

**(12) STANDARD PATENT**  
**(19) AUSTRALIAN PATENT OFFICE**

(11) Application No. **AU 2020229714 B2**

(54) Title  
**Cancer therapy using 3,5-disubstituted benzene alkynyl compound and pembrolizumab**

(51) International Patent Classification(s)  
**A61K 39/395** (2006.01) **A61P 35/00** (2006.01)  
**A61K 31/519** (2006.01) **A61P 43/00** (2006.01)  
**A61K 45/00** (2006.01)

(21) Application No: **2020229714** (22) Date of Filing: **2020.02.28**

(87) WIPO No: **WO20/175697**

(30) Priority Data

(31)	Number	(32)	Date	(33)	Country
	<b>2019-035603</b>		<b>2019.02.28</b>		<b>JP</b>
	<b>2019-112619</b>		<b>2019.06.18</b>		<b>JP</b>

(43) Publication Date: **2020.09.03**

(44) Accepted Journal Date: **2025.02.27**

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(56) Related Art  
**WO 2013/108809 A1**  
**EP 3424505 A1**

(12) 特許協力条約に基づいて公開された国際出願

(19) 世界知的所有権機関  
国際事務局

(43) 国際公開日  
2020年9月3日(03.09.2020)



(10) 国際公開番号

WO 2020/175697 A1

(51) 国際特許分類:

A61K 39/395 (2006.01) A61P 43/00 (2006.01)  
A61K 45/00 (2006.01) A61K 31/519 (2006.01)  
A61P 35/00 (2006.01)

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(21) 国際出願番号: PCT/JP2020/008509

(22) 国際出願日: 2020年2月28日(28.02.2020)

(25) 国際出願の言語: 日本語

(26) 国際公開の言語: 日本語

(30) 優先権データ:

特願 2019-035603 2019年2月28日(28.02.2019) JP  
特願 2019-112619 2019年6月18日(18.06.2019) JP

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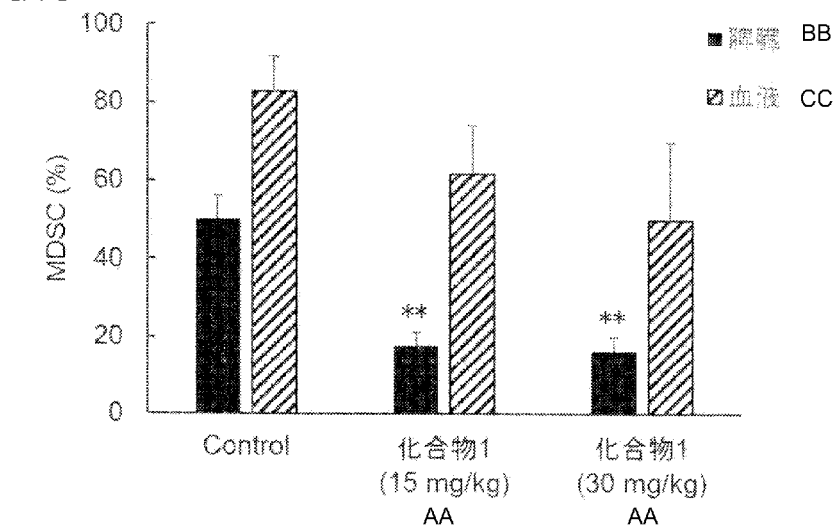
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(54) Title: CANCER THERAPY USING 3,5-DISUBSTITUTED BENZENE ALKYNYL COMPOUND AND PEM-BROLIZUMAB

(54) 発明の名称: 3, 5-二置換ベンゼンアルキニル化合物とペムブロリズマブとを用いた癌治療法

[図1]



\*\* P < 0.01

AA Compound 1  
BB Spleen  
CC Blood

(57) Abstract: The present disclosure addresses the problem of providing a new combination therapy that exhibits a superior anti-tumor effect in cancer patients who have a resistance to immune checkpoint inhibitors, said combination therapy involving (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidine-1-yl)pyrrolidine-1-yl)prop-2-en-1-one or a salt thereof. The present disclosure provides an anti-tumor agent for concomitant administration with pembrolizumab to cancer patients who have a resistance to immune checkpoint inhibitors, said anti-tumor

[続葉有]

(81) 指定国(表示のない限り、全ての種類の国内保護が可能): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) 指定国(表示のない限り、全ての種類の広域保護が可能): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), ユーラシア (AM, AZ, BY, KG, KZ, RU, TJ, TM), ヨーロッパ (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

添付公開書類:

一 国際調査報告(条約第21条(3))

agent including (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidine-1-yl)pyrrolidine-1-yl)prop-2-en-1-one or a salt thereof as an active component.

(57) 要約: 本開示が解決すべき課題は、(S)-1-(3-(4-アミノ-3-((3,5-ジメトキシフェニル)エチニル)-1H-ピラゾロ[3,4-d]ピリミジン-1-イル)ピロリジン-1-イル)プロパー-2-エン-1-オン又はその塩を用い、免疫チェックポイント阻害薬に対する耐性を有する癌患者に対して優れた抗腫瘍効果を示す新たな併用療法を提供することである。本開示は、(S)-1-(3-(4-アミノ-3-((3,5-ジメトキシフェニル)エチニル)-1H-ピラゾロ[3,4-d]ピリミジン-1-イル)ピロリジン-1-イル)プロパー-2-エン-1-オン又はその塩を有効成分として含む、免疫チェックポイント阻害薬に対する耐性を有する癌患者に対して、ペムブロリズマブと併用投与される抗腫瘍剤を提供する。

DESCRIPTION

Title of Invention: CANCER THERAPY USING 3,5-DISUBSTITUTED  
BENZENE ALKYNYL COMPOUND AND PEMBROLIZUMAB

5 Technical Field

[0001]

Cross-Reference to Related Applications

This application claims priority based on Japanese  
Patent Application No. 2019-035603 filed on February 28, 2019,  
10 and Japanese Patent Application No. 2019-112619 filed on June 18,  
2019, the entire contents of which are incorporated herein by  
reference. The present disclosure relates to an antitumor agent,  
an antitumor effect enhancer, and a kit preparation.

15 Background Art

[0002]

Fibroblast growth factors (FGFs) are expressed in  
various tissues, and are one of the growth factors that regulate  
cell proliferation and differentiation. The physiological  
20 activity of the FGFs is mediated by fibroblast growth factor  
receptors (FGFRs), which are specific cell surface receptors.  
FGFRs belong to a receptor protein tyrosine kinase family, and  
comprise an extracellular ligand-binding domain, a single  
transmembrane domain, and an intracellular tyrosine kinase  
25 domain. Four types of FGFRs (FGFR1, FGFR2, FGFR3, and FGFR4) have  
been heretofore identified. FGFRs bind to FGFs to form dimers,  
and are activated by phosphorylation. Activation of the receptors  
induces mobilization and activation of specific downstream signal  
transduction molecules, thereby developing physiological  
30 functions. Some reports have been made about the relationship  
between aberrant FGF/FGFR signaling and various human tumors.  
Aberrant activation of FGF/FGFR signaling in human tumors is  
considered to be attributable to overexpression of FGFRs and/or  
gene amplification, gene mutation, chromosomal translocation,  
35 insertion, and inversion, gene fusion, or an autocrine or

paracrine mechanism by overproduction of FGFs (ligands) (NPL 1, 2, 3, and 4).

[0003]

On the other hand, the development of cancer  
5 immunotherapy has progressed as a new cancer treatment method.

[0004]

Activation of the adaptive immune response is initiated by the binding of antigenic peptide-MHC complexes to T-cell receptors (TCRs). This binding is further defined by  
10 costimulation or coinhibition by binding between the costimulatory molecule B7 family and their receptor CD28 family. That is, in order for T cells to activate an antigen specifically, two characteristic signal transduction events are required, and T cells that have received only antigen stimulation  
15 without costimulation from the B7 family enter a state of anergy, and immune tolerance is induced.

[0005]

Taking advantage of this mechanism to suppress the activation of antigen-specific T cells, cancer cells escape from  
20 the immune surveillance system and continue to grow. Therefore, it is considered to be effective for cancer treatment to induce antitumor immune responses in the bodies of cancer patients by strengthening costimulation and blocking coinhibition, and to prevent tumor immune escape. Various proposals have been made for  
25 cancer immunotherapy targeting costimulatory molecules (stimulatory costimulatory molecules) or coinhibitory molecules (inhibitory costimulatory molecules) (NPL 5). For example, nivolumab (human IgG4 monoclonal antibody against human PD-1) is used for the treatment of malignant melanoma etc. as an immune  
30 checkpoint inhibitor that activates T cells by inhibiting the binding of PD-1 with its ligands (PD-L1 and PD-L2) (PTL 1 and NPL 6). Further, as an immune checkpoint inhibitor that is different from nivolumab in terms of antibody type, pembrolizumab is used for the treatment of malignant melanoma, non-small cell lung  
35 cancer, etc. (NPL 6).

[0006]

(S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one, which is a 3,5-disubstituted benzene alkynyl compound, or a salt thereof is known as an FGFR inhibitor. Combinations of FGFR inhibitors and other antitumor agents have been reported so far (PTL 2 and PTL 3). With regard to combined administration of an FGFR inhibitor and an immune checkpoint inhibitor, for example, PTL 4 discloses a method using an FGFR inhibitor and an anti-PD-1 antibody or an anti-PD-L1 antibody in combination.

[0007]

Many cases have been reported regarding immune checkpoint inhibitors, it has been clarified that continued administration results in resistance to drugs, and the mechanism thereof has been studied (NPL 9, NPL 10, and NPL 11). As an example of the use of an immune checkpoint inhibitor and an FGFR inhibitor, for example, a phase II trial (NCT02365597) of erdafitinib (JNJ-42756493) for urothelial cancer has reported a test in which FGFR inhibitors were administered to subjects who had been pretreated with PD-1 or PD-L1. Further, a combination test of vofatamab, which is an anti-FGFR3 antibody, and pembrolizumab is in progress (NCT03123055). As continued administration, reports have been made on the combined use of everolimus and pazopanib, which is a multikinase inhibitor that has an FGFR inhibitory effect, the combined use of vofatamab and docetaxel, and continued administration of atezolizumab (NPL 12).

