diarrhea) toxicities in clinical trials (Byrd, Furman et al. N Engl J Med (July 4, 2013), 369:32-42; Byrd, Harrington et al. N Engl J Med (January 28, 2016); 374:323-332).

There remains a need to provide alternative treatment therapies for patients suffering from cancer and autoimmune diseases. In addition, there remains a need to provide alternative therapies for patients suffering from cGVHD. In particular, there remains a need to provide alternative treatment therapies for patients who develop resistance or become intolerant to current therapies, to provide alternative BTK inhibitors with activity against resistant mutants of BTK and that possess better tolerability profiles, or to provide alternative therapies that allow for maximum BTK inhibition with limited adverse events and fewer dose interruptions or discontinuations.

SUMMARY

In an aspect of the present disclosure, there is provided a use of a compound which is (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer wherein the compound or salt is to be administered at a daily dose of between 118.75 mg and 315 mg.

We claim:

1. Use of a compound which is (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer wherein the compound or salt is to be administered at a daily dose of between 118.75 mg and 315 mg.

2. The use according to claim 1, wherein the dose is between 142.5 mg and 315 mg.

3. The use according to claim 1, wherein the dose is 200 ±5% mg.

4. The use according to any one of claims 1 to 3, wherein the dose is to be administered once daily.

5. The use according to any one of claims 1 to 3 wherein the dose is to be administered daily for a 28-day cycle.

6. The use according to any one of claims 1 to 5, wherein (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide or a pharmaceutically acceptable salt thereof is to be administered to patients in an oral form.

7. The use according to claim 6, wherein (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide or a pharmaceutically acceptable salt thereof is to be administered to patients in tablets or capsules.

8. The use according to claim 7, wherein each of the tablets or capsules are formulated to contain 25 ±5% mg, or 50 ±5% mg, or 100 ±5% mg of (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide or a pharmaceutically acceptable salt thereof.

9. The use according to any one of claims 1 to 8, wherein the cancer is selected from B-cell malignancy, B-cell lymphoma, diffuse large B-cell lymphoma, mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL), non-Hodgkin lymphoma (NHL), small lymphocytic lymphoma (SLL), Waldenstrom’s macroglobulinemia, marginal zone lymphoma (MZL), activated B-cell-like diffuse large B-cell lymphoma (ABC-DLBCL),

follicular lymphoma, hairy cell leukemia, multiple myeloma, B-cell prolymphocytic leukemia, and B-cell non-Hodgkin lymphoma (B-cell NHL).

10. The use according to any one of claims 1 to 8 wherein the cancer is mantle cell lymphoma.

11. The use according to any one of claims 1 to 8 wherein the cancer is chronic lymphocytic leukemia/small lymphocytic lymphoma.

12. The use according to any one of claims 9 to 11, wherein the patient has a C481S BTK mutation.

13. The use according to claim 3 wherein the dose is reduced to 100 mg.

14. The use according to claim 3 or 13 wherein the dose is reduced to 50 mg.

15. The use according to claim 1 wherein the starting dose of 200 mg of (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide or salt is reduced to 100 mg dose and then to 50 mg dose.

16. The use according to claim 15 wherein the dose is reduced due to toxicity.

17. The use according to claim 15 wherein the dose is reduced due to a clinically significant adverse event.

18. The use according to claim 15 wherein the dose is reduced due to intolerability.

19. The use according to any one of claims 1 to 18 wherein the compound or salt is to be administered to a patient who is relapsed or refractory.

20. The use according to claim 19 wherein for the relapsed patient there is evidence of disease progression according to disease-defined criteria in a patient who has previously achieved a complete response or partial response for $\geq$ 6 months.

21. The use according to claim 19 wherein for the refractory patient there is treatment failure as defined by less than complete response or partial response or progression within 6 months from the last dose of therapy.

22. The use according to any one of claims 1 to 18 wherein the compound or salt is to be administered to a patient who is treatment naive.

23. The use according to any one of claims 1 to 21 wherein the compound or salt is to be administered to a patient who received at least one prior anti-cancer therapy.

24. The use according to any one of claims 1 to 21 or 23 wherein the compound or salt is to be administered to a patient who received at least one prior anti-cancer therapy that includes at least one BTK inhibitor based therapy.

25. The use according claim 24 wherein the BTK inhibitor based therapy is selected from ibrutinib, acalabrutinib, zanubrutinib, and tirabrutinib.

26. The use according to any one of claims 1 to 21 or 23 wherein the compound or salt is to be administered to a patient who received no prior anti-cancer therapy containing a BTK inhibitor

27. The use according to any one of claims 1 to 26 wherein the compound or salt is to be administered in simultaneous, separate, or sequential administration with a BCL-2 inhibitor and/or an anti-CD20 based therapy.

28. The use according to claim 27 wherein the BCL-2 inhibitor is venetoclax.

29. The use according to claim 27 wherein the BCL-2 inhibitor is N-[[(3S)-3-benzyl-5-nitro-3,4-dihydro-2H-1,4-benzoxazin-7-yl]sulfonyl]-4-[4-[[2-(4-chlorophenyl)-4,4-dimethyl-cyclohexen-1-yl]methyl]piperazin-1-yl]-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide or a pharmaceutically acceptable salt thereof.

30. The use according to any one of claims 27 to 29 wherein the anti-CD20 based therapy is rituximab.

31. The use according to any one of claims 1 to 30 wherein the administration of (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide or salt does not induce the severity of adverse effects observed with ibrutinib and acalabrutinib, wherein the adverse effect is selected from atrial fibrillation, hemorrhage, cytopenia, cardiac arrhythmias, along with severe leukopenia neutropenia, decreased platelet count, reticulocyte count, and red cell mass consistent with bone marrow suppression/toxicity.

32. The use according to any one of claims 1-31, wherein the compound is (S)-5-amino-3-(4-((5-fluoro-2-methoxybenzamido)methyl)phenyl)-1-(1,1,1-trifluoropropane-2-yl)-1H-pyrazole-4-carboxamide.