

mutations, and difficulty in separating the drivers from the passenger mutations. The Oncologist 24(12):e1303-e1314 (2019). The role of HER2-directed therapy in these HER2-mutated cancers is the subject of active exploration.

[0008] Targeted therapy of multiple non-redundant molecular pathways regulating immune responses can enhance antitumor immunotherapy. However, not all combinations have acceptable safety and/or efficacy. There remains a need for combination therapies with an acceptable safety profile and high efficacy for the treatment of cancer, in particular for the treatment of breast cancer and cervical cancer. Targeted therapy of multiple non-redundant molecular pathways regulating immune responses can enhance antitumor immunotherapy. However, not all combinations have acceptable safety and/or efficacy. There remains a need for combination therapies with an acceptable safety profile and high efficacy for the treatment of cancer, in particular for the treatment of HER2+ solid tumors.

[0009] All references cited herein, including patent applications, patent publications, and scientific literature, are herein incorporated by reference in their entirety, as if each individual reference were specifically and individually indicated to be incorporated by reference.

SUMMARY

[0010] In one aspect, the present disclosure provides a use of tucatinib, or a salt or solvate thereof, in the manufacture of a first medicament and use of an antibody or an antigen-binding fragment thereof in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat cancer in a subject, wherein the antibody binds to Programmed Death-1 (PD-1) and inhibits PD-1 activity, and wherein the cancer is a solid tumor. In another aspect, the present disclosure provides a use of tucatinib, or a salt or solvate thereof, in the manufacture of a medicament for use in combinatorial therapy for treating cancer in a subject, wherein said medicament is to be administered in combination with an antibody, or antigen-binding fragment thereof; wherein the antibody binds to PD-1 and inhibits PD-1 activity, and wherein the cancer is a solid tumor. In yet another aspect, the present disclosure provides a use of an antibody or an antigen-binding fragment thereof in the manufacture of a medicament for use in combinatorial therapy for treating cancer in a subject, wherein said medicament is to be administered in combination with tucatinib, or a salt or solvate

thereof; wherein the antibody binds to PD-1 and inhibits PD-1 activity, and wherein the cancer is a solid tumor. In a further aspect, the present disclosure provides a use of tucatinib, or a salt or solvate thereof, and an antibody or an antigen-binding fragment thereof in the manufacture of a medicament for combination therapy to treat cancer in a subject, wherein the antibody binds to PD-1 and inhibits PD-1 activity, and wherein the cancer is a solid tumor.

[0010a] In one aspect, the present disclosure provides a use of tucatinib, or a salt or solvate thereof, in the manufacture of a first medicament and use of an antibody or an antigen-binding fragment thereof in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat cancer in a subject, wherein the antibody binds to Programmed Death Ligand-1 (PD-L1) and inhibits PD-L1 activity, and wherein the cancer is a solid tumor. In another aspect, the present disclosure provides a use of tucatinib, or a salt or solvate thereof, in the manufacture of a medicament for use in combinatorial therapy for treating cancer in a subject, wherein said medicament is to be administered in combination with an antibody, or antigen-binding fragment thereof; wherein the antibody binds to PD-L1 and inhibits PD-L1 activity, and wherein the cancer is a solid tumor. In yet another aspect, the present disclosure provides a use of an antibody or an antigen-binding fragment thereof in the manufacture of a medicament for use in combinatorial therapy for treating cancer in a subject, wherein said medicament is to be administered in combination with tucatinib, or a salt or solvate thereof; wherein the antibody binds to PD-L1 and inhibits PD-L1 activity, and wherein the cancer is a solid tumor. In a further aspect, the present disclosure provides a use of tucatinib, or a salt or solvate thereof, and an antibody, or antigen-binding fragment thereof in the manufacture of a medicament for use in combination therapy to treat cancer in a subject, wherein the antibody binds to PD-L1 and inhibits PD-L1 activity, and wherein the cancer is a solid tumor.

[0010b] Provided herein is a method of treating cancer in a subject, the method comprising administering to the subject an antibody or an antigen-binding fragment thereof, wherein the antibody binds to Programmed Death-1 (PD-1) and inhibits PD-1 activity, and tucatinib, or salt or solvate thereof, to the subject, wherein the cancer is a solid tumor. In some **embodiment examples**, the anti-PD-1 antibody or antigen-binding fragment thereof comprises the complementary determining regions (CDRs) of an antibody or antigen-binding fragment selected from the group consisting of pembrolizumab, nivolumab, Amp-514, tislelizumab, cemiplimab, TSR-042, JNJ-63723283,

CBT-501, PF-06801591, JS-001, camrelizumab, PDR001, BCD-100, AGEN2034, IBI-308, BI-754091, GLS-010, LZM-009, AK-103, MGA-012, Sym-021 and CS1003, or a biosimilar thereof. In some embodiment examples, the anti-PD-1 antibody or antigen-binding fragment thereof comprises the complementary determining regions (CDRs) of an antibody or antigen-binding fragment of pembrolizumab. In some embodiment examples, the anti-PD-1 antibody or antigen-binding fragment thereof comprises the complementary determining regions (CDRs) of an

antibody or antigen-binding fragment of nivolumab. In some embodimentexamples, the anti-PD-1 antibody or antigen-binding fragment thereof comprises the heavy chain variable region and the light chain variable region of an antibody or antigen-binding fragment selected from the group consisting of pembrolizumab , nivolumab, Amp-514, tislelizumab, cemiplimab, TSR-042, JNJ-63723283, CBT-501, PF-06801591, JS-001, camrelizumab, PDR001, BCD-100, AGEN2034, IBI-308, BI-754091, GLS-010, LZM-009, AK-103, MGA-012, Sym-021 and CS1003, or a biosimilar thereof. In some embodimentexamples, the anti-PD-1 antibody or antigen-binding fragment thereof comprises the heavy chain variable region and the light chain variable region of an antibody or antigen-binding fragment selected from the group consisting of pembrolizumab, nivolumab, Amp-514, tislelizumab, cemiplimab, TSR-042, JNJ-63723283, CBT-501, PF-06801591, JS-001, camrelizumab, PDR001, BCD-100, AGEN2034, IBI-308, BI-754091, GLS-010, LZM-009, AK-103, MGA-012, Sym-021 and CS1003. In some embodimentexamples, the anti-PD-1 antibody or antigen-binding fragment thereof is selected from the group consisting of pembrolizumab, nivolumab, Amp-514, tislelizumab, cemiplimab, TSR-042, JNJ-63723283, CBT-501, PF-06801591, JS-001, camrelizumab, PDR001, BCD-100, AGEN2034, IBI-308, BI-754091, GLS-010, LZM-009, AK-103, MGA-012, Sym-021 and CS1003, or a biosimilar thereof. In some embodimentexamples, the anti-PD-1 antibody or antigen-binding fragment thereof is selected from the group consisting of pembrolizumab, nivolumab, Amp-514, tislelizumab, cemiplimab, TSR-042, JNJ-63723283, CBT-501, PF-06801591, JS-001, camrelizumab, PDR001, BCD-100, AGEN2034, IBI-308, BI-754091, GLS-010, LZM-009, AK-103, MGA-012, Sym-021 and CS1003. In some embodimentexamples, the anti-PD-1 antibody or antigen-binding fragment thereof is pembrolizumab. In some embodimentexamples, the anti-PD-1 antibody or antigen-binding fragment thereof is nivolumab. In some embodimentexamples, the anti-PD-1 antibody or antigen-binding fragment thereof is administered intravenously. In some embodimentexamples, one or more therapeutic effects in the subject is improved after administration of the tucatinib, or salt or solvate thereof, and the anti-PD-1 antibody or antigen-binding fragment thereof relative to a baseline. In some embodimentexamples, the one or more therapeutic effects is selected from the group consisting of: size of a tumor derived from the cancer, objective response rate, duration of response, time to response, progression free survival, and overall survival. In some embodimentexamples, the size of a tumor derived from the cancer is reduced by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%,

