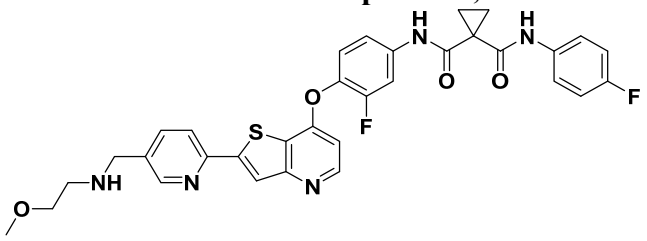
CLAIMS

1. Use of a multi-tyrosine kinase inhibitor, in combination with a therapeutically effective amount of a PD-1 antagonist, in the preparation of a medicament for the prevention, delay of progression or treatment of cancer in a subject,

wherein the multi-tyrosine kinase inhibitor is **Compound 1,**



Compound 1

or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof,

wherein the PD-1 antagonist is an antibody or a fragment antigen binding thereof, which specifically binds to human PD-1 comprising a heavy chain variable region (Vh) and a light chain variable region (Vk) that contain complement determinant regions (CDRs) listed as follows:

a) mu317 CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 11, 12, 13, respectively); and CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 14, 15, 16, respectively);

b) mu326 CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 17, 18, 19, respectively); and CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 20, 21, 22, respectively);

c) 317-4B6 CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 31, 32, 33, respectively); and CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 34, 35, 36, respectively);

d) 326-4A3 CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 37, 38, 39, respectively); and CDR-L1, CDR--L2 and CDR-L3 (SEQ ID NOs: 40, 41, 42, respectively);

e) 317-1H CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 11, 59, 13, respectively); and CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 14, 15, 16, respectively);

f) 317-4B2 CDR-HL CDR-H2 and CDR-H3 (SEQ ID NOs: 11, 60, 13, respectively); and CDR-L1 , CDR-L2 and CDR-L3 (SEQ ID NOs: 61, 15, 16, respectively);

g) 317-4B5 CDR-Hl, CDR-H2 and CDR-H3 (SEQ ID NOs: 11, 60, 13, respectively); and CDR-L1 , CDR-L2 and CDR-L3 (SEQ ID NOs: 61, 15, 16, respectively);

h) 317-4B6 CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 11, 32, 13, respectively); and CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 61, 15, 16, respectively);

i) 326-1 CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 17, 62, 19, respectively); and CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 20, 21, 22, respectively);

j) 326-3B1 CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 17, 62, 19, respectively); and CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 20, 21, 22, respectively); or

k) 326-3G1 CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 17, 62, 19, respectively); and CDR-L1, CDR-I 2 and CDR-L3 (SEQ ID NOs: 20, 21, 22, respectively).

2. The use of claim 1, wherein the PD-1 antagonist is an antibody which comprises a heavy chain variable region (Vh) and a light chain variable region (Vk) comprising:

a) mu317 (SEQ ID NOs: 4 and 6, respectively);
b) mu326 (SEQ ID NOs: 8 and 10, respectively);
c) 317-4B6 (SEQ ID NOs: 24 and 26, respectively);
d) 326-4A3 (SEQ ID NOs: 28 and 30, respectively);
e) 317-4B2 (SEQ ID NOs: 43 and 44, respectively);
f) 317-4B5 (SEQ ID NOs: 45 and 46, respectively);
g) 317-1 (SEQ ID NOs: 48 and 50, respectively);
h) 326-3B1 (SEQ ID NOs: 51 and 52, respectively);
i) 326-3GI (SEQ ID NOs: 53 and 54, respectively);
j) 326-1 (SEQ ID NOs: 56 and 58, respectively);
k) 317-3A1 (SEQ ID NOs: 64 and 26, respectively);
l) 317-3C1 (SEQ ID NOs: 65 and 26, respectively);
m) 317-3E1 (SEQ ID NOs: 66 and 26, respectively);
n) 317-3F1 (SEQ ID NOs: 67 and 26, respectively);
o) 317-3G1 (SEQ ID NOs: 68 and 26, respectively);
p) 317-3H1 (SEQ ID NOs: 69 and 26, respectively);
q) 317-311 (SEQ ID NOs: 70 and 26, respectively);
r) 317-4B 1 (SEQ ID NOs: 71 and 26, respectively);
s) 317-4B3 (SEQ ID NOs: 72 and 26, respectively);
t) 317-4B4 (SEQ ID NOs: 73 and 26, respectively);
u) 317-4A2 (SEQ ID NOs: 74 and 26, respectively);
v) 326-3 A 1 (SEQ ID NOs: 75 and 30, respectively);
w) 326-3C1 (SEQ ID NOs: 76 and 30, respectively);
x) 326-3D1 (SEQ ID NOs: 77 and 30, respectively);
y) 326-3E1 (SEQ ID NOs: 78 and 30, respectively);
z) 326-3F1 (SEQ ID NOs: 79 and 30, respectively);
aa) 326-3B N55D (SEQ ID NOs: 80 and 30, respectively);
ab) 326-4A1 (SEQ ID NOs: 28 and 81, respectively); or
ac) 326-4A2 (SEQ ID NOs: 28 and 82, respectively).

