

NTRK1 and its related TRK family members *NTRK2* and *NTRK3* have been described (Vaishnavi et al., *Cancer Disc.* 5:25-34, 2015; Vaishnavi et al., *Nature Med.* 19:1469-1472, 2013). Although there are numerous different 5' gene fusion partners identified, all share an in-frame, intact TRK kinase domain. A variety of different Trk inhibitors have been developed to treat cancer (see, e.g., U.S. Patent Application Publication No. 62/080,374, International Application Publication Nos. WO 11/006074, WO 11/146336, WO 10/033941, and WO 10/048314, and U.S. Patent Nos. 8,933,084, 8,791,123, 8,637,516, 8,513,263, 8,450,322, 7,615,383, 7,384,632, 6,153,189, 6,027,927, 6,025,166, 5,910,574, 5,877,016, and 5,844,092).

SUMMARY

The present disclosure is based on the discovery of Trk inhibitor-resistance *NTRK1*, *NTRK2*, and *NTRK3* mutations. In view of this discovery, provided herein are methods of treating a subject having a cancer, methods of selecting a treatment for a subject having a cancer, methods of selecting a subject having a cancer for a treatment that does not include a Trk inhibitor, methods of determining the likelihood that a subject having a cancer will have a positive response to a treatment with a Trk inhibitor, methods of predicting the efficacy of a Trk inhibitor in a subject having cancer, methods of determining a subject's risk for developing a Trk inhibitor-resistant cancer, and methods of determining the presence of a Trk inhibitor-resistant cancer in a subject. In some embodiments, the methods provided herein are based, in part, on a determination of whether the subject has a cell that has (i) at least one point mutation in a *NTRK1* gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a *NTRK2* gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a *NTRK3* gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705. Also provided are kits

Also provided herein are methods of treating a subject having a cancer, that include: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first Trk inhibitor, has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); (b) administering a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, and another anticancer agent or anticancer therapy to a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); or (c) administering additional doses of the first Trk inhibitor to a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

In one aspect, there is provided use of a first Trk inhibitor in the manufacture of a medicament for treating a subject having a cancer, wherein:

(a) one or more doses of the medicament is to be administered to the subject for a period of time;

(b) after (a), a cancer cell in a sample obtained from the subject is to be determined whether it has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) a point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at amino acid position 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

(c) a treatment including one or more doses of a second Trk inhibitor or a pharmaceutically acceptable salt thereof, is to be administered to a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; or

(d) additional doses of the first Trk inhibitor are to be administered to a subject having a cancer cell that does not have (i) a point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, or (ii) a point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, or (iii) a point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

In one aspect, there is provided a method of treating a subject having a cancer, the method comprising:

(a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first Trk inhibitor, has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705;

(b) administering a second Trk inhibitor or a treatment that does not include the first Trk inhibitor of step (a) as a monotherapy to a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a

mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; or

(c) administering additional doses of the first Trk inhibitor of step (a) to a subject having a cancer cell that does not have (i) a point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, or (ii) a point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, or (iii) a point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

In one aspect, there is provided a method of treating a subject having a cancer, the method comprising:

identifying a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

administering to the identified subject a treatment that does not include a first Trk inhibitor as a monotherapy.

In one aspect, there is provided a use of one or more compounds in the manufacture of a medicament for treating a subject having a cancer, the use comprising:

identifying a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; wherein the medicament is to be administered to the identified subject, and wherein the one or more compounds is selected from the group consisting of:

- (R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- (R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;
- 5 (R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;
- (R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;
- (R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- 10 (R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;
- (R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;
- (R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;
- 15 (R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- (R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;
- 20 (R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
- (R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
- 25 (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;
- (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
- 30 (6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;
- (6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11, 19(26),20,23-heptaen-18-one;
- (6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.0^{2,6}.0^{7,12}.0^{23,27}]-heptacos-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.17,11.0^{2,6}.0^{21,25}]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

5 1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

10 (6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.17,11.0^{2,6}.0^{20,24}]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof.

In one aspect, there is provided a method of treating a subject identified as having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting

of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705, the method comprising administering to the subject a treatment that does not include a first Trk inhibitor as a monotherapy.

In one aspect, there is provided a use of one or more compounds in the manufacture of a medicament for treating a subject identified as having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705, wherein the one or more compounds is selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5 (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

10 (6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.0^{2,6}.0^{7,12}.0^{23,27}]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

15 (6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,11}.0^{21,25}]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

20 (6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

25 (6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.0^{2,6}.0^{7,11}.0^{20,24}]-pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

30 (15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof.

In one aspect, there is provided a method of treating a subject, the method comprising administering a therapeutically effective amount of a treatment that does not include a first Trk inhibitor as a monotherapy, to a subject having a clinical record that indicates that the subject has a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

In one aspect, there is provided a use of one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

- (R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- (R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;
- 5 (R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
- (R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
- 10 (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;
- (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
- 15 (6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;
- (6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11, 19(26),20,23-heptaen-18-one;
- (6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.0^{2,6}.0^{7,12}.0^{23,27}]-heptacos-1(26),7,9,11,20(27),21,24-heptaen-19-one;
- 20 (6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;
- (6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,11}.0^{21,25}]-hexacos-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;
- 25 1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacos-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;
- (6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one;
- 30 (6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;
- (6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.0^{2,6}.0^{7,11}.0^{20,24}]-pentacos-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for treating a subject having a clinical record that indicates that the subject has a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

In one aspect, there is provided a method of treating a subject having a cancer, the method comprising:

(a) administering one or more doses of a first Trk inhibitor to the subject for a period of time;

(b) after (a), determining whether a cancer cell in a sample obtained from the subject has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

(c) administering a second Trk inhibitor or a treatment that does not include the first Trk inhibitor of step (a) as a monotherapy to a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; or

(d) administering additional doses of the Trk inhibitor of step (a) to a subject having a cancer cell that does not have (i) a point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, or (ii) a point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, or (iii) a point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

Also provided herein are methods of selecting a treatment for a subject having a cancer (e.g., any of the cancers described herein or known in the art) that include: identifying a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and selecting a treatment that does not include a first Trk inhibitor as a monotherapy for the identified subject.

