. Patients with esophageal SCC, cervical SCC or TNBC regardless of prior anti-PD-1 therapy are also eligible. However, patients with esophageal SCC, cervical SCC, or TNBC who had received prior anti-PD-1 therapy must have had a best response of progressive disease to that therapy. • the Compound of Formula (I) with PDR001: **Dose expansion:** patients with pancreatic cancer, or TNBC, or melanoma or head and neck squamous cell cancer. 2. Age 18 years or older 3. WHO Performance Status of 0-2 4. During the dose escalation part of the study patients must have evaluable disease. During the expansion part of the study patients must have measurable disease as defined by RECIST v1.1 (at least one lesion ≥ 10 mm in at least one dimension when assessed by CT or MRI, or a cutaneous lesion with clearly defined margins that measures ≥ 10 mm in at least one dimension) 6. Willingness and ability to comply with all study procedures 7. Written informed consent obtained prior to any screening procedures 8. Patient must be willing to undergo a new tumor biopsy at screening.
Investigational and reference therapy	Investigational Drug: LGK974 [2-(2',3-dimethyl-2,4'-bipyridin-5-yl)-N-(5-(pyrazin-2-yl)pyridin-2-yl) acetamide] 2.5-mg, 10-mg, and 50-mg capsule PDR001: 100-mg powder for infusion
Efficacy assessments	Compound of Formula (I) in combination with PDR001: Tumor response will be determined by local investigator interpretation according to two sets of criteria: 1. RECIST v1.1 2. irRC

	At baseline all patients will undergo CT with i.v. contrast of the chest, abdomen and pelvis. If there is clinical evidence of disease in the head or neck, a CT of the head and/or neck will also be performed. MRI should only be used to evaluate sites of disease that are not adequately imaged by CT. If a patient is intolerant of iodine-based contrast agents, CTs may be performed without contrast; however, MRI may be used to evaluate sites of disease where a CT without i.v. contrast is not adequate. Visible skin lesions and easily palpable subcutaneous tumors may be measured by physical examination using a ruler or calipers. Ultrasound should not be used to measure sites of disease. Subsequent tumor evaluations for patients treated with the Compound of Formula (I) in combination with PDR001 will be obtained during treatment starting on Cycle 3 Day 1, every 2 cycles until Cycle 11 Day 1, and then every 3 cycles until progression of disease as per irRC or patient withdrawal and during follow-up for progession every 8 weeks for 40 week, then every 12 weeks until progression of disease per irRC or lost to follow-up. Tumor evaluations will also be performed at EOT for both portions of the study. If the last prior tumor evaluation was within 28 days of EOT, then it does not need to be repeated at EOT. Tumor evaluations after the baseline assessment will include evaluation of all sites of disease identified at baseline, using the same technique that was used at baseline. If there was no evidence of disease in a body region at baseline, that region does not need to be imaged at subsequent assessments, unless there is clinical concern for a new lesion in that body region. For the Compound of Formula (I) in combination with PDR001, the local investigator's assessment will be used for the analysis of response according to both RECIST 1.1 and irRC, and for treatment decision making (study discontinuation due to PD as per irRC). Patients experiencing progressive disease per RECIST v. 1.1 criteria may continue to be treated according to irRC guidelines until progression is documented via irRC. During the course of the study, the study sponsor may decide to have a central review of the radiological assessments performed. In such case, the investigator's staff will be instructed on how to send data from these radiological assessments to a Contract Research Organization (CRO) for central review when needed.
Safety assessments	Safety will be monitored by assessing changes from baseline in laboratory values, physical examination, and vital signs as well as collecting of the adverse events at every visit. • Evaluation of all AEs and SAEs including injection site hypersensitivity reactions, vital signs, laboratory assessments and occurrence of infections. • Physical examination • Vital signs • Height and weight • Laboratory evaluations

	• Hematology • Clinical chemistry • Bone-related laboratory assessments • Urinalysis • Pregnancy and assessments of fertility • Thyroid function panel • Cytokines • Cardiac assessments • Bone density scans • Lumbar x-rays • Pharmacokinetics and immunogenicity (IG) assessments
Data analysis	Data will be summarized using descriptive statistics (continuous data) and/or contingency tables (categorical data) for demographic and baseline characteristics, efficacy measurements, safety measurements, and all relevant pharmacokinetic and pharmacodynamic measurements. The primary CSR will be based on all patient data from the escalation and expansion parts up to the time when all patients have completed at least four cycles of treatment or discontinued the study. Any additional data for patients continuing to receive study treatment past the cutoff date of the primary CSR, as allowed by protocol, will be reported once all patients have completed SEC follow-up visit. Within this analysis, cohorts of patients treated at the same dose or combination, regimen, and formulation will be pooled into treatment groups. Also, within the combination portion of the study, patients treated during the escalation part will be pooled with those receiving the same dosing regimen during the expansion part. All listings, summaries, figures, and analyses will be performed by treatment group unless otherwise specified. Within the dose expansion part, additional descriptive analyses by indication group and route of administration may be performed if appropriate.

The clinical trial design is shown in Figure 8.

Example 3: Suppression of pancreatic growth alone and in combination with immunotherapy

The following experimental study will be used to confirm the rationale, findings, and conclusions of Example 1. The efficacy expected from Example 1 will also be further evaluated.

The study will examine the ability of the Compound of Formula (I), either alone or in combination with an anti-PD1 molecule to suppress the growth of pancreatic tumor cells in PDX-CRE $KRAS^{G12D}$ $P53^{R172H/+}$ mice.

Treatment groups:

A) Vehicle
B) Compound of Formula (I), 5mg/kg BID, PO
C) Compound of Formula (I), 5mg/kg BID, PO and anti-PD1 (twice weekly ip)
D) Compound of Formula (I), 5mg/kg BID, PO and isotype control (twice weekly ip)

Approximately 10-15 mice will be in each treatment group

Treatment period: Treatment will begin when the mice have palpable tumor burden. Mice will be harvested when exhibiting symptoms of pancreatic cancer (median 120 days). Cohorts of treatment and control animals will be sample following short term treatment (less than 7 days) for analysis of tumour immune and inflammatory infiltrate.

Tumor growth will be monitored via ultrasound. Time to symptoms of pancreatic cancers and metastatic spread will also be monitored. HC for markers of differentiation, apoptosis, proliferation and senescence will be monitored, as well.

Readouts: IHC for nuclear β-catenin, BrdU incorporation, CD4+, CD8+, CD3+ (T-lymphosycets), F4/8- (macrophage) and NIMP (neutrophils). Material and dta in the form of isolated RNA for cohort animals and whole transciptome analysis by RNASeq in combination with GSEA for immune and inflammatory signatures following short term intervention will be determined.

Example 4: Suppression of melanoma growth alone and in combination with immunotherapy
The following experimental study will be used to confirm the rationale, findings, and conclusions of Example 1. The efficacy expected from Example 1 will also be further evaluated.