3. The use of claim 1, wherein the PD-1 antagonist is an antibody which contains an IgG4 heavy chain effector or constant domain comprising any of SEQ ID NOs: 83-88.

4. The use of claim 1, wherein the PD-1 antagonist is an antibody which contains an F(ab) or F(ab)2 comprising a domain of claim 2.

5. The use according to Claim 1, wherein the PD-1 antagonist is an antibody which comprises a heavy chain variable region (Vh) and a light chain variable region (Vk), and a IgG4 heavy chain effector or constant domain comprising SEQ ID NOs: 87 or 88, wherein the heavy chain variable region (Vh) and the light chain variable region (Vk) comprise:

a) mu317 (SEQ ID NOs: 4 and 6, respectively);
b) mu326 (SEQ ID NOs: 8 and 10, respectively);
c) 317-4B6 (SEQ ID NOs: 24 and 26, respectively);
d) 326-4A3 (SEQ ID NOs: 28 and 30, respectively);
e) 317-4B2 (SEQ ID NOs: 43 and 44, respectively);
f) 317-4B5 (SEQ ID NOs: 45 and 46, respectively);
g) 317-1 (SEQ ID NOs: 48 and 50, respectively);
h) 326-3B1 (SEQ ID NOs: 51 and 52, respectively);
i) 326-3GI (SEQ ID NOs: 53 and 54, respectively);
j) 326-1 (SEQ ID NOs: 56 and 58, respectively);
k) 317-3A1 (SEQ ID NOs: 64 and 26, respectively);
l) 317-3C1 (SEQ ID NOs: 65 and 26, respectively);
m) 317-3E1 (SEQ ID NOs: 66 and 26, respectively);
n) 317-3F1 (SEQ ID NOs: 67 and 26, respectively);
o) 317-3G1 (SEQ ID NOs: 68 and 26, respectively);
p) 317-3H1 (SEQ ID NOs: 69 and 26, respectively);
q) 317-311 (SEQ ID NOs: 70 and 26, respectively);
r) 317-4B 1 (SEQ ID NOs: 71 and 26, respectively);
s) 317-4B3 (SEQ ID NOs: 72 and 26, respectively);
t) 317-4B4 (SEQ ID NOs: 73 and 26, respectively);
u) 317-4A2 (SEQ ID NOs: 74 and 26, respectively);
v) 326-3 A 1 (SEQ ID NOs: 75 and 30, respectively);
w) 326-3C1 (SEQ ID NOs: 76 and 30, respectively);
x) 326-3D1 (SEQ ID NOs: 77 and 30, respectively);
y) 326-3E1 (SEQ ID NOs: 78 and 30, respectively);
z) 326-3F1 (SEQ ID NOs: 79 and 30, respectively);
aa) 326-3B N55D (SEQ ID NOs: 80 and 30, respectively);
ab) 326-4A1 (SEQ ID NOs: 28 and 81, respectively); or
ac) 326-4A2 (SEQ ID NOs: 28 and 82, respectively).

6. The use according to claim 1, wherein the PD-1 antagonist is an antibody which comprises a heavy chain variable region (Vh) and a light chain variable region (Vk), and an IgG4 heavy chain effector or constant domain comprising SEQ ID NO: 88, wherein the heavy chain variable region (Vh) and the light chain variable region (Vk) comprises SEQ ID NO: 24 and SEQ ID NO: 26, respectively.