Also provided herein are methods of selecting a treatment for a subject having a cancer (e.g., any of the cancers described herein or known in the art) that include: identifying a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and selecting a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, for the identified subject.

Also provided herein are methods of selecting a treatment for a subject having a cancer (e.g., any of the cancers described herein or known in the art) that include: identifying a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the

mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and selecting the identified subject for a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, and another anticancer agent or anticancer therapy.

Some embodiments of these methods further include administering the selected treatment to the identified subject.

Some embodiments of these methods further include recording the selected treatment in the identified subject's clinical record (e.g., a computer readable medium). For example, recording that the subject is selected for a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof. In some embodiments, these methods further include recording that the subject is selected for a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, and another anticancer agent or anticancer therapy in the subject's clinical record (e.g., a computer readable medium). In some embodiments, these methods further include recording that the subject is selected for a treatment that does not include a first Trk inhibitor as a monotherapy in the subject's clinical record (e.g., a computer readable medium).

In one aspect, there is provided a method of selecting a treatment for a subject having a cancer, the method comprising:

identifying a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

selecting a treatment for the identified subject that does not include a first Trk inhibitor as a monotherapy.

In one aspect, there is provided a method of selecting a treatment for a subject having a cancer, the method comprising:

identifying a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

selecting a treatment for the identified subject that includes one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

5 (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-
10 [17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.0^{2,6}.0^{7,12}.0^{23,27}]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

15 (6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.0^{2,6}.0^{21,25}]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

20 (6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

25 (6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.0^{2,6}.0^{20,24}]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

30 (15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

35

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof.

5 In one aspect, there is provided a method of selecting a treatment for a subject having a cancer, the method comprising:

selecting a treatment that does not include a first Trk inhibitor as a monotherapy for a subject identified as having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

15 In one aspect, there is provided a method of selecting a treatment for a subject having a cancer, the method comprising:

20 selecting a treatment that includes one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

25 (R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

30 (R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

35 (R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

- (R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- (R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;
- 5 (R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
- (R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
- 10 (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;
- (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
- (6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;
- 15 (6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11, 19(26),20,23-heptaen-18-one;
- (6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.0^{2,6}.0^{7,12}.0^{23,27}]-heptacos-1(26),7,9,11,20(27),21,24-heptaen-19-one;
- 20 (6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;
- (6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.0^{2,6}.0^{21,25}]-hexacos-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;
- 1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;
- 25 (6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one;
- (6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;
- 30 (6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.0^{2,6}.0^{20,24}]pentacos-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof;

for a subject identified as having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

In one aspect, there is provided a method of selecting a subject having a cancer for a treatment that does not include a first Trk inhibitor as a monotherapy, the method comprising:

identifying a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

selecting the identified subject for a treatment that does not include a first Trk inhibitor as a monotherapy.

In one aspect, there is provided a method of selecting a subject having a cancer for a treatment that includes one or more compounds selected from the group consisting of:

- (R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- (R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;
- 5 (R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;
- (R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;
- (R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- 10 (R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;
- (R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;
- (R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;
- 15 (R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- (R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;
- 20 (R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
- (R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
- 25 (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;
- (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
- 30 (6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;
- (6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11, 19(26),20,23-heptaen-18-one;
- (6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.0^{2,6}.0^{7,12}.0^{23,27}]-heptacos-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosal(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.0^{2,6}.0^{21,25}]-hexacosal(24),7(26),8,10,18(25),19,22-heptaen-17-one;

5 1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosal(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxo-2,11,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacosal(24),7,9,11,18(25),19,22-heptaen-17-one;

10 (6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosal(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.0^{2,6}.0^{20,24}]pentacosal(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosal(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosal(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosal(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosal(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof;
the method comprising:

identifying a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid

position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

selecting the identified subject for a treatment that includes one or more compounds selected from the group consisting of:

- 5 (R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- (R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;
- (R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;
- 10 (R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;
- (R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- (R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;
- 15 (R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;
- (R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;
- (R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- 20 (R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;
- (R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- 25 (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
- (R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
- (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;
- 30 (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
- (6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;

- (6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-
[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;
- (6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.0^{2,6}.0^{7,12}.0^{23,27}]-
heptacos-1(26),7,9,11,20(27),21,24-heptaen-19-one;
- 5 (6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-
1(25),7,9,11,19(26),20,23-heptaen-18-one;
- (6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-hexacos-
1(24),7(26),8,10,18(25),19,22-heptaen-17-one;
- 10 1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-
pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacos-1(24),7,9,11,18(25),19,22-
heptaen-16-yl]ethan-1-one;
- (6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-
pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one;
- (6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-
15 hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-
heptaen-18-one;
- (6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-
hexaazapentacyclo[15.5.2.0^{2,6}.0^{7,12}.0^{20,24}]-pentacos-1(23),7,9,17(24),18,21-hexaene-
16,25-dione;
- 20 (6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17
.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;
- (15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22,25-
pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7(12),8,10,19(26),20,23-
heptaen-18-one;
- 25 (6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-
hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacos-1(24),7,9,11,18(25),19,22-
heptaen-17-one; and
- (6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-
hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacos-1(24),7,9,11,18(25),19,22-
30 heptaen-17-one;

or a pharmaceutically acceptable salt thereof.