The study will examine the ability of the Compound of Formula (I), either alone or in combination with an anti-PD1 molecule to suppress the growth of melanoma tumor cells in TyrCreER $BRaf^{V600E/+}$ $Pten^{fl/+}$ and TyrCreER $BRaf^{V600E/+}$ $Pten^{fl/+}$ $Catnb^{lox(ex3)/+}$ mice.

Treatment groups:

A) Vehicle
B) Compound of Formula (I), 5mg/kg BID, PO
C) Compound of Formula (I), 5mg/kg BID, PO and anti-PD1 (twice weekly ip)
D) Compound of Formula (I), 5mg/kg BID, PO and isotype control (twice weekly ip)

Approximately 10-15 mice will be in each treatment group

Treatment period: Treatment will begin upon establishment of melanoma (5 mm diameter) and continue until tumors reach endpoint (15 mm diameter).Tumor growth will be monitored by caliper measurement.

Readouts: Tumor growth by caliper measurement, tumor cellularity by pathological examination, IHC for β-catenin and qPCR for Wnt target genes, stromal cell/infiltrating immune cell markers by IHC.

Example 5: Suppression of melanoma growth alone and in combination with immunotherapy
The following experimental study will be used to confirm the rationale, findings, and conclusions of Example 1. The efficacy expected from Example 1 will also be further evaluated.

The study will examine the ability of the Compound of Formula (I), either alone or in combination with an anti-PD1 molecule to suppress the growth of melanoma tumor cells in CD-1 nude or C57BL/^

mice grafted with mouse derived melanoma (TyrCreER $BRaf^{V600E/+}$ $Pten^{fl/+}$ and TyrCreER $BRaf^{V600E/+}$ $Pten^{fl/+}$ $Catnb^{lox(ex3)/+}$ mice.

Treatment groups:

A) Vehicle
B) Compound of Formula (I), 5mg/kg BID, PO
C) Compound of Formula (I), 5mg/kg BID, PO and anti-PD1 (twice weekly ip)
D) Compound of Formula (I), 5mg/kg BID, PO and isotype control (twice weekly ip)

Approximately 10-15 mice will be in each treatment group

Treatment period: Treatment will begin upon establishment of melanoma (5 mm diameter) and continue until tumors reach endpoint (15 mm diameter). Tumor growth will be monitored by caliper measurment.

Readouts: Tumor growth by caliper measurement, tumor cellularity by pathological examination, IHC for β-catenin and qPCR for Wnt target genes, stromal cell/infiltrating immune cell markers by IHC.

CLAIMS

1. A pharmaceutical combination comprising (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof, and (ii) anti-PD-1 antibody molecule or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, wherein (i) is administered daily on days 1 to 15 of each cycle for up to 4 cycles and (ii) is administered at least once per cycle.

2. The pharmaceutical combination for use in the treatment of cancer according to claim 1, wherein (i) is administered during days 1 to 8 of each cycle for up to 4 cycles.

3. The pharmaceutical combination for use in the treatment of cancer according to claim 1 or 2, wherein (i) is administered during the first cycle only.

4. The pharmaceutical combination for use in the treatment of cancer according to claim 1 or 2, wherein (i) is administered during 4 cycles only.

5. The pharmaceutical combination for use in the treatment of cancer according to any one of claims 1 to 4, wherein each cycle is 28 days.

6. The pharmaceutical combination for use in the treatment of cancer according to any one of claims 1 to 5, wherein (i) is administered twice daily.

7. The pharmaceutical combination for use in the treatment of cancer according to claim 6, wherein (i) is administered at 12-hour intervals.

8. The pharmaceutical combination for use in the treatment of cancer according to any one of claims 1 to 7, wherein the daily dose of (i) is 2.5 mg/day, 5 mg/day, 7.5 mg/day, 10 mg/day, 20 mg/day, 40 mg/day, 80 mg/day, 120 mg/day, or 180 mg/day.

9. The pharmaceutical combination for use in the treatment of cancer according to claim 8, wherein the daily dose of (i) is 2.5 mg/day, 5 mg/day, or 10 mg/day.

10. The pharmaceutical combination for use in the treatment of cancer according to anyone of claims 8 to 9, wherein the daily dose of (i) is 10 mg/day.

11. The pharmaceutical combination for use in the treatment of cancer according to any one of claims 1 to 10, wherein (ii) is administered every 2 weeks or every 4 weeks in a cycle.

12. The pharmaceutical combination for use in the treatment of cancer according to claim 11, wherein (ii) is administered, every 4 weeks.

13. The pharmaceutical combination for use in the treatment of cancer according to claims 11or 12, wherein (ii) is selected from nivolumab, pembrolizumab, pidilizumab, PDR-001, or a pharmaceutical salt thereof.

14. The pharmaceutical combination for use in the treatment of cancer according to claim 13, wherein (ii) is PDR-001, or a pharmaceutical salt thereof.

15. The pharmaceutical combination for use in the treatment of cancer according to claim13, wherein (ii) is administered intravenously in a single dose of 300 to 400 mg/day.

16. The pharmaceutical combination for use in the treatment of cancer according to claim 15, wherein the single dose is 400 mg/day.

17. The pharmaceutical combination for use in the treatment of cancer according to any one of claims 1, 2, 5 to 9 or 11 to 16, wherein 2.5 mg/day of (i) is administered on days 1-8 and 400 mg/day of (ii) is administered once every 4 weeks for up to 4 cycles.

18. The pharmaceutical combination for use in the treatment of cancer according to any one of claims 1, 5 to 9 or 11 to 16, wherein 2.5 mg/day of (i) is administered on days 1-15 and 400 mg/day of (ii) is administered once every 4 weeks for up to 4 cycles.

19. The pharmaceutical combination for use in the treatment of cancer according to any one of claims 3 to 9 or 11 to 18, wherein 2.5 mg/day of (i) is administered during cycle 1 only and 400 mg/day of (ii) is administered every 4 weeks.

20. The pharmaceutical combination for use in the treatment of cancer according to any one of claims 1, 2, 5 to 9 or 11 to 16, wherein 5 mg/day of (i) is administered on days 1-8 and 400 mg/day of (ii) is administered once every 4 weeks for up to 4 cycles.

21. The pharmaceutical combination for use in the treatment of cancer according to any one of claims 1, 5 to 9 or 11 to 16, wherein 5 mg/day of (i) is administered on days 1-15 and 400 mg/day of (ii) is administered once every 4 weeks for up to 4 cycles.

22. The pharmaceutical combination for use in the treatment of cancer according to any one of claims 3 to 9, 11 to 16, 20 or 21, wherein 5 mg/day of (i) is administered during cycle 1 only and 400 mg/day of (ii) is administered every 4 weeks.