#### Citation List

##### Patent Literature

[0008]

PTL 1: WO2004/004771

PTL 2: WO2013/108809

PTL 3: WO2017/150725

PTL 4: WO2016/161239

Non-patent Literature

2020229714 04 Feb 2025

[0009]

- NPL 1: Nat. Rev. Cancer, 10, 116-129 (2010)  
NPL 2: J. Clin. Oncol., 24, 3664-3671 (2006)  
NPL 3: Mol. Cancer Res., 3, 655-667 (2005)  
5 NPL 4: Cancer Res., 70, 2085-2094 (2010)  
NPL 5: Nat. Rev. Cancer, 12, 252-264 (2012)  
NPL 6: N. Engl. J. Med., 366, 2443-2454 (2012)  
NPL 7: The Breast, 37, 126-133 (2018)  
NPL 8: Oncotarget, 8, 16052-16074 (2017)  
10 NPL 9: Cell, 168, 707-723 (2017)  
NPL 10: N. Engl. J. Med., 375, 819-829 (2016)  
NPL 11: Sci. Transl. Med. 9, eaal 3604 (2017)  
NPL 12: JCO Precision Oncology (DOI: 10.1200/P0.18.00117),  
July 24, 2018  
15 NPL 13: Cellular Physiology and Biochemistry, 33, pp. 633-645  
(2014)  
NPL 14: Frontiers in Immunology, 9, 2018, Article  
1310.doi:10.3389/fimmu.2018.01310

20 Summary of Invention

[0010]

It would be advantageous to provide a novel combination  
therapy that has excellent antitumor effects for cancer patients  
who are resistant to immune checkpoint inhibitors by using (S)-1-  
25 (3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-  
d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt  
thereof.

[0011]

30 In view of such circumstances, the present inventors  
found the combined use of (S)-1-(3-(4-amino-3-((3,5-  
dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-  
yl)pyrrolidin-1-yl)prop-2-en-1-one

(hereinafter also referred to as "compound 1"), which is a compound having FGFR inhibitory activity, or a salt thereof with an immune checkpoint inhibitor.

[0012]

5                   Therefore, the present disclosure provides the following Items 1 to 55.

[0013]

Item 1. An antitumor agent comprising (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-  
10 d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof as an active ingredient, the antitumor agent being administered in combination with pembrolizumab to a cancer patient with resistance to immune checkpoint inhibitors.

[0014]

15                   Item 2. The antitumor agent according to Item 1, wherein a tumor has an aberration in the FGFR pathway.

[0015]

Item 3. The antitumor agent according to Item 2, wherein the aberration in the FGFR pathway is at least one member  
20 selected from the group consisting of FGFR overexpression, FGFR genetic aberration, and aberrant FGFR signaling.

[0016]

Item 4. The antitumor agent according to any one of Items 1 to 3, wherein treatment with the antitumor agent results  
25 in a sustained response in an individual after cessation of the treatment.

[0017]

Item 5. The antitumor agent according to any one of Items 1 to 4, wherein (S)-1-(3-(4-amino-3-((3,5-  
30 dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof is used before, simultaneously with, or after pembrolizumab.

[0018]

Item 6. The antitumor agent according to any one of  
35 Items 1 to 5, wherein (S)-1-(3-(4-amino-3-((3,5-



dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof is used continuously or intermittently.

[0019]

5           Item 7. The antitumor agent according to any one of Items 1 to 6, wherein (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof and pembrolizumab are administered in treatment with one therapeutic  
10 regimen.

[0020]

          Item 8. The antitumor agent according to any one of Items 1 to 7, wherein for a tumor with resistance to immune checkpoint inhibitors, the antitumor agent is used to administer  
15 (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof once a day at a dose selected from the group consisting of 4 mg, 8 mg, 12 mg, 16 mg, and 20 mg, and to administer nivolumab at a dose selected from the group consisting  
20 of 1 mg/kg in 3-week intervals, 2 mg/kg in 3-week intervals, 3 mg/kg in 3-week intervals, 80 mg in 3-week intervals, 240 mg in 3-week intervals, 1 mg/kg in 2-week intervals, 2 mg/kg in 2-week intervals, 3 mg/kg in 2-week intervals, 80 mg in 2-week intervals, and 240 mg in 2-week intervals.

25 [0021]

          Item 9. The antitumor agent according to any one of Items 1 to 8, wherein for a tumor with resistance to immune checkpoint inhibitors, (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof is  
30 administered once a day at a dose selected from the group consisting of 8 mg, 12 mg, 16 mg, and 20 mg, and pembrolizumab is administered at a dose of 200 mg in 3-week intervals.

[0022]

35           Item 10. The antitumor agent according to any one of

Items 1 to 9, wherein the tumor with resistance to immune checkpoint inhibitors is esophageal cancer or non-small cell lung cancer.

[0023]

5           Item 11. A pharmaceutical composition comprising pembrolizumab and (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof as active ingredients.

10   [0024]

          Item 12. The pharmaceutical composition according to Item 11, for the treatment of cancer with resistance to immune checkpoint inhibitors.

[0025]

15           Item 13. Use of pembrolizumab and (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof for the manufacture of an antitumor agent for treating cancer with resistance to immune checkpoint inhibitors.

20   [0026]

          Item 14. Use of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof for the manufacture of an antitumor agent to be administered in combination with pembrolizumab to a patient with resistance to immune checkpoint inhibitors.

[0027]

          Item 15. Use of pembrolizumab for the manufacture of an antitumor agent to be administered in combination with (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof to a patient with resistance to immune checkpoint inhibitors.

[0028]

Item 16. A combination of pembrolizumab and (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof for use in treatment of cancer with resistance to immune  
5 checkpoint inhibitors.

[0029]

Item 17. (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof for use in  
10 combination therapy with pembrolizumab in treatment of cancer with resistance to immune checkpoint inhibitors.

[0030]

Item 18. Pembrolizumab for use in combination therapy with (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or  
15 a salt thereof in treatment of cancer with resistance to immune checkpoint inhibitors.

[0031]

Item 19. Use of pembrolizumab and (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof for the  
20 treatment of cancer with resistance to immune checkpoint inhibitors.

[0032]

Item 20. Use of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof for the  
25 treatment of cancer with resistance to immune checkpoint inhibitors by combination therapy with pembrolizumab.

[0033]

Item 21. Use of pembrolizumab for the treatment of cancer with resistance to immune checkpoint inhibitors by combination therapy with (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof.  
35

[0034]

Item 22. A method for treating cancer with resistance to immune checkpoint inhibitors, the method comprising administering a therapeutically effective amount of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof, and a therapeutically effective amount of pembrolizumab to a human in need thereof.

[0035]

10 Item 23. An antitumor agent comprising (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof as an active ingredient, the antitumor agent being administered in combination with pembrolizumab to a cancer  
15 patient who has not been administered immune checkpoint inhibitors.

[0036]

Item 24. A pharmaceutical composition comprising pembrolizumab and (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof as active ingredients, for the treatment of cancer in a cancer patient who has not been administered immune checkpoint inhibitors.

[0037]

25 Item 25. The pharmaceutical composition according to Item 24, for the treatment of cancer with resistance to immune checkpoint inhibitors.

[0038]

Item 26. Use of pembrolizumab and (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof for the manufacture of an antitumor agent for treating cancer in a cancer patient who has not been administered immune checkpoint inhibitors.

35 [0039]

Item 27. Use of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof for the manufacture of an antitumor agent to be administered in combination with pembrolizumab to a cancer patient who has not been administered immune checkpoint inhibitors.  
[0040]

Item 28. Use of pembrolizumab for the manufacture of an antitumor agent to be administered in combination with (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof to a cancer patient who has not been administered immune checkpoint inhibitors.  
[0041]

Item 29. A combination of pembrolizumab and (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof for use in treatment of cancer in a cancer patient who has not been administered immune checkpoint inhibitors.  
[0042]

Item 30. (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof for use in combination therapy with pembrolizumab in treatment of cancer in a cancer patient who has not been administered immune checkpoint inhibitors.  
[0043]

Item 31. Pembrolizumab for use in combination therapy with (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof in treatment of cancer in a cancer patient who has not been administered immune checkpoint inhibitors.  
[0044]

Item 32. Use of pembrolizumab and (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-

yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof for the treatment of cancer in a cancer patient who has not been administered immune checkpoint inhibitors.

[0045]

5           Item 33. Use of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof for the treatment of cancer in a cancer patient who has not been administered immune checkpoint inhibitors by combination therapy  
10 with pembrolizumab.

[0046]

          Item 34. Use of pembrolizumab for the treatment of cancer in a cancer patient who has not been administered immune checkpoint inhibitors by combination therapy with (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof.

[0047]

          Item 35. A method for treating cancer in a cancer  
20 patient who has not been administered immune checkpoint inhibitors, the method comprising administering a therapeutically effective amount of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof, and a  
25 therapeutically effective amount of pembrolizumab to a human in need thereof.

[0048]

          Item 36. The composition, use, combination, (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof, pembrolizumab, or method according to any one of Items 11 to 22, wherein a tumor has an aberration in the FGFR pathway.

[0049]

          Item 37. The composition, use, combination, (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-

35

d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof, pembrolizumab, or method according to Item 36, wherein the aberration in the FGFR pathway is at least one member selected from the group consisting of FGFR overexpression, FGFR genetic aberration, and aberrant FGFR signaling.

[0050]

Item 38. An antitumor agent comprising (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof as an active ingredient, the antitumor agent being administered in combination with pembrolizumab to a cancer patient with resistance to immune checkpoint inhibitors and without aberrations in the FGFR pathway.

[0051]

Item 39. A pharmaceutical composition comprising pembrolizumab and (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof as active ingredients, for the treatment of cancer without aberrations in the FGFR pathway.

[0052]

Item 40. The pharmaceutical composition according to Item 24, for the treatment of cancer with resistance to immune checkpoint inhibitors.

[0053]

Item 41. Use of pembrolizumab and (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof for the manufacture of an antitumor agent for treating cancer without aberrations in the FGFR pathway.

[0054]

Item 42. Use of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof for the manufacture of an antitumor agent to be administered in

combination with pembrolizumab to a cancer patient without aberrations in the FGFR pathway.

[0055]

Item 43. Use of pembrolizumab for the manufacture of an  
5 antitumor agent to be administered in combination with (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof to a cancer patient without aberrations in the FGFR pathway.

10 [0056]

Item 44. A combination of pembrolizumab and (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof for use in treatment of cancer without aberrations in the  
15 FGFR pathway.

[0057]

Item 45. (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof for use in  
20 combination therapy with pembrolizumab in treatment of cancer without aberrations in the FGFR pathway.

[0058]

Item 46. Pembrolizumab for use in combination therapy with (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or  
25 a salt thereof in treatment of cancer without aberrations in the FGFR pathway.

[0059]

Item 47. Use of pembrolizumab and (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof for the  
30 treatment of cancer without aberrations in the FGFR pathway.

[0060]

Item 48. Use of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-

35



yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof for the treatment of cancer without aberrations in the FGFR pathway by combination therapy with pembrolizumab.

[0061]

5           Item 49. Use of pembrolizumab for the treatment of cancer without aberrations in the FGFR pathway by combination therapy with (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof.

10   [0062]

          Item 50. A method for treating cancer without aberrations in the FGFR pathway, the method comprising administering a therapeutically effective amount of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof, and a therapeutically effective amount of pembrolizumab to a human in need thereof.