In one aspect, there is provided a method of selecting a subject having a cancer for a treatment that does not include a first Trk inhibitor as a monotherapy, the method comprising:

selecting a subject identified as having a cancer cell that has (i) at least one point
35 mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a

mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705, for a treatment that does not include a first Trk inhibitor as a monotherapy.

In one aspect, there is provided a method of selecting a subject having a cancer for a treatment that includes one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

- (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;
- (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
- 5 (6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;
- (6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11, 19(26),20,23-heptaen-18-one;
- 10 (6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.0^{2,6}.0^{7,12}.0^{23,27}]-heptacos-1(26),7,9,11,20(27),21,24-heptaen-19-one;
- (6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;
- (6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.0^{2,6}.0^{21,25}]-hexacos-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;
- 15 1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;
- (6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one;
- 20 (6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;
- (6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.0^{2,6}.0^{20,24}]pentacos-1(23),7,9,17(24),18,21-hexaene-16,25-dione;
- 25 (6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;
- (15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;
- 30 (6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof;

the method comprising:

selecting a subject identified as having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705, for a treatment that includes one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

- (R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
- 5 (R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
- (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;
- (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
- 10 (6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;
- (6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11, 19(26),20,23-heptaen-18-one;
- (6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.0^{2,6}.0^{7,12}.0^{23,27}]-heptacos-1(26),7,9,11,20(27),21,24-heptaen-19-one;
- 15 (6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;
- (6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.1^{7,11}.0^{2,6}.0^{21,25}]-hexacos-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;
- 20 1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;
- (6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one;
- 25 (6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;
- (6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.1^{7,11}.0^{2,6}.0^{20,24}]pentacos-1(23),7,9,17(24),18,21-hexaene-16,25-dione;
- 30 (6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof.

Also provided herein are methods of determining the likelihood that a subject having a cancer will have a positive response to treatment with a first Trk inhibitor as a monotherapy, that include: determining whether a cancer cell in a sample obtained from the subject has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and determining that a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3) has a decreased likelihood of having a positive response to treatment with a first Trk inhibitor as a monotherapy.

Also provided herein are methods of determining the likelihood that a subject having a cancer will have a positive response to treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, that include: determining whether a cancer cell in a sample obtained from the subject has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more

In one aspect, there is provided a method of determining the likelihood that a subject having a cancer will have a positive response to treatment with a first Trk inhibitor as a monotherapy, the method comprising:

determining whether a cancer cell in a sample obtained from the subject has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

determining that a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705, has a decreased likelihood of having a positive response to treatment with a first Trk inhibitor as a monotherapy.

In one aspect, there is provided a method of determining the likelihood that a subject having a cancer will have a positive response to treatment that includes one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

5 (R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

10 (R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

15 (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

20 (6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.0^{2,6}.0^{7,12}.0^{23,27}]-heptacos-1(26),7,9,11,20(27),21,24-heptaen-19-one;

25 (6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.1^{7,11}.0^{2,6}.0^{21,25}]-hexacos-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

30 1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.0^{17,11}.0^{2,6}.0^{20,24}]pentacos-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof;
the method comprising:

determining whether a cancer cell in a sample obtained from the subject has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

determining that a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630,

675, 685, 686, 696, and 705, has a increased likelihood of having a positive response to treatment that includes one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

5 (R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

10 (R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

15 (R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

20 (R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

25 (R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

30 (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.0^{2,6}.0^{7,12}.0^{23,27}]-heptacos-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;

5 (6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-hexacos-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

10 (6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;

15 (6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.0^{2,6}.0^{7,12}.0^{20,24}]pentacos-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;

20 (15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

25 (6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof.

30 In one aspect, there is provided a method of determining the likelihood that a subject having cancer will have a positive response to treatment with a first Trk inhibitor as a monotherapy, the method comprising:

determining that a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or
35 more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2

gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705, has a decreased likelihood of having a positive response to treatment with a first Trk inhibitor as a monotherapy.

In one aspect, there is provided a method of determining the likelihood that a subject having cancer will have a positive response to treatment that includes one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5 (6R)-9-fluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;

10 (6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.0^{2,6}.0^{7,12}.0^{23,27}]-heptacos-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-hexacos-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

15 1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacos-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one;

20 (6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.0^{2,6}.0^{7,12}.0^{20,24}]-pentacos-1(23),7,9,17(24),18,21-hexaene-25 16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

30 (6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof;

the method comprising:

determining that a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705, has an increased likelihood of having a positive response to treatment including one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(6R)-9-fluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.0^{2,6}.0^{7,12}.0^{23,27}]-heptacos-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,11}.0^{21,25}]-hexacos-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacos-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.0^{2,6}.0^{7,11}.0^{20,24}]-pentacos-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

5 (6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one;

10 or a pharmaceutically acceptable salt thereof.

cancer, that include: determining that treatment including one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, is more likely to be effective in a subject having a cancer cell in a sample obtained from the subject that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3). Some embodiments of these methods further include administering one or more compound of Table 5, or a pharmaceutically acceptable salt thereof, to the subject.