23. The pharmaceutical combination for use in the treatment of cancer according to any one of claims 1, 2, 5 to 16, wherein 10 mg/day of (i) is administered daily on days 1-8 and 400 mg/day of (ii) is administered every 4 weeks for up to 4 cycles.

24. The pharmaceutical combination for use in the treatment of cancer according to any one of claims 1 or 5 to 16, wherein 10 mg/day of (i) is administered on days 1-15 and 400 mg/day of (ii) is administered every 4 weeks for up to 4 cycles.

25. The pharmaceutical combination for use in the treatment of cancer according to any one of claims 1, 3 to 16, 23 or 24, wherein 10 mg/day of (i) is administered during cycle 1 only and 400 mg/day of (ii) is administered every 4 weeks.

26. The pharmaceutical combination for use in the treatment of cancer according to any one of claims 1 to 25, wherein (ii) is administered continuously every 4 weeks.

27. Use of (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof, in combination with anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt, for the manufacture of a medicament for the treatment of cancer, wherein (i) and (ii) are administered as define in any one of the claims 1 to 26, preferably wherein (i) is administered daily on days 1 to 16 of each cycle for up to 4 cycles and (ii) is administered at least once per cycle.

28. The use of (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof, in combination with (ii) anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of cancer according to claim 27 wherein (i) is to be administered on days 1 to 16 of each cycle, on days 1 to 8 of each cycle for up to 4 cycles or only during the first cycle.

29. The use of (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof, in combination with (ii) anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of cancer according to claims 27 or 28 wherein the daily dose of (i) is 2.5 mg/day, 5 mg/day, 7.5 mg/day, 10 mg/day, 20 mg/day, 40 mg/day, 80 mg/day, 120 mg/day, or 180 mg/day.

30. The use of (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof, in combination with (ii) anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of cancer according to any one of claims 27 to 29 wherein the daily dose of (i) is 10 mg/day.

31. The use of (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof, in combination with (ii) anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of cancer according to any one of claims 27 to 30 wherein (ii) is to be administered in a single dose of 300-400 mg/day.

32. The use of (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof, in combination with (ii) anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of cancer according to any one of claims 27 to 30 wherein (ii) is administered in a single dose of 400 mg/day.

33. The use of (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof, in combination with (ii) anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, for the manufacture

of a medicament for the treatment of cancer according to claim 27 wherein (i) and (ii) are administered as defined in any one of claims 17 to 25.

34. A method for the treatment of cancer, said method comprising administering an effective amount of (i) and (ii) to a patient in need thereof, wherein (i) is administered daily during days 1 to 15 of each cycle for up to 4 cycles and (ii) is administered at least once per cycle.

35. The method for the treatment of cancer according to claim 34, said method comprising administering an effective amount of (i) and (ii) as defined in any one of claims 1 to 26.

36. The pharmaceutical combination for use in the treatment of cancer according to claims 1 to 26, the use of (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof, in combination with (ii) anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, according to claims 27 to 33, or the method for the treatment of cancer according to claim 34 to 36 wherein the cancer is triple-negative breast cancer (TNBC), head and neck squamous cell carcinoma, pancreatic cancer, gastrointestinal cancer, colorectal cancer, squamous cell cancer of the lung, squamous cell cancer of the esophagus, squamous cell cancer of the cervix or melanoma.

37. The pharmaceutical combination for use in the treatment of cancer according to claim 1 to 26 or 36, the use of 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof, in combination with an anti-PD-1 antibody molecule, or a pharmaceutical salt thereof according to claims 27 to 33 or 36, or the method for the treatment of cancer according to claims 34 to 36, wherein the cancer is triple-negative breast cancer (TNBC), pancreatic cancer or melanoma.

38. The pharmaceutical combination for use in the treatment of cancer according to claims 1 to 26, 36 or 37, the use of (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof, in combination with (ii) anti-PD-1 antibody molecule, or a pharmaceutically acceptable salt thereof, according to claims 27 to 33, 36 or 37, or the method for the treatment of cancer according to claim 34 to 37, wherein (i) and (ii) are synergistically active at reducing bone resorption.

39. The pharmaceutical combination for use in the treatment of cancer according to claims 1 to 26, or 36 to 38, the use of (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof, in combination with an anti-PD-1 antibody molecule, or a pharmaceutical salt thereof, according to claims 27 to 33, or 36 to 38, or the method for the treatment of cancer according to claims 34 to 38, wherein (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof, is administered orally or intravenously, most preferably orally.

40. The pharmaceutical combination for use in the treatment of cancer according to claims 1 to 26 or 36 to 39, the use of (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-

2-yl)acetamide, or a pharmaceutically acceptable salt thereof, in combination with an anti-PD-1 antibody molecule according to claims 27 to 33 or 36 to 39, or the method for the treatment of cancer according to claims 34 to 39, wherein the anti-PD-1 antibody molecule (ii) is selected from nivolumab, pembrolizumab, pidilizumab, PDR-001, or a pharmaceutical salt thereof.

41. The pharmaceutical combination for use in the treatment of cancer according to claims 1 to 26 or 36 to 40, the use of (i) 2-(2',3-dimethyl-[2,4'-bipyridin]-5-yl)-*N*-(5-(pyrazin-2-yl)pyridin-2-yl)acetamide, or a pharmaceutically acceptable salt thereof in combination with an anti-PD-1 antibody molecule according to claims 27 to 33 or 36 to 40, or a method for the treatment of cancer according to claims 34 to 40, wherein the anti-PD-1 antibody molecule (ii) is PDR-001, or a pharmaceutical salt thereof.