[0063]

          Item 51. The composition, use, combination, (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof, pembrolizumab, or method according to any one of Items 11 to 50, wherein treatment with (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or the salt thereof and pembrolizumab results in a sustained response in an individual after cessation of the treatment.

[0064]

          Item 52. The composition, use, combination, (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof, pembrolizumab, or method according to any one of Items 11 to 51, wherein (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-

yl)pyrrolidin-1-yl)prop-2-en-1-one or the salt thereof is used before, simultaneously with, or after pembrolizumab.

[0065]

Item 53. The composition, use, combination, (S)-1-(3-  
5 (4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-  
d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof, pembrolizumab, or method according to any one of Items 11 to 52, wherein (S)-1-(3-(4-amino-3-((3,5-  
dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-  
10 yl)pyrrolidin-1-yl)prop-2-en-1-one or the salt thereof is used continuously or intermittently.

[0066]

Item 54. The composition, use, combination, (S)-1-(3-  
(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-  
15 d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof, pembrolizumab, or method according to any one of Items 11 to 53, wherein (S)-1-(3-(4-amino-3-((3,5-  
dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-  
yl)pyrrolidin-1-yl)prop-2-en-1-one or the salt thereof and  
20 pembrolizumab are administered in treatment with one therapeutic regimen.

[0067]

Item 55. The composition, use, combination, (S)-1-(3-  
(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-  
25 d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof, pembrolizumab, or method according to any one of Items 11 to 54, wherein (S)-1-(3-(4-amino-3-((3,5-  
dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-  
yl)pyrrolidin-1-yl)prop-2-en-1-one or the salt thereof and  
30 pembrolizumab are used in the following manner: to a cancer patient with resistance to immune checkpoint inhibitors, (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-  
d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or the salt thereof is administered once a day at a dose selected from the  
35 group consisting of 4 mg, 8 mg, 12 mg, 16 mg, and 20 mg; and

pembrolizumab is administered at a dose selected from the group consisting of 1 mg/kg in 3-week intervals, 2 mg/kg in 3-week intervals, and 200 mg in 3-week intervals.

5 [0067a]

The present invention as claimed herein is described in the following items 1 to 16:

[Item 1]

10 Use of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof for the treatment of cancer in a patient with resistance to immune checkpoint inhibitors by combination therapy with pembrolizumab, 15 wherein (S)-1-(3-(4-amino-3-((3,5 dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof is administered once a day at a dose selected from the group consisting of 4 mg, 8 mg, 12 mg, 16 mg, and 20 mg, and pembrolizumab is administered at a dose selected from the group 20 consisting of 1 mg/kg in 3-week intervals, 2 mg/kg in 3-week intervals, and 200 mg in 3-week intervals.

[Item 2]

25 Use of pembrolizumab for the treatment of cancer in a patient with resistance to immune checkpoint inhibitors by combination therapy with of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof, wherein pembrolizumab is administered at a dose selected from the group 30 consisting of 1 mg/kg in 3-week intervals, 2 mg/kg in 3-week intervals, and 200 mg in 3-week intervals , and (S)-1-(3-(4-amino-3-((3,5 -dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof is administered once a day at a dose selected from the 35 group consisting of 4 mg, 8 mg, 12 mg, 16 mg, and 20 mg.

## [Item 3]

A method for treating cancer in a patient with resistance to immune checkpoint inhibitors, the method comprising administering (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof, and pembrolizumab to the patient in need thereof, wherein (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof is administered once a day at a dose selected from the group consisting of 4 mg, 8 mg, 12 mg, 16 mg, and 20 mg, and pembrolizumab is administered at a dose selected from the group consisting of 1 mg/kg in 3-week intervals, 2 mg/kg in 3-week intervals, and 200 mg in 3-week intervals.

## [Item 4]

Use of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof for the treatment of cancer in a patient who has not been administered immune checkpoint inhibitors by combination therapy with pembrolizumab, wherein (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof is administered once a day at a dose selected from the group consisting of 4 mg, 8 mg, 12 mg, 16 mg, and 20 mg, and pembrolizumab is administered at a dose selected from the group consisting of 1 mg/kg in 3-week intervals, 2 mg/kg in 3-week intervals, and 200 mg in 3-week intervals.

## [Item 5]

Use of pembrolizumab for the treatment of cancer in a patient who has not been administered immune checkpoint inhibitors by combination therapy with (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-

yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof, wherein pembrolizumab is administered at a dose selected from the group consisting of 1 mg/kg in 3-week intervals, 2 mg/kg in 3-week intervals, and 200 mg in 3-week intervals , and (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof is administered once a day at a dose selected from the group consisting of 4 mg, 8 mg, 12 mg, 16 mg, and 20 mg.

10 [Item 6]

A method for treating cancer in a patient who has not been administered immune checkpoint inhibitors, the method comprising administering (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof, and 15 pembrolizumab to the patient in need thereof, wherein (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof is administered once a day at a dose selected from the group consisting of 4 mg, 8 mg, 12 mg, 16 mg, and 20 mg, and 20 pembrolizumab is administered at a dose selected from the group consisting of 1 mg/kg in 3-week intervals, 2 mg/kg in 3-week intervals, and 200 mg in 3-week intervals.

25 [Item 7]

Use of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof for the treatment of cancer in a patient without aberrations in the FGFR pathway by combination therapy with pembrolizumab, wherein (S)-1-(3-(4-amino-3-((3,5 dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof is administered once a day at a dose selected from the group consisting of 4 mg, 8 mg, 12 mg, 16 mg, and 20 mg, and 30 pembrolizumab is administered at a dose selected from the group

consisting of 1 mg/kg in 3-week intervals, 2 mg/kg in 3-week intervals, and 200 mg in 3-week intervals.

[Item 8]

5           Use of pembrolizumab for the treatment of cancer in a patient without aberrations in the FGFR pathway by combination therapy with (S)-1-(3-(4-amino-3-((3,5 dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof, wherein pembrolizumab is administered at a  
10       dose selected from the group consisting of 1 mg/kg in 3-week intervals, 2 mg/kg in 3-week intervals, and 200 mg in 3-week intervals , and (S)-1-(3-(4-amino-3-((3,5 - dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof is  
15       administered once a day at a dose selected from the group consisting of 4 mg, 8 mg, 12 mg, 16 mg, and 20 mg.

[Item 9]

20           A method for treating cancer in a patient without aberrations in the FGFR pathway, the method comprising administering (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof, and pembrolizumab to the patient in need thereof, wherein (S)-1-(3-(4-amino-3-((3,5  
25       dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof is administered once a day at a dose selected from the group consisting of 4 mg, 8 mg, 12 mg, 16 mg, and 20 mg, and pembrolizumab is administered at a dose selected from the group  
30       consisting of 1 mg/kg in 3-week intervals, 2 mg/kg in 3-week intervals, and 200 mg in 3-week intervals.

[Item 10]

Use of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof for the  
5 manufacture of an agent for:

the treatment of cancer in a patient with resistance to immune checkpoint inhibitors,

the treatment of cancer in a patient who has not been administered immune checkpoint inhibitors, or

10 the treatment of cancer in a patient without aberrations in the FGFR pathway,

by combination therapy with pembrolizumab, wherein (S)-1-(3-(4-amino-3-((3,5 dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt  
15 thereof is administered once a day at a dose selected from the group consisting of 4 mg, 8 mg, 12 mg, 16 mg, and 20 mg, and pembrolizumab is administered at a dose selected from the group consisting of 1 mg/kg in 3-week intervals, 2 mg/kg in 3-week intervals, and 200 mg in 3-week intervals.

20

[Item 11]

Use of pembrolizumab for the manufacture of an agent for:

25 the treatment of cancer in a patient with resistance to immune checkpoint inhibitors,

the treatment of cancer in a patient who has not been administered immune checkpoint inhibitors, or

the treatment of cancer in a patient without aberrations in the FGFR pathway,

by combination therapy with (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof, wherein pembrolizumab is administered at a dose selected from the group consisting of 1 mg/kg in 3-week intervals, 2 mg/kg in 3-week intervals, and 200 mg in 3-week intervals, and (S)-1-(3-(4-amino-3-((3,5 -dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof is administered once a day at a dose selected from the group consisting of 4 mg, 8 mg, 12 mg, 16 mg, and 20 mg.

[Item 12]

Use of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof and pembrolizumab for the manufacture of an agent for:

the treatment of cancer in a patient with resistance to immune checkpoint inhibitors,

the treatment of cancer in a patient who has not been administered immune checkpoint inhibitors, or

the treatment of cancer in a patient without aberrations in the FGFR pathway,

wherein (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof is administered once a day at a dose selected from the group consisting of 4 mg, 8 mg, 12 mg, 16 mg, and 20 mg, and pembrolizumab is administered at a dose selected from the group consisting of 1 mg/kg in 3-week intervals, 2 mg/kg in 3-week intervals, and 200 mg in 3-week intervals.



[Item 13]

Use or method according to any one of items 1 to 12, wherein treatment with (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof and pembrolizumab results in a sustained response in an individual after cessation of the treatment.

[Item 14]

Use or method according to any one of items 1 to 13, wherein (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof is used before, simultaneously with, or after pembrolizumab.

[Item 15]

Use or method according to any one of items 1 to 14, wherein (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof is used continuously or intermittently.

[Item 16]

Use or method according to any one of items 1 to 15, wherein the cancer is esophageal cancer, non-small cell lung cancer, or urothelial cancer.

#### Advantageous Effects of Invention

[0068]

The present disclosure can provide a novel combination therapy that has excellent antitumor effects for cancer patients who are resistant to immune checkpoint inhibitors by using (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof.

## Brief Description of Drawings

[0069]

Fig. 1 shows the results of Example 2 (influence of compound 1 on myeloid-derived suppressor cells (MDSCs)).

5

## Description of Embodiments

[0070]

The present disclosure relates to the provision of, for example, combined use of a compound having FGFR inhibitory activity and an immune checkpoint inhibitor, that is, an antitumor agent comprising a compound having FGFR inhibitory activity and being administered in combination with an immune checkpoint inhibitor, an antitumor effect enhancer comprising a compound having FGFR inhibitory activity, a combination of a compound having FGFR inhibitory activity and an immune checkpoint inhibitor, and use of a compound having FGFR inhibitory activity in the production of a medicament for the treatment of tumors performed in combination with an immune checkpoint inhibitor.

