

WHAT IS CLAIMED IS:

- 1 1. A method of treating cancer in a subject in need thereof, said method
2 comprising administering to said subject a therapeutically effective amount of a Bruton's tyrosine
3 kinase (BTK) antagonist and a tyrosine kinase-like orphan receptor 1 (ROR-1) antagonist.
- 1 2. The method of claim 1, wherein said BTK antagonist is a small molecule.
- 1 3. The method of claim 1, wherein said BTK antagonist is ibrutinib, idelalisib,
2 fostamatinib, acalabrutinib, ONO/GS-4059, BGB-3111 or CC-292 (AVL-292).
- 1 4. The method of claim 1, wherein said BTK antagonist is ibrutinib.
- 1 5. The method of claim 1, wherein said ROR-1 antagonist is an antibody or a
2 small molecule.
- 1 6. The method of claim 1, wherein said ROR-1 antagonist is an anti-ROR-1
2 antibody.
- 1 7. The method of claim 5, wherein said antibody comprises a humanized heavy
2 chain variable region and a humanized light chain variable region,
3 wherein said humanized heavy chain variable region comprises the sequences set
4 forth in SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3; and
5 wherein said humanized light chain variable region comprises the sequences set forth
6 in SEQ ID NO:4, SEQ ID NO:5, and SEQ ID NO:6.
- 1 8. The method of claim 5, wherein said antibody is cirmtuzumab.
- 1 9. The method of claim 5, wherein said antibody comprises a humanized heavy
2 chain variable region and a humanized light chain variable region,
3 wherein said humanized heavy chain variable region comprises the sequences set
4 forth in SEQ ID NO:7, SEQ ID NO:8, and SEQ ID NO:9; and
5 wherein said humanized light chain variable region comprises the sequences set forth
6 in SEQ ID NO:10, SEQ ID NO:11, and SEQ ID NO:12.

1 10. The method of claim 1, wherein said BTK antagonist and said ROR-1
2 antagonist are administered in a combined synergistic amount.

1 11. The method of claim 1, wherein said BTK antagonist and said ROR-1
2 antagonist are administered simultaneously or sequentially.

1 12. The method of claim 1, wherein said ROR-1 antagonist is administered at a
2 first time point and said BTK antagonist is administered at a second time point, wherein said first
3 time point precedes said second time point.

1 13. The method of claim 1, wherein said BTK antagonist and said ROR-1
2 antagonist are admixed prior to administration.

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

1 15. The method of claim 1, wherein said BTK antagonist is administered at an
2 amount of about 5 mg/kg.

1 16. The method of claim 1, wherein said BTK antagonist is administered at an
2 amount of about 420 mg.

1 17. The method of claim 1, wherein said ROR-1 antagonist is administered at an
2 amount of about 1 mg/kg, 2 mg/kg, 3 mg/kg, 5 mg/kg or 10 mg/kg.

1 18. The method of claim 1, wherein said ROR-1 antagonist is administered at an
2 amount of about 2 mg/kg.

1 19. The method claim 1, wherein said BTK antagonist is administered at an
2 amount of about 5 mg/kg and said ROR-1 antagonist is administered at about 2 mg/kg.

1 20. The method of claim 1, wherein said BTK antagonist is administered at an
2 amount of about 5 mg/kg and said ROR-1 antagonist is administered at about 1 mg/kg.

1 21. The method of claim 1, wherein said BTK antagonist is administered daily
2 over the course of at least 14 days.

1 22. The method of claim 1, wherein said BTK antagonist is administered daily
2 over the course of about 28 days.

1 23. The method of claim 1, wherein said ROR-1 antagonist is administered once
2 over the course of about 28 days.

1 24. The method of claim 1, wherein said BTK antagonist is administered
2 intravenously.

1 25. The method of claim 1, wherein said ROR-1 antagonist is administered
2 intravenously.

1 26. The method of claim 1, wherein said subject is a mammal.

1 27. The method of claim 1, wherein said subject is a human.

1 28. The method of claim 1, wherein said cancer is lymphoma, leukemia,
2 myeloma, AML, B-ALL, T-ALL, renal cell carcinoma, colon cancer, colorectal cancer, breast
3 cancer, epithelial squamous cell cancer, melanoma, stomach cancer, brain cancer, lung cancer,
4 pancreatic cancer, cervical cancer, ovarian cancer, liver cancer, bladder cancer, prostate cancer,
5 testicular cancer, thyroid cancer, head and neck cancer, uterine cancer, adenocarcinoma, or adrenal
6 cancer.

1 29. The method of claim 1, wherein said cancer is chronic lymphocytic leukemia
2 (CLL), small lymphocytic lymphoma, marginal cell B-Cell lymphoma, Burkitt's Lymphoma, or B
3 cell leukemia.

1 30. A pharmaceutical composition comprising a BTK antagonist, a ROR-1
2 antagonist and a pharmaceutically acceptable excipient.

1 31. A pharmaceutical composition comprising a BTK antagonist, an anti-ROR-1
2 antibody and a pharmaceutically acceptable excipient, wherein said BTK antagonist and said anti-

3 ROR-1 antibody are present in a combined synergistic amount, wherein said combined synergistic
4 amount is effective to treat cancer in a subject in need thereof.

1 32. The pharmaceutical composition of claim 30, wherein said BTK antagonist is
2 a small molecule.

1 33. The pharmaceutical composition of claim 30, wherein said BTK antagonist is
2 ibrutinib, idelalisib, fostamatinib, acalabrutinib, ONO/GS-4059, BGB-3111 or CC-292 (AVL-292).

1 34. The pharmaceutical composition of claim 30, wherein said BTK antagonist is
2 ibrutinib.

1 35. The pharmaceutical composition of claim 30, wherein said ROR-1 antagonist
2 is an antibody or a small molecule.

1 36. The pharmaceutical composition of claim 30, wherein said ROR-1 antagonist
2 is an anti-ROR-1 antibody.

1 37. The pharmaceutical composition of claim 35, wherein said antibody
2 comprises a humanized heavy chain variable region and a humanized light chain variable region,
3 wherein said humanized heavy chain variable region comprises the sequences set
4 forth in SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3; and
5 wherein said humanized light chain variable region comprises the sequences set forth
6 in SEQ ID NO:4, SEQ ID NO:5, and SEQ ID NO:6.

1 38. The pharmaceutical composition of claim 35, wherein said antibody is
2 cirmtuzumab.

1 39. The pharmaceutical composition of claim 35, wherein said antibody
2 comprises a humanized heavy chain variable region and a humanized light chain variable region,
3 wherein said humanized heavy chain variable region comprises the sequences set
4 forth in SEQ ID NO:7, SEQ ID NO:8, and SEQ ID NO:9; and
5 wherein said humanized light chain variable region comprises the sequences set forth
6 in SEQ ID NO:10, SEQ ID NO:11, and SEQ ID NO:12.