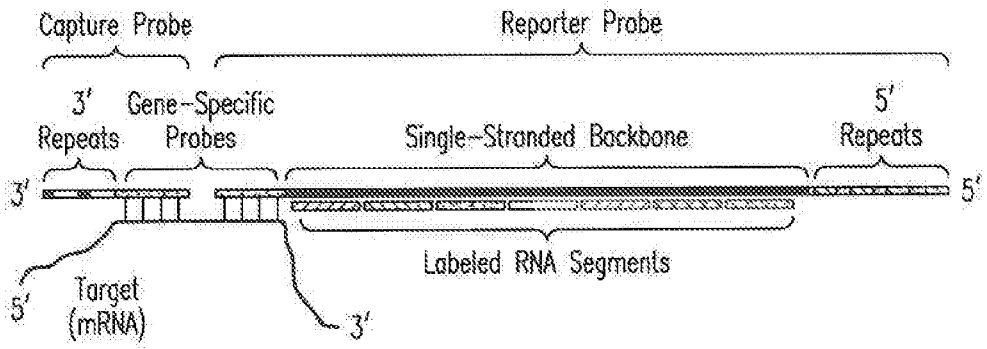


FIG. 1A

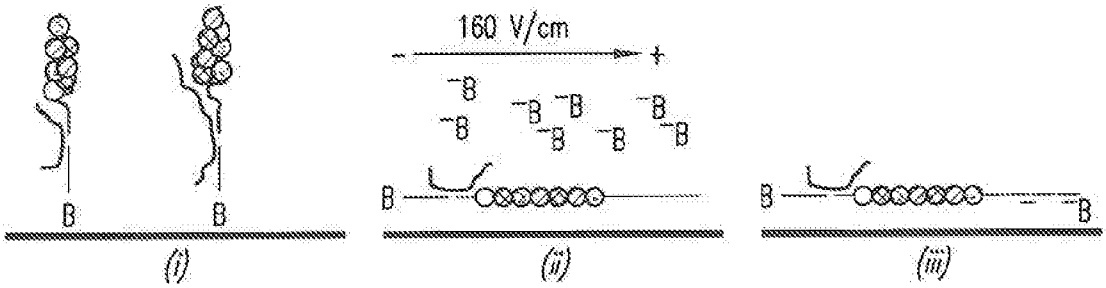


FIG. 1B

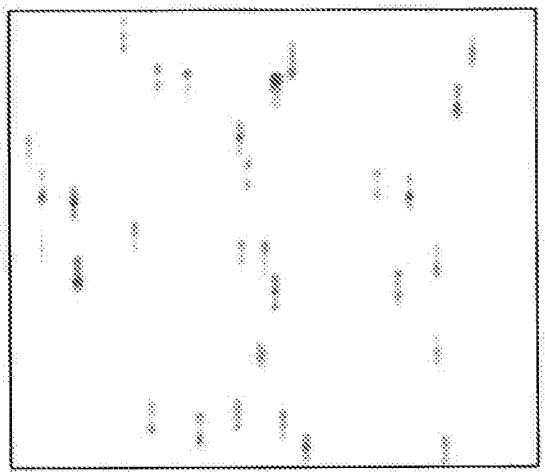


FIG. 1C

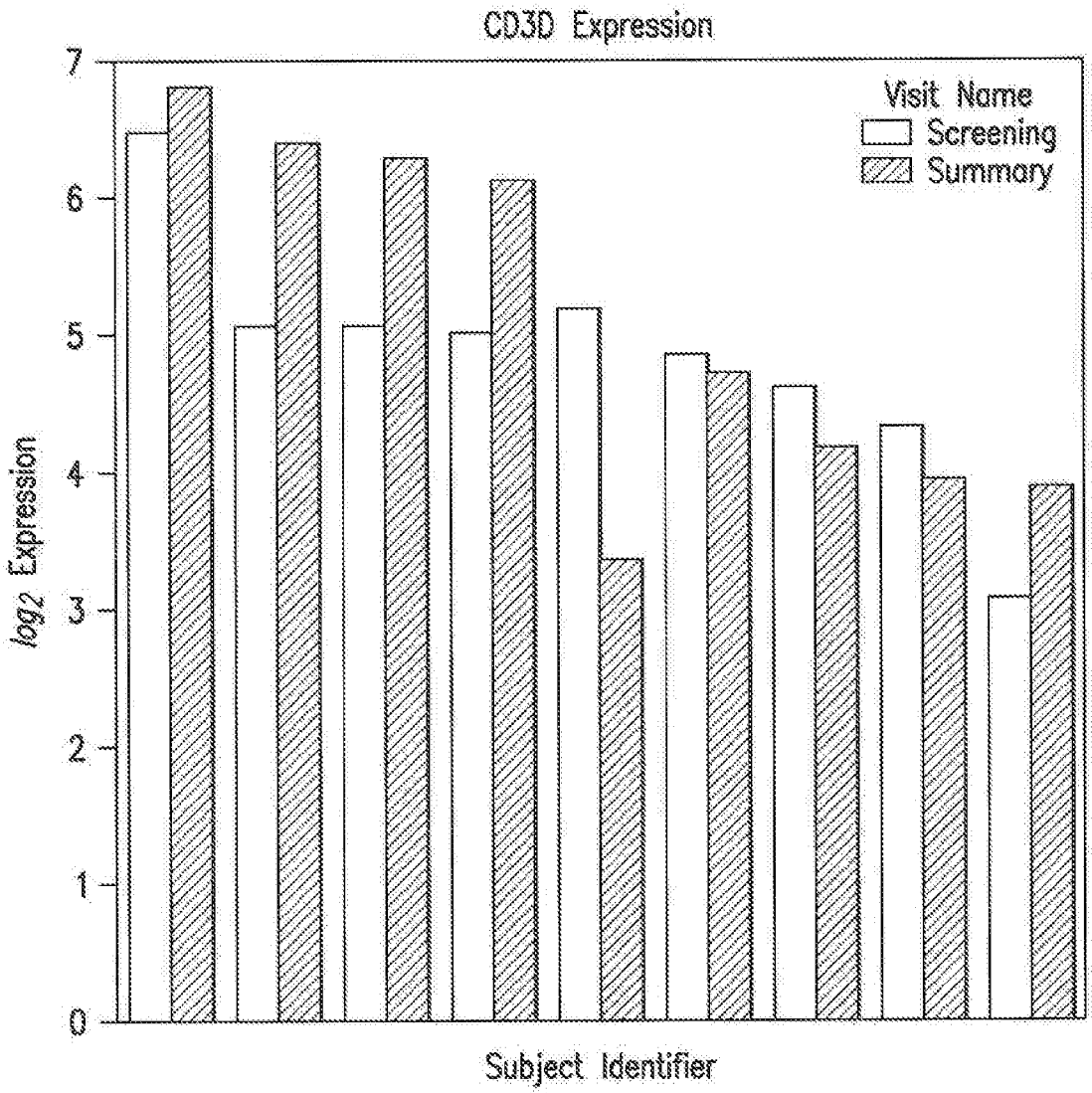


FIG.2

Genes In The T-Cell Signature: CD2, CD247, CD3D, CD3E, CD3EAP, CD3G, CD48, CD53, CD8A, CD8B, CXCR6, GZMK, LY9, SH2D1A, SLAMF6, TARP, TCF7, CD337.