10

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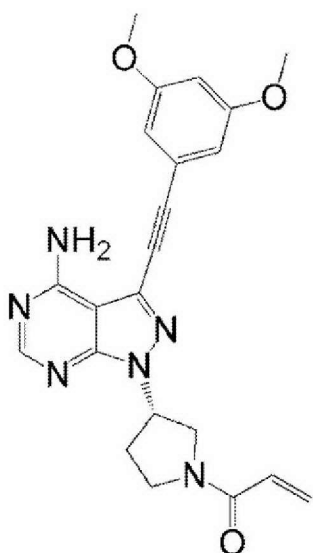
[0071]

20

In the present disclosure, (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one, which exhibits an excellent

antitumor effect when used in combination with an immune checkpoint inhibitor, is a disubstituted benzene alkynyl compound having the following structure. In the present specification, this compound is simply referred to as "compound 1." Compound 1 is described as Example Compound 2 in PTL 2 mentioned above. It has been reported that compound 1 or a salt thereof has an excellent FGFR inhibitory effect and inhibits the ability of receptor protein tyrosine kinases (FGFR1, FGFR3, and FGFR4) to phosphorylate tyrosine in the substrate peptide sequence (PTL 2).

10 [0072]



(I)

[0073]

Compound 1 or a pharmaceutically acceptable salt thereof in the present disclosure can be synthesized by any method; for example, it can be synthesized according to the production method described in PTL 2.

[0074]

In the present disclosure, compound 1 can be used as is or in the form of a pharmaceutically acceptable salt. The pharmaceutically acceptable salt of compound 1 is not particularly limited, and examples include addition salts with inorganic acids such as hydrochloric acid and sulfuric acid, or with organic acids such as acetic acid, citric acid, tartaric

acid, and maleic acid; salts with alkali metals such as potassium and sodium; salts with alkaline earth metals such as calcium and magnesium; salts with organic bases such as ammonium salts, ethylamine salts, and arginine salts; and the like.

5 [0075]

In the present disclosure, immune checkpoint inhibitors act on immune checkpoint molecules, and have the effects of inducing antitumor immune responses in the bodies of subjects and preventing tumor immune escape.

10 [0076]

Examples of such immune checkpoint inhibitors include substances that promote the function of costimulatory molecules (stimulatory costimulatory molecules), and substances that inhibit the function of coinhibitory molecules (inhibitory costimulatory molecules). Examples of immune checkpoint molecules include B7 family (B7-1, B7-2, PD-L1, PD-L2, etc.), CD28 family (CTLA-4, PD-1, etc.), TNF superfamily (4-1BBL, OX40L), and TNF receptor superfamily (4-1BB, OX40) molecules. Substances that target immune checkpoint molecules can be used as immune checkpoint inhibitors. Examples include PD-1 pathway antagonists, ICOS pathway agonists, CTLA-4 pathway antagonists, CD28 pathway agonists, BTLA pathway antagonists, 4-1BB pathway agonists, and the like.

[0077]

25 PD-1 pathway antagonists inhibit immunosuppressive signals of PD-1 expressed on T cells and its ligand PD-L1 or PD-L2. Examples include anti-PD-1 antibodies, anti-PD-L1 antibodies, anti-PD-L2 antibodies, PD-1 extracellular domains, PD-L1 extracellular domains, PD-L2 extracellular domains, PD-1-Ig (fusion protein of a PD-1 extracellular domain and the FC region of Ig), PD-L1-Ig, PD-L2-Ig, PD-1 siRNA, PD-L1 siRNA, PD-L2 siRNA, and the like.

[0078]

35 Examples of these antibodies include immunoglobulins (IgA, IgD, IgE, IgG, IgM, IgY, etc.), Fab fragments, F(ab')<sub>2</sub>

fragments, single-chain antibody fragments (scFv), single-domain antibodies, and Diabody (Nat. Rev. Immunol., 6:343-357, 2006). These include monoclonal antibodies and polyclonal antibodies, such as human antibodies, humanized antibodies, chimeric  
5 antibodies, mouse antibodies, llama antibodies, and chicken antibodies. Preferred is a humanized IgG monoclonal antibody or a human IgG monoclonal antibody.

[0079]

These agonists or antagonists can be produced by a  
10 generally known production method.

[0080]

Further, anti-PD-1 antibodies have already been sold as pembrolizumab, and this can also be used.

[0081]

15 In the present disclosure, the immune checkpoint inhibitors can be used singly or in combination of two or more.

[0082]

In the present disclosure, when two or more immune checkpoint inhibitors are used, for example, an anti-PD-1  
20 antibody, an anti-CTLA-4 antibody, and like immune checkpoint inhibitors can be used in combination, or bispecific antibodies that can bind to different immune checkpoint molecules can also be used. Examples of bispecific antibodies include XmAb20717 (PD-1 x CTLA-4), which can bind to both PD-1 and CTLA-4.

25 [0083]

The treatment in the present disclosure includes procedures performed for the purpose of curing or ameliorating diseases, or for the purpose of suppressing disease progression or relapse or alleviating the symptoms. The treatment includes  
30 administration of drugs before or after surgical procedure, or administration of drugs during, before, or after radiation therapy.

[0084]

The therapeutically effective amounts of antibodies and  
35 compound 1 or a salt thereof that block the interaction with

immune checkpoint molecules are not limited, and depend on several factors, including the stage and severity of cancer, as well as other factors related to the patient's health. Persons skilled in the art would know how to determine the therapeutically effective amounts.

[0085]

An embodiment of the present disclosure is used for tumors having aberrations in the FGFR pathway. In an embodiment, the FGFR is selected from the group consisting of FGFR1, FGFR2, FGFR3, and FGFR4.

[0086]

In an embodiment, the tumors to which the present disclosure is to be applied are preferably tumors having aberrations in the FGFR pathway. The aberrations in the FGFR pathway include FGFR overexpression, FGFR genetic aberration, and aberrant FGFR signaling.

[0087]

In an embodiment of the present disclosure, the presence of FGF/FGFR aberrations does not matter; however, the administration subject is preferably one having aberrations in the FGFR pathway. Compound 1 can promote the antitumor effect of immune checkpoint inhibitors even in cancer types without FGFR genetic aberrations. The susceptibility of cancer to immune checkpoint inhibitors is known to be also affected by the tumor microenvironment. The microenvironment includes, but is not limited to, cell groups controlled by FGF/FGFR pathway activation, such as cancer-associated fibroblasts (CAFs). These cell groups are known to diminish the susceptibility of cancer to immune checkpoint inhibitors. The administration of compound 1 is considered to cause changes in the microenvironment, including inactivation of CAFs, thereby promoting the effects of immune checkpoint inhibitors on cancer.

[0088]

Examples of FGFR overexpression include gene expression and high expression of gene product proteins. The expression of

FGFR can be detected by methods known to persons skilled in the art. Gene expression and high expression of gene product proteins can be detected by known methods, such as methods using antibodies (immunohistochemistry, enzyme immunoassay (ELISA),  
5 flow cytometry, immunoblotting, etc.), methods using nucleic acids (*in situ* hybridization, PCR, Northern blotting, etc.), and methods based on a common principle of these methods. The detection device can be any known device (GeneChip, microarray, etc.).

10 [0089]

An embodiment of the present disclosure is used for tumors having FGFR genetic aberrations. Genetic aberrations in the FGFR pathway include gene amplification, gene mutation, chromosomal translocation, insertion, and inversion, gene fusion,  
15 genetic rearrangement, etc. Some of the FGFR genetic aberrations in tumors have already been reported in documents available to persons skilled in the art (NPL 7 and NPL 8). FGFR genetic aberrations can be detected by methods known to persons skilled in the art, for example, pyrosequence, DNA sequencing including  
20 next-generation sequencing (NGS), PCR-based methods including allele-specific PCR chain reactions, microarray-based comparative genomic hybridization (aCGH), fluorescence *in situ* hybridization (FISH), and chromogenic *in situ* hybridization (CISH).  
[0090]

25 Further, an embodiment of the present disclosure is used for tumors with activated FGFR signaling. FGFRs bind to FGFs to form dimers and are activated by phosphorylation, which induces mobilization and activation of specific downstream signal transduction molecules, thereby developing physiological  
30 functions.  
[0091]

Activation of FGFR signaling can be detected by methods known to persons skilled in the art. Signaling activation can be detected, for example, by detecting FGFs, which are substrates  
35 for FGFRs; by detecting direct phosphorylation state of FGFRs,

which are phosphorylated enzymes, or biological activity including enzymatic activity; by detecting phosphorylation state of intracellular substrates and intracellular proteins existing in the FGFR signaling cascade downstream, or biological activity including enzymatic activity; or by detecting gene products or gene transcripts.

[0092]

In another embodiment, the tumors to which the present disclosure is to be applied also include tumors having no aberrations in the FGFR pathway.

[0093]

In the present disclosure, preferred examples of the dose of compound 1 or a salt thereof per day on the day of administration include 4 mg to 160 mg, 4 mg to 24 mg, 12 to 24 mg, 16 to 24 mg, 20 mg, and the like. More specifically, examples of the number of doses and the dose per day on the day of administration include once a day, 4 mg, 8 mg, 12 mg, 16 mg, 20 mg, and the like. In another embodiment, preferred examples of the number of doses and the dose per day on the day of administration include 8 mg, 12 mg, 16 mg, 20 mg, and the like. In another embodiment, preferred examples of the number of doses and the dose per day on the day of administration include 12 mg, 16 mg, 20 mg, and the like. In another embodiment, preferred examples of the number of doses and the dose per day on the day of administration include 20 mg and the like.

[0094]

In an embodiment of the present disclosure, in the case of a cancer type for which a stronger effect is desired (e.g., brain tumor), the dose of compound 1 or a salt thereof includes a dose larger than 20 mg once a day.

[0095]

When the dose of compound 1 or a salt thereof per day is administered intermittently, the dose of compound 1 or a salt thereof per day is, for example, about 2 to 1000 mg, preferably 10 to 500 mg, more preferably 20 to 200 mg, and even more



preferably 50 to 160 mg.

[0096]

Regarding the administration schedule, compound 1 or a salt thereof can be administered every day or intermittently.

5 [0097]

In the present disclosure, "administered every day" may be an administration schedule based on a cycle in which dosing is performed for 21 days every day (one cycle), and a drug holiday may be provided as each cycle ends.

10 [0098]

In the present disclosure, "administered intermittently" is not particularly limited as long as the conditions of at least twice a week and an administration interval of at least one day between dosing (the number of days between a certain day of administration and the next day of administration) are satisfied.

[0099]

Examples include an administration schedule based on a 1-week cycle, in which compound 1 or a salt thereof is administered at least twice every one to three days per cycle (with an interval between a certain day of administration and the next day of administration of 1 to 3 days), and this cycle is performed once or repeated twice or more;

an administration schedule based on a 14-day cycle, in which compound 1 or a salt thereof is administered 4 to 7 times every one to three days per cycle (with an interval between a certain day of administration and the next day of administration of 1 to 3 days), and this cycle is performed once or repeated twice or more;

an administration schedule based on a 14-day cycle, in which, among 14 days contained in one cycle, compound 1 or a salt thereof is administered on days 1, 4, 8, and 11;

an administration schedule based on a 14-day cycle, in which, among 14 days contained in one cycle, compound 1 or a salt thereof is administered on days 1, 3, 5, 7, 9, 11, and 13; and

an administration schedule based on a 14-day cycle, in which, among 14 days contained in one cycle, compound 1 or a salt thereof is administered on days 1, 3, 5, 8, 10, and 12.

