

combination of anti-ROR-1 antibody with BCR inhibitors to treat chronic lymphocytic leukemia (CLL).

[0006a] In one aspect, the present disclosure refers to a pharmaceutical composition comprising a BTK antagonist, an anti-ROR-1 antibody, and a pharmaceutically acceptable excipient, wherein said anti-ROR-1 antibody comprises a humanized heavy chain variable region and a humanized light chain variable region, wherein said humanized heavy chain variable region comprises the sequences set forth in SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3; and wherein said humanized light chain variable region comprises the sequences set forth in SEQ ID NO:4, SEQ ID NO:5, and SEQ ID NO:6~~use of a Bruton's tyrosine kinase (BTK) antagonist in the manufacture of a first medicament and an anti ROR-1 antibody in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat an ROR-1 expressing cancer or a cancer susceptible to a BTK antagonist in a subject in need thereof, comprising that a therapeutically effective amount of said BTK antagonist and said anti-ROR-1 antibody is to be administered to said subject, wherein said anti ROR-1 antibody comprises a humanized heavy chain variable region and a humanized light chain variable region, wherein said humanized heavy chain variable region comprises the sequences set forth in SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3; and wherein said humanized light chain variable region comprises the sequences set forth in SEQ ID NO:4, SEQ ID NO:5, and SEQ ID NO:6.~~

[0006b] In another aspect, the present disclosure refers to a use of the pharmaceutical composition as described herein in the manufacture of a medicament for treating an ROR-1 expressing cancer or a cancer susceptible to a BTK antagonist in a subject in need thereof~~pharmaceutical composition comprising a BTK antagonist, an anti-ROR-1 antibody, and a pharmaceutically acceptable excipient, wherein said anti ROR-1 antibody comprises a humanized heavy chain variable region and a humanized light chain variable region, wherein said humanized heavy chain variable region comprises the sequences set forth in SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3; and wherein said humanized light chain variable region comprises the sequences set forth in SEQ ID NO:4, SEQ ID NO:5, and SEQ ID NO:6.~~

[0007] In an example is provided a method of treating cancer in a subject in need thereof, the method including administering to the subject a therapeutically effective amount of a Bruton's tyrosine kinase (BTK) antagonist and a tyrosine kinase-like orphan receptor 1 (ROR-1) antagonist.

[0008] In an example is provided a pharmaceutical composition including a BTK antagonist, a ROR-1 antagonist and a pharmaceutically acceptable excipient.

[0009] In an example is provided a pharmaceutical composition including a BTK antagonist, an anti-ROR-1 antibody and a pharmaceutically acceptable excipient, wherein the BTK antagonist and the anti-ROR-1 antibody are present in a combined synergistic amount, wherein the combined synergistic amount is effective to treat cancer in a subject in need thereof.

[0010] In an example, there is provided a method of treating cancer in a subject in need thereof. The method includes administering to the subject a therapeutically effective amount of a Bruton's tyrosine kinase (BTK) antagonist and an anti-ROR-1 antibody.

[0011] In another example, there is provided a pharmaceutical composition including a Bruton's tyrosine kinase (BTK) antagonist, an anti-ROR-1 antibody, and a pharmaceutically acceptable excipient.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] FIGS. 1A-1D. UC-961 inhibits Wnt5a-induced Rac1 activation in ibrutinib-treated CLL cells. (FIG. 1A) Activated Rac1 was measured in CLL cells incubated with or without Wnt5a and treated with UC-961 or ibrutinib, as indicated on the top of each lane. (FIG. 1B) Wnt5a-induced activation of Rac1 in CLL cells without treatment or treated with UC-961 (10 µg/ml) and/or ibrutinib (0.5 µM). Mean Rac1 activation observed in five independent experiments is shown (n=5). (FIG. 1C) CLL cells were collected from ibrutinib treated patients (n=5). Activated Rac1 was measured in these CLL cells treated with or without Wnt5a or UC-961 indicated above each lane *in vitro*. (FIG. 1D) Rac1 activation was measured in CLL cells collected from patient treated with ibrutinib, which were treated with Wnt5a and/or UC-961. Mean Rac1 activation observed in five independent experiments is shown (n=5). The numbers below each lane are ratios of band IOD of activated *versus* total GTPase normalized to untreated samples. Data are shown as mean ± SEM for

WHAT IS CLAIMED IS:

1. ——— Use of a Bruton's tyrosine kinase (BTK) antagonist in the manufacture of a first medicament and an anti-ROR-1 antibody in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to treat an ROR-1 expressing cancer or a cancer susceptible to a BTK antagonist in a subject in need thereof, comprising that a therapeutically effective amount of said BTK antagonist and said anti-ROR-1 antibody is to be administered to said subject, wherein said anti-ROR-1 antibody comprises a humanized heavy chain variable region and a humanized light chain variable region, wherein said humanized heavy chain variable region comprises the sequences set forth in SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3; and wherein said humanized light chain variable region comprises the sequences set forth in SEQ ID NO:4, SEQ ID NO:5, and SEQ ID NO:6.

