

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 examples, 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

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 Trk inhibitor of step (a) 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 examples of these methods include 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 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 examples of these methods include administering additional doses of the first Trk inhibitor of step (a) 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).

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, 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).

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, the present disclosure refers to 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,

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)); dovatinib (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)), and 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;

(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;
 15 (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;
 20 (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, the present disclosure refers to use of a second Trk inhibitor or a treatment that does not include the first Trk inhibitor of step (a) in the manufacture of a medicament for treating a subject having a cancer, the use 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) wherein the medicament is to be administered 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) wherein additional doses of the first Trk inhibitor of step (a) 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, wherein in step (b) one or more doses of the second Trk inhibitor is to be administered, 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;

(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^{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[15.5.2.0^{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.

Disclosed is 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, the present disclosure refers to 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)-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-15 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),19,22-20 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),20,23-25 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;
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),19,22-35 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.

Disclosed is 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.

Also disclosed is 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;
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}]-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-
10 [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[16.5.2.17,11.0^{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}]-
20 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;
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;
35 or a pharmaceutically acceptable salt thereof.

Disclosed is a method of treating a subject, the method comprising administering a
40 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
45 (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 disclosed is 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;
- (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.^{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;

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.

Disclosed is 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

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

Some examples 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 examples, 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 examples, 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).

Disclosed is 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.

Disclosed is 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;

(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 Disclosed is 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
10 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
15 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 disclosed is 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;

(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;

(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.

Further disclosed is 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.

Also disclosed is a method of selecting a subject having a cancer for a treatment that includes one or more compounds selected from the group consisting of:

(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

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}]pentacos-1(24),7,9,11,18(25),19,22-
heptaen-17-one;

or a pharmaceutically acceptable salt thereof.

Disclosed is 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:

35 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 does not include a first Trk inhibitor as a monotherapy.

Also disclosed is 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;

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 increased likelihood of having a positive response to treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof.

Also provided herein are methods of determining the likelihood that a subject having cancer will have a positive response to treatment with a first Trk inhibitor as a monotherapy, 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) 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 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 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 increased likelihood of having a positive response to treatment including one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof.

Some examples of these methods further include: administering a treatment not including a first Trk inhibitor as a monotherapy to the subject determined to have a decreased likelihood of having a positive response to treatment with a first Trk inhibitor as a monotherapy. Some examples of these methods further include: administering a treatment including one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, to the subject determined to have an increased likelihood of having a positive response to treatment including one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof.

Disclosed is 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.

Disclosed is 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;

(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^{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;

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^{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;

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 Disclosed is 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 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.

Also disclosed is 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;

Also provided herein are methods of predicting the efficacy of treatment with a first Trk inhibitor as a monotherapy in a subject having cancer, 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 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 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 predicting the efficacy of treatment with a treatment including one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, in a subject having cancer, 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 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).

Also provided herein are methods of predicting the efficacy of treatment with a first Trk inhibitor as a monotherapy in a subject having cancer, that include: 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 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 examples of these methods further include administering a treatment not including a first Trk inhibitor as a monotherapy to the subject.

Also provided herein are methods of predicting the efficacy of treatment including one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, in a subject having

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 examples of these methods further include administering one or more compound of Table 5, or a pharmaceutically acceptable salt thereof, to the subject.

Disclosed is 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.

Disclosed is 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;

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.

Disclosed is 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 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.

Also disclosed is 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-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;

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 examples of these methods include 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).

Some examples of these methods include 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) 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) selecting a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, 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).

Also provided herein are methods of selecting a treatment for 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) 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 examples 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 examples of any of the methods described herein further include administering selected treatment to the subject.

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

In some examples 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 examples 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 examples 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.

Disclosed is 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.

Disclosed is 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

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.

Disclosed is 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;

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.

Disclosed is 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.

Disclosed is 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;

(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-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}]pentacosal-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof;

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.

Disclosed is 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

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 examples 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.

Disclosed is 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.

Disclosed is 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).

Disclosed is 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

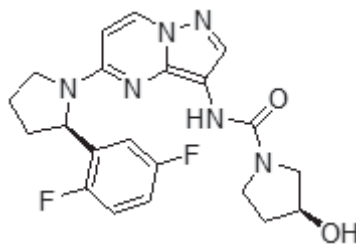
determining that a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646,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

Disclosed is 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 examples 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-

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)); dovatinib (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); AZD7451 ((S)-N-(1-(5-fluoropyrimidin-2-yl)ethyl)-3-(5-isopropoxy-1H-pyrazol-3-yl)-3H-imidazo[4,5-b]pyridin-5-amine). In some examples, the first Trk inhibitor (e.g., the first Trk inhibitor in step (a)) is entrectinib. In some examples, the first Trk inhibitor (e.g., the first Trk inhibitor in step (a)) is the compound of Formula I:



or a hydrogen sulfate salt thereof. In some examples, the first Trk inhibitor (e.g., the first Trk inhibitor in step (a)) is a crystalline form of the compound of Formula I or a hydrogen sulfate salt thereof (e.g., a compound of Formula I-HS).