[0100]

5 In an embodiment of the present disclosure, an example of the administration schedule is such that 160 mg of compound 1 or a salt thereof is administered once a day on days 1, 3, 5, 8, 10, and 12. The dose of compound 1 or a salt thereof can be reduced to 120 mg, 80 mg, 56 mg, 36 mg, 24 mg, 16 mg, or 8 mg.

10 [0101]

In the present disclosure, in terms of enhancing the antitumor effect of pembrolizumab by compound 1 or a salt thereof, the daily dose of pembrolizumab on the day of administration is preferably 30 to 100%, more preferably 50 to 100%, even more preferably 70 to 100%, still more preferably 80 to 100%, further still more preferably 90 to 100%, and further still more preferably 100%, of the recommended dose in the case of administering pembrolizumab alone.

[0102]

20 The preferred dose of pembrolizumab when administered alone is, for example, 100 to 200 mg per dose, or 200 or 400 mg per dose. In another embodiment, the preferred dose of pembrolizumab when administered alone is, for example, 1.0 to 2.0 mg/kg (body weight) per dose, or 2.0 mg/kg (body weight) per dose.

25 [0103]

In the present disclosure, the preferred dose of pembrolizumab per day on the day of administration is, for example, 100 to 400 mg per dose, or 200 or 400 mg per dose. In another embodiment of the present disclosure, the preferred dose of pembrolizumab per day on the day of administration is, for example, 1.0 to 2.0 mg/kg (body weight) per dose, or 2.0 mg/kg (body weight) per dose. Further, the administration interval of pembrolizumab is preferably 3 to 4 weeks, and more preferably 3 weeks.

35

[0104]

Examples of the dose of compound 1 or a salt thereof of the present disclosure per day on the day of administration, and the dose of pembrolizumab per day, or a preferred combination of usage and dosage include the following:

4 mg to 160 mg of compound 1 or a salt thereof of the present disclosure and 100 to 400 mg of pembrolizumab per dose.

4 mg to 160 mg of compound 1 or a salt thereof of the present disclosure and 100 to 200 mg of pembrolizumab per dose.

4 mg to 160 mg of compound 1 or a salt thereof of the present disclosure and 200 mg of pembrolizumab per dose.

4 mg to 160 mg of compound 1 or a salt thereof of the present disclosure and 400 mg of pembrolizumab per dose.

4 mg to 160 mg of compound 1 or a salt thereof of the present disclosure and 1.0 to 2.0 mg/kg (body weight) per dose of pembrolizumab.

4 mg to 160 mg of compound 1 or a salt thereof of the present disclosure and 2.0 mg/kg (body weight) per dose of pembrolizumab.

4 mg to 160 mg of compound 1 or a salt thereof of the present disclosure and 200 mg of pembrolizumab in 3-week intervals.

4 mg to 160 mg of compound 1 or a salt thereof of the present disclosure and 400 mg of pembrolizumab in 3-week intervals.

4 mg to 24 mg of compound 1 or a salt thereof of the present disclosure and 100 to 400 mg of pembrolizumab per dose.

4 mg to 24 mg of compound 1 or a salt thereof of the present disclosure and 100 to 200 mg of pembrolizumab per dose.

4 mg to 24 mg of compound 1 or a salt thereof of the present disclosure and 200 mg of pembrolizumab per dose.

4 mg to 24 mg of compound 1 or a salt thereof of the present disclosure and 400 mg of pembrolizumab per dose.

4 mg to 24 mg of compound 1 or a salt thereof of the present disclosure and 1.0 to 2.0 mg/kg (body weight) per dose of pembrolizumab.

4 mg to 24 mg of compound 1 or a salt thereof of the present

disclosure and 2.0 mg/kg (body weight) per dose of pembrolizumab.

4 mg to 24 mg of compound 1 or a salt thereof of the present disclosure and 200 mg of pembrolizumab in 3-week intervals.

4 mg to 24 mg of compound 1 or a salt thereof of the present disclosure and 400 mg of pembrolizumab in 3-week intervals.

5 12 to 24 mg of compound 1 or a salt thereof of the present disclosure and 100 to 400 mg of pembrolizumab per dose.

12 to 24 mg of compound 1 or a salt thereof of the present disclosure and 100 to 200 mg of pembrolizumab per dose.

10 12 to 24 mg of compound 1 or a salt thereof of the present disclosure and 200 mg of pembrolizumab per dose.

12 to 24 mg of compound 1 or a salt thereof of the present disclosure and 400 mg of pembrolizumab per dose.

15 12 to 24 mg of compound 1 or a salt thereof of the present disclosure and 1.0 to 2.0 mg/kg (body weight) per dose of pembrolizumab.

12 to 24 mg of compound 1 or a salt thereof of the present disclosure and 2.0 mg/kg (body weight) per dose of pembrolizumab.

12 to 24 mg of compound 1 or a salt thereof of the present disclosure and 200 mg of pembrolizumab in 3-week intervals.

20 12 to 24 mg of compound 1 or a salt thereof of the present disclosure and 400 mg of pembrolizumab in 3-week intervals.

16 to 24 mg of compound 1 or a salt thereof of the present disclosure and 100 to 400 mg of pembrolizumab per dose.

25 16 to 24 mg of compound 1 or a salt thereof of the present disclosure and 100 to 200 mg of pembrolizumab per dose.

16 to 24 mg of compound 1 or a salt thereof of the present disclosure and 200 mg of pembrolizumab per dose.

30 16 to 24 mg of compound 1 or a salt thereof of the present disclosure and 400 mg of pembrolizumab per dose.

16 to 24 mg of compound 1 or a salt thereof of the present disclosure and 1.0 to 2.0 mg/kg (body weight) per dose of pembrolizumab.

16 to 24 mg of compound 1 or a salt thereof of the present disclosure and 2.0 mg/kg (body weight) per dose of pembrolizumab.

16 to 24 mg of compound 1 or a salt thereof of the present disclosure and 200 mg of pembrolizumab in 3-week intervals.

16 to 24 mg of compound 1 or a salt thereof of the present disclosure and 400 mg of pembrolizumab in 3-week intervals.

5 [0105]

Examples of the number of doses and the dose of compound 1 or a salt thereof of the present disclosure per day on the day of administration, and the dose of pembrolizumab per day, or a combination of usage and dosage include the following:

10 4 mg of compound 1 or a salt thereof of the present disclosure once a day and 100 to 400 mg of pembrolizumab per dose.

4 mg of compound 1 or a salt thereof of the present disclosure once a day and 100 to 200 mg of pembrolizumab per dose.

15 4 mg of compound 1 or a salt thereof of the present disclosure once a day and 200 mg of pembrolizumab per dose.

4 mg of compound 1 or a salt thereof of the present disclosure once a day and 400 mg of pembrolizumab per dose.

20 4 mg of compound 1 or a salt thereof of the present disclosure once a day and 1.0 to 2.0 mg/kg (body weight) per dose of pembrolizumab.

4 mg of compound 1 or a salt thereof of the present disclosure once a day and 2.0 mg/kg (body weight) per dose of pembrolizumab.

4 mg of compound 1 or a salt thereof of the present disclosure once a day and 200 mg of pembrolizumab in 3-week intervals.

25 4 mg of compound 1 or a salt thereof of the present disclosure once a day and 400 mg of pembrolizumab in 3-week intervals.

8 mg of compound 1 or a salt thereof of the present disclosure once a day and 100 to 400 mg of pembrolizumab per dose.

30 8 mg of compound 1 or a salt thereof of the present disclosure once a day and 100 to 200 mg of pembrolizumab per dose.

8 mg of compound 1 or a salt thereof of the present disclosure once a day and 200 mg of pembrolizumab per dose.

8 mg of compound 1 or a salt thereof of the present disclosure once a day and 400 mg of pembrolizumab per dose.

8 mg of compound 1 or a salt thereof of the present disclosure once a day and 1.0 to 2.0 mg/kg (body weight) per dose of pembrolizumab.

8 mg of compound 1 or a salt thereof of the present disclosure  
5 once a day and 2.0 mg/kg (body weight) per dose of pembrolizumab.

8 mg of compound 1 or a salt thereof of the present disclosure once a day and 200 mg of pembrolizumab in 3-week intervals.

8 mg of compound 1 or a salt thereof of the present disclosure once a day and 400 mg of pembrolizumab in 3-week intervals.

10 12 mg of compound 1 or a salt thereof of the present disclosure once a day and 100 to 400 mg of pembrolizumab per dose.

12 mg of compound 1 or a salt thereof of the present disclosure once a day and 100 to 200 mg of pembrolizumab per dose.

12 mg of compound 1 or a salt thereof of the present disclosure  
15 once a day and 200 mg of pembrolizumab per dose.

12 mg of compound 1 or a salt thereof of the present disclosure once a day and 400 mg of pembrolizumab per dose.

12 mg of compound 1 or a salt thereof of the present disclosure once a day and 1.0 to 2.0 mg/kg (body weight) per dose of  
20 pembrolizumab.

12 mg of compound 1 or a salt thereof of the present disclosure once a day and 2.0 mg/kg (body weight) per dose of pembrolizumab.

12 mg of compound 1 or a salt thereof of the present disclosure once a day and 200 mg of pembrolizumab in 3-week intervals.

25 12 mg of compound 1 or a salt thereof of the present disclosure once a day and 400 mg of pembrolizumab in 3-week intervals.

16 mg of compound 1 or a salt thereof of the present disclosure once a day and 100 to 400 mg of pembrolizumab per dose.

16 mg of compound 1 or a salt thereof of the present disclosure  
30 once a day and 100 to 200 mg of pembrolizumab per dose.

16 mg of compound 1 or a salt thereof of the present disclosure once a day and 200 mg of pembrolizumab per dose.

16 mg of compound 1 or a salt thereof of the present disclosure once a day and 400 mg of pembrolizumab per dose.

16 mg of compound 1 or a salt thereof of the present disclosure once a day and 1.0 to 2.0 mg/kg (body weight) per dose of pembrolizumab.

16 mg of compound 1 or a salt thereof of the present disclosure  
5 once a day and 2.0 mg/kg (body weight) per dose of pembrolizumab.

16 mg of compound 1 or a salt thereof of the present disclosure once a day and 200 mg of pembrolizumab in 3-week intervals.

16 mg of compound 1 or a salt thereof of the present disclosure once a day and 400 mg of pembrolizumab in 3-week intervals.