at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80% relative to the size of the tumor derived from the cancer before administration of the tucatinib, or salt or solvate thereof, and the anti-PD-1 antibody or antigen-binding fragment thereof. In some embodimentexamples, the objective response rate is at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80%. In some embodimentexamples, the subject exhibits progression-free survival of at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after administration of the tucatinib, or salt or solvate thereof, and the anti-PD-1 antibody or antigen-binding fragment thereof. In some embodimentexamples, the subject exhibits overall survival of at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after administration of the tucatinib, or salt or solvate thereof, and the anti-PD-1 antibody or antigen-binding fragment thereof. In some embodimentexamples, the duration of response to the tucatinib, or salt or solvate thereof, and the anti-PD-1 antibody or antigen-binding fragment thereof is at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after administration of the tucatinib, or salt or solvate thereof, and the anti-PD-1 antibody or antigen-binding fragment thereof. In some embodimentexamples, infiltration of natural killer (NK) cells is increased in the solid tumor following administration of tucatinib, or salt or solvate thereof. In some embodimentexamples, infiltration of CD8⁺ T cells expressing PD-1 is increased in the solid tumor following administration of tucatinib, or salt or solvate thereof. In some embodimentexamples, infiltration of CD8⁺ T cells expressing IFN γ is increased in the solid tumor

following administration of tucatinib, or salt or solvate thereof. In some [embodimentexamples](#), infiltration of CD8+ T cells expressing TIM3 is increased in the solid tumor following administration of tucatinib, or salt or solvate thereof. In some [embodimentexamples](#), infiltration of CD8+ T cells expressing OX40 is increased in the solid tumor following administration of tucatinib, or salt or solvate thereof. In some [embodimentexamples](#), infiltration of CD4+ T cells expressing FOXP3 is increased in the solid tumor following administration of tucatinib, or salt or solvate thereof. In some [embodimentexamples](#), infiltration of CD4+ T cells not expressing FOXP3 is increased in the solid tumor following administration of tucatinib, or salt or solvate thereof. In some [embodimentexamples](#), infiltration of CD4+ T cells expressing Ki67 is increased in the solid tumor following administration of tucatinib, or salt or solvate thereof. In some [embodimentexamples](#), the ratio of CD4+ to CD8+ T cells is increased in the solid tumor following administration of tucatinib, or salt or solvate thereof. In some [embodimentexamples](#), infiltration of neutrophils is decreased in the solid tumor following administration of tucatinib, or salt or solvate thereof. In some [embodimentexamples](#), the percentage of CD11b dendritic cells is increased in the solid tumor following administration of tucatinib, or salt or solvate thereof. In some [embodimentexamples](#), the percentage of MHC-II high expressing macrophages is increased in the solid tumor following administration of tucatinib, or salt or solvate thereof. In some [embodimentexamples](#), the percentage of MHC-II low expressing macrophages is decreased in the solid tumor following administration of tucatinib, or salt or solvate thereof. In some [embodimentexamples](#), the solid tumor is a HER2+ solid tumor. In some [embodimentexamples](#), the cancer has been determined to express a mutant form of HER2. In some [embodimentexamples](#), the cancer expresses a mutant form of HER2. In some [embodimentexamples](#), the mutant form of HER2 is determined by DNA sequencing. In some [embodimentexamples](#), wherein the mutant form of HER2 is determined by determining RNA sequencing. In some [embodimentexamples](#), the mutant form of HER2 is determined by nucleic acid sequencing. In some [embodimentexamples](#), the nucleic acid sequencing is next-generation sequencing (NGS). In some [embodimentexamples](#), the mutant form of HER2 is determined by polymerase chain reaction (PCR). In some [embodimentexamples](#), the mutant form of HER2 is determined by analyzing a sample obtained from the subject. In some [embodimentexamples](#), the sample obtained from the subject is a cell-free plasma sample. In some [embodimentexamples](#), the sample obtained from the subject is a tumor biopsy. In some [embodimentexamples](#), the HER2 mutation comprises at least one amino acid substitution, insertion, or deletion compared to the amino acid sequence of SEQ ID NO:1. In some [embodimentexamples](#), the HER2 mutation is an

activating mutation. In some [embodimentexamples](#), the HER2 mutation is a mutation in the extracellular domain, the kinase domain, or the transmembrane/juxtamembrane domain, or any combination thereof. In some [embodimentexamples](#), the HER2 mutation is a mutation in the extracellular domain selected from the group consisting of G309A, G309E, S310F, S310Y, C311R, C311S, and C334S. In some [embodimentexamples](#), the HER2 mutation is a mutation in the kinase domain at an amino acid residue selected from the group consisting of Y772, G776, G778, and T798. In some [embodimentexamples](#), the HER2 mutation is a G776 YVMA insertion. In some [embodimentexamples](#), the HER2 mutation is a mutation in the kinase domain selected from the group consisting of T733I, L755P, L755S, I767M, L768S, D769N, D769Y, D769H, V777L, V777M, L841V, V842I, N857S, T862A, L869R, H878Y, and R896C. In some [embodimentexamples](#), the HER2 mutation is a mutation in the kinase domain at an amino acid residue V697. In some [embodimentexamples](#), the HER2 mutation is a mutation in the transmembrane/juxtamembrane domain selected from the group consisting of S653C, I655V, V659E, G660D, and R678Q. In some [embodimentexamples](#), the cancer does not have HER2 amplification, and wherein the absence of HER2 amplification is determined by immunohistochemistry (IHC). In some [embodimentexamples](#), the cancer has a HER2 amplification score of 0 or 1+, and wherein the HER2 amplification score is determined by immunohistochemistry (IHC). In some [embodimentexamples](#), the cancer has less than a 2 fold increase in HER2 protein levels. In some [embodimentexamples](#), the solid tumor the solid tumor has been determined to comprise HER2 overexpression/amplification. In some [embodimentexamples](#), the solid tumor comprises HER2 overexpression/amplification. In some [embodimentexamples](#), the HER2 overexpression is 3+ overexpression as determined by immunohistochemistry (IHC). In some [embodimentexamples](#), the HER2 amplification is determined by an *in situ* hybridization assay. In some [embodimentexamples](#), the *in situ* hybridization assay is fluorescence *in situ* hybridization (FISH) assay. In some [embodimentexamples](#), the *in situ* hybridization assay is chromogenic *in situ* hybridization. In some [embodimentexamples](#), the HER2 amplification is determined in tissue by NGS. In some [embodimentexamples](#), the HER2 amplification is determined in circulating tumor DNA (ctDNA) by a blood-based NGS assay. In some [embodimentexamples](#), the solid tumor is a metastatic solid tumor. In some [embodimentexamples](#), the solid tumor is locally-advanced. In some [embodimentexamples](#), the solid tumor is unresectable. In some [embodimentexamples](#), the solid tumor is selected from the group consisting of cervical cancer, uterine cancer, gallbladder cancer, cholangiocarcinoma, urothelial cancer, lung cancer, breast cancer, gastroesophageal cancer, and colorectal cancer. In some [embodimentexamples](#), the breast cancer

is a HER2+ breast cancer. In some [embodimentexamples](#), the breast cancer is hormone receptor positive (HR+) breast cancer. In some [embodimentexamples](#), the lung cancer is non-small cell lung cancer. In some [embodimentexamples](#), the solid tumor is sensitive to trastuzumab. In some [embodimentexamples](#), the solid tumor is resistant to trastuzumab. In some [embodimentexamples](#), the tucatinib, or salt or solvate thereof, is administered to the subject at a dose of about 150 mg to about 650 mg. In some [embodimentexamples](#), the tucatinib, or salt or solvate thereof, is administered to the subject at a dose of about 300 mg. In some [embodimentexamples](#), the tucatinib, or salt or solvate thereof, is administered once or twice per day. In some [embodimentexamples](#), the tucatinib, or salt or solvate thereof, is administered to the subject at a dose of about 300 mg twice per day. In some [embodimentexamples](#), the tucatinib, or salt or solvate thereof, is administered to the subject orally. In some [embodimentexamples](#), the method further comprises administering one or more additional therapeutic agents to the subject to treat the cancer. In some [embodimentexamples](#), the one or more additional therapeutic agents is an anti-CTLA4 antibody or antigen-binding fragment thereof. In some [embodimentexamples](#), the anti-CTLA4 antibody or antigen-binding fragment thereof comprises the CDRs of ipilimumab, or a biosimilar thereof. In some [embodimentexamples](#), the anti-CTLA4 antibody or antigen-binding fragment thereof comprises the heavy chain variable region and the light chain variable region of ipilimumab, or a biosimilar thereof. In some [embodimentexamples](#), the anti-CTLA4 antibody or antigen-binding fragment thereof is ipilimumab, or a biosimilar thereof. In some [embodimentexamples](#), at least about 0.1%, at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80% of T-cells from the subject express CTLA4. In some [embodimentexamples](#), at least about 0.1%, at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80% of T-cells from the subject express PD-1. In some [embodimentexamples](#), at least about 0.1%, at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at

