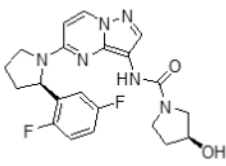


selected from the group of 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 608, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 677, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 730, 731, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810, the method comprising administering to the subject a therapeutically effective amount of a Trk inhibitor.

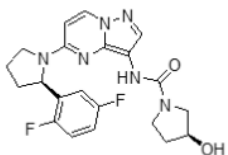
In one aspect, provided herein is use of a Trk inhibitor, wherein the Trk inhibitor is



the compound of formula I: or a hydrogen sulfate salt thereof, in the manufacture of a medicament for treating a subject identified as having a cancer cell that has: 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 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750; 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 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 677, 678, 679, 680, 689, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805, or an amino acid substitution of Q666L; and/or 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 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810, or an amino acid substitution of G608C, G608E, M731I, M731L, or L732I.

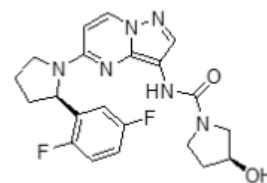
In one aspect, provided herein are methods of selecting a treatment for a cancer, the methods comprising: (a) identifying a cancer cell that has: at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group of 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750; 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 of 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 677, 678, 679, 680, 689, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805, or an amino acid substitution of Q666L; and/or 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 of 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539,

- 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810, or an amino acid substitution of G608C, G608E, M731I, M731L, or L732I; and (b) selecting a treatment comprising a therapeutically effective amount of a Trk inhibitor for the identified cancer cell, wherein the Trk inhibitor is the compound of formula



I: or a hydrogen sulfate salt thereof.

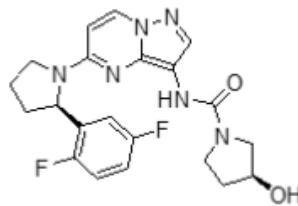
In one aspect, provided herein are methods of selecting a treatment for a cancer, the methods comprising selecting a treatment comprising a therapeutically effective amount of a



- 10 Trk inhibitor, wherein the Trk inhibitor is the compound of formula I:
or a hydrogen sulfate salt thereof, for a cancer cell identified as having: 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 of 241, 314, 318,
319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687,
15 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750; 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 of 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 677, 678, 679, 680, 689, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805, or an amino acid substitution of Q666L; and/or 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 of 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810, or an amino acid substitution of G608C, G608E, M731I, M731L, or L732I.

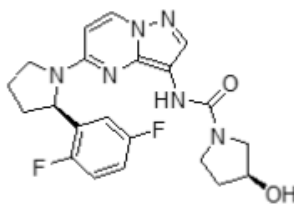
In one aspect, provided herein are methods of determining the likelihood that a subject having a cancer will have a positive response to treatment with a Trk inhibitor,



wherein the Trk inhibitor is the compound of formula I: or a hydrogen sulfate salt thereof, the methods comprising: (a) determining whether a cancer cell in a sample obtained from the subject has: 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 of 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750; 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 of 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 677, 678, 679, 680, 689, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805, or an amino acid substitution of Q666L; and/or 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 of 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810, or an amino acid substitution of G608C, G608E, M731I, M731L, or L732I; and (b) determining that a subject having a cancer cell that has at least one point mutation in a NTRK1 gene, the at least one point mutation in a NTRK2 gene,

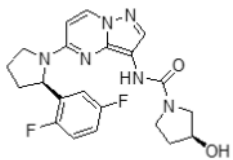
and/or at least one point mutation in a NTRK3 gene, has an increased likelihood of having a positive response to treatment with the Trk inhibitor.

5 In one aspect, provided herein are methods of determining the likelihood that a cancer will have a positive response to treatment with a Trk inhibitor, wherein the Trk



inhibitor is the compound of formula I: or a hydrogen sulfate salt thereof, the methods comprising: determining that a cancer cell that has: 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 of: 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750; 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 of 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 677, 678, 679, 680, 689, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805, or an amino acid substitution of Q666L; and/or 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 of 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810, or an amino acid substitution of G608C, G608E, M731I, M731L, or L732I, has an increased likelihood of having a positive response to treatment with the Trk inhibitor.