In one aspect, there is provided a method of predicting the efficacy of treatment with a first Trk inhibitor as a monotherapy in a subject having cancer, the method comprising:

determining whether a cancer cell in a sample obtained from the subject has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

determining that treatment with a first Trk inhibitor as a monotherapy is less likely to be effective in a subject having a cancer cell in a sample obtained from the subject that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

In one aspect, there is provided a method of predicting the efficacy of treatment with a treatment including one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

5 (R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

10 (R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

15 (R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

20 (R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

25 (R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

30 (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.0^{2,6}.0^{7,12}.0^{23,27}]-heptacos-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;

5 (6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,11}.0^{21,25}]-hexacos-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

10 (6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;

15 (6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.0^{2,6}.0^{7,11}.0^{20,24}]pentacos-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;

20 (15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

25 (6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof;

30 in a subject having cancer, the method comprising:

determining whether a cancer cell in a sample obtained from the subject has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570,

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596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

5 determining that treatment including one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

10 (R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

15 (R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

20 (R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

25 (R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

30 (R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

5 (6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.0^{2,6}.0^{7,12}.0^{23,27}]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

10 (6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.1^{7,11}.0^{2,6}.0^{21,25}]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

15 (6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

20 (6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.1^{7,11}.0^{2,6}.0^{20,24}]-pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

25 (15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

30 (6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof;

is more likely to be effective in a subject having a cancer cell in a sample obtained from the

35 subject that has (i) at least one point mutation in a NTRK1 gene that results in the expression of

a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group
5 consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

In one aspect, there is provided a method of predicting the efficacy of treatment with a
10 first Trk inhibitor as a monotherapy in a subject having cancer, the method comprising:

determining that treatment with a first Trk inhibitor as a monotherapy is less likely to be effective in a subject having a cancer cell in a sample obtained from the subject that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting
15 of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a
20 mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

In one aspect, there is provided a method of predicting the efficacy of treatment including one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-
25 hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-
dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-
30 methylurea;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-
hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-
hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-
35 hydroxy-3-methylazetidine-1-carboxamide;

- (R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;
- (R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- 5 (R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;
- (R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
- 10 (R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
- (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;
- (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
- 15 (6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;
- (6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11, 19(26),20,23-heptaen-18-one;
- 20 (6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.0^{2,6}.0^{7,12}.0^{23,27}]-heptacos-1(26),7,9,11,20(27),21,24-heptaen-19-one;
- (6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;
- (6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,11}.0^{21,25}]-hexacos-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;
- 25 1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacos-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;
- (6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one;
- 30 (6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;

- (6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.0^{2,6}.0^{20,24}]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;
- 5 (6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;
- (15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;
- 10 (6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and
- (6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;
- 15 or a pharmaceutically acceptable salt thereof;
in a subject having cancer, the method comprising:
determining that treatment including one or more compounds selected from the group consisting of:
- 20 (R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- (R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;
- (R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;
- 25 (R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;
- (R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- (R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;
- 30 (R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;
- (R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;
- (R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- 35 (R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;
- (R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
5 (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;
(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;
10 (6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;
(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.0^{2,6}.0^{7,12}.0^{23,27}]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;
(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;
15 (6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;
1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;
20 (6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;
(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;
25 (6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.0^{2,6}.0^{7,11}.0^{20,24}]-pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;
(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;
30 (15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;
(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and
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(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof;

is more likely to be effective in a subject having a cancer cell in a sample obtained from the subject that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

Also provided herein are methods of selecting a treatment for a subject having a cancer that include: (a) administering one or more doses of a first Trk inhibitor to the subject for a period of time; (b) after (a), determining whether a cancer cell in a sample obtained from the subject has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and (c) selecting a second Trk inhibitor or a treatment that does not include the first Trk inhibitor of step (a) as a monotherapy for a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); or (d) selecting additional doses of the first Trk inhibitor of step (a) for a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

Also provided herein are methods of selecting a treatment for a subject having a cancer, that include: (a) administering one or more doses of a first Trk inhibitor to the subject for a period of time; (b) after (a), determining whether a cancer cell in a sample obtained from the subject has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and (c) selecting a treatment including one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, for a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a

mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); (b) selecting a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, and another anticancer agent or anticancer therapy to a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); or (c) selecting additional doses of the first Trk inhibitor to a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

Some embodiments of any of the methods described herein further include recording the selected treatment in the subject's clinical record (e.g., a computer readable medium). Some embodiments of any of the methods described herein further include administering selected treatment to the subject.

In some embodiments of any of the methods described herein, the subject is previously identified or diagnosed as having the cancer.

In some embodiments of the methods described herein, the treatment that does not include a first Trk inhibitor as a monotherapy is selected from a treatment that includes one or more of: surgery, radiation therapy, chemotherapy, immunotherapy, hormone therapy, small molecule drugs targeting other kinases in a Trk-signaling pathway, recombinant antibodies, and stem cell transplant. In some embodiments of the methods described herein, the treatment that does not include a first Trk inhibitor as a monotherapy includes: one or more of surgery, radiation therapy, chemotherapy, immunotherapy, hormone therapy, small molecule drugs targeting other kinases in a Trk-signaling pathway, recombinant antibodies, and stem cell transplant; and one or more Trk inhibitors. In some embodiments of the methods described herein, the treatment that does not include a first Trk inhibitor as a monotherapy includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, as a monotherapy.

In one aspect, there is provided a method of selecting a treatment for a subject having a cancer, the method comprising:

(a) administering one or more doses of a first Trk inhibitor to the subject for a period of time;

(b) after (a), determining whether a cancer cell in a sample obtained from the subject has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

(c) selecting a second Trk inhibitor or a treatment that does not include the Trk inhibitor of step (a) as a monotherapy for a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; or

(d) selecting additional doses of the first Trk inhibitor of step (a) for a subject having a cancer cell that does not have (i) a point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, or (ii) a point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, or (iii) a point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

In one aspect, there is provided a method of selecting a treatment for a subject having a cancer, the method comprising:

(a) administering one or more doses of a first Trk inhibitor to the subject for a period of time;

(b) after (a), determining whether a cancer cell in a sample obtained from the subject has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein

comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545,
5 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

(c) selecting a treatment including one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