least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80% of cancer cells from the subject express PD-L1. In some embodimentexamples, treating the subject results in a tumor growth inhibition (TGI) index of at least about 85%. In some embodimentexamples, treating the subject results in a TGI index of about 100%. In some embodimentexamples, the subject has one or more adverse events and is further administered an additional therapeutic agent to eliminate or reduce the severity of the one or more adverse events. In some embodimentexamples, the subject is at risk of developing one or more adverse events and is further administered an additional therapeutic agent to prevent or reduce the severity of the one or more adverse events. In some embodimentexamples, the one or more adverse events is a grade 3 or greater adverse event. In some embodimentexamples, the one or more adverse events is a serious adverse event. In some embodimentexamples, the subject is a human. In some embodimentexamples, the tucatinib, or salt or solvate thereof, is in a pharmaceutical composition comprising the tucatinib, or salt or solvate thereof, and a pharmaceutical acceptable carrier. In some embodimentexamples, the anti-PD-1 antibody or antigen-binding fragment thereof is in a pharmaceutical composition comprising the anti-PD-1 antibody or antigen-binding fragment thereof and a pharmaceutical acceptable carrier. In some embodimentexamples, the anti-CTLA4 antibody or antigen-binding fragment thereof is in a pharmaceutical composition comprising the anti-CTLA4 antibody or antigen-binding fragment thereof and a pharmaceutical acceptable carrier.

[0011] Also provided herein is a kit comprising tucatinib, or salt or solvate thereof, an antibody or an antigen-binding fragment thereof, wherein the antibody binds to Programmed Death-1 (PD-1) and inhibits PD-1 activity; and instructions for use of the tucatinib, or salt or solvate thereof, and the anti-PD-1 antibody or antigen-binding fragment thereof according to any of the embodimentexamples herein.

[0012] Also provided herein is a method of treating cancer in a subject, the method comprising administering to the subject an antibody or an antigen-binding fragment thereof, wherein the antibody binds to Programmed Death Ligand-1 (PD-L1) and inhibits PD-L1 activity, and tucatinib, or salt or solvate thereof, to the subject, wherein the cancer is a solid tumor. In some embodimentexamples, the anti-PD-L1 antibody or antigen-binding fragment thereof comprises the complementary determining regions (CDRs) of an antibody or antigen-binding fragment selected from the group consisting of atezolizumab, BMS-936559, durvalumab, avelumab, envafolelimab,

CK-301, CS-1001, SHR-1316, CBT-502, and BGB-A333, or a biosimilar thereof. In some [embodimentexamples](#), the anti-PD-L1 antibody or antigen-binding fragment thereof comprises the complementary determining regions (CDRs) of an antibody or antigen-binding fragment of atezolizumab. In some [embodimentexamples](#), the anti-PD-L1 antibody or antigen-binding fragment thereof comprises the complementary determining regions (CDRs) of an antibody or antigen-binding fragment of BMS936559. In some [embodimentexamples](#), the anti-PD-L1 antibody or antigen-binding fragment thereof comprises the complementary determining regions (CDRs) of an antibody or antigen-binding fragment of durvalumab. In some [embodimentexamples](#), the anti-PD-L1 antibody or antigen-binding fragment thereof comprises the complementary determining regions (CDRs) of an antibody or antigen-binding fragment of avelumab. In some [embodimentexamples](#), the anti-PD-L1 antibody or antigen-binding fragment thereof comprises the heavy chain variable region and the light chain variable region of an antibody or antigen-binding fragment selected from the group consisting of atezolizumab, BMS-936559, durvalumab, avelumab, envafoimab, CK-301, CS-1001, SHR-1316, CBT-502, and BGB-A333, or a biosimilar thereof. In some [embodimentexamples](#), the anti-PD-L1 antibody or antigen-binding fragment thereof comprises the heavy chain variable region and the light chain variable region of an antibody or antigen-binding fragment selected from the group consisting of atezolizumab, BMS-936559, durvalumab, avelumab, envafoimab, CK-301, CS-1001, SHR-1316, CBT-502, and BGB-A333. In some [embodimentexamples](#), the anti-PD-L1 antibody or antigen-binding fragment thereof is selected from the group consisting of atezolizumab, BMS-936559, durvalumab, avelumab, envafoimab, CK-301, CS-1001, SHR-1316, CBT-502, and BGB-A333, or a biosimilar thereof. In some [embodimentexamples](#), the anti-PD-L1 antibody or antigen-binding fragment thereof is selected from the group consisting of atezolizumab, BMS-936559, durvalumab, avelumab, envafoimab, CK-301, CS-1001, SHR-1316, CBT-502, and BGB-A333. In some [embodimentexamples](#), the anti-PD-L1 antibody or antigen-binding fragment thereof is atezolizumab. In some [embodimentexamples](#), the anti-PD-L1 antibody or antigen-binding fragment thereof is BMS-936559. In some [embodimentexamples](#), the anti-PD-L1 antibody or antigen-binding fragment thereof is durvalumab. In some [embodimentexamples](#), the anti-PD-L1 antibody or antigen-binding fragment thereof is avelumab. In some [embodimentexamples](#), the anti-PD-L1 antibody or antigen-binding fragment thereof is administered intravenously. In some [embodimentexamples](#), one or more therapeutic effects in the subject is improved after administration of the tucatinib, or salt or solvate thereof, and the anti-PD-L1 antibody or antigen-

binding fragment thereof relative to a baseline. In some embodimentexamples, the one or more therapeutic effects is selected from the group consisting of: size of a tumor derived from the cancer, objective response rate, duration of response, time to response, progression free survival, and overall survival. In some embodimentexamples, the size of a tumor derived from the cancer is reduced by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80% relative to the size of the tumor derived from the cancer before administration of the tucatinib, or salt or solvate thereof, and the anti-PD-L1 antibody or antigen-binding fragment thereof. In some embodimentexamples, the objective response rate is at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80%. In some embodimentexamples, the subject exhibits progression-free survival of at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after administration of the tucatinib, or salt or solvate thereof, and the anti-PD-L1 antibody or antigen-binding fragment thereof. In some embodimentexamples, the subject exhibits overall survival of at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after administration of the tucatinib, or salt or solvate thereof, and the anti-PD-L1 antibody or antigen-binding fragment thereof. In some embodimentexamples, the duration of response to the tucatinib, or salt or solvate thereof, and the anti-PD-L1 antibody or antigen-binding fragment thereof is at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after administration of the tucatinib, or salt or

solvate thereof, and the anti-PD-L1 antibody or antigen-binding fragment thereof. In some [embodimentexamples](#), infiltration of natural killer (NK) cells is increased in the solid tumor following administration of tucatinib, or salt or solvate thereof. In some [embodimentexamples](#), infiltration of CD8+ T cells expressing PD-1 is increased in the solid tumor following administration of tucatinib, or salt or solvate thereof. In some [embodimentexamples](#), infiltration of CD8+ T cells expressing IFN γ is increased in the solid tumor following administration of tucatinib, or salt or solvate thereof. In some [embodimentexamples](#), infiltration of CD8+ T cells expressing TIM3 is increased in the solid tumor following administration of tucatinib, or salt or solvate thereof. In some [embodimentexamples](#), infiltration of CD8+ T cells expressing OX40 is increased in the solid tumor following administration of tucatinib, or salt or solvate thereof. In some [embodimentexamples](#), infiltration of CD4+ T cells expressing FOXP3 is increased in the solid tumor following administration of tucatinib, or salt or solvate thereof. In some [embodimentexamples](#), infiltration of CD4+ T cells not expressing FOXP3 is increased in the solid tumor following administration of tucatinib, or salt or solvate thereof. In some [embodimentexamples](#), infiltration of CD4+ T cells expressing Ki67 is increased in the solid tumor following administration of tucatinib, or salt or solvate thereof. In some [embodimentexamples](#), the ratio of CD4+ to CD8+ T cells is increased in the solid tumor following administration of tucatinib, or salt or solvate thereof. In some [embodimentexamples](#), infiltration of neutrophils is decreased in the solid tumor following administration of tucatinib, or salt or solvate thereof. In some [embodimentexamples](#), the percentage of CD11b dendritic cells is increased in the solid tumor following administration of tucatinib, or salt or solvate thereof. In some [embodimentexamples](#), the percentage of MHC-II high expressing macrophages is increased in the solid tumor following administration of tucatinib, or salt or solvate thereof. In some [embodimentexamples](#), the percentage of MHC-II low expressing macrophages is decreased in the solid tumor following administration of tucatinib, or salt or solvate thereof. In some [embodimentexamples](#), the solid tumor is a HER2+ solid tumor. In some [embodimentexamples](#), the cancer has been determined to express a mutant form of HER2. In some [embodimentexamples](#), the cancer expresses a mutant form of HER2. In some [embodimentexamples](#), the mutant form of HER2 is determined by DNA sequencing. In some [embodimentexamples](#), wherein the mutant form of HER2 is determined by determining RNA sequencing. In some [embodimentexamples](#), the mutant form of HER2 is determined by nucleic acid sequencing. In some [embodimentexamples](#), the nucleic acid sequencing is next-generation sequencing (NGS). In some [embodimentexamples](#), the mutant form of HER2 is determined by polymerase chain reaction (PCR). In