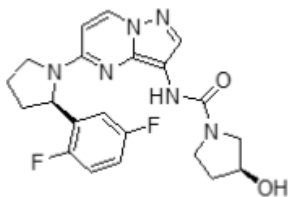
25 In one aspect, provided herein are methods of predicting the efficacy of a Trk inhibitor in a subject having cancer, wherein the Trk inhibitor is the compound of formula I:



or a hydrogen sulfate salt thereof, the methods comprising: (a) determining whether a cancer cell in a sample obtained from the subject has: 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 of 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750; 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 of 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 677, 678, 679, 680, 689, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805, or an amino acid substitution of Q666L; and/or 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 of 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810, or an amino acid substitution of G608C, G608E, M731I, M731L, or L732I; and (b) determining that the Trk inhibitor is more likely to be effective in a subject having a cancer cell in a sample obtained from the subject that has the at least one point mutation in a NTRK1 gene, the at least one point mutation in a NTRK2 gene, and/or the at least one point mutation in a NTRK3 gene.

In one aspect, provided are methods of predicting the efficacy of a Trk inhibitor in a subject having cancer, wherein the Trk inhibitor is the compound of formula I:



- or a hydrogen sulfate salt thereof, the methods comprising:
- determining that the Trk inhibitor 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 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 of 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750; 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 of 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 677, 678, 679, 680, 689, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805, or an amino acid substitution of Q666L; and/or 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 of 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810, or an amino acid substitution of G608C, G608E, M731I, M731L, or L732I.

In some embodiments of any of the use or methods described herein, the cancer is selected from the group 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-

NTRK2 gene, and/or the at least one point mutation in a NTRK3 gene as having an increased likelihood of developing a cancer.

Provided herein are methods of determining a cell's risk for developing a cancer, the methods comprising identifying a cell that has: at least one point mutation in a NTRK1 gene
5 that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group of 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750; 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)
10 selected from the group of: 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 666, 677, 678, 679, 680, 689, 691, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805; and/or 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 of 221, 222, 223,
15 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 608, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 677, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 730, 731, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810,
20 as having an increased likelihood of developing a cancer.

In one aspect, provided herein are methods of assisting in the diagnosis of a cancer in a subject, the methods comprising: (a) determining whether a cell in a sample obtained from the subject has: 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)
25 selected from the group of 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750; 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 of 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599,
30 600, 602, 603, 664, 665, 677, 678, 679, 680, 689, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805, or an amino acid substitution of Q666L; and/or 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 of 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282,

35

283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810, or an amino acid substitution of G608C, G608E, M731I, M731L, or L732I; and (b) determining that a subject having a cell that has the at least one point mutation in a NTRK1 gene, the at least one point mutation in a NTRK2 gene, and/or the at least one point mutation in a NTRK3 gene, has an increased likelihood of having a cancer.

Provided are methods of assisting in the diagnosis of a cancer, the methods comprising determining that a cell that has: 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 of 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750; 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 of 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 666, 677, 678, 679, 680, 689, 691, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805; and/or 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 of 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 608, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 677, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 730, 731, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810, has an increased likelihood of having a cancer.

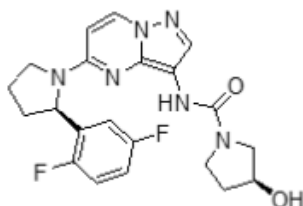
In some embodiments of any of the methods described herein, the subject is identified as having been exposed to a significant level of carcinogen(s). In some embodiments of any of the methods described herein, the subject is suspected of having a cancer. In some embodiments of any of the methods described herein, the subject has one or more symptoms of cancer. In some embodiments of any of the methods described herein, the cancer is selected from the group of: adenocarcinoma, adrenal gland cortical carcinoma, adrenal gland neuroblastoma, anus squamous cell carcinoma, appendix adenocarcinoma,

240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 677, 678, 679, 680, 689, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805, or an amino acid substitution of Q666L in TrkB protein; or a segment of a NTRK3 gene that encodes a mutation at one of amino acid positions 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810, or an amino acid substitution of G608C, G608E, M731I, M731L, or L732I in a TrkC protein.