10 (R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

15 (R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

20 (R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

25 (R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

30 (R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

35 (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

- (6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;
- (6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;
- 5 (6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.0^{2,6}.0^{7,12}.0^{23,27}]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;
- (6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;
- 10 (6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.0^{2,6}.0^{21,25}]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;
- 1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;
- 15 (6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;
- (6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;
- 20 (6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.0^{2,6}.0^{20,24}]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;
- (6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;
- 25 (15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;
- (6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and
- 30 (6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof;

- for a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid
- 35

position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; or

(d) selecting additional doses of the first Trk inhibitor for a subject having a cancer cell that does not have (i) a point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, or (ii) a point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, or (iii) a point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

In one aspect, there is provided a method of selecting a treatment for a subject having a cancer, the method comprising:

(a) administering one or more doses of a first Trk inhibitor to the subject for a period of time;

(b) after (a), determining whether a cancer cell in a sample obtained from the subject has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

(c) selecting a treatment including one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

- (R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;
- (R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- 5 (R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;
- (R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;
- 10 (R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;
- (R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- (R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;
- 15 (R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
- (R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
- 20 (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;
- (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
- 25 (6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;
- (6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;
- (6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.0^{2,6}.0^{7,12}.0^{23,27}]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;
- 30 (6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;
- (6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.0^{7,11}.0^{2,6}.0^{21,25}]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.0^{2,6}.0^{7,11}.0^{20,24}]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof;

and another anticancer agent or anticancer therapy for a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; or

(d) selecting additional doses of the first Trk inhibitor for a subject having a cancer cell that does not have (i) a point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, or (ii) a

point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, or (iii) a point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

In one aspect, there is provided a method of selecting a treatment for a subject having a cancer, the method comprises:

(a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first Trk inhibitor, has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705;

(b) selecting a second Trk inhibitor or a treatment that does not include the first Trk inhibitor of step (a) as a monotherapy to a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; or

(c) selecting additional doses of the first Trk inhibitor of step (a) to a subject having a cancer cell that does not have (i) a point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, or (ii) a point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, or (iii) a point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

In one aspect, there is provided a method of selecting a treatment for a subject having a cancer, the method comprises:

(a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first Trk inhibitor, has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705;

(b) selecting a treatment that includes one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
5 (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;
(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
(6R)-9-fluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;
10 (6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;
(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.0^{2,6}.0^{7,12}.0^{23,27}]-heptacos-1(26),7,9,11,20(27),21,24-heptaen-19-one;
(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;
15 (6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,11}.0^{21,25}]-hexacos-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;
1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;
20 (6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one;
(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;
25 (6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.0^{2,6}.0^{7,11}.0^{20,24}]pentacos-1(23),7,9,17(24),18,21-hexaene-16,25-dione;
(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;
30 (15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

5 (6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof;

10 to a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; or

15 (c) selecting additional doses of the first Trk inhibitor to a subject having a cancer cell that does not have (i) a point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, or (ii) a point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, or (iii) a point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

In one aspect, there is provided a method of selecting a treatment for a subject having a cancer, the method comprises:

30 (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first Trk inhibitor, has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a

mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705;

(b) selecting a treatment that includes one or more compounds selected from the group consisting of:

- 5 (R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- (R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;
- (R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;
- 10 (R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;
- (R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- (R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;
- 15 (R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;
- (R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;
- 20 (R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- (R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;
- (R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- 25 (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
- (R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
- (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;
- 30 (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
- (6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;

- (6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-
[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;
- (6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.0^{2,6}.0^{7,12}.0^{23,27}]-
heptacos-1(26),7,9,11,20(27),21,24-heptaen-19-one;
- 5 (6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-
1(25),7,9,11,19(26),20,23-heptaen-18-one;
- (6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.0^{2,6}.0^{21,25}]-hexacos-
1(24),7(26),8,10,18(25),19,22-heptaen-17-one;
- 10 1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-
pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacos-1(24),7,9,11,18(25),19,22-
heptaen-16-yl]ethan-1-one;
- (6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-
pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one;
- 15 (6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-
hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-
heptaen-18-one;
- (6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-
hexaazapentacyclo[15.5.2.^{17,11}.0^{2,6}.0^{20,24}]-pentacos-1(23),7,9,17(24),18,21-hexaene-
16,25-dione;
- 20 (6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17
.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;
- (15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22,25-
pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7(12),8,10,19(26),20,23-
heptaen-18-one;
- 25 (6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-
hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacos-1(24),7,9,11,18(25),19,22-
heptaen-17-one; and
- (6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-
hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacos-1(24),7,9,11,18(25),19,22-
30 heptaen-17-one;

or a pharmaceutically acceptable salt thereof;

and an another anticancer agent or anticancer therapy to a subject having a cancer cell that has
(i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein
comprising a mutation at one or more amino acid position(s) selected from the group consisting
35 of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least

one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; or

(c) selecting additional doses of the first Trk inhibitor to a subject having a cancer cell that does not have (i) a point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, or (ii) a point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, or (iii) a point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

Also provided herein are methods of determining a subject's risk for developing a Trk inhibitor-resistant cancer that include: determining whether a cell in a sample obtained from the subject has at least one point mutation in a NTRK gene that results in the

expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and identifying a subject having a cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3), as having an increased likelihood of developing a Trk inhibitor-resistant cancer. Also provided herein are methods of determining a subject's risk for developing a Trk inhibitor-resistant cancer that include: identifying a subject having a cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3), as having an increased likelihood of developing a Trk inhibitor-resistant cancer. Some embodiments of these methods further include confirming a diagnosis of a Trk inhibitor-resistant cancer in a subject determined to have an increased likelihood of developing a Trk inhibitor-resistant cancer.