some [embodimentexamples](#), the mutant form of HER2 is determined by analyzing a sample obtained from the subject. In some [embodimentexamples](#), the sample obtained from the subject is a cell-free plasma sample. In some [embodimentexamples](#), the sample obtained from the subject is a tumor biopsy. In some [embodimentexamples](#), the HER2 mutation comprises at least one amino acid substitution, insertion, or deletion compared to the amino acid sequence of SEQ ID NO:1. In some [embodimentexamples](#), the HER2 mutation is an activating mutation. In some [embodimentexamples](#), the HER2 mutation is a mutation in the extracellular domain, the kinase domain, or the transmembrane/juxtamembrane domain, or any combination thereof. In some [embodimentexamples](#), the HER2 mutation is a mutation in the extracellular domain selected from the group consisting of G309A, G309E, S310F, S310Y, C311R, C311S, and C334S. In some [embodimentexamples](#), the HER2 mutation is a mutation in the kinase domain at an amino acid residue selected from the group consisting of Y772, G776, G778, and T798. In some [embodimentexamples](#), the HER2 mutation is a G776 YVMA insertion. In some [embodimentexamples](#), the HER2 mutation is a mutation in the kinase domain selected from the group consisting of T733I, L755P, L755S, I767M, L768S, D769N, D769Y, D769H, V777L, V777M, L841V, V842I, N857S, T862A, L869R, H878Y, and R896C. In some [embodimentexamples](#), the HER2 mutation is a mutation in the kinase domain at an amino acid residue V697. In some [embodimentexamples](#), the HER2 mutation is a mutation in the transmembrane/juxtamembrane domain selected from the group consisting of S653C, I655V, V659E, G660D, and R678Q. In some [embodimentexamples](#), the cancer does not have HER2 amplification, and wherein the absence of HER2 amplification is determined by immunohistochemistry (IHC). In some [embodimentexamples](#), the cancer has a HER2 amplification score of 0 or 1+, and wherein the HER2 amplification score is determined by immunohistochemistry (IHC). In some [embodimentexamples](#), the cancer has less than a 2 fold increase in HER2 protein levels. In some [embodimentexamples](#), the solid tumor the solid tumor has been determined to comprise HER2 overexpression/amplification. In some [embodimentexamples](#), the solid tumor comprises HER2 overexpression/amplification. In some [embodimentexamples](#), the HER2 overexpression is 3+ overexpression as determined by immunohistochemistry (IHC). In some [embodimentexamples](#), the HER2 amplification is determined by an *in situ* hybridization assay. In some [embodimentexamples](#), the *in situ* hybridization assay is fluorescence *in situ* hybridization (FISH) assay. In some [embodimentexamples](#), the *in situ* hybridization assay is chromogenic *in situ* hybridization. In some [embodimentexamples](#), the HER2 amplification is determined in tissue by NGS. In some [embodimentexamples](#), the HER2 amplification is determined in circulating tumor DNA (ctDNA) by a

blood-based NGS assay. In some [embodimentexamples](#), the solid tumor is a metastatic solid tumor. In some [embodimentexamples](#), the solid tumor is locally-advanced. In some [embodimentexamples](#), the solid tumor is unresetable. In some [embodimentexamples](#), the solid tumor is selected from the group consisting of cervical cancer, uterine cancer, gallbladder cancer, cholangiocarcinoma, urothelial cancer, lung cancer, breast cancer, gastroesophageal cancer, and colorectal cancer. In some [embodimentexamples](#), the breast cancer is a HER2+ breast cancer. In some [embodimentexamples](#), the breast cancer is hormone receptor positive (HR+) breast cancer. In some [embodimentexamples](#), the lung cancer is non-small cell lung cancer. In some [embodimentexamples](#), the solid tumor is sensitive to trastuzumab. In some [embodimentexamples](#), the solid tumor is resistant to trastuzumab. In some [embodimentexamples](#), the tucatinib, or salt or solvate thereof, is administered to the subject at a dose of about 150 mg to about 650 mg. In some [embodimentexamples](#), the tucatinib, or salt or solvate thereof, is administered to the subject at a dose of about 300 mg. In some [embodimentexamples](#), the tucatinib, or salt or solvate thereof, is administered once or twice per day. In some [embodimentexamples](#), the tucatinib, or salt or solvate thereof, is administered to the subject at a dose of about 300 mg twice per day. In some [embodimentexamples](#), the tucatinib, or salt or solvate thereof, is administered to the subject orally. In some [embodimentexamples](#), the method further comprises administering one or more additional therapeutic agents to the subject to treat the cancer. In some [embodimentexamples](#), the one or more additional therapeutic agents is an anti-CTLA4 antibody or antigen-binding fragment thereof. In some [embodimentexamples](#), the anti-CTLA4 antibody or antigen-binding fragment thereof comprises the CDRs of ipilimumab, or a biosimilar thereof. In some [embodimentexamples](#), the anti-CTLA4 antibody or antigen-binding fragment thereof comprises the heavy chain variable region and the light chain variable region of ipilimumab, or a biosimilar thereof. In some [embodimentexamples](#), the anti-CTLA4 antibody or antigen-binding fragment thereof is ipilimumab, or a biosimilar thereof. In some [embodimentexamples](#), at least about 0.1%, at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80% of T-cells from the subject express CTLA4. In some [embodimentexamples](#), at least about 0.1%, at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 15%, at least about 20%, at least

about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80% of T-cells from the subject express PD-1. In some embodimentexamples, at least about 0.1%, at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80% of cancer cells from the subject express PD-L1. In some embodimentexamples, treating the subject results in a tumor growth inhibition (TGI) index of at least about 85%. In some embodimentexamples, treating the subject results in a TGI index of about 100%. In some embodimentexamples, the subject has one or more adverse events and is further administered an additional therapeutic agent to eliminate or reduce the severity of the one or more adverse events. In some embodimentexamples, the subject is at risk of developing one or more adverse events and is further administered an additional therapeutic agent to prevent or reduce the severity of the one or more adverse events. In some embodimentexamples, the one or more adverse events is a grade 3 or greater adverse event. In some embodimentexamples, the one or more adverse events is a serious adverse event. In some embodimentexamples, the subject is a human. In some embodimentexamples, the tucatinib, or salt or solvate thereof, is in a pharmaceutical composition comprising the tucatinib, or salt or solvate thereof, and a pharmaceutical acceptable carrier. In some embodimentexamples, the anti-PD-L1 antibody or antigen-binding fragment thereof is in a pharmaceutical composition comprising the anti-PD-L1 antibody or antigen-binding fragment thereof and a pharmaceutical acceptable carrier. In some embodimentexamples, the anti-CTLA4 antibody or antigen-binding fragment thereof is in a pharmaceutical composition comprising the anti-CTLA4 antibody or antigen-binding fragment thereof and a pharmaceutical acceptable carrier.

[0013] Also provided herein is a kit comprising tucatinib, or salt or solvate thereof, an antibody or an antigen-binding fragment thereof, wherein the antibody binds to Programmed Death ligant-1 (PD-L1) and inhibits PD-L1 activity; and instructions for use of the tucatinib, or salt or solvate thereof, and the anti-PD-L1 antibody or antigen-binding fragment thereof according to any of the embodimentexamples herein.