2. ——— The use of claim 1, wherein said BTK antagonist is a small molecule.

3. ——— The use of claim 1, wherein said BTK antagonist comprises ibrutinib, acalabrutinib, ONO/GS-4059, BGB-3111, or CC-292 (AVL-292).

4. ——— The use of claim 1, wherein said BTK antagonist is ibrutinib.

5. ——— The use of claim 1, wherein said anti-ROR-1 antibody is cirtuzumab.

6. ——— The use of claim 1, wherein said BTK antagonist and said anti-ROR-1 antibody are to be administered in a combined synergistic amount.

7. ——— The use of claim 1, wherein said BTK antagonist and said anti-ROR-1 antibody are to be administered simultaneously or sequentially.

8. ——— The use of claim 1, wherein said anti-ROR-1 antibody is to be administered at a first time point and said BTK antagonist is to be administered at a second time point, wherein said first time point precedes said second time point.

9. — The use of claim 1, wherein said BTK antagonist and said anti-ROR-1 antibody are admixed prior to administration.

10. — The use of claim 1, wherein said BTK antagonist is to be administered at an amount of about 1 mg/kg, 2 mg/kg, 5 mg/kg, 10 mg/kg or 15 mg/kg.

11. — The use of claim 1, wherein said BTK antagonist is to be administered at an amount of about 5 mg/kg.

12. — The use of claim 1, wherein said BTK antagonist is to be administered at an amount of about 420 mg.

13. — The use of claim 1, wherein said anti-ROR-1 antibody is to be administered at an amount of about 1 mg/kg, 2 mg/kg, 3 mg/kg, 5 mg/kg or 10 mg/kg.

14. — The use of claim 1, wherein said anti-ROR-1 antibody is to be administered at an amount of about 2 mg/kg.

15. — The use of claim 1, wherein said BTK antagonist is to be administered at an amount of about 5 mg/kg and said anti-ROR-1 antibody is to be administered at about 2 mg/kg.

16. — The use of claim 1, wherein said BTK antagonist is to be administered at an amount of about 5 mg/kg and said anti-ROR-1 antibody is to be administered at about 1 mg/kg.

17. — The use of claim 1, wherein said BTK antagonist is to be administered daily over the course of at least 14 days.

18. — The use of claim 1, wherein said BTK antagonist is to be administered daily over the course of about 28 days.

19. — The use of claim 1, wherein said anti-ROR-1 antibody is to be administered once over the course of about 28 days.

~~20. The use of claim 1, wherein said BTK antagonist is to be administered intravenously.~~

~~21. The use of claim 1, wherein said anti-ROR-1 antibody is to be administered intravenously.~~

~~22. The use of claim 1, wherein said subject is a mammal.~~

~~23. The use of claim 1, wherein said subject is a human.~~

~~24. The use of claim 1, wherein said ROR-1 expressing cancer or said cancer susceptible to a BTK antagonist is lymphoma, leukemia, myeloma, AML, B-ALL, T-ALL, renal cell carcinoma, colon cancer, colorectal cancer, breast cancer, epithelial squamous cell cancer, melanoma, stomach cancer, brain cancer, lung cancer, pancreatic cancer, cervical cancer, ovarian cancer, liver cancer, bladder cancer, prostate cancer, testicular cancer, thyroid cancer, head and neck cancer, uterine cancer, adenocarcinoma, or adrenal cancer.~~

~~25. The use of claim 1, wherein said ROR-1 expressing cancer or said cancer susceptible to a BTK antagonist is chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma, marginal cell B-Cell lymphoma, Burkitt's Lymphoma, or B-cell leukemia.~~

~~26. The use of claim 1, wherein said BTK antagonist and said anti-ROR-1 antibody are to be administered on different treatment schedules.~~

~~27. The use of claim 1, wherein said BTK antagonist and said anti-ROR-1 antibody are to be administered on different days.~~

~~28. The use of claim 1, wherein said BTK antagonist and said anti-ROR-1 antibody are to be administered separately.~~

291. A pharmaceutical composition comprising a BTK antagonist, an anti-ROR-1 antibody, and a pharmaceutically acceptable excipient, wherein said anti-ROR-1 antibody comprises a humanized heavy chain variable region and a humanized light chain variable region, wherein said humanized heavy chain variable region comprises the sequences set forth in SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3; and wherein said humanized light chain variable region comprises the sequences set forth in SEQ ID NO:4, SEQ ID NO:5, and SEQ ID NO:6.