In one aspect, there is provided a method of determining a subject's risk for developing a Trk inhibitor-resistant cancer, the method comprising:

determining whether a cell in a sample obtained from the subject has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

identifying a subject having a cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705, as having an increased likelihood of developing a Trk inhibitor-resistant cancer.

In one aspect, there is provided a method of determining a subject's risk for developing a Trk inhibitor-resistant cancer, the method comprising:

identifying a subject having a cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705, as having an increased likelihood of developing a Trk inhibitor-resistant cancer.

Also provided herein are methods of determining the presence of a Trk inhibitor-resistant cancer in a subject that include: determining whether a cancer cell in a sample obtained from the subject has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and determining that a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3), has an a Trk inhibitor-resistant cancer. Also provided herein are methods of determining the presence of a Trk inhibitor-resistant cancer in a subject that include: determining that a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

In one aspect, there is provided a method of determining the presence of a Trk inhibitor-resistant cancer in a subject, the method comprising:

determining whether a cancer cell in a sample obtained from the subject has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising

a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

determining that a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705, has an a Trk inhibitor-resistant cancer.

In one aspect, there is provided a method of determining the presence of a Trk inhibitor-resistant cancer in a subject, the method comprising:

determining that a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705, has a Trk inhibitor-resistant cancer.

In some embodiments of any of the methods described herein, the first Trk inhibitor (e.g., the first Trk inhibitor in step (a)) is selected from the group consisting of: entrectinib (N-[5-(3,5-difluoro-benzyl)-1H-indazol-3-yl]-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-

F617L, F617C, F617I, G623S, G623R, D624V, R630K, C682Y, C682F, L683V, G693S, and G713S. In some embodiments of any of the methods described herein, the TrkC protein includes one or more of the following amino acid substitutions: G545R, A570V, F617L, G623R, D624V, C685Y, C685F, L686V, and G696A.

5 In one aspect, there is provided a method for inhibiting a Trk kinase activity in a mammalian cell, the method comprising:

determining that the mammalian cell comprises (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 10 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid 15 position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

contacting the mammalian cell with one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3- 20 hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3- 25 methylurea;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

- (R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;
- (R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;
- 5 (R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- (R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;
- 10 (R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
- (R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
- (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;
- 15 (R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
- (6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;
- 20 (6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11, 19(26),20,23-heptaen-18-one;
- (6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.0^{2,6}.0^{7,12}.0^{23,27}]-heptacos-1(26),7,9,11,20(27),21,24-heptaen-19-one;
- (6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;
- 25 (6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.0^{17,11}.0^{2,6}.0^{21,25}]-hexacos-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.0^{2,6}.0^{20,24}]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof.

In one aspect, there is provided a kit comprising: one or more probes that each specifically hybridize to a segment of a NTRK1 gene that encodes a mutation at one of amino acid positions 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676 in TrkA protein; and/or one or more probes that each specifically hybridize to a segment of a NTRK2 gene that encodes a mutation at one of amino acid

positions 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702 in TrkB protein; and/or one or more probes that each specifically hybridize to a segment of a NTRK3 gene that encodes a mutation at one or amino acid positions 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705 in TrkC protein. Some embodiments of these kits include: one or more probes that each specifically hybridize to a segment of a NTRK1 gene that encodes a mutation selected from the group consisting of: G517R, A542V, V573M, F589L, F589C, G595S, G595R, D596V, F600L, F646V, C656Y, C656F, L657V, G667S, G667C, and Y676S in TrkA protein; and/or one or more probes that each specifically hybridize to a segment of a NTRK2 gene that encodes a mutation selected from the group consisting of: G545R, A570V, Q596E, Q596P, V601G, F617L, F617C, F617I, G623S, G623R, D624V, R630K, C682Y, C682F, L683V, G693S, and G713S in TrkB protein; and/or one or more probes that each specifically hybridize to a segment of a NTRK3 gene that encodes a mutation selected from the group consisting of: G545R, A570V, F617L, G623R, D624V, C685Y, C685F, L686V, and G696A in TrkC protein. In some embodiments of any of the kits described herein, the one or more probes are labeled with a detectable probe. In some embodiments of any of the kits described herein, the one or more probes are covalently attached to a substrate (e.g., a film, a plate, or a bead).

As used herein, the word “a” before a noun represents one or more of the particular noun. For example, the phrase “a cell” represents “one or more cells.”

The term “subject” means a vertebrate, including any member of the class mammalia, including humans, sports or pet animals, such as horse (e.g., race horse) or dog (e.g., race dogs), and higher primates. In some embodiments, the subject is a human.

The term “treating” or “positive response to treatment” means an improvement in the condition of a subject having a cancer, e.g., one or more of a decrease in the size of one or more tumor(s) in a subject, a decrease or no substantial change in the growth rate of one or more tumor(s) in a subject, a decrease in metastasis in a subject, and an increase in the period of remission for a subject (e.g., as compared to the one or more metric(s) in a subject having a similar cancer receiving no treatment or a different treatment, or as compared to the one or more metric(s) in the same subject prior to treatment). Additional metrics for assessing response to a treatment in a subject having a cancer are known in the art.

The term “point mutation” means a change in the nucleotide sequence of a gene that results in a single amino acid change in a protein encoded by the gene. For example, a point mutation in a gene can result in the deletion of a single amino acid in a protein encoded by the gene or can result in the substitution of an amino acid in a wildtype version of the encoded protein with a different amino acid. Non-limiting examples of point mutations in a NTRK1 genes, NTRK2 genes, and NTRK3 genes are described herein.

The phrase “significant level of carcinogen” is meant a level of exposure to a carcinogen that is known to increase (e.g., a statistically significant increase) the likelihood of a subject to develop a cancer (e.g., as compared to a subject that has not been exposed to the same level of exposure or has been exposed to a non-detectable amount of the carcinogen).