[0014] It is to be understood that one, some, or all of the properties of the various embodimentexamples described herein may be combined to form other embodimentexamples of the present inventiondisclosure. These and other aspectexamples of the inventiondisclosure will become apparent to one of skill in the art. These and other embodimentexamples of the inventiondisclosure are further described by the detailed description that follows.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] FIG. 1A-1D is a series of graphs showing the effect of tucatinib on the tumor microenvironment using a trastuzumab resistant Fo5 murine tumor model.

[0016] FIG. 2A-2L is a series of graphs showing the effect of tucatinib on the tumor microenvironment using a trastuzumab sensitive H2N113 murine tumor model.

[0017] FIG. 3A-3B is a heatmap RNA profile for trastuzumab resistant Fo5 tumors that have been treated with tucatinib or vehicle control. The IFN γ -related gene signature is shown in FIG. 3A and the expanded immune signature is shown in FIG. 3B.

[0018] FIG. 4A-4B is a series of graphs showing the effect of tucatinib and various combination treatments on Fo5 tumor growth (FIG. 4A) and survival (FIG. 4B) using the treatments indicated in the legends. N=5 per treatment group.

[0019] FIG. 5A-5C shows the *in vitro* effect on cell growth of tucatinib at various doses in the cell lines (FIG. 5A) BT474, (FIG. 5B) SKBR3, and (FIG. 5C) H2N113.

[0020] FIG. 6 shows the H2N113 trastuzumab-sensitive HER2-positive murine tumor model scheme for assessing the effect of tucatinib on tumor size and mouse survival.

[0021] FIG. 7 shows the Fo5 trastuzumab-resistant HER2-positive murine tumor model scheme for assessing the effect of tucatinib on tumor size and mouse survival.

[0022] FIG. 8A-8B shows results of tucatinib in a H2N113 trastuzumab-sensitive HER2-positive murine tumor model. BALB/c MMTV mice inoculated with H2N113 by subcutaneous injection were treated with tucatinib or vehicle control by oral gavage at the indicated doses, and (FIG. 8A) tumor volume and (FIG. 8B) percent survival were assessed at the indicated time points. Data shown for tumor volume represent mean tumor volume (mm³) +/- SEM. P values

CLAIMS

~~1. A method of treating cancer in a subject, the method comprising administering to the subject an antibody or an antigen-binding fragment thereof, wherein the antibody binds to Programmed Death-1 (PD-1) and inhibits PD-1 activity, and tucatinib, or salt or solvate thereof, to the subject, wherein the cancer is a solid tumor.~~

1. Use of tucatinib, or a salt or solvate thereof, in the manufacture of a first medicament and use of an antibody or an antigen-binding fragment thereof in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat cancer in a subject, wherein the antibody binds to Programmed Death-1 (PD-1) and inhibits PD-1 activity, and wherein the cancer is a solid tumor.

2. Use of tucatinib, or a salt or solvate thereof, in the manufacture of a medicament for use in combinatorial therapy for treating cancer in a subject, wherein said medicament is to be administered in combination with an antibody, or antigen-binding fragment thereof; wherein the antibody binds to PD-1 and inhibits PD-1 activity, and wherein the cancer is a solid tumor.

3. Use of an antibody or an antigen-binding fragment thereof in the manufacture of a medicament for use in combinatorial therapy for treating cancer in a subject, wherein said medicament is to be administered in combination with tucatinib, or a salt or solvate thereof; wherein the antibody binds to PD-1 and inhibits PD-1 activity, and wherein the cancer is a solid tumor.

4. Use of tucatinib, or a salt or solvate thereof, and an antibody or an antigen-binding fragment thereof in the manufacture of a medicament for combination therapy to treat cancer in a subject, wherein the antibody binds to PD-1 and inhibits PD-1 activity, and wherein the cancer is a solid tumor.

52. The use of any one of claims 1-4~~method of claim 1~~, wherein:

(i) the anti-PD-1 antibody or antigen-binding fragment thereof comprises the complementary determining regions (CDRs) of an antibody or antigen-binding fragment selected

from the group consisting of pembrolizumab, nivolumab, Amp-514, tislelizumab, cemiplimab, TSR-042, JNJ-63723283, CBT-501, PF-06801591, JS-001, camrelizumab, PDR001, BCD-100, AGEN2034, IBI-308, BI-754091, GLS-010, LZM-009, AK-103, MGA-012, Sym-021 and CS1003, or a biosimilar thereof;

(ii) the anti-PD-1 antibody or antigen-binding fragment thereof comprises the heavy chain variable region and the light chain variable region of an antibody or antigen-binding fragment selected from the group consisting of pembrolizumab , nivolumab, Amp-514, tislelizumab, cemiplimab, TSR-042, JNJ-63723283, CBT-501, PF-06801591, JS-001, camrelizumab, PDR001, BCD-100, AGEN2034, IBI-308, BI-754091, GLS-010, LZM-009, AK-103, MGA-012, Sym-021 and CS1003, or a biosimilar thereof; and/or

(iii) the anti-PD-1 antibody or antigen-binding fragment thereof is selected from the group consisting of pembrolizumab, nivolumab, Amp-514, tislelizumab, cemiplimab, TSR-042, JNJ-63723283, CBT-501, PF-06801591, JS-001, camrelizumab, PDR001, BCD-100, AGEN2034, IBI-308, BI-754091, GLS-010, LZM-009, AK-103, MGA-012, Sym-021 and CS1003, or a biosimilar thereof.

~~3. The method of claim 1, wherein the anti PD-1 antibody or antigen-binding fragment thereof comprises the complementary determining regions (CDRs) of an antibody or antigen-binding fragment of pembrolizumab.~~

~~4. The method of claim 1, wherein the anti PD-1 antibody or antigen-binding fragment thereof comprises the complementary determining regions (CDRs) of an antibody or antigen-binding fragment of nivolumab.~~

~~5. The method of claim 1, wherein the anti PD-1 antibody or antigen-binding fragment thereof comprises the heavy chain variable region and the light chain variable region of an antibody or antigen-binding fragment selected from the group consisting of pembrolizumab , nivolumab, Amp-514, tislelizumab, cemiplimab, TSR-042, JNJ-63723283, CBT-501, PF-06801591, JS-001, camrelizumab, PDR001, BCD-100, AGEN2034, IBI-308, BI-754091, GLS-010, LZM-009, AK-103, MGA-012, Sym-021 and CS1003, or a biosimilar thereof.~~

~~6. The method of claim 1, wherein the anti PD-1 antibody or antigen-binding fragment thereof comprises the heavy chain variable region and the light chain variable region of an antibody or antigen-binding fragment selected from the group consisting of pembrolizumab, nivolumab, Amp-514, tislelizumab, cemiplimab, TSR-042, JNJ-63723283, CBT-501, PF-06801591, JS-001, camrelizumab, PDR001, BCD-100, AGEN2034, IBI-308, BI-754091, GLS-010, LZM-009, AK-103, MGA-012, Sym-021 and CS1003.~~

~~7. The method of claim 1, wherein the anti PD-1 antibody or antigen-binding fragment thereof is selected from the group consisting of pembrolizumab, nivolumab, Amp-514, tislelizumab, cemiplimab, TSR-042, JNJ-63723283, CBT-501, PF-06801591, JS-001, camrelizumab, PDR001, BCD-100, AGEN2034, IBI-308, BI-754091, GLS-010, LZM-009, AK-103, MGA-012, Sym-021 and CS1003, or a biosimilar thereof.~~

~~8. The method of claim 1, wherein the anti PD-1 antibody or antigen-binding fragment thereof is selected from the group consisting of pembrolizumab, nivolumab, Amp-514, tislelizumab, cemiplimab, TSR-042, JNJ-63723283, CBT-501, PF-06801591, JS-001, camrelizumab, PDR001, BCD-100, AGEN2034, IBI-308, BI-754091, GLS-010, LZM-009, AK-103, MGA-012, Sym-021 and CS1003.~~

~~9. The method of claim 1, wherein the anti PD-1 antibody or antigen-binding fragment thereof is pembrolizumab.~~

~~10. The method of claim 1, wherein the anti PD-1 antibody or antigen-binding fragment thereof is nivolumab.~~

611. The ~~method-use~~ of any one of claims 1-~~510~~, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is to be administered intravenously.