10 20 mg of compound 1 or a salt thereof of the present disclosure once a day and 100 to 400 mg of pembrolizumab per dose.

20 mg of compound 1 or a salt thereof of the present disclosure once a day and 100 to 200 mg of pembrolizumab per dose.

20 mg of compound 1 or a salt thereof of the present disclosure  
15 once a day and 200 mg of pembrolizumab per dose.

20 mg of compound 1 or a salt thereof of the present disclosure once a day and 400 mg of pembrolizumab per dose.

20 mg of compound 1 or a salt thereof of the present disclosure once a day and 1.0 to 2.0 mg/kg (body weight) per dose of  
20 pembrolizumab.

20 mg of compound 1 or a salt thereof of the present disclosure once a day and 2.0 mg/kg (body weight) per dose of pembrolizumab.

20 mg of compound 1 or a salt thereof of the present disclosure once a day and 200 mg of pembrolizumab in 3-week intervals.

25 20 mg of compound 1 or a salt thereof of the present disclosure once a day and 400 mg of pembrolizumab in 3-week intervals.

[0106]

The use ratio of compound 1 or a salt thereof to pembrolizumab in the present disclosure is not particularly  
30 limited, but can be set so that the amount of pembrolizumab is preferably within a range of 10 to 10000 parts by mass, and more preferably 100 to 1000 parts by mass, based on 100 parts by mass of compound 1 or the salt thereof.

[0107]

35 In the present disclosure, the mixing ratio of compound

1 or a salt thereof in a dosage form comprising compound 1 or the salt thereof is not particularly limited, but can be appropriately set within a range of, for example, 100 to 100000 mass%, and preferably 1000 to 10000 mass%. In the present disclosure, the mixing ratio of an immune checkpoint inhibitor in a dosage form comprising the immune checkpoint inhibitor is not particularly limited, but can be appropriately set within a range of, for example, 100 to 100000 mass%, and preferably 1000 to 10000 mass%. In an embodiment in which an antitumor agent is formulated into a plurality of dosage forms, the above-mentioned preferable mixing ratio means the mixing ratio of the active ingredient with respect to the mass of the dosage form comprising the active ingredient, rather than the mixing ratio of the active ingredient with respect to the total amount of the dosage form comprising the active ingredient and the dosage form not comprising the active ingredient. For example, the mixing ratio of compound 1 or a salt thereof means mass% of compound 1 or the salt thereof with respect to the mass of only the dosage form comprising compound 1 or the salt thereof.

[0108]

In one embodiment of the present disclosure, the combination therapy of the present invention is administered to patients who have not been treated with hormonal therapy, immunotherapy (cancer peptide vaccine therapy, etc.), surgery, radiation therapy, or treatment with chemotherapeutic agents, i.e., treatment-naïve patients. In another embodiment, the combination therapy is administered to patients who fail to achieve sustained responses after the previous treatment with chemotherapeutic agents.

[0109]

In one embodiment of the present disclosure, the combination therapy of the present invention is administered to patients with no treatment experience with immune checkpoint inhibitors. In another embodiment, the combination therapy is administered to patients with treatment experience with FGFR



inhibitors.

[0110]

In one embodiment of the present disclosure, "sustained responses" mean that immune responses to cancer are expanded and maintained by performing immunotherapy using an immune checkpoint inhibitor etc. on the subject. Sustained responses can be detected, for example, by measuring the binding of T-lymphocytes to the immune checkpoint inhibitor.

[0111]

In the present disclosure, the "recommended dose" is a dose that produces the maximum therapeutic effect within a range that can be safely used without developing serious side effects, determined by clinical trials etc. Specific examples include doses that are described in package inserts, interview forms, treatment guidelines, etc., and that have been approved, recommended, or advised by public institutions or organizations, such as the Japan Pharmaceuticals and Medical Devices Agency (PMDA), the U.S. Food and Drug Administration (FDA), and the European Medicines Agency (EMA). Doses that have been approved by any of the public agencies PMDA, FDA, and EMA are preferable.

[0112]

The administration schedule of the antitumor agent of the present disclosure can be appropriately selected according to the type of cancer, the stage of cancer, and the like.

[0113]

In the case of compound 1 or a salt thereof, a daily administration schedule of 1 to 21 days (e.g., 3 weeks (21 days)) is preferred; however, there may be a drug holiday after this schedule, and daily administration for 3 weeks (21 days) is more preferable. The administration schedule of the immune checkpoint inhibitor is preferably 2-week to 4-week intervals, for example. The administration schedule of pembrolizumab is preferably 2-week, 3-week, or 4-week intervals, and more preferably 3-week intervals. In the present disclosure, the administration of drug A at intervals of X days means that when the day on which drug A

is administered is day 1, the next day is day 2, and the day after is day 3 . . . , drug A will be next administered on day X + 1. In addition, when the administration schedule is calculated, "1 week," "2 weeks," "3 weeks," and "4 weeks" mean "7 days," "14 days," "21 days," and "28 days," respectively. Therefore, in the present disclosure, the administration of drug A at intervals of 3 weeks means that when the day on which drug A is administered is day 1, drug A will be next administered on day 22.

[0114]

The number of daily doses of the antitumor agent of the present disclosure can be appropriately selected according to the type of cancer, the stage of cancer, and the like. In the case of combined administration with pembrolizumab, the number of doses is preferably once a day.

[0115]

The order of administration of compound 1 or a salt thereof and pembrolizumab may be appropriately selected according to the type of cancer, the stage of cancer, and the like; however, in one therapeutic regimen, either of them may be administered first, or both of them may be administered simultaneously.

[0116]

In one embodiment of the present disclosure, compound 1 or a salt thereof enhances the effect of pembrolizumab. In another embodiment, pembrolizumab enhances the action of compound 1 or a salt thereof.

[0117]

In one embodiment of the present disclosure, although PD-L1 may or may not be expressed, the administration subject is preferably one expressing 1% or more, and more preferably 50% or more, PD-L1.

[0118]

In one embodiment of the present disclosure, the subject is one having a tumor with a positive test result for PD-L1 expression. PD-L1 expression can be detected using an anti-

human PD-L1 antibody for diagnostic purposes, or an antigen-binding fragment thereof, in an IHC assay on FFPE or frozen tissue sections of tumor samples taken from a patient. In general, a doctor is considered to instruct diagnostic tests to  
5 determine PD-L1 expression using tumor tissue samples taken from the subject prior to the start of combined administration of an immune checkpoint inhibitor and an FGFR inhibitor; however, it is assumed that the doctor can instruct diagnostic tests before or after the start of treatment, after the start of treatment, e.g.,  
10 at the end of the treatment cycle.  
[0119]

In the present disclosure, "cancer" or "tumor" refers to the physiological conditions of a mammal characterized by unregulated cell growth. "Cancer" and "tumor" have the same  
15 meaning in the present specification and are used interchangeably. Cancers include solid and hematologic cancers. Examples include, but are not limited to, carcinoma, lymphoma, leukemia, blastoma, sarcoma, and borderline malignancy (carcinoid).  
20 [0120]

Examples of cancers targeted by the combination method of the present disclosure include head and neck cancer, digestive organ cancer (esophageal cancer, gastric cancer, duodenal cancer, liver cancer, biliary tract cancer (e.g., gallbladder and  
25 cholangiocarcinoma), pancreatic cancer, urothelial cancer, small intestine cancer, large intestine cancer (e.g., colorectal cancer, colon cancer, and rectal cancer)), lung cancer (e.g., non-small cell lung cancer, small cell lung cancer, and mesothelioma (e.g., malignant pleural mesothelioma, peritoneal  
30 mesothelioma, and pericardial mesothelioma)), breast cancer, genital cancer (ovarian cancer, uterine cancer (e.g., cervical cancer, uterine body cancer, and endometrial cancer), etc.), renal cancer, bladder cancer, prostate cancer, testicular tumor, skin cancer (e.g., malignant melanoma and epidermal cancer),  
35 blood cancer (e.g., multiple myeloma and acute myeloid leukemia),

bone and soft tissue tumor, rhabdomyosarcoma, brain tumor, malignant schwannoma, neuroendocrine tumor, thyroid cancer, and the like. In one embodiment, the targets are bladder cancer, urothelial cancer, digestive organ cancer (esophageal cancer, gastric cancer, duodenal cancer, liver cancer, biliary tract cancer (e.g., gallbladder and cholangiocarcinoma), pancreatic cancer, small intestine cancer, large intestine cancer (e.g., colorectal cancer, colon cancer, and rectal cancer)), ovarian cancer, head and neck cancer, and uterine cancer (e.g., cervical cancer and uterine body cancer). Preferred are urothelial cancer, esophageal cancer, and non-small cell lung cancer; and more preferred are esophageal cancer and non-small cell lung cancer. The cancers mentioned herein include not only the primary lesion, but also cancer metastasized to other organs (e.g., liver). The antitumor agent of the present disclosure may also be used in postoperative adjuvant chemotherapy performed in order to prevent recurrence after surgical removal of the tumor, or may be used in preoperative adjuvant chemotherapy performed in order to surgically remove the tumor.

[0121]

In one embodiment of the present disclosure, examples of cancers targeted by the combination method include malignant melanoma, non-small cell lung cancer, Hodgkin's lymphoma, urothelial cancer, solid cancer with high-frequency microsatellite instability (MSI-High), renal cell cancer, head and neck cancer, esophageal cancer, and gastric cancer.

[0122]

As used in the present specification, the term "combination (therapy)" is intended to define a therapy that includes the use of a combination of two or more compounds/drugs (as defined above). Thus, "combination (therapy)," "combination," and the use of compounds/drugs "in combination" in the present application may mean compounds/drugs administered as part of the same overall therapeutic regimen. The dose of each of the two or more compounds/drugs may be different: each may be administered

simultaneously or at different times. Therefore, it is understood that the compounds/drugs of the combination may be administered sequentially (e.g., before or after) or simultaneously, either in the same pharmaceutical formulation (i.e., together) or in  
5 different pharmaceutical formulations (i.e., separately). The same formulation is simultaneously a single formulation. On the other hand, different pharmaceutical formulations are non-integral.

[0123]

10 In the present specification, the terms "regimen" and "therapeutic regimen" refer to a plan that shows, in chronological order, the type and amount of drugs, duration, procedure, etc., in drug treatment, and that shows the dose, administration method, administration order, and administration  
15 day of each drug. The treatment in one therapeutic regimen is, for example, a method that starts administration of drugs to be combined, simultaneously or substantially simultaneously on the first day of the cycle. The treatment in one therapeutic regimen also includes, for example, one cycle with three weeks in which  
20 administration of drug A is started first, and administration of drug B is started one week later; however, both drugs are substantially simultaneously administered as one cycle.