In some embodiments of any of the kits provided herein, the kit includes 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 S241F, S241H, S241Y, R314G, R314H, R314L, R314P, N318S, G319S, S320F, V321M, I510T, V511M, L512F, L512R, S552R, A553T, R554P, R554Q, R554W, A636E, A636T, A636V, G637E, G637W, M638V, R649L, R649W, R654C, R654H, N655Y, D679N, D679Y, Y680H, T687I, M688I, L689M, P690H, R692C, R692H, P695S, P696L, E697K, E747K, R748L, R748Q, R748W, P749Q, R750C, R750H, and R750L in a TrkA protein; a segment of a NTRK2 gene that encodes a mutation selected from the group consisting of M240I, N241D, E242K, R251G, R251K, I252V, S256L, S257F, D258N, I264M, A314E, A314G, A314V, L315F, G401A, G401E, G401R, T426I, G427S, R428Q, A440S, A440T, A440V, R598C, R598S, K599M, D600H, H602N, R603S, L664M, T665M, T665S, Q666L, Q666R, A677T, A678T, A678V, G679D, M680I, V689M, R691C, D692N, F746I, T747M, T748M, E749K, Q784H, G785V, R786Q, V787F, L788M, Q789E, G804E, C805R, and C805Y in TrkB protein; or a segment of a NTRK3 gene that encodes a mutation selected from the group consisting of V221I, R222Q, E223D, D242N, W243C, I244T, T269A, T269M, T270M, T270Q, T270V, V271L, V271M, E276D, D277E, D277G, D277N, T281I, T281P, T282M, T283A, T283K, T283M, S296I, S296R, V297I, V325M, R326C, R326G, R326H, R326L, R326P, N328S, P329N, P329S, P330Q, E344G, E344V, S345F, K346N, H349Y, V350E, E351D, Y353F, Q354K, D537E, D537Y, I538N, V539M, L540M, G545C, G545D, G550R, K551E, L560V, P562L, P562Q, P562R, P562T, K575E, D576N, P577S, P582Q, P582W, K583%, D584E, D584N, V601A, V601I, K602R, F603L, Y604F, Y604H, Y604N, C607F, G608C, G608E, G608S, D609G, D609H, D609N, D609V, G610R, P612A, P612L, P612S, P612T, D624Y, L625M, N626K, K627N, K627R, F628L, L629F, L629I, P634L, P634T, D635H, A636E, A636V, M637I, M637K,

WHAT IS CLAIMED IS:

1. Use of a Trk inhibitor, wherein the Trk inhibitor is the compound of formula I:



or a hydrogen sulfate salt thereof, 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:

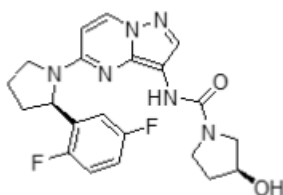
at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750;

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 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 677, 678, 679, 680, 689, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805, or an amino acid substitution of Q666L; and/or

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 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810, or an amino acid substitution of G608C, G608E, M731I, M731L, or L732I;

wherein the medicament is to be administered to the identified subject.

2. Use of a Trk inhibitor, wherein the Trk inhibitor is the compound of formula I:



or a hydrogen sulfate salt thereof, in the manufacture of a medicament for treating a subject identified as having a cancer cell that has: 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 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750; 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 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 677, 678, 679, 680, 689, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805, or an amino acid substitution of Q666L; and/or 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 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810, or an amino acid substitution of G608C, G608E, M731I, M731L, or L732I.

3. A method of selecting a treatment for a cancer, the method comprising:

(a) identifying a cancer cell that has:

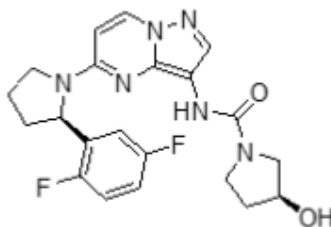
at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750;

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 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 677, 678, 679, 680, 689, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805, or an amino acid substitution of Q666L; and/or

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 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297,

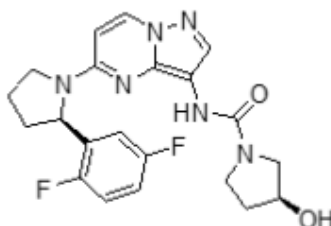
325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810, or an amino acid substitution of G608C, G608E, M731I, M731L, or L732I; and

(b) selecting a treatment comprising a therapeutically effective amount of a Trk inhibitor for the identified cancer cell, wherein the Trk inhibitor is the compound of formula I:



or a hydrogen sulfate salt thereof.