712. The ~~method-use~~ of any one of claims 1-611, wherein one or more therapeutic effects in the subject is improved after administration of the tucatinib, or salt or solvate thereof, and the anti-PD-1 antibody or antigen-binding fragment thereof relative to a baseline, optionally wherein

the one or more therapeutic effects is selected from the group consisting of: size of a tumor derived from the cancer, objective response rate, duration of response, time to response, progression free survival, and overall survival.

13. — ~~The method of claim 12, wherein the one or more therapeutic effects is selected from the group consisting of: size of a tumor derived from the cancer, objective response rate, duration of response, time to response, progression free survival, and overall survival.~~

14. — ~~The method of any one of claims 1-13, wherein the size of a tumor derived from the cancer is reduced by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80% relative to the size of the tumor derived from the cancer before administration of the tucatinib, or salt or solvate thereof, and the anti PD-1 antibody or antigen-binding fragment thereof.~~

15. — ~~The method of any one of claims 1-14, wherein the objective response rate is at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80%.~~

16. — ~~The method of any one of claims 1-15, wherein the subject exhibits progression-free survival of at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after administration of the tucatinib, or salt or solvate thereof, and the anti PD-1 antibody or antigen-binding fragment thereof.~~

17. — ~~The method of any one of claims 1-16, wherein the subject exhibits overall survival of at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at~~

least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after administration of the tucatinib, or salt or solvate thereof, and the anti-PD-1 antibody or antigen-binding fragment thereof.

18. — The method of any one of claims 1-16, wherein the duration of response to the tucatinib, or salt or solvate thereof, and the anti-PD-1 antibody or antigen-binding fragment thereof is at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after administration of the tucatinib, or salt or solvate thereof, and the anti-PD-1 antibody or antigen-binding fragment thereof.

19. A method of treating cancer in a subject, the method comprising administering to the subject an antibody or an antigen-binding fragment thereof, wherein the antibody binds to Programmed Death Ligand-1 (PD-L1) and inhibits PD-L1 activity, and tucatinib, or salt or solvate thereof, to the subject, wherein the cancer is a solid tumor.

8. Use of tucatinib, or a salt or solvate thereof, in the manufacture of a first medicament and use of an antibody or an antigen-binding fragment thereof in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat cancer in a subject, wherein the antibody binds to Programmed Death Ligand-1 (PD-L1) and inhibits PD-L1 activity, and wherein the cancer is a solid tumor.

9. Use of tucatinib, or a salt or solvate thereof, in the manufacture of a medicament for use in combinatorial therapy for treating cancer in a subject, wherein said medicament is to be administered in combination with an antibody, or antigen-binding fragment thereof; wherein the antibody binds to PD-L1 and inhibits PD-L1 activity, and wherein the cancer is a solid tumor.

10. Use of an antibody or an antigen-binding fragment thereof in the manufacture of a medicament for use in combinatorial therapy for treating cancer in a subject, wherein said medicament is to be administered in combination with tucatinib, or a salt or solvate thereof; wherein the antibody binds to PD-L1 and inhibits PD-L1 activity, and wherein the cancer is a solid tumor.

11. Use of tucatinib, or a salt or solvate thereof, and an antibody or an antigen-binding fragment thereof in the manufacture of a medicament for combination therapy to treat cancer in a subject, wherein the antibody binds to PD-L1 and inhibits PD-L1 activity, and wherein the cancer is a solid tumor.

1220. The use of any one of claims 8-11~~method of claim 19~~, wherein:

(i) the anti-PD-L1 antibody or antigen-binding fragment thereof comprises the complementary determining regions (CDRs) of an antibody or antigen-binding fragment selected from the group consisting of atezolizumab, BMS-936559, durvalumab, avelumab, envafolimab, CK-301, CS-1001, SHR-1316, CBT-502, and BGB-A333, or a biosimilar thereof;

(ii) the anti-PD-L1 antibody or antigen-binding fragment thereof comprises the heavy chain variable region and the light chain variable region of an antibody or antigen-binding fragment selected from the group consisting of atezolizumab, BMS-936559, durvalumab, avelumab, envafolimab, CK-301, CS-1001, SHR-1316, CBT-502, and BGB-A333, or a biosimilar thereof; and/or

(iii) the anti-PD-L1 antibody or antigen-binding fragment thereof is selected from the group consisting of atezolizumab, BMS-936559, durvalumab, avelumab, envafolimab, CK-301, CS-1001, SHR-1316, CBT-502, and BGB-A333, or a biosimilar thereof.

~~21. The method of claim 19, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof comprises the complementary determining regions (CDRs) of an antibody or antigen-binding fragment of atezolizumab.~~

~~22. The method of claim 19, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof comprises the complementary determining regions (CDRs) of an antibody or antigen-binding fragment of BMS936559.~~

~~23. The method of claim 19, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof comprises the complementary determining regions (CDRs) of an antibody or antigen-binding fragment of durvalumab.~~

~~24. The method of claim 19, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof comprises the complementary determining regions (CDRs) of an antibody or antigen-binding fragment of avelumab.~~

~~25. The method of claim 19, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof comprises the heavy chain variable region and the light chain variable region of an antibody or antigen-binding fragment selected from the group consisting of atezolizumab, BMS-936559, durvalumab, avelumab, envafolelimab, CK-301, CS-1001, SHR-1316, CBT-502, and BGB-A333, or a biosimilar thereof.~~

~~26. The method of claim 19, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof comprises the heavy chain variable region and the light chain variable region of an antibody or antigen-binding fragment selected from the group consisting of atezolizumab, BMS-936559, durvalumab, avelumab, envafolelimab, CK-301, CS-1001, SHR-1316, CBT-502, and BGB-A333.~~

~~27. The method of claim 19, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof is selected from the group consisting of atezolizumab, BMS-936559, durvalumab, avelumab, envafolelimab, CK-301, CS-1001, SHR-1316, CBT-502, and BGB-A333, or a biosimilar thereof.~~

~~28. The method of claim 19, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof is selected from the group consisting of atezolizumab, BMS-936559, durvalumab, avelumab, envafolelimab, CK-301, CS-1001, SHR-1316, CBT-502, and BGB-A333.~~

~~29. The method of claim 19, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof is atezolizumab.~~

~~30. The method of claim 19, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof is BMS-936559.~~

~~31. The method of claim 19, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof is durvalumab.~~

~~32. The method of claim 19, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof is avelumab.~~

1333. The method-use of any one of claims ~~19-328-12~~, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof is to be administered intravenously.

1434. The method-use of any one of claims ~~19-328-13~~, wherein one or more therapeutic effects in the subject is improved after administration of the tucatinib, or salt or solvate thereof, and the anti-PD-L1 antibody or antigen-binding fragment thereof relative to a baseline, optionally wherein the one or more therapeutic effects is selected from the group consisting of: size of a tumor derived from the cancer, objective response rate, duration of response, time to response, progression free survival, and overall survival.

~~35.—The method of claim 34, wherein the one or more therapeutic effects is selected from the group consisting of: size of a tumor derived from the cancer, objective response rate, duration of response, time to response, progression free survival, and overall survival.~~

36. — ~~The method of any one of claims 19-35, wherein the size of a tumor derived from the cancer is reduced by at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80% relative to the size of the tumor derived from the cancer before administration of the tucatinib, or salt or solvate thereof, and the anti-PD-L1 antibody or antigen-binding fragment thereof.~~

37. — ~~The method of any one of claims 19-36, wherein the objective response rate is at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80%.~~

38. — ~~The method of any one of claims 19-37, wherein the subject exhibits progression-free survival of at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after administration of the tucatinib, or salt or solvate thereof, and the anti-PD-L1 antibody or antigen-binding fragment thereof.~~

39. — ~~The method of any one of claims 19-37, wherein the subject exhibits overall survival of at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after administration of the tucatinib, or salt or solvate thereof, and the anti-PD-L1 antibody or antigen-binding fragment thereof.~~

40. — ~~The method of any one of claims 19-39, wherein the duration of response to the tucatinib, or salt or solvate thereof, and the anti-PD-L1 antibody or antigen-binding fragment thereof is at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at~~

~~least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 12 months, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after administration of the tucatinib, or salt or solvate thereof, and the anti-PD-L1 antibody or antigen-binding fragment thereof.~~