302. The pharmaceutical composition of claim 291, wherein said BTK antagonist and said anti-ROR-1 antibody are present in a combined synergistic amount, wherein said combined synergistic amount is effective to treat an ROR-1 expressing cancer or a cancer susceptible to a BTK antagonist in a subject in need thereof.

313. The pharmaceutical composition of claim 291, wherein said BTK antagonist is a small molecule.

324. The pharmaceutical composition of claim 291, wherein said BTK antagonist is ibrutinib, acalabrutinib, ONO/GS-4059, BGB-3111 or CC-292 (AVL-292).

335. The pharmaceutical composition of claim 291, wherein said BTK antagonist is ibrutinib.

346. The pharmaceutical composition of claim 291, wherein said anti-ROR-1 antibody is cirmtuzumab.

7. Use of the pharmaceutical composition of claim 1 in the manufacture of a medicament for treating an ROR-1 expressing cancer or a cancer susceptible to a BTK antagonist in a subject in need thereof.

8. The use of claim 7, wherein said BTK antagonist is a small molecule.

9. The use of claim 7, wherein said BTK antagonist comprises ibrutinib, acalabrutinib, ONO/GS-4059, BGB-3111, or CC-292 (AVL-292).
10. The use of claim 7, wherein said BTK antagonist is ibrutinib.
11. The use of claim 7, wherein said anti-ROR-1 antibody is cirmtuzumab.
12. The use of claim 7, wherein said BTK antagonist and said anti-ROR-1 antibody are to be administered in a combined synergistic amount.
13. The use of claim 7, wherein said BTK antagonist and said anti-ROR-1 antibody are to be administered simultaneously or sequentially.
14. The use of claim 7, wherein said anti-ROR-1 antibody is to be administered at a first time point and said BTK antagonist is to be administered at a second time point, wherein said first time point precedes said second time point.
15. The use of claim 7, wherein said BTK antagonist and said anti-ROR-1 antibody are admixed prior to administration.
16. The use of claim 7, wherein said BTK antagonist is to be administered at an amount of about 1 mg/kg, 2 mg/kg, 5 mg/kg, 10 mg/kg or 15 mg/kg.
17. The use of claim 7, wherein said BTK antagonist is to be administered at an amount of about 5 mg/kg.
18. The use of claim 7, wherein said BTK antagonist is to be administered at an amount of about 420 mg.
19. The use of claim 7, wherein said anti-ROR-1 antibody is to be administered at an amount of about 1 mg/kg, 2 mg/kg, 3 mg/kg, 5 mg/kg or 10 mg/kg.

20. The use of claim 7, wherein said anti-ROR-1 antibody is to be administered at an amount of about 2 mg/kg.

21. The use of claim 7, wherein said BTK antagonist is to be administered at an amount of about 5 mg/kg and said anti-ROR-1 antibody is to be administered at about 2 mg/kg.

22. The use of claim 7, wherein said BTK antagonist is to be administered at an amount of about 5 mg/kg and said anti-ROR-1 antibody is to be administered at about 1 mg/kg.

23. The use of claim 7, wherein said BTK antagonist is to be administered daily over the course of at least 14 days.

24. The use of claim 7, wherein said BTK antagonist is to be administered daily over the course of about 28 days.

25. The use of claim 7, wherein said anti-ROR-1 antibody is to be administered once over the course of about 28 days.

26. The use of claim 7, wherein said BTK antagonist is to be administered intravenously.

27. The use of claim 7, wherein said anti-ROR-1 antibody is to be administered intravenously.

28. The use of claim 7, wherein said subject is a mammal.

29. The use of claim 7, wherein said subject is a human.

30. The use of claim 7, wherein said ROR-1 expressing cancer or said cancer susceptible to a BTK antagonist is lymphoma, leukemia, myeloma, AML, B-ALL, T-ALL, renal cell carcinoma, colon cancer, colorectal cancer, breast cancer, epithelial squamous cell cancer, melanoma, stomach cancer, brain cancer, lung cancer, pancreatic cancer, cervical cancer, ovarian

cancer, liver cancer, bladder cancer, prostate cancer, testicular cancer, thyroid cancer, head and neck cancer, uterine cancer, adenocarcinoma, or adrenal cancer.

31. The use of claim 7, wherein said ROR-1 expressing cancer or said cancer susceptible to a BTK antagonist is chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma, marginal cell B-Cell lymphoma, Burkitt's Lymphoma, or B cell leukemia.

32. The use of claim 7, wherein said BTK antagonist and said anti-ROR-1 antibody are to be administered on different treatment schedules.

33. The use of claim 7, wherein said BTK antagonist and said anti-ROR-1 antibody are to be administered on different days.

34. The use of claim 7, wherein said BTK antagonist and said anti-ROR-1 antibody are to be administered separately.