4. A method of selecting a treatment for a cancer, the method comprising:
selecting a treatment comprising a therapeutically effective amount of a Trk inhibitor, wherein the Trk inhibitor is the compound of formula I:



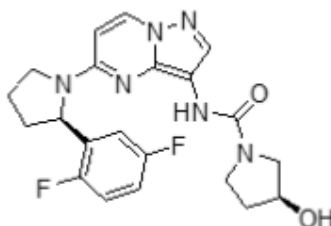
or a hydrogen sulfate salt thereof, for a cancer cell identified as having:

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 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750;

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 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 677, 678, 679, 680, 689, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805, or an amino acid substitution of Q666L; and/or

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 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810, or an amino acid substitution of G608C, G608E, M731I, M731L, or L732I.

5. A method of determining the likelihood that a subject having a cancer will have a positive response to treatment with a Trk inhibitor, wherein the Trk inhibitor is the compound of formula I:



or a hydrogen sulfate salt thereof, the method comprising:

(a) determining whether a cancer cell in a sample obtained from the subject has:

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 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750;

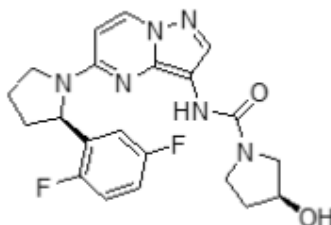
at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 677, 678, 679, 680, 689, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805, or an amino acid substitution of Q666L; and/or

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 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 678, 679, 687, 688, 689,

705, 706, 707, 708, 715, 716, 717, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810, or an amino acid substitution of G608C, G608E, M731I, M731L, or L732I; and

(b) determining that a subject having a cancer cell that has at least one point mutation in a NTRK1 gene, the at least one point mutation in a NTRK2 gene, and/or at least one point mutation in a NTRK3 gene, has an increased likelihood of having a positive response to treatment with the Trk inhibitor.

6. A method of determining the likelihood that a cancer will have a positive response to treatment with a Trk inhibitor, wherein the Trk inhibitor is the compound of formula I:



or a hydrogen sulfate salt thereof, the method comprising:

determining that a cancer cell that has:

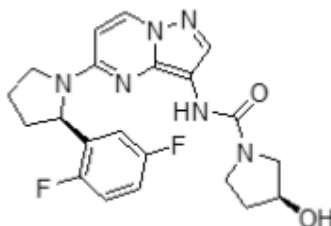
at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750;

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 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 677, 678, 679, 680, 689, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805, or an amino acid substitution of Q666L; and/or

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 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810, or an amino acid substitution of G608C, G608E, M731I, M731L, or L732I,

has an increased likelihood of having a positive response to treatment with the Trk inhibitor.

7. A method of predicting the efficacy of a Trk inhibitor in a subject having cancer, wherein the Trk inhibitor is the compound of formula I:



or a hydrogen sulfate salt thereof, the method comprising:

(a) determining whether a cancer cell in a sample obtained from the subject has:

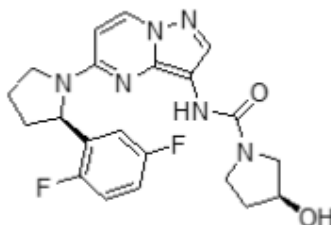
at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750;

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 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 677, 678, 679, 680, 689, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805, or an amino acid substitution of Q666L; and/or

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 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810, or an amino acid substitution of G608C, G608E, M731I, M731L, or L732I; and

(b) determining that the Trk inhibitor is more likely to be effective in a subject having a cancer cell in a sample obtained from the subject that has the at least one point mutation in a NTRK1 gene, the at least one point mutation in a NTRK2 gene, and/or the at least one point mutation in a NTRK3 gene.