~~1541.~~ The ~~method-use~~ of any one of claims 1-~~1440~~, wherein:

- ~~(i) infiltration of natural killer (NK) cells, CD8+ T cells expressing PD-1, CD8+ T cells expressing IFN γ , CD8+ T cells expressing TIM3, CD8+ T cells expressing OX40, CD4+ T cells expressing FOXP3, CD4+ T cells not expressing FOXP3, and/or CD4+ T cells expressing Ki67 is increased in the solid tumor following administration of tucatinib, or salt or solvate thereof;~~
- ~~(ii) the ratio of CD4+ to CD8+ T cells is increased in the solid tumor following administration of tucatinib, or salt or solvate thereof;~~
- ~~(iii) infiltration of neutrophils is decreased in the solid tumor following administration of tucatinib, or salt or solvate thereof;~~
- ~~(iv) the percentage of CD11b dendritic cells and/or MHC-II high expressing macrophages is increased in the solid tumor following administration of tucatinib, or salt or solvate thereof; and/or~~
- ~~(v) the percentage of MHC-II low expressing macrophages is decreased in the solid tumor following administration of tucatinib, or salt or solvate thereof.~~

~~42. The method of any one of claims 1-41, wherein infiltration of CD8+ T cells expressing PD-1 is increased in the solid tumor following administration of tucatinib, or salt or solvate thereof.~~

~~43. The method of any one of claims 1-42, wherein infiltration of CD8+ T cells expressing IFN γ is increased in the solid tumor following administration of tucatinib, or salt or solvate thereof.~~

~~44. The method of any one of claims 1-43, wherein infiltration of CD8+ T cells expressing TIM3 is increased in the solid tumor following administration of tucatinib, or salt or solvate thereof.~~

~~45. The method of any one of claims 1-44, wherein infiltration of CD8+ T cells expressing OX40 is increased in the solid tumor following administration of tucatinib, or salt or solvate thereof.~~

~~46. The method of any one of claims 1-45, wherein infiltration of CD4+ T cells expressing FOXP3 is increased in the solid tumor following administration of tucatinib, or salt or solvate thereof.~~

~~47. The method of any one of claims 1-46, wherein infiltration of CD4+ T cells not expressing FOXP3 is increased in the solid tumor following administration of tucatinib, or salt or solvate thereof.~~

~~48. The method of any one of claims 1-47, wherein infiltration of CD4+ T cells expressing Ki67 is increased in the solid tumor following administration of tucatinib, or salt or solvate thereof.~~

~~49. The method of any one of claims 1-48, wherein the ratio of CD4+ to CD8+ T cells is increased in the solid tumor following administration of tucatinib, or salt or solvate thereof.~~

~~50. The method of any one of claims 1-49, wherein infiltration of neutrophils is decreased in the solid tumor following administration of tucatinib, or salt or solvate thereof.~~

~~51. The method of any one of claims 1-50, wherein the percentage of CD11b dendritic cells is increased in the solid tumor following administration of tucatinib, or salt or solvate thereof.~~

~~52. The method of any one of claims 1-51, wherein the percentage of MHC-II high expressing macrophages is increased in the solid tumor following administration of tucatinib, or salt or solvate thereof.~~

~~53. The method of any one of claims 1-52, wherein the percentage of MHC-II low expressing macrophages is decreased in the solid tumor following administration of tucatinib, or salt or solvate thereof.~~

~~1654.~~ The ~~method-use~~ of any one of claims 1-~~1553~~, wherein the solid tumor is a HER2+ solid tumor.

~~1755.~~ The ~~method-use~~ of any one of claims 1-~~1654~~, wherein the cancer has been determined to express a mutant form of HER2 or the cancer expresses a mutant form of HER2.

~~56. The method of any one of claims 1-55, wherein the cancer expresses a mutant form of HER2.~~

~~1857.~~ The ~~method-use~~ of claim ~~1755 or claim 56~~, wherein the mutant form of HER2 is determined by:

~~(i) -DNA sequencing,~~

~~(ii) RNA sequencing,~~

~~(iii) next-generation sequencing (NGS), and/or~~

~~(iv) polymerase chain reaction (PCR);~~

~~optionally wherein the mutant form of HER2 is determined by analyzing a sample obtained from the subject, further optionally wherein the sample obtained from the subject is a cell-free plasma sample or a tumor biopsy.~~

~~58. The method of claim 55 or claim 56, wherein the mutant form of HER2 is determined by determining RNA sequencing.~~

~~59. The method of any one of claims 55-58, wherein the mutant form of HER2 is determined by nucleic acid sequencing.~~

~~60. The method of claim 59, wherein the nucleic acid sequencing is next-generation sequencing (NGS).~~

~~61. The method of claim 55 or claim 56, wherein the mutant form of HER2 is determined by polymerase chain reaction (PCR).~~

~~62. The method of any one of claims 55-61, wherein the mutant form of HER2 is determined by analyzing a sample obtained from the subject.~~

~~63. The method of claim 62, wherein the sample obtained from the subject is a cell-free plasma sample.~~

~~64. The method of claim 62, wherein the sample obtained from the subject is a tumor biopsy.~~

1965. The ~~method-use~~ of claim 17 or claim 18~~any one of claims 55-64~~, wherein the HER2 mutation comprises at least one amino acid substitution, insertion, or deletion compared to the amino acid sequence of SEQ ID NO:1.

2066. The ~~method-use~~ of claim 1965, wherein the HER2 mutation is an activating mutation and/or is a mutation in the extracellular domain, the kinase domain, or the transmembrane/juxtamembrane domain, or any combination thereof.

~~67. The method of claim 65 or claim 66, wherein the HER2 mutation is a mutation in the extracellular domain, the kinase domain, or the transmembrane/juxtamembrane domain, or any combination thereof.~~

2168. The ~~method-use~~ of claim 19 or claim 2067, wherein the HER2 mutation is

- (i) a mutation in the extracellular domain selected from the group consisting of G309A, G309E, S310F, S310Y, C311R, C311S, and C334S;
- (ii) a mutation in the kinase domain at an amino acid residue selected from the group consisting of Y772, G776, G778, and T798;
- (iii) a G776 YVMA insertion;
- (iv) a mutation in the kinase domain selected from the group consisting of T733I, L755P, L755S, I767M, L768S, D769N, D769Y, D769H, V777L, V777M, L841V, V842I, N857S, T862A, L869R, H878Y, and R896C;
- (v) a mutation in the kinase domain at an amino acid residue V697; or

(vi) a mutation in the transmembrane/juxtamembrane domain selected from the group consisting of S653C, I655V, V659E, G660D, and R678Q.

~~69. The method of claim 67, wherein the HER2 mutation is a mutation in the kinase domain at an amino acid residue selected from the group consisting of Y772, G776, G778, and T798.~~

~~70. The method of claim 67, wherein the HER2 mutation is a G776 YVMA insertion.~~

~~71. The method of claim 67, wherein the HER2 mutation is a mutation in the kinase domain selected from the group consisting of T733I, L755P, L755S, I767M, L768S, D769N, D769Y, D769H, V777L, V777M, L841V, V842I, N857S, T862A, L869R, H878Y, and R896C.~~

~~72. The method of claim 67, wherein the HER2 mutation is a mutation in the kinase domain at an amino acid residue V697.~~

~~73. The method of claim 67, wherein the HER2 mutation is a mutation in the transmembrane/juxtamembrane domain selected from the group consisting of S653C, I655V, V659E, G660D, and R678Q.~~

2274. The ~~method-use~~ of any one of claims ~~17-2155-73~~, wherein:

(i) the cancer does not have HER2 amplification, and wherein the absence of HER2 amplification is determined by immunohistochemistry (IHC); or

(ii) the cancer has a HER2 amplification score of 0 or 1+, and wherein the HER2 amplification score is determined by immunohistochemistry (IHC).

~~75. The method of any one of claims 55-73, wherein the cancer has a HER2 amplification score of 0 or 1+, and wherein the HER2 amplification score is determined by immunohistochemistry (IHC).~~

2376. The ~~method-use~~ of any one of claims ~~17-2255-75~~, wherein the cancer has less than a 2 fold increase in HER2 protein levels.

2477. The ~~method-use~~ of any one of claims 1-~~2373~~, wherein the solid tumor the solid tumor has been determined to comprise HER2 overexpression/amplification; or the solid tumor comprises HER2 overexpression/amplification.