As used herein, a “first Trk kinase inhibitor” or “first Trk inhibitor” is a Trk inhibitor as described herein but does not include compounds of Table 5, or a pharmaceutically acceptable salt thereof, as defined herein. As used herein, a “second Trk kinase inhibitor” or a “second Trk inhibitor” is a Trk inhibitor as described herein and includes the compounds of Table 5, or a pharmaceutically acceptable salt thereof, as described herein. When both a first and a second Trk inhibitor are present in a method provided herein, the first and second Trk kinase inhibitors are different.

The term “monotherapy” means the use of a single drug to treat a particular disorder or disease.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Methods and materials are described herein for use in the present disclosure; other,

suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

Other features and advantages of the disclosure will be apparent from the following detailed description and figures, and from the claims.

DESCRIPTION OF DRAWINGS

Figure 1 is a flow chart of the experimental methods used in Example 1.

Figure 2 is a crystal structure of TrkA showing the location of some of the Trk inhibitor-resistance amino acid substitutions.

Figure 3 is a diagram showing the position of some of the Trk inhibitor-resistance amino acid substitutions.

Figure 4 is a graph of the POC of cells expressing a MPRIP-NTRK1 fusion protein including one of the Trk inhibitor resistance mutations at different concentrations of (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate (Cmpd A).

Figure 5 is a flow chart of the experimental methods used in Example 3.

Figure 6A is a graph representing the frequency of mutations and the dose of (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate (Cmpd A) from which they were isolated.

Figure 6B is a schematic of RIP-TRKA (encoded by MPRIP-NTRK1) with selected protein domains and resistance mutations that were identified.

Figure 6C is a ribbon representation of the crystallographic structure of the TRKA kinase domain in complex with the TRK inhibitor AZ-23 (PDB 4AOJ) showing localization of mutations that were identified.

Figure 7 is a graph of the percent of control of cells expressing a MPRIP-NTRK1 fusion protein including certain of the identified TrkA inhibitor resistance mutations at different concentrations of (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate (Cmpd A).

WHAT IS CLAIMED IS:

1. Use of a first Trk inhibitor in the manufacture of a medicament for treating a subject having a cancer, wherein:

(a) one or more doses of the medicament is to be administered to the subject for a period of time;

(b) after (a), a cancer cell in a sample obtained from the subject is to be determined whether it has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) a point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at amino acid position 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

(c) a treatment including one or more doses of a second Trk inhibitor or a pharmaceutically acceptable salt thereof, is to be administered to a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; or

(d) additional doses of the first Trk inhibitor are to be administered to a subject having a cancer cell that does not have (i) a point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, or (ii) a point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, or (iii) a point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or

more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

2. The use of claim 1 or 2, wherein the first Trk inhibitor is selected from the group consisting of: entrectinib (N-[5-(3,5-difluoro-benzyl)-1H-indazol-3-yl]-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-pyran-4-ylamino)-benzamide); (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate; cabozantinib ((N-(4-((6,7-Dimethoxyquinolin-4-yl)oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide)); dovatini (4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one mono 2-hydroxypropanoate hydrate); belizatinib (4-fluoro-N-(6-((4-(2-hydroxypropan-2-yl)piperidin-1-yl)methyl)-1-((1s,4s)-4-(isopropylcarbamoyl)cyclohexyl)-1H-benzo[d]imidazol-2-yl)benzamide); sitravatinib (N-(3-fluoro-4-((2-(5-((2-methoxyethyl)amino)methyl)pyridin-2-yl)thieno[3,2-b]pyridin-7-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide); PLX7486; altiratinib (N-(4-((2-(cyclopropanecarboxamido)pyridin-4-yl)oxy)-2,5-difluorophenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide); and AZD7451 ((S)-N-(1-(5-fluoropyrimidin-2-yl)ethyl)-3-(5-isopropoxy-1H-pyrazol-3-yl)-3H-imidazo[4,5-b]pyridin-5-amine)).

3. The use of claim 1, wherein the first Trk inhibitor is selected from the group consisting of: entrectinib (N-[5-(3,5-difluoro-benzyl)-1H-indazol-3-yl]-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-pyran-4-ylamino)-benzamide); and (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate.

4. The use of any one of claims 1-3, wherein the second Trk inhibitor is selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidione-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.0^{2,6}.0^{21,25}]-hexacos-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.0^{2,6}.0^{20,24}]pentacos-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof.

5. The use of any one of claims 1-4, wherein the second Trk inhibitor is selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

or a pharmaceutically acceptable salt thereof.

6. The use of any one of claims 1-4, wherein the second Trk inhibitor is selected from the group consisting of:

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

or a pharmaceutically acceptable salt thereof.

7. The use of any one of claims 1-4, wherein the second Trk inhibitor is selected from the group consisting of:

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

or a pharmaceutically acceptable salt thereof.

8. The use of any one of claims 1-4, wherein the second Trk inhibitor is selected from the group consisting of:

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.0^{2,6}.0^{7,12}.0^{23,27}]-heptacos-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.0^{2,6}.0^{21,25}]-hexacos-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacos-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.0^{2,6}.0^{20,24}]-pentacos-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(1S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacos-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof

9. The use of claim 1, wherein the first Trk inhibitor is entrectinib (N-[5-(3,5-difluorobenzyl)-1H-indazol-3-yl]-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-pyran-4-ylamino)-benzamide); and the second Trk inhibitor is selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

or a pharmaceutically acceptable salt thereof.

10. The use of claim 1, wherein the first Trk inhibitor is entrectinib (N-[5-(3,5-difluorobenzyl)-1H-indazol-3-yl]-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-pyran-4-ylamino)-benzamide); and the second Trk inhibitor is selected from the group consisting of:

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

or a pharmaceutically acceptable salt thereof.