FIG.3

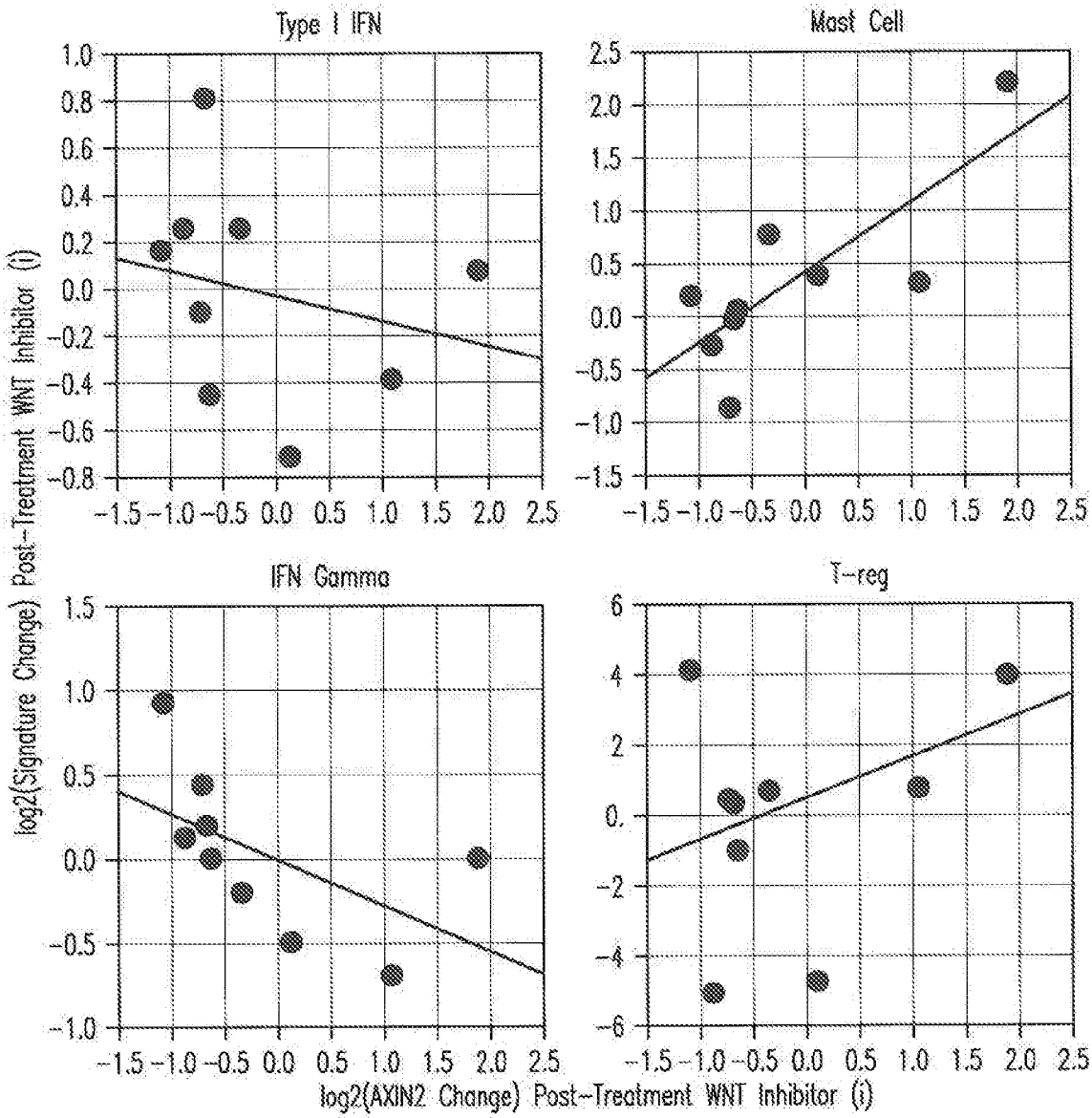

Type I IFN
Mast Cell
IFN Gamma
T-reg
log2(Signature Change) Post-Treatment WNT Inhibitor (i)
log2(AXIN2 Change) Post-Treatment WNT Inhibitor (i)

FIG.4

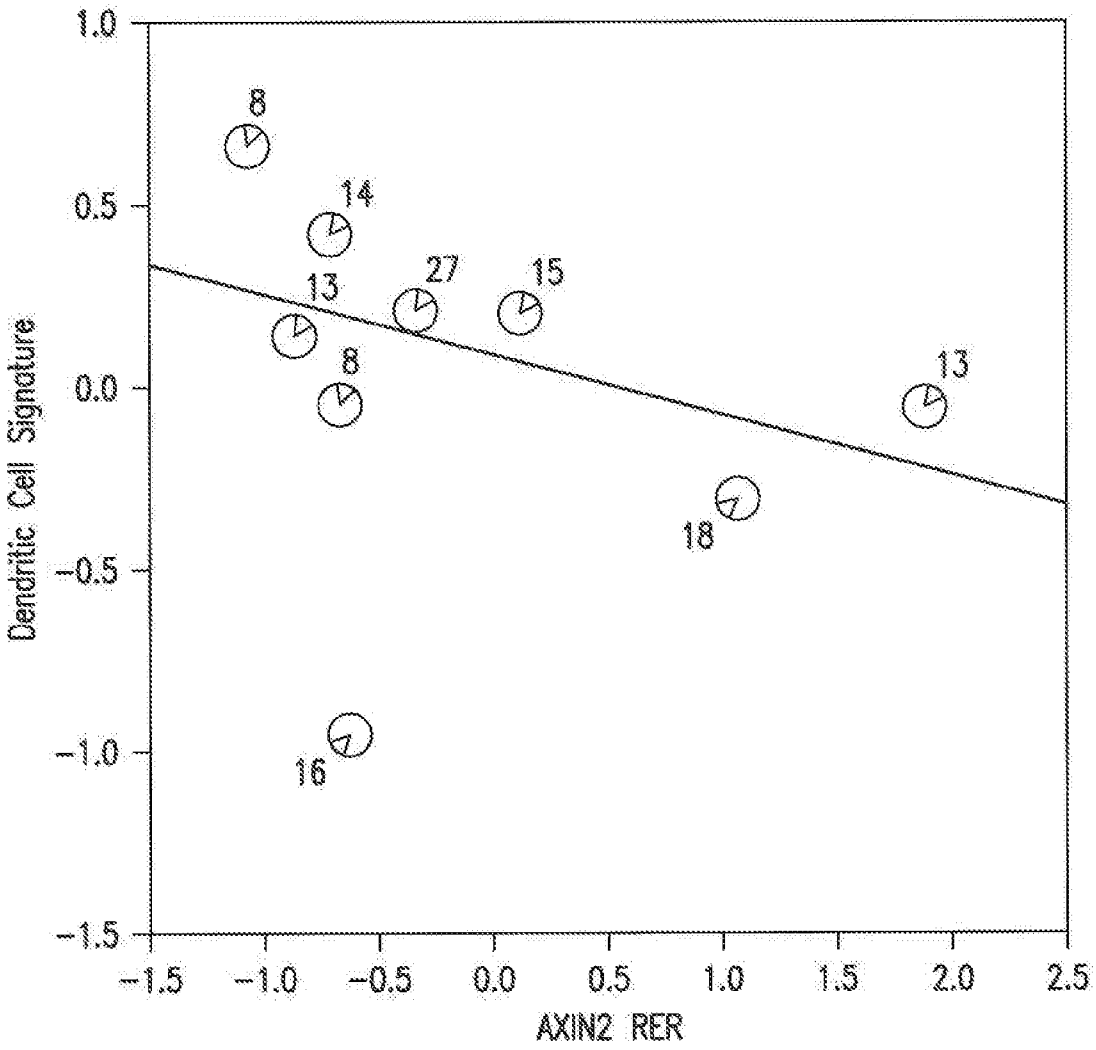

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−1.5
Dendritic Cell Signature
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14
13
27
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8
13
18
16
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−0.5
0.0
0.5
1.0
1.5
2.0
2.5
AXIN2 RER