8. A method of predicting the efficacy of a Trk inhibitor in a subject having cancer, wherein the Trk inhibitor is the compound of formula I:



or a hydrogen sulfate salt thereof, the method comprising:

determining that the Trk inhibitor 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 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 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750;

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 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 677, 678, 679, 680, 689, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805, or an amino acid substitution of Q666L; and/or

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 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810, or an amino acid substitution of G608C, G608E, M731I, M731L, or L732I.

9. The use of claim 1 or 2, or the method of any one of claims 3-8, 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, esophagus and stomach carcinoma, 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, kidney carcinoma, leukemia lymphocytic, leukemia lymphocytic chronic, liver cholangiocarcinoma, liver hepatocellular carcinoma, liver 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, upper aerodigestive tract squamous cell carcinoma, upper aerodigestive tract 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, lymphoma, non-Hodgkins, 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), large intestine/colon carcinoma, large intestine adenocarcinoma, 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, lymphoid 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.

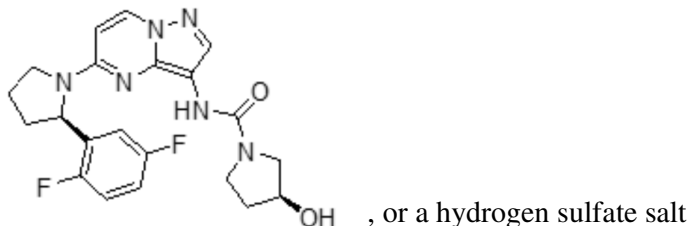
10. The use or method of any one of claims 1-9, wherein the subject is previously identified or diagnosed as having the cancer.

11. The use of claim 1 or the method of any one of claims 3, 5, and 7, wherein the step of identifying a cancer cell or a subject having a cancer cell that has the at least one point mutation in a NTRK1 gene, the at least one point mutation in a NTRK2 gene, and/or the at least one point mutation in a NTRK3 gene comprises performing an assay to determine the presence of the at least one point mutation in a NTRK1 gene, the at least one point mutation in a NTRK2 gene, and/or the at least one point mutation in a NTRK3 gene, in a cancer cell in a sample from the subject.

12. The use or method of claim 11, wherein 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, and denaturing high performance liquid chromatography.

13. The use or method of claim 11, wherein the assay comprises sequencing a segment of the NTRK1 gene comprising the at least one point mutation, a segment of the NTRK2 gene comprising the at least one point mutation, and/or a segment of the NTRK3 gene comprising the at least one point mutation.

14. The use or method of any one of claims 1-13, wherein the Trk inhibitor is a crystalline form of the compound of Formula I:



thereof.

15. The method of claim 3 or 4, wherein:

a therapeutically effective amount of the selected treatment is to be administered to the identified subject.

16. The method of claim 3, 4, and 15, further comprising:

recording the selected treatment in the identified subject's clinical record.

17. The method of claim 16, wherein the subject's clinical record is a computer

readable medium.

18. The method of claim 5 or 6, wherein:

a therapeutically effective amount of the Trk inhibitor is to be administered to a subject or a cancer determined to have an increased likelihood of having a positive response to treatment with the Trk inhibitor.

19. A method of determining a subject's risk for developing a cancer, the method comprising:

(a) determining whether a cell in a sample obtained from the subject has:

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 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750;

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 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440,

598, 599, 600, 602, 603, 664, 665, 677, 678, 679, 680, 689, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805, or an amino acid substitution of Q666L; and/or

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 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810, or an amino acid substitution of G608C, G608E, M731I, M731L, or L732I; and

(b) identifying a subject having a cell that has the at least one point mutation in a NTRK1 gene, the at least one point mutation in a NTRK2 gene, and/or the at least one point mutation in a NTRK3 gene as having an increased likelihood of developing a cancer.

20. A method of assisting in the diagnosis of a cancer in a subject, the method comprising:

(a) determining whether a cell in a sample obtained from the subject has:

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 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750;

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 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 677, 678, 679, 680, 689, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805, or an amino acid substitution of Q666L; and/or

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 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810, or an amino acid substitution of G608C, G608E, M731I, M731L, or L732I; and

(b) determining that a subject having a cell that has the at least one point mutation in a NTRK1 gene, the