7. The use of claim 1, wherein **Compound 1** is in Crystalline Form D.

8. The use of claim 7, wherein the Crystalline Form D has an XRPD pattern substantially as shown in **Figure 1A.**

9. The use of claim 1, wherein the cancer is a solid cancer or tumor.

10. The use of claim 9, wherein the cancer is selected from lung cancer including non-small cell lung cancer (NSCLC), ovarian cancer (OC), renal cell carcinoma (RCC) or melanoma.

11. The use of claim 9, wherein cancer is multi-tyrosine kinase-associated cancer.

12. The use of claim 9, the cancer is resistant or refractory to a checkpoint inhibitor selected from anti-PD-1 antibody and / or anti-PD-L1 antibody.

13. The use of claim 9, the cancer is PD-L1 expression.

14. The use of claim 9, the cancer is selected by its stage including locally advanced, recurrent or metastatic.

15. The use of claim 10, wherein the cancer is non-squamous non-small cell lung cancer (NSCLC), squamous non-small cell lung cancer (NSCLC), epithelial ovarian cancer (OC), renal cell carcinoma (RCC) or melanoma.

16. The use of claim 15, wherein the non-squamous non-small cell lung cancer (NSCLC) is: anti-PD-1/PD-L1 antibody refractory/resistant metastatic, non-squamous NSCLC; anti-PD-1/PD-L1 antibody naïve metastatic, non-squamous NSCLC; or, PD-L1 positive, locally advanced or metastatic, non-squamous NSCLC without prior systemic treatment in metastatic setting.

17. The use of claim 15, wherein the squamous non-small cell lung cancer (NSCLC) is: anti-PD-1/PD-L1 antibody refractory/resistant metastatic, squamous NSCLC; anti-PD-1/PD-L1 antibody naïve metastatic, squamous NSCLC; or, PD-L1 positive, locally advanced or metastatic, squamous NSCLC without prior systemic treatment in metastatic setting.

18. The use of claim 15, wherein the renal cell carcinoma (RCC) is anti-PD-1/PD-L1 antibody refractory/resistant metastatic or advanced RCC, or metastatic or advanced RCC without prior systemic therapy.

19. The use of claim 15, wherein the melanoma is anti-PD-1/PD-L1 antibody refractory/resistant unresectable or metastatic melanoma.

20. The use of claim 15, wherein the ovarian cancer (OC) is naïve recurrent and platinum-resistant epithelial OC.

21. The use of any one of claims 1-6, wherein the PD-1 antagonist is to be administered parenterally at a dose of 30-300 mg QW, or Q2W, or Q3W, or Q4W.

22. The use of any one of claims 1-6, wherein the PD-1 antagonist is to be administered parenterally at a dose of 200 mg Q3W.

23. The use of any one of claims 1- 7, wherein **Compound 1** is to be administered orally at a dose of 40-150 mg QD.

24. The use of any one of claims 1- 7, wherein **Compound 1** is to be administered orally at a dose of 60-150 mg QD.

25. The use of any one of claims 1- 7, wherein **Compound 1** is to be administered orally at a dose of 120 mg QD.

26. The method of any one of claims 1-7, wherein **Compound 1** is to be administered orally at a dose of 120 mg QD in combination with the PD-1 antagonist at a dose of 200 mg IV Q3W.

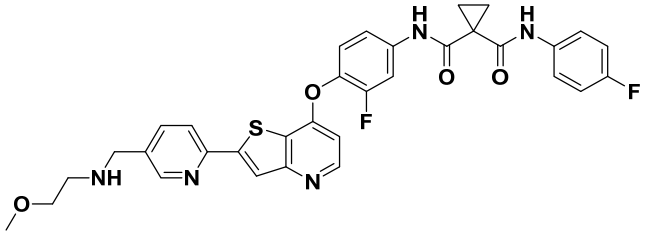
27. A pharmaceutical combination comprising a PD-1 antagonist and a multi-tyrosine kinase inhibitor,

wherein the PD-1 antagonist is an antibody or a fragment antigen binding thereof, which specifically binds to human PD-1, comprising a heavy chain variable region (Vh) and a light chain variable region (Vk) that contain complement determinant regions (CDRs) listed as follows:

CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 31, 32, 33, respectively); and

CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 34, 35, 36, respectively); and

wherein the multi-tyrosine kinase inhibitor is **Compound 1,**



Compound 1

or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.