~~78. The method of any one of claims 1-73, wherein the solid tumor comprises HER2 overexpression/amplification.~~

2579. The ~~method-use~~ of claim ~~2477 or claim 78~~, wherein the HER2 overexpression is 3+ overexpression as determined by immunohistochemistry (IHC); or the HER2 amplification is determined by an *in situ* hybridization assay.

~~80. The method of claim 77 or claim 78, wherein the HER2 amplification is determined by an *in situ* hybridization assay.~~

2681. The ~~method-use~~ of claim ~~8024~~, wherein the *in situ* hybridization assay is fluorescence *in situ* hybridization (FISH) assay or chromogenic *in situ* hybridization.

~~82. The method of claim 80, wherein the *in situ* hybridization assay is chromogenic *in situ* hybridization.~~

2783. The ~~method-use~~ of claim ~~77 or claim 7824~~, wherein the HER2 amplification is determined in tissue by NGS or in circulating tumor DNA (ctDNA) by a blood-based NGS assay.

~~84. The method of claim 77 or claim 78, wherein the HER2 amplification is determined in circulating tumor DNA (ctDNA) by a blood-based NGS assay.~~

2885. The ~~method-use~~ of any one of claims 1-~~2784~~, wherein the solid tumor is
(i) a metastatic solid tumor;
(ii) locally-advanced; and/or
(iii) unresetable.

~~86. The method of any one of claims 1-85, wherein the solid tumor is locally advanced.~~

~~87. The method of any one of claims 1-86, wherein the solid tumor is unresetable.~~

2988. The ~~method-use~~ of any one of claims 1-~~2887~~, wherein the solid tumor is selected from the group consisting of cervical cancer, uterine cancer, gallbladder cancer, cholangiocarcinoma, urothelial cancer, lung cancer, breast cancer, gastroesophageal cancer, and colorectal cancer.

3089. The ~~method-use~~ of claim 2988, wherein the breast cancer is a HER2+ breast cancer and/or hormone receptor positive (HR+) breast cancer.

~~90. The method of claim 88 or claim 89, wherein the breast cancer is hormone receptor positive (HR+) breast cancer.~~

3191. The ~~method-use~~ of claim 2988, wherein the lung cancer is non-small cell lung cancer.

3292. The ~~method-use~~ of any one of claims 1-3191, wherein the solid tumor is sensitive to trastuzumab.

3393. The ~~method-use~~ of any one of claims 1-3191, wherein the solid tumor is resistant to trastuzumab.

3494. The ~~method-use~~ of any one of claims 1-3393, wherein the tucatinib, or salt or solvate thereof, is to be administered to the subject at a dose of ~~about~~ 150 mg to ~~about~~ 650 mg, optionally at a dose of about 300 mg.

~~95. The method of claim 94, wherein the tucatinib, or salt or solvate thereof, is administered to the subject at a dose of about 300 mg.~~

3596. The ~~method-use~~ of claim 3494 or 95, wherein the tucatinib, or salt or solvate thereof, is to be administered once or twice per day.

~~3697.~~ The ~~method-use~~ of claim ~~3596~~, wherein the tucatinib, or salt or solvate thereof, is to be administered to the subject at a dose of about 300 mg twice per day.

~~3798.~~ The ~~method-use~~ of any one of claims 1-~~3697~~, wherein the tucatinib, or salt or solvate thereof, is to be administered to the subject orally.

~~3899.~~ The ~~method-use~~ of any one of claims 1-~~3798~~, further comprising ~~administering-that~~ one or more additional therapeutic agents is to be administered to the subject to treat the cancer, optionally wherein the one or more additional therapeutic agents is an anti-CTLA4 antibody or antigen-binding fragment thereof.

~~100.~~ The ~~method of claim 99, wherein the one or more additional therapeutic agents is an anti-CTLA4 antibody or antigen-binding fragment thereof.~~

~~39101.~~ The ~~method-use~~ of claim ~~38100~~, wherein the anti-CTLA4 antibody or antigen-binding fragment thereof

(i) comprises the CDRs of ipilimumab, or a biosimilar thereof;

(ii) comprises the heavy chain variable region and the light chain variable region of ipilimumab, or a biosimilar thereof; or

(iii) is ipilimumab, or a biosimilar thereof.

~~102.~~ The ~~method of claim 100, wherein the anti-CTLA4 antibody or antigen-binding fragment thereof comprises the heavy chain variable region and the light chain variable region of ipilimumab, or a biosimilar thereof.~~

~~103.~~ The ~~method of claim 100, wherein the anti-CTLA4 antibody or antigen-binding fragment thereof is ipilimumab, or a biosimilar thereof.~~

~~40104.~~ The ~~method-use~~ of claim 39~~any one of claims 100-103~~, wherein:

(i) at least about 0.1%, at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least

about 9%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80% of T-cells from the subject express CTLA4;

(ii) at least about 0.1%, at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80% of T-cells from the subject express PD-1; and/or

(iii) at least about 0.1%, at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80% of cancer cells from the subject express PD-L1.

~~105.—The method of any one of claims 1–104, wherein at least about 0.1%, at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80% of T-cells from the subject express PD-1.~~

~~106.—The method of any one of claims 1–105, wherein at least about 0.1%, at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, or at least about 80% of cancer cells from the subject express PD-L1.~~

~~41107.~~ The ~~method-use~~ of any one of claims 1-~~40106~~, wherein treating the subject results in a tumor growth inhibition (TGI) index of at least about 85%.

~~108. The method of any one of claims 1-107, wherein treating the subject results in a TGI index of about 100%.~~

~~42109.~~ The ~~method-use~~ of any one of claims 1-~~41108~~, wherein the subject has one or more adverse events and is to be further administered an additional therapeutic agent to eliminate or reduce the severity of the one or more adverse events.

~~43110.~~ The ~~method-use~~ of any one of claims 1-~~42109~~, wherein the subject is at risk of developing one or more adverse events and is to be further administered an additional therapeutic agent to prevent or reduce the severity of the one or more adverse events.

~~44111.~~ The ~~method-use~~ of claim ~~42109~~ or claim ~~43110~~, wherein the one or more adverse events is a grade 3 or greater adverse event or a serious adverse event.

~~112. The method of claim 109 or claim 110, wherein the one or more adverse events is a serious adverse event.~~

~~45113.~~ The ~~method-use~~ of any one of claims 1-~~44112~~, wherein the subject is a human.

~~114. The method of any one of claims 1-113, wherein the tucatinib, or salt or solvate thereof, is in a pharmaceutical composition comprising the tucatinib, or salt or solvate thereof, and a pharmaceutical acceptable carrier.~~

~~115. The method of any one of claims 1-18, wherein the anti-PD-1 antibody or antigen-binding fragment thereof is in a pharmaceutical composition comprising the anti-PD-1 antibody or antigen-binding fragment thereof and a pharmaceutical acceptable carrier.~~

~~116. — The method of any one of claims 19-40, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof is in a pharmaceutical composition comprising the anti-PD-L1 antibody or antigen-binding fragment thereof and a pharmaceutical acceptable carrier.~~

~~117. — The method of any one of claims 100-104, wherein the anti-CTLA4 antibody or antigen-binding fragment thereof is in a pharmaceutical composition comprising the anti-CTLA4 antibody or antigen-binding fragment thereof and a pharmaceutical acceptable carrier.~~

~~118. — A kit comprising:~~

- ~~(a) — tucatinib, or salt or solvate thereof;~~
- ~~(b) — an antibody or an antigen-binding fragment thereof, wherein the antibody binds to Programmed Death 1 (PD-1) and inhibits PD-1 activity; and~~
- ~~(c) — instructions for use of the tucatinib, or salt or solvate thereof and the anti-PD-1 antibody or antigen-binding fragment thereof according to the method of any one of claims 1-18.~~

~~119. — A kit comprising:~~

- ~~(a) — tucatinib, or salt or solvate thereof;~~
- ~~(b) — an antibody or an antigen-binding fragment thereof, wherein the antibody binds to Programmed Death Ligand 1 (PD-L1) and inhibits PD-L1 activity; and~~
- ~~(c) — instructions for use of the tucatinib, or salt or solvate thereof and the anti-PD-L1 antibody or antigen-binding fragment thereof according to the method of any one of claims 19-40.~~