CLAIMS

What is claimed is:

1. A method of treating cancer comprising adminstering to a subject in need thereof a pharmaceutical composition comprising (3S,4S)-8-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-amine, or pharmaceutically acceptable salt thereof, in combination with a second therapeutic agent.

2. The method of claim 1, wherein the cancer is selected from: EGFR-mutant non-small cell lung cancer (NSCLC); KRAS mutant non-small cell lung cancer; head and neck squamous cell carcinoma (HNSCC); melanoma; gastrointestinal stromal tumors (GIST); colorectal cancer (CRC); medullary thyroid cancers; and ALK-rearranged NSCLC.

3. The method according to claim 1 or 2, wherein (3S,4S)-8-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-amine, or pharmaceutically acceptable salt thereof, and the second therapeutic agent are are administered simultaneously, separately or over a period of time.

4. The method according to any one of claims 1 to 3, wherein the amount of (3S,4S)-8-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-amine, or pharmaceutically acceptable salt thereof, administered to the subject in need therof is effective to treat the cancer.

5. The method according to any one of claims 1 to 4, wherein the amount of (3S,4S)-8-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-amine, or pharmaceutically acceptable salt thereof, and the second therapeutic agent, administered to the subject in need therof, is effective to treat the cancer.

6. The method according to any one of claims 1 to 5, wherein the second therapeutic agent is an EGFR inhibitor.

7. The method of claim 6 wherein the EGFR inhibitor is (R,E)-N-(7-chloro-1-(1-(4-(dimethylamino)but-2-enoyl)azepan-3-yl)-1H-benzo[d]imidazol-2-yl)-2-methylisonicotinamide, or a pharmaceutically acceptable salt thereof.

8. The method according to any one of claims 1 to 7, wherein (3S,4S)-8-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-amine is administered orally at a dose ranging from about 1.5 to about 100 mg per day, (e.g., from about 1.5 mg to about 60 mg per day, and from about 20 mg to about 60 mg per day).

9. The method according to any one of claims 1 to 8, wherein (3S,4S)-8-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-amine is administered orally at a dose of about 1.5 mg per day, or 3 mg per day, or 6 mg per day, or 10 mg per day, or 20 mg per day, or 30 mg per day, or 40 mg per day, or 50 mg per day, or 60 mg per day, or 80 mg per day or 100 mg per day.

10. The method of claim 9 wherein (R,E)-N-(7-chloro-1-(1-(4-(dimethylamino)but-2-enoyl)azepan-3-yl)-1H-benzo[d]imidazol-2-yl)-2-methylisonicotinamide is administered orally at a dose ranging from about 75 mg to about 350 mg per day.

11. The method of claim 10, wherein (R,E)-N-(7-chloro-1-(1-(4-(dimethylamino)but-2-enoyl)azepan-3-yl)-1H-benzo[d]imidazol-2-yl)-2-methylisonicotinamide is admnistered orally at about a dose of of about 75 mg per day, or 100 mg per day, or 150 mg per day, or 200 mg per day, or 250 mg per day, or 300 mg per day, or 350 mg per day.

12. The method of claim 11, wherein (R,E)-N-(7-chloro-1-(1-(4-(dimethylamino)but-2-enoyl)azepan-3-yl)-1H-benzo[d]imidazol-2-yl)-2-methylisonicotinamide is administered orally at 100 mg or 150 mg per day.

13. The method of claim 11, wherein (R,E)-N-(7-chloro-1-(1-(4-(dimethylamino)but-2-enoyl)azepan-3-yl)-1H-benzo[d]imidazol-2-yl)-2-methylisonicotinamide is administered orally at 150 mg per day.

14. A method of treating cancer comprising administering, to a patient in need thereof, (3S,4S)-8-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-

amine is administered orally at a dose of about 1.5 mg per day, or 3 mg per day, or 6 mg per day, or 10 mg per day, or 20 mg per day, or 30 mg per day, or 40 mg per day, or 50 mg per day, or 60 mg per day, or 80 mg per day or 100 mg per day.

15. The method of claim 14, wherein the dose per day is on a 21 day cycle of 2 weeks on drug followed by 1 week off drug.

16. The method of claim 14 or 15, wherein the cancer is selected from: EGFR-mutant non-small cell lung cancer (NSCLC); KRAS mutant non-small cell lung cancer; head and neck squamous cell carcinoma (HNSCC); melanoma; gastrointestinal stromal tumors (GIST); colorectal cancer (CRC); medullary thyroid cancers; and ALK-rearranged NSCLC.

17. The method of claim 14 further comprising a second therapeutic agent.

18. The method of claim 17 wherein (3S,4S)-8-(6-amino-5-((2-amino-3-chloropyridin-4-yl)thio)pyrazin-2-yl)-3-methyl-2-oxa-8-azaspiro[4.5]decan-4-amine, or pharmaceutically acceptable salt thereof, and the second therapeutic agent are are administered simultaneously, separately or over a period of time.

19. The method according to any one of claims 14 to 18, wherein the second therapeutic agent is an EGFR inhibitor.

20. The method of claim 19 wherein the EGFR inhibitor is (R,E)-N-(7-chloro-1-(1-(4-(dimethylamino)but-2-enoyl)azepan-3-yl)-1H-benzo[d]imidazol-2-yl)-2-methylisonicotinamide, or a pharmaceutically acceptable salt thereof.

21. The method of claim 20 wherein (R,E)-N-(7-chloro-1-(1-(4-(dimethylamino)but-2-enoyl)azepan-3-yl)-1H-benzo[d]imidazol-2-yl)-2-methylisonicotinamide is administered orally at a dose of about 75 mg per day, or 100 mg per day, or 150 mg per day, or 200 mg per day, or 250 mg per day, or 300 mg per day, or 350 mg per day.

22. The method of claim 21 wherein (R,E)-N-(7-chloro-1-(1-(4-(dimethylamino)but-2-enoyl)azepan-3-yl)-1H-benzo[d]imidazol-2-yl)-2-methylisonicotinamide is administered orally at 150 mg per day.

23. The method of anyone of claims 1 to 22, wherin the patient or subject is a patient suffering from advanced NSCLC harboring an activating EGFR mutation and having progressed on standard-of-care (SOC) EGFR tyrosine kinase inhibitor (TKI) (or have no SOC EGFR TKI available) and having progressed on platinum-containing combination chemotherapy; or advanced NSCLC harboring a KRAS G12 mutation having progressing on SOC; or advanced HNSCC having progressed on platinum-containing combination chemotherapy; or advanced esophageal SCC having progressed on platinum-containing chemotherapy; or advanced NRAS/BRAF WT cutaneous melanoma having progressed on SOC; or advanced GIST having progressed on SOC.

24. The method of any one of claims 1 to 23, wherein the cancer to be treated is NSCLC which is resistant or refractory to treatment with osimertinib, or a pharmaceutically acceptable salt thereof.

25. A compound for use in a method of treating cancer, wherein the compound is TNO155, or a pharmaceutically acceptable salt thereof and TNO155 is co-administered with nazartinib, or a pharmaceutically acceptable salt thereof.

26. A compound for use in a method of treating cancer, wherein the compound is nazrtinib, or a pharmaceutically acceptable salt thereof and nazartinib is co-administered with TNO155, or a pharmaceutically acceptable salt thereof.

27. The compound for use according to claim 25 or 26, wherein the method is according to any one of claims 1 to 21.

28. A pharmaceutical combination comprising TNO155, or a pharmaceutically acceptable salt thereof, and nazartinib, or a pharmaceutically acceptable salt thereof.