[0124]

The therapeutic regimen of compound 1 or a salt thereof  
25 and pembrolizumab of the present disclosure may include not only compound 1 or the salt thereof and pembrolizumab, but also other drugs.

[0125]

The administration form of the antitumor agent of the  
30 present disclosure is not limited, and can be appropriately selected depending on the therapeutic purpose. Specific examples thereof include oral preparations (tablets, coated tablets, powders, granules, capsules, solutions, etc.), injections, suppositories, patches, ointments, and the like. In the case of  
35 compound 1 or a salt thereof, oral preparations are preferable.

In the case of pembrolizumab, the above-mentioned administration forms can be used, and injections are preferable.

[0126]

According to the antitumor agent of the present  
5 disclosure, pembrolizumab and compound 1 or a salt thereof, which  
are active ingredients, may be directly used as an antitumor  
agent. Depending on the administration form thereof, a  
pharmaceutically acceptable carrier may be used to prepare a  
pharmaceutical composition by a generally known method. Examples  
10 of such carriers include various carriers commonly used in  
general drugs, such as excipients, binders, disintegrants,  
lubricants, diluents, solubilizing agents, suspending agents,  
isotonizing agents, pH adjusters, buffers, stabilizers, coloring  
agents, flavoring agents, and the like.

15 [0127]

The antitumor agent of the present disclosure may be  
formulated into a plurality of dosage forms, or may be formulated  
into a single dosage form, based on the administration form and  
administration schedule of each active ingredient. Further,  
20 formulations may be produced and sold in a single package  
suitable for combined administration, or formulations may be  
produced and sold in separate packages. The same applies to the  
embodiments of the pharmaceutical composition. Accordingly, the  
"pharmaceutical composition comprising pembrolizumab and compound  
25 1 or a salt thereof as active ingredients" includes a  
pharmaceutical composition prepared by separately formulating the  
active ingredients in a plurality of dosage forms, and a  
pharmaceutical composition prepared by formulating the active  
ingredients in a single dosage form. The pharmaceutical  
30 composition prepared by separately formulating the active  
ingredients in a plurality of dosage forms includes a  
pharmaceutical composition prepared by formulating formulations  
in a single package suitable for combined administration, and a  
pharmaceutical composition prepared by formulating formulations  
35 in separate packages.

[0128]

The present disclosure relates to a kit preparation comprising an antitumor agent comprising compound 1 or a salt thereof, and an instruction manual stating that compound 1 or the salt thereof is administered to cancer patients in combination with pembrolizumab. The "instruction manual" as used herein may be one stating the above-mentioned dose. Regardless of whether it is legally binding, an instruction manual that recommends the above-mentioned dose is preferable. Specific examples include package inserts, brochures, and the like. The kit preparation comprising an instruction manual may be one in which the instruction manual is printed or attached to the package of the kit preparation, or may be one in which the instruction manual is enclosed together with an antitumor agent in the package of the kit preparation.

[0129]

Examples of methods for detecting the mechanism of action by FGFR inhibitors and the expression of resistance to immune checkpoint inhibitors include, but are not limited to, a method for examining the modulation of the tumor immune microenvironment (NPL 13).

[0130]

The microenvironment of the cancer is important for the efficacy of immune checkpoint inhibitors, and cancer-associated fibroblasts (CAFs) are known to play an important role. FGFs are factors that regulate the growth of fibroblast cells, and their receptors, FGFRs, are molecules that receive signals from FGFs in cells and promote cell growth. Myeloid-derived suppressor cells (MDSC) are immature myeloid cells that increase in tumor tissues, lymph nodes, and peripheral blood under pathological conditions, and are known to have potent immunosuppressive activity.

[0131]

It has been reported that MDSC can be used as a predictive marker for the effect of immune checkpoint inhibitors and can contribute to the patient resistance to immune checkpoint

inhibitors (NPL 14).

[0132]

In the present specification, the resistance (also referred to as tolerance or intractableness) to immune checkpoint inhibitors includes subject conditions in which no therapeutic effect is expected after administration of an immune checkpoint inhibitor, and in which progression of disease is confirmed in at least one clinical evaluation; and subject conditions in which therapeutic effects of immune checkpoint inhibitors cannot be expected, although the subject does not have intolerance to immune checkpoint inhibitors, recurrence after administration of immune checkpoint inhibitors, or treatment experience with immune checkpoint inhibitors. In one embodiment, it is also included that no effective effects are exhibited for immune checkpoint inhibitors in pharmacological tests, such as responses of cell lines that are not considered to show efficacy. Resistance includes natural resistance that an anticancer agent does not show efficacy from the beginning of the treatment, and acquired resistance that an anticancer agent that has initially been effective becomes ineffective as the treatment is continued and leads to the exacerbation of the cancer. In the present specification, resistance includes the meaning of both natural resistance and acquired resistance.

[0133]

In the present specification, refractory to immune checkpoint inhibitors means that an immune checkpoint inhibitor become ineffective and exhibits no effect after administration of the immune checkpoint inhibitor. One of the causes of refractory is considered to be due to resistance.

[0134]

The antitumor agent of the present disclosure can be used for the treatment of cancer. The "antitumor effect" when referring to a cancer patient who receives treatment with a therapeutic regimen, such as the combination therapy described in the present specification, means at least one evaluation of, for



example, PFS (progression-free survival), DCR (disease control rate), DOR (duration of response), OS (overall survival), ORR (objective response rate), DCR (disease control rate), TTR (time to response), PROs (patient-reported outcomes), and the like. In one embodiment, tumor evaluation for the combination therapy described in the present specification for solid tumors is based on the RECIST 1.1 criteria (Response Evaluation Criteria in Solid Tumors), and the antitumor effect is expressed by SD (stable disease), PR (partial response), CR (complete response), and PD (progressive disease). Tumor evaluation of brain tumors can be carried out by standard brain tumor MRI, including pre- and post-enhancement MRI, using a Gd-MRI (gadolinium (Gd)) chelate contrast agent.

## Examples

[0135]

The present disclosure is explained in more detail below with reference to Examples; however, the present disclosure is not limited to these Examples, and many modifications can be made by a person who has ordinary knowledge in this field within the technical idea of the present disclosure.

[0136]

Example 1: Clinical trial for cancer immunotherapy-resistant cancer (e.g., non-small cell lung cancer, esophageal cancer, and urothelial cancer) patients by combined use of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof and pembrolizumab

This study evaluates the efficacy and safety of the combined use of compound 1 or a salt thereof and pembrolizumab in FGFR-overexpressing cancer patients (with, e.g., non-small cell lung cancer, esophageal cancer, or urothelial cancer), based on the clinical trial registered as JapicCTI-195063 with the Japan Pharmaceutical Information Center. Specifically, administration is performed for a predetermined period of time (e.g., 24 weeks).

Compound 1 or a salt thereof is orally administered to the patients at various doses (e.g., 20 mg) for 21 days, and pembrolizumab (e.g., 200 mg per administration) is administered by intravenous drip infusion every three weeks (every 21 days).

5 One cycle is 21 days, and this is repeated. In some cases, a placebo may be used as a control, and compound 1 or a salt thereof and/or pembrolizumab may be additionally administered to other patients. Moreover, combined administration with compound 1 or a salt thereof may be performed on patients who have treatment  
10 experience with pembrolizumab.

[0137]

The combined use of compound 1 or a salt thereof and pembrolizumab can provide therapeutic effects that cannot be expected from monotherapies separately using each of them. For  
15 example, in an embodiment of the present disclosure, it can be found that this combined use has a higher degree of effects than at least one of the measurement results of treatment with either of them. Moreover, for example, in an embodiment of the present disclosure, a synergistic effect can be obtained by the combined  
20 use of compound 1 or a salt thereof and pembrolizumab.

[0138]

The combined use of compound 1 or a salt thereof and pembrolizumab can be more effective than the single use of either of them, according to at least one of the following measurement  
25 results: reduced number of cancer cells, regression of tumor size, reduced rate of cancer cell infiltration into peripheral organs, reduced rate of tumor metastasis or tumor growth, overall response rate, and extended progression-free survival or overall survival.

30 [0139]

Example 2: Influence on tumor immunity in model subcutaneously implanted with mouse breast cancer cell 4T1

Mouse breast cancer cell line 4T1 was subcutaneously implanted in a 6-week-old male BALB/cAJcl mouse. The day of cell  
35 implantation was set to Day 0, and compound 1 was orally

administered daily from the next day (Day 1) for 14 days at a dose of 15 mg/kg/day. On the day following the final administration (Day 15), lymphocyte fractions were isolated from the tumor, spleen, and peripheral blood, and myeloid-derived suppressor cells (MDSCs) (CD11b<sup>+</sup>/Gr-1<sup>+</sup> cells), CD4-positive T cells, and CD8-positive T cells were measured using a cell sorter. Moreover, the production of the model subcutaneously implanted with mouse breast cancer cell 4T1, drug administration, and the measurement of each cell were performed in the same manner as described above, except that the dose of compound 1 was changed to 30 mg/kg/day. As a control, the same operation as described above was performed, except that compound 1 was not administered. Fig. 1 shows the results.

[0140]

The administration of compound 1 at any dose resulted in a significant reduction in MDSCs in the spleen lymphocyte fractions (Student's t-test,  $P < 0.01$ ), compared with the non-drug administration control. MDSCs in the peripheral blood lymphocyte fractions tended to decrease in a dose-dependent manner compared with the control. The CD4-positive T cells in the peripheral blood lymphocyte fractions, and the CD8-positive T cells in the spleen lymphocyte fractions and peripheral blood lymphocyte fractions, tended to increase in a dose-dependent manner compared with the control.

[0141]

These results confirmed the inhibitory effect of compound 1 on MDSCs in the in vivo models, and thus suggested the possibility that compound 1 had an antitumor effect via an immunosuppression mechanism. Further, since CD4-positive T cells and CD8-positive T cells increased due to the administration of compound 1, the activation of immune activity in the cancer-bearing mice by compound 1 was confirmed. The above results suggested that the combined use of compound 1 or a salt thereof with an immune checkpoint inhibitor enhances the antitumor effect.

[0142]

Although the mouse breast cancer cell line 4T1 used in Example 2 is breast cancer cells that have no FGFR genetic aberration, the administration of compound 1 confirmed the inhibitory effect on MDSCs, as well as increased CD4-positive T cells and CD8-positive T cells, indicating that compound 1 has an antitumor effect via an immunosuppression mechanism. Moreover, the administration of vofatamab, which is an anti-FGFR3 antibody, to urothelial cancer patients causes the cancer to change from a "cold" state (low sensitivity to immune checkpoint inhibitors) to a "hot" state (high sensitivity to immune checkpoint inhibitors); thus, response by combined use with pembrolizumab is observed even in patients without FGFR genetic aberration (W. Choi et al., presentation at AACR Special Conference on Bladder Cancer: Transforming the Field, May 18-21, 2019, Denver, USA).