FIG.5

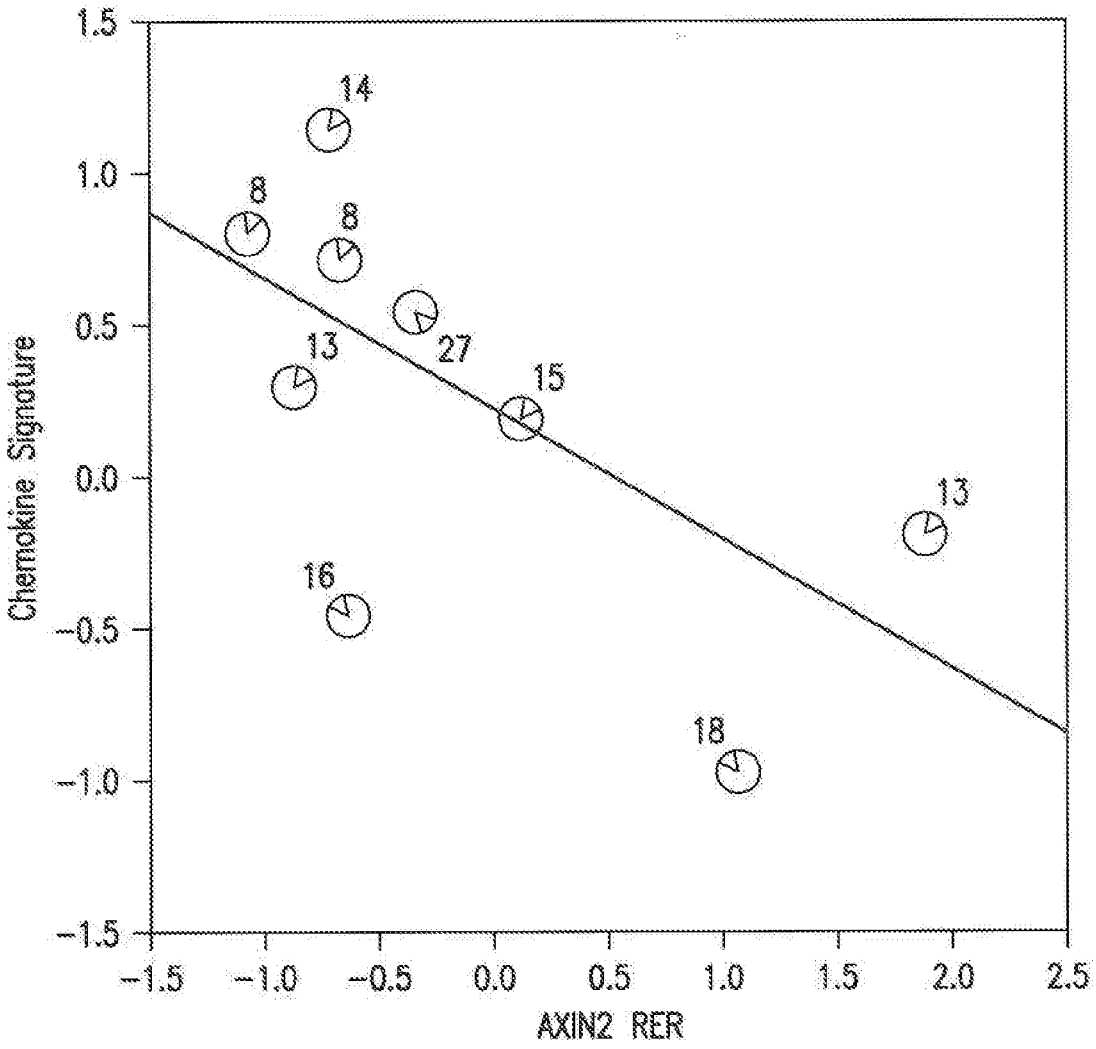

Chemokine Signature
AXIN2 RER
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−0.5
0.0
0.5
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2.5
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15
13
16
18