In some examples of any of the methods described herein, the second Trk inhibitor is selected from the group consisting of: a (R)-2-phenylpyrrolidine substituted imadazopyridazine, AZD6918, GNF-4256, GTx-186, GNF-5837, AZ623, AG-879, altiratinib, CT327, ARRY-470, AR-772, AR-523, AR-786, AR-256, AR-618, AZ-23, AZD7451, cabozantinib, CEP-701, CEP-751, PHA-739358, dovitinib, entrectinib (N-[5-(3,5-difluoro-benzyl)-1H-indazol-3-yl]-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-pyran-4-ylamino)-benzamide), PLX7486, Gö 6976, GW441756, MGCD516, ONO-5390556, PHA-848125AC, regorafenib, sorafenib, sunitinib, TSR-011, VM-902A, K252a, a 4-

aminopyrazolylpyrimidine, and a substituted pyrazolo[1,5-a] pyrimidine compound. In some examples of any of the methods described herein, the second Trk inhibitor is selected from the compounds of Table 5, or a pharmaceutically acceptable salt thereof.

In some examples of any of the methods described herein, the subject is suspected of having a cancer. In some examples of any of the methods described herein, the subject has one or more symptoms of cancer. In some examples of any of the methods described herein, the subject is previously identified or diagnosed as having a cancer.

In some examples of any of the methods described herein, the step of 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), comprises performing an assay to determine the presence of the at least one point mutation in a NTRK1 gene and/or a NTRK2 gene and/or a NTRK3 gene in a cell in the sample. In some examples of any of the methods described herein, the step of 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), comprises performing an assay to determine the presence of the at least one point mutation in a NTRK1 gene and/or a NTRK2 gene and/or a NTRK3 gene in a cancer cell in the sample. In some examples of any of the methods described herein, the assay is selected from the group consisting of: denaturing gradient gel electrophoresis (DGGE), temperature gradient gel electrophoresis (TGGE), temperature gradient capillary electrophoresis, a single strand conformational polymorphism assay, a molecular beacon assay, a dynamic hybridization assay, a PCR-based assay, denaturing high performance liquid chromatography. In some examples of any of the methods described herein, the assay includes sequencing a segment of the NTRK1 gene and/or the NTRK2 gene and/or the NTRK3 gene including the at least one point mutation.

In some examples of any of the methods described herein, the cancer is selected from the group consisting of: adenocarcinoma, adrenal gland cortical carcinoma, adrenal gland neuroblastoma, anus squamous cell carcinoma, appendix adenocarcinoma, bladder

adenocarcinoma, small intestine gastrointestinal stromal tumors (GISTs), soft tissue angiosarcoma, soft tissue Ewing sarcoma, soft tissue hemangioendothelioma, soft tissue inflammatory myofibroblastic tumor, soft tissue leiomyosarcoma, soft tissue liposarcoma, soft tissue neuroblastoma, soft tissue paraganglioma, soft tissue perivascular epithelioid cell tumor, soft tissue sarcoma, soft tissue synovial sarcoma, stomach adenocarcinoma, stomach adenocarcinoma diffuse-type, stomach adenocarcinoma intestinal type, stomach adenocarcinoma intestinal type, stomach leiomyosarcoma, thymus carcinoma, thymus thymoma lymphocytic, thyroid papillary carcinoma, unknown primary adenocarcinoma, unknown primary carcinoma, unknown primary malignant neoplasm, unknown primary melanoma, unknown primary sarcomatoid carcinoma, unknown primary squamous cell 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.

In some of examples of any of the methods described herein, the 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 can be selected from (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein including 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 including 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 including 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 some examples of any of the methods described herein, the TrkA protein includes one or more of the following amino acid substitutions: G517R, A542V, V573M, F589L, F589C, G595S, G595R, D596V, F600L, F646V, C656Y, C656F, L657V, G667S, G667C, and Y676S. In some examples of any of the methods described herein, the TrkB protein includes one or more of the following amino acid substitutions: G545R, A570V, Q596E, Q596P, V601G,

F617L, F617C, F617I, G623S, G623R, D624V, R630K, C682Y, C682F, L683V, G693S, and G713S. In some examples 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 Disclosed is 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,
10 599, 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
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;

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.

Disclosed is 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 examples of these kits
5 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
10 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 examples of
15 any of the kits described herein, the one or more probes are labeled with a detectable probe. In some examples 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.”

20 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 examples, the subject is a human.

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,

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)); dovatatinib (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-(isopropylcarbonyl)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)), and

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;
- (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;

(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.

2. 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.

3. 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)-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[15.5.2.0^{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;

(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.

4. 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.

5. 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}]-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^{7,12}.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;

(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^{7,12}.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;

(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;

(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.

6. Use of a second Trk inhibitor or a treatment that does not include the first Trk inhibitor of step (a) in the manufacture of a medicament for treating a subject having a cancer, the use 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) wherein the medicament is to be administered 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) wherein additional doses of the first Trk inhibitor of step (a) 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, wherein in step (b) one or more doses of the second Trk inhibitor is to be administered, 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;
- (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;
- (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}]pentacos-1(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}]-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.