[0143]

It is to be understood that, if any prior art publication is referred to herein, such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art, in Australia or any other country.

[0144]

In the claims which follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary implication, the word "comprise" or variations such as "comprises" or "comprising" is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

30

## CLAIMS

## [Claim 1]

Use of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof for the treatment of cancer in a patient with resistance to immune checkpoint inhibitors by combination therapy with pembrolizumab, wherein (S)-1-(3-(4-amino-3-((3,5 dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof is administered once a day at a dose selected from the group consisting of 4 mg, 8 mg, 12 mg, 16 mg, and 20 mg, and pembrolizumab is administered at a dose selected from the group consisting of 1 mg/kg in 3-week intervals, 2 mg/kg in 3-week intervals, and 200 mg in 3-week intervals.

## [Claim 2]

Use of pembrolizumab for the treatment of cancer in a patient with resistance to immune checkpoint inhibitors by combination therapy with of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof, wherein pembrolizumab is administered at a dose selected from the group consisting of 1 mg/kg in 3-week intervals, 2 mg/kg in 3-week intervals, and 200 mg in 3-week intervals , and (S)-1-(3-(4-amino-3-((3,5 -dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof is administered once a day at a dose selected from the group consisting of 4 mg, 8 mg, 12 mg, 16 mg, and 20 mg.

## [Claim 3]

A method for treating cancer in a patient with resistance to immune checkpoint inhibitors, the method comprising administering (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof, and pembrolizumab to the patient in need

2020229714 04 Feb 2025

thereof, wherein (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof is administered once a day at a dose selected from the group consisting of 4 mg, 8 mg, 12 mg, 16 mg, and 20 mg, and pembrolizumab is administered at a dose selected from the group consisting of 1 mg/kg in 3-week intervals, 2 mg/kg in 3-week intervals, and 200 mg in 3-week intervals.

[Claim 4]

Use of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof for the treatment of cancer in a patient who has not been administered immune checkpoint inhibitors by combination therapy with pembrolizumab, wherein (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof is administered once a day at a dose selected from the group consisting of 4 mg, 8 mg, 12 mg, 16 mg, and 20 mg, and pembrolizumab is administered at a dose selected from the group consisting of 1 mg/kg in 3-week intervals, 2 mg/kg in 3-week intervals, and 200 mg in 3-week intervals.

[Claim 5]

Use of pembrolizumab for the treatment of cancer in a patient who has not been administered immune checkpoint inhibitors by combination therapy with (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof, wherein pembrolizumab is administered at a dose selected from the group consisting of 1 mg/kg in 3-week intervals, 2 mg/kg in 3-week intervals, and 200 mg in 3-week intervals, and (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt

thereof is administered once a day at a dose selected from the group consisting of 4 mg, 8 mg, 12 mg, 16 mg, and 20 mg.

[Claim 6]

5 A method for treating cancer in a patient who has not been administered immune checkpoint inhibitors, the method comprising administering (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof, and  
10 pembrolizumab to the patient in need thereof, wherein (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof is administered once a day at a dose selected from the group consisting of 4 mg, 8 mg, 12 mg, 16 mg, and 20 mg, and  
15 pembrolizumab is administered at a dose selected from the group consisting of 1 mg/kg in 3-week intervals, 2 mg/kg in 3-week intervals, and 200 mg in 3-week intervals.

[Claim 7]

20 Use of (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof for the treatment of cancer in a patient without aberrations in the FGFR pathway by combination therapy with pembrolizumab, wherein (S)-1-  
25 (3-(4-amino-3-((3,5 dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof is administered once a day at a dose selected from the group consisting of 4 mg, 8 mg, 12 mg, 16 mg, and 20 mg, and pembrolizumab is administered at a dose selected from the group  
30 consisting of 1 mg/kg in 3-week intervals, 2 mg/kg in 3-week intervals, and 200 mg in 3-week intervals.

[Claim 8]

35 Use of pembrolizumab for the treatment of cancer in a patient without aberrations in the FGFR pathway by combination

therapy with (S)-1-(3-(4-amino-3-((3,5 dimethoxyphenyl)ethynyl)-  
1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one  
or a salt thereof, wherein pembrolizumab is administered at a  
dose selected from the group consisting of 1 mg/kg in 3-week  
5 intervals, 2 mg/kg in 3-week intervals, and 200 mg in 3-week  
intervals , and (S)-1-(3-(4-amino-3-((3,5 -  
dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-  
yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof is  
administered once a day at a dose selected from the group  
10 consisting of 4 mg, 8 mg, 12 mg, 16 mg, and 20 mg.

[Claim 9]

A method for treating cancer in a patient without  
aberrations in the FGFR pathway, the method comprising  
15 administering (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-  
1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one  
or a salt thereof, and pembrolizumab to the patient in need  
thereof, wherein (S)-1-(3-(4-amino-3-((3,5  
dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-  
20 yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof is  
administered once a day at a dose selected from the group  
consisting of 4 mg, 8 mg, 12 mg, 16 mg, and 20 mg, and  
pembrolizumab is administered at a dose selected from the group  
consisting of 1 mg/kg in 3-week intervals, 2 mg/kg in 3-week  
25 intervals, and 200 mg in 3-week intervals.

[Claim 10]

Use of (S)-1-(3-(4-amino-3-((3,5-  
dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-  
30 yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof for the  
manufacture of an agent for:

the treatment of cancer in a patient with resistance to  
immune checkpoint inhibitors,



the treatment of cancer in a patient who has not been administered immune checkpoint inhibitors, or

the treatment of cancer in a patient without aberrations in the FGFR pathway,

5 by combination therapy with pembrolizumab, wherein (S)-1-(3-(4-amino-3-((3,5 dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof is administered once a day at a dose selected from the group consisting of 4 mg, 8 mg, 12 mg, 16 mg, and 20 mg, and  
10 pembrolizumab is administered at a dose selected from the group consisting of 1 mg/kg in 3-week intervals, 2 mg/kg in 3-week intervals, and 200 mg in 3-week intervals.

[Claim 11]

15 Use of pembrolizumab for the manufacture of an agent for:

the treatment of cancer in a patient with resistance to immune checkpoint inhibitors,

the treatment of cancer in a patient who has not been administered immune checkpoint inhibitors, or

20 the treatment of cancer in a patient without aberrations in the FGFR pathway,

by combination therapy with (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof, wherein  
25 pembrolizumab is administered at a dose selected from the group consisting of 1 mg/kg in 3-week intervals, 2 mg/kg in 3-week intervals, and 200 mg in 3-week intervals , and (S)-1-(3-(4-amino-3-((3,5 -dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt  
30

thereof is administered once a day at a dose selected from the group consisting of 4 mg, 8 mg, 12 mg, 16 mg, and 20 mg.

[Claim 12]

5 Use of (S)-1-(3-(4-amino-3-((3,5-

dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof and pembrolizumab for the manufacture of an agent for:

10 the treatment of cancer in a patient with resistance to immune checkpoint inhibitors,

the treatment of cancer in a patient who has not been administered immune checkpoint inhibitors, or

the treatment of cancer in a patient without aberrations in the FGFR pathway,

15 wherein (S)-1-(3-(4-amino-3-((3,5-

dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof is administered once a day at a dose selected from the group consisting of 4 mg, 8 mg, 12 mg, 16 mg, and 20 mg, and

20 pembrolizumab is administered at a dose selected from the group consisting of 1 mg/kg in 3-week intervals, 2 mg/kg in 3-week intervals, and 200 mg in 3-week intervals.

[Claim 13]

25 Use or method according to any one of claims 1 to 12, wherein treatment with (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or a salt thereof and pembrolizumab results in a sustained response in an individual  
30 after cessation of the treatment.

## [Claim 14]

Use or method according to any one of claims 1 to 13,  
wherein (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-  
pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or  
5 a salt thereof is used before, simultaneously with, or after  
pembrolizumab.

## [Claim 15]

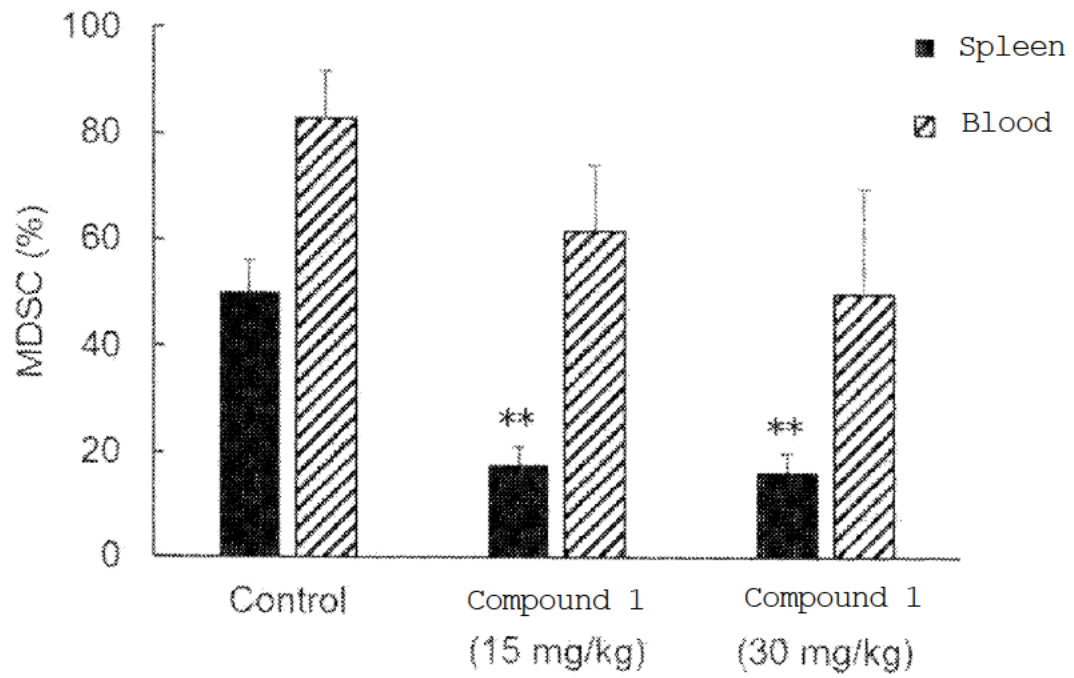
Use or method according to any one of claims 1 to 14,  
10 wherein (S)-1-(3-(4-amino-3-((3,5-dimethoxyphenyl)ethynyl)-1H-  
pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one or  
a salt thereof is used continuously or intermittently.

## [Claim 16]

15 Use or method according to any one of claims 1 to 15,  
wherein the cancer is esophageal cancer, non-small cell lung  
cancer, or urothelial cancer.

## DRAWINGS

Fig. 1



\*\*;  $P < 0.01$