FIG.6

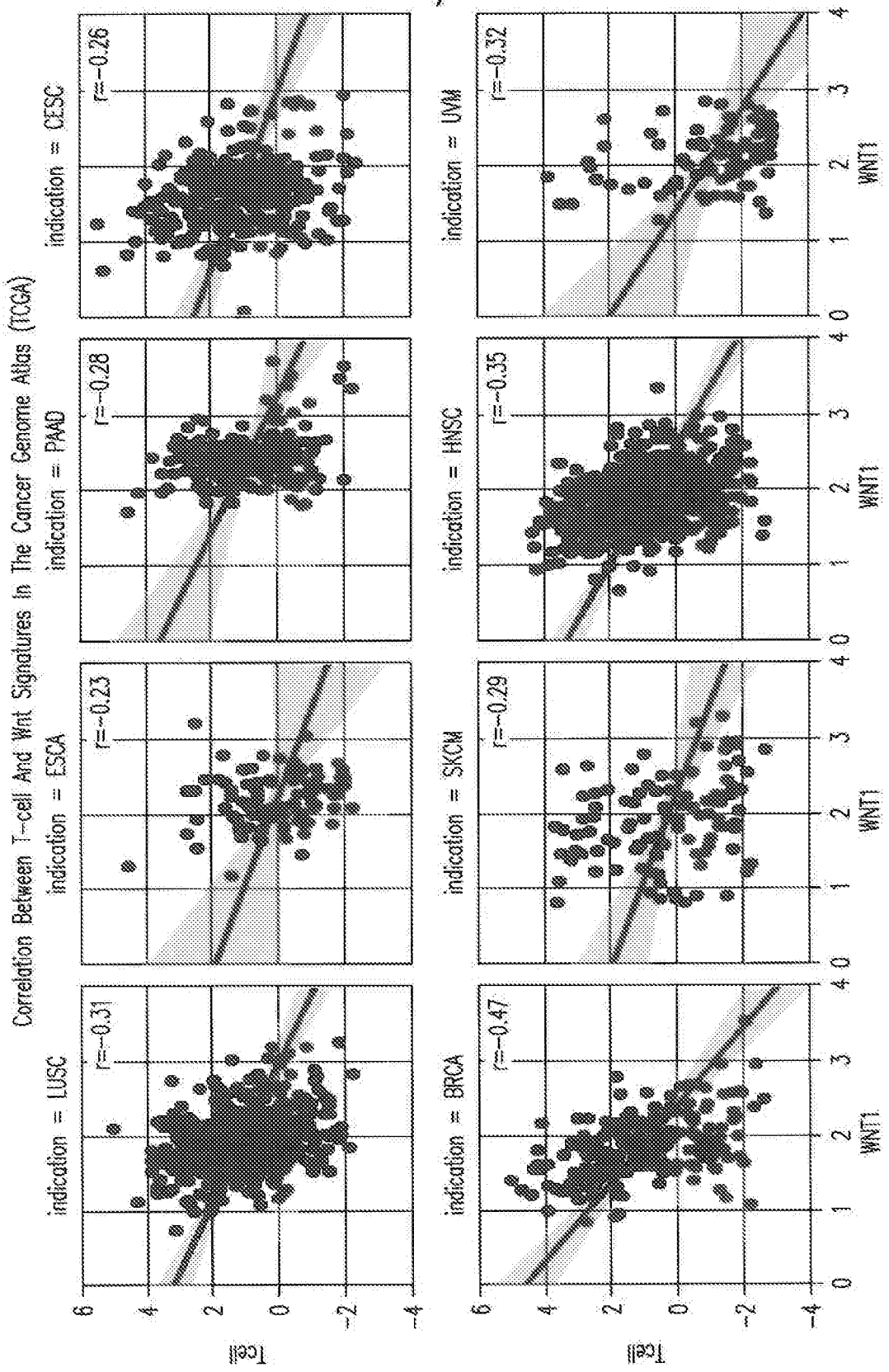

Correlation Between T-cell And Wnt Signatures In The Cancer Genome Atlas (TCGA)
indication = LUSC
r=−0.31
indication = ESCA
r=−0.23
indication = PAAD
r=−0.28
indication = CESC
r=−0.26
indication = BRCA
r=−0.47
indication = SKCM
r=−0.29
indication = HNSC
r=−0.35
indication = UVM
r=−0.32
Tcell
WNT1

FIG. 7A

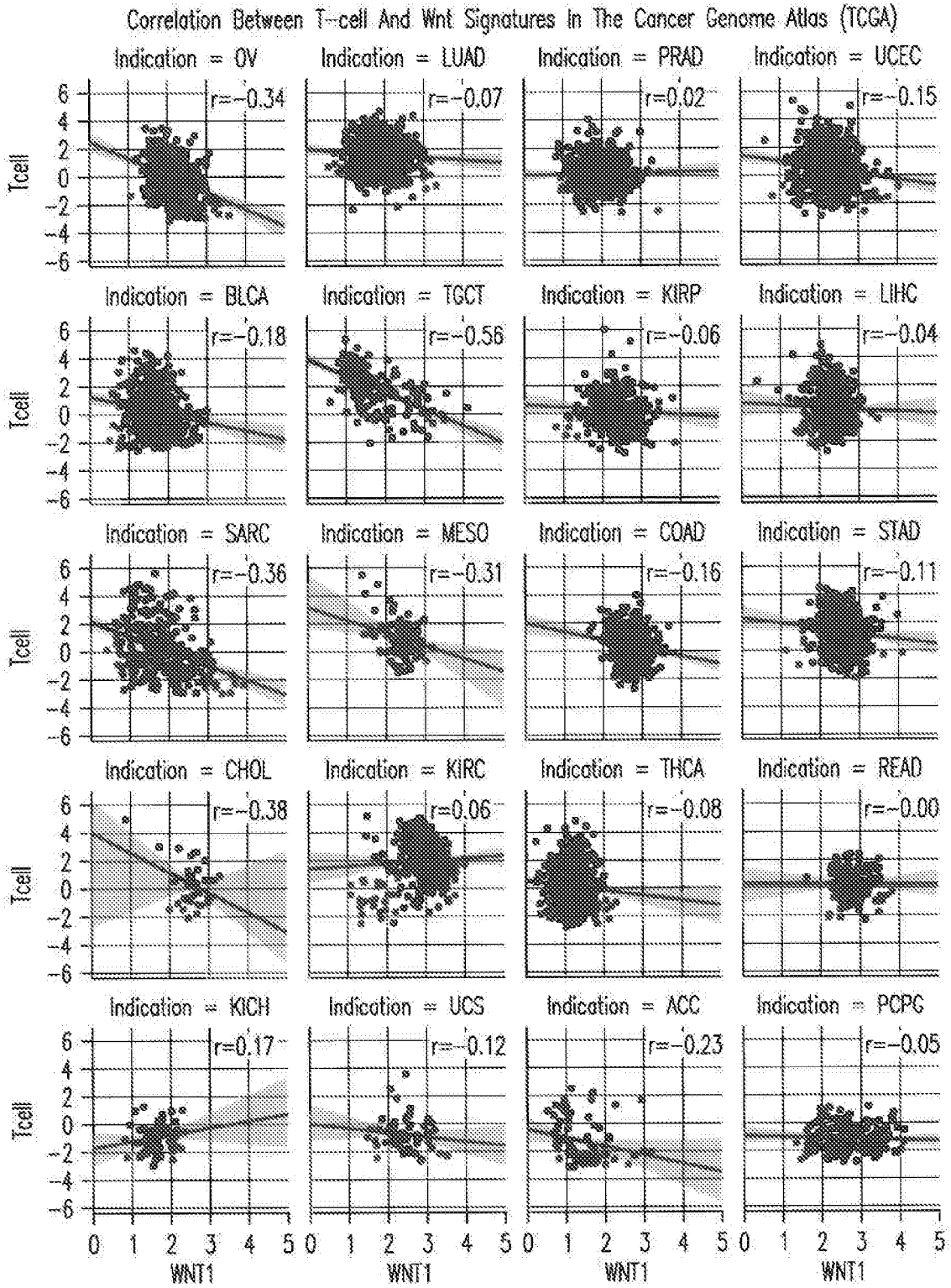

Correlation Between T-cell And Wnt Signatures In The Cancer Genome Atlas (TCGA)
Indication = OV
r=-0.34
Indication = LUAD
r=-0.07
Indication = PRAD
r=0.02
Indication = UCEC
r=-0.15
Indication = BLCA
r=-0.18
Indication = TGCT
r=-0.56
Indication = KIRP
r=-0.06
Indication = LIHC
r=-0.04
Indication = SARC
r=-0.36
Indication = MESO
r=-0.31
Indication = COAD
r=-0.16
Indication = STAD
r=-0.11
Indication = CHOL
r=-0.38
Indication = KIRC
r=0.06
Indication = THCA
r=-0.08
Indication = READ
r=-0.00
Indication = KICH
r=0.17
Indication = UCS
r=-0.12
Indication = ACC
r=-0.23
Indication = PCPG
r=-0.05
Tcell
WNT1