7. 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)-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}]-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;

(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}]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.

8. The use of claim 6 or claim 7, wherein said second Trk inhibitor or said compound is (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.

9. The use of any one of claims 1-8, 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 in situ, breast invasive ductal carcinoma, breast invasive lobular carcinoma, breast metaplastic carcinoma, cervix neuroendocrine carcinoma, cervix squamous cell carcinoma, colon adenocarcinoma, colon carcinoid tumor, duodenum adenocarcinoma, endometrioid tumor, esophagus adenocarcinoma, eye intraocular melanoma, eye intraocular squamous cell carcinoma, eye lacrimal duct carcinoma, fallopian tube serous carcinoma, gallbladder adenocarcinoma, gallbladder glomus tumor, gastroesophageal junction adenocarcinoma, head and neck adenoid cystic carcinoma, head and neck carcinoma, head and neck neuroblastoma, head and neck squamous cell carcinoma, kidney chromophore carcinoma, kidney medullary carcinoma, kidney renal cell carcinoma, kidney renal papillary carcinoma, kidney sarcomatoid carcinoma, kidney urothelial carcinoma, leukemia lymphocytic, liver cholangiocarcinoma, liver hepatocellular carcinoma, lung adenocarcinoma, lung adenosquamous carcinoma, lung atypical carcinoid, lung carcinosarcoma, lung large cell neuroendocrine carcinoma, lung non-small cell lung carcinoma, lung sarcoma, lung sarcomatoid carcinoma, lung small cell carcinoma, lung small cell undifferentiated carcinoma, lung squamous cell carcinoma, lymph node lymphoma diffuse large B cell, lymph node lymphoma follicular lymphoma, lymph node lymphoma mediastinal B-cell, lymph node lymphoma plasmablastic lung adenocarcinoma, lymphoma follicular lymphoma, non-Hodgkin's lymphoma, nasopharynx and paranasal sinuses undifferentiated carcinoma, ovary carcinoma, ovary carcinosarcoma, ovary clear cell carcinoma, ovary epithelial carcinoma, ovary granulosa cell tumor, ovary serous carcinoma, pancreas carcinoma, pancreas ductal adenocarcinoma, pancreas neuroendocrine carcinoma, peritoneum mesothelioma, peritoneum serous carcinoma, placenta choriocarcinoma, pleura mesothelioma, prostate acinar adenocarcinoma, prostate carcinoma, rectum adenocarcinoma, rectum squamous cell carcinoma, skin adnexal carcinoma, skin basal cell carcinoma, skin melanoma, skin Merkel cell carcinoma, skin squamous cell carcinoma, small intestine adenocarcinoma, small intestine gastrointestinal stromal tumors (GISTs), soft tissue angiosarcoma, soft tissue Ewing sarcoma, soft tissue hemangioendothelioma, soft tissue inflammatory myofibroblastic tumor, soft tissue leiomyosarcoma, soft tissue liposarcoma, soft tissue neuroblastoma, soft tissue paraganglioma, soft tissue perivascular epithelioid cell tumor, soft tissue sarcoma, soft tissue synovial sarcoma, stomach adenocarcinoma, stomach adenocarcinoma diffuse-type, stomach adenocarcinoma intestinal type, stomach adenocarcinoma intestinal type, stomach leiomyosarcoma, thymus carcinoma, thymus thymoma lymphocytic, thyroid papillary carcinoma, unknown primary adenocarcinoma, unknown primary carcinoma, unknown primary malignant neoplasm, unknown primary melanoma, unknown primary sarcomatoid carcinoma, unknown primary squamous cell

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.

10. The use of any one of claims 1-9, wherein the TrkA protein comprises one or more of the following amino acid substitutions: G517R, A542V, V573M, F589L, F589C, G595S, G595R, F600L, F646V, C656Y, C656F, L657V, G667S, G667C, and Y676S, and/or the TrkB protein comprises one or more of the following amino acid substitutions: G545R, A570V, Q596E, Q596P, V601G, F617L, F617C, F617I, G623S, G623R, D624V, R630K, C682Y, C682F, L683V, and G693S, and/or the TrkC protein comprises one or more of the following amino acid substitution G545R, A570V, F617L, G623R, D624V, C685Y, C685F, L686V, and G696A.

11. The use of any one of claims 1-9, wherein (i) said 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: 573, 589, 595, 599, 600, 646, 667, and 676, and/or (ii) said 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: 596, 601, 617, 623, and 630, and/or (iii) said a point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at amino acid position 617 and 623.

12. The use of any one of claims 1-9, wherein the TrkA protein comprises one or more of the following amino acid substitutions: V573M, F589L, F589C, G595S, G595R, F600L, F646V, G667S, G667C, and Y676S, and/or the TrkB protein comprises one or more of the following amino acid substitutions: Q596E, Q596P, V601G, F617L, F617C, F617I, G623S, G623R, and R630K, and/or the TrkC protein comprises one or more of the following amino acid substitution F617L and G623R.