11. The use of claim 1, wherein the first Trk inhibitor is entrectinib (N-[5-(3,5-difluorobenzyl)-1H-indazol-3-yl]-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-pyran-4-ylamino)-benzamide); and the second Trk inhibitor is selected from the group consisting of:

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

or a pharmaceutically acceptable salt thereof.

12. The use of claim 1, wherein the first Trk inhibitor is entrectinib (N-[5-(3,5-difluorobenzyl)-1H-indazol-3-yl]-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-pyran-4-ylamino)-benzamide); and the second Trk inhibitor is selected from the group consisting of:

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacos-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof.

13. The use of claim 1, wherein the first Trk inhibitor is (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate; and the second Trk inhibitor is selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

or a pharmaceutically acceptable salt thereof.

14. The use of claim 1, wherein the first Trk inhibitor is (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate; and the second Trk inhibitor is selected from the group consisting of:

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

or a pharmaceutically acceptable salt thereof.

15. The use of claim 1, wherein the first Trk inhibitor is (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate; and the second Trk inhibitor is selected from the group consisting of:

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

or a pharmaceutically acceptable salt thereof.

16. The use of claim 1, wherein the first Trk inhibitor is (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate; and the second Trk inhibitor is selected from the group consisting of:

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacosan-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacosan-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.0^{2,6}.0^{7,12}.0^{23,27}]-heptacosan-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]-hexacosan-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.0^{17,11}.0^{2,6}.0^{21,25}]-hexacosan-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.0^{17,11}.0^{2,6}.0^{20,24}]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof.

17. The use of any one of claims 1-16, wherein step (c) further comprises administration of another anticancer agent or anticancer therapy.

18. A method of treating a subject having a cancer, the method comprising:

(a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first Trk inhibitor, has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542,

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-

hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof.

20. The method of claim 18 or 19, wherein step (b) further comprises administering another anticancer agent or anticancer therapy.

21. A method of treating a subject having a cancer, the method comprising:

identifying a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

administering to the identified subject a treatment that does not include a first Trk inhibitor as a monotherapy.

22. Use of one or more compounds in the manufacture of a medicament for treating a subject having a cancer, the use comprising:

identifying a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705;

wherein the medicament is to be administered to the identified subject, and wherein the one or more compounds is selected from the group consisting of:

- (R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- (R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;
- (R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;
- (R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;
- (R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- (R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;
- (R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;
- (R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;
- (R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- (R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;
- (R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
- (R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
- (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof.

23. The use of claim 22, wherein the use further comprises administration of another anticancer agent or anticancer therapy.

24. A method of treating a subject identified as having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705, the method comprising administering to the subject a treatment that does not include a first Trk inhibitor as a monotherapy.

25. Use of one or more compounds in the manufacture of a medicament for treating a subject identified as having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623,

624, 628, 630, 675, 685, 686, 696, and 705, wherein the one or more compounds is selected from the group consisting of:

- (R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- (R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;
- (R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;
- (R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;
- (R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- (R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;
- (R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;
- (R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;
- (R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- (R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;
- (R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;
- (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
- (R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;
- (R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof.

26. The use of claim 25, wherein the use further comprises administration of another anticancer agent or anticancer therapy.

27. A method of treating a subject, the method comprising administering a therapeutically effective amount of a treatment that does not include a first Trk inhibitor as a monotherapy, to a subject having a clinical record that indicates that the subject has a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

28. Use of one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.0^{2,6}.0^{21,25}]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.0^{2,6}.0^{20,24}]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for treating a subject having a clinical record that indicates that the subject has a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting

of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

29. The use of claim 28, wherein the use further comprises administering another anticancer agent or anticancer therapy.

30. A method of selecting a treatment for a subject having a cancer, the method comprising:

identifying a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

selecting a treatment for the identified subject that does not include a first Trk inhibitor as a monotherapy.

31. A method of selecting a treatment for a subject having a cancer, the method comprising:

identifying a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof;

and another anticancer agent or anticancer therapy to a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; or

(c) selecting additional doses of the first Trk inhibitor to a subject having a cancer cell that does not have (i) a point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, or (ii) a point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, or (iii) a point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

58. The use or method of any one of claims 1-57, wherein the cancer is selected from the group consisting of: adenocarcinoma, adrenal gland cortical carcinoma, adrenal gland neuroblastoma, anus squamous cell carcinoma, appendix adenocarcinoma, bladder urothelial carcinoma, bile duct adenocarcinoma, bladder carcinoma, bladder urothelial carcinoma, bone chordoma, bone marrow leukemia lymphocytic chronic, bone marrow leukemia non-lymphocytic acute myelocytic, bone marrow lymph proliferative disease, bone marrow multiple myeloma, bone sarcoma, brain astrocytoma, brain glioblastoma, brain medulloblastoma, brain meningioma, brain oligodendroglioma, breast adenoid cystic carcinoma, breast carcinoma, breast ductal

carcinoma, unknown undifferentiated neuroendocrine carcinoma, unknown primary undifferentiated small cell carcinoma, uterus carcinosarcoma, uterus endometrial adenocarcinoma, uterus endometrial adenocarcinoma endometrioid, uterus endometrial adenocarcinoma papillary serous, and uterus leiomyosarcoma.

59. The use or method of any one of claims 1-58, wherein the subject is previously identified or diagnosed as having the cancer.

60. A method of determining a subject's risk for developing a Trk inhibitor-resistant cancer, the method comprising:

determining whether a cell in a sample obtained from the subject has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

identifying a subject having a cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705, as having an increased likelihood of developing a Trk inhibitor-resistant cancer.