FIG.7B

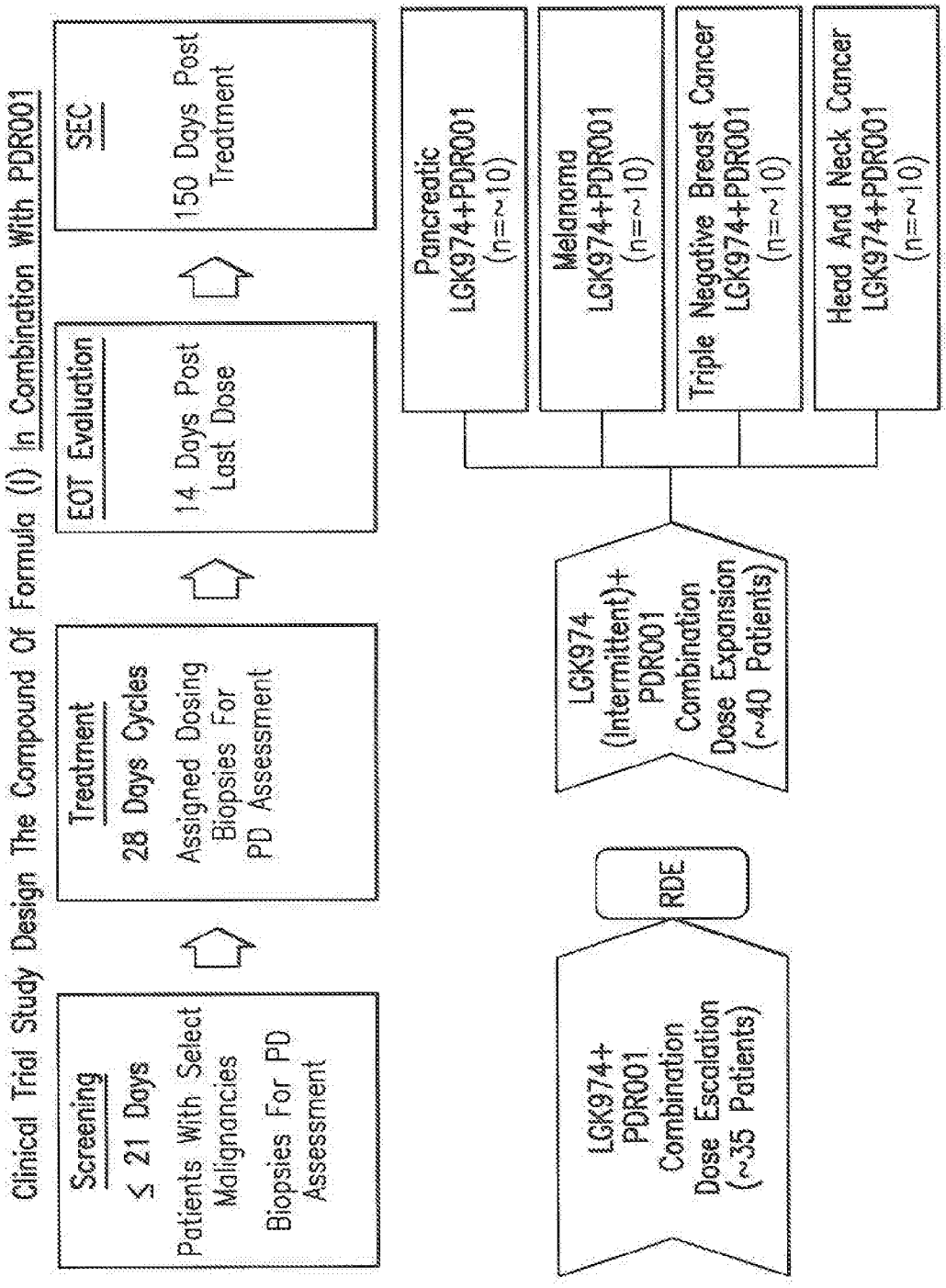

Clinical Trial Study Design The Compound Of Formula (I) In Combination With PDR001
Screening
≤ 21 Days
Patients With Select Malignancies
Biopsies For PD Assessment
Treatment
28 Days Cycles
Assigned Dosing
Biopsies For PD Assessment
EOT Evaluation
14 Days Post Last Dose
SEC
150 Days Post Treatment
LGK974+ PDR001 Combination Dose Escalation (~35 Patients)
RDE
LGK974 (Intermittent)+ PDR001 Combination Dose Expansion (~40 Patients)
Pancreatic LGK974+PDR001 (n=~10)
Melanoma LGK974+PDR001 (n=~10)
Triple Negative Breast Cancer LGK974+PDR001 (n=~10)
Head And Neck Cancer LGK974+PDR001 (n=~10)

FIG. 8

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2018/050846

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K39/395 A61K45/06 A61K31/496 A61P35/00
ADD.

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2016/196218 A1 (CUREGENIX CORP [US]) 8 December 2016 (2016-12-08) page 3, paragraph 11-12 claims 1, 16 page 42, paragraph 88-89 -----	1-41
X	anonymous: "A study of LGK974 in patients with malignancies dependent on wnt ligands", clinical Trials , 10 May 2011 (2011-05-10), XP002780915, Retrieved from the Internet: URL:https://clinicaltrials.gov/ct2/show/NCT01351103?term=LGK974&rank=1 [retrieved on 2018-05-09] page 3 ----- -/--	1-41

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 May 2018	06/06/2018

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2018/050846

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	F. JANKU ET AL: "Abstract C45: Phase I study of WNT974, a first in class porcupine inhibitor, in advanced solid tumors", MOLECULAR CANCER THERAPEUTICS, vol. 14, no. 12 suppl 2, December 2015 (2015-12), XP002780916, DOI: 10.1158/1535-7163.TARG-15-C45 the whole document ----	1-41
Y	A.NAING ET AL: "A first in human phase I study of the anti-PD-1 antibody PDR001 in patients with advanced solid tumors", JOURNAL OF CLINICAL ONCOLOGY, vol. 34, no. 15 suppl, 3060, 20 May 2016 (2016-05-20), XP002780917, DOI: 10.1200/JCO.2016.34.15_suppl.3060 the whole document ----	1-41
Y	J. LIU ET AL: "Targeting Wnt-driven cancer through the inhibition of Porcupine by LGK974", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, vol. 110, no. 50, 25 November 2013 (2013-11-25), pages 20224-20229, XP055121007, ISSN: 0027-8424, DOI: 10.1073/pnas.1314239110 page 20227, column 1, paragraph 2 page 20229, column 1, paragraph 2 - column 2, paragraph 1 ----	1,27,34
Y	US 2016/303137 A1 (RADOVICH MILAN [US] ET AL) 20 October 2016 (2016-10-20) page 2, paragraphs 22, 23 ----	1,27,34

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2018/050846

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2016196218 A1	08-12-2016	AU 2016271101 A1	30-11-2017
		CA 2985818 A1	08-12-2016
		CN 107613980 A	19-01-2018
		EP 3302467 A1	11-04-2018
		KR 20180011117 A	31-01-2018
		WO 2016196218 A1	08-12-2016
US 2016303137 A1	20-10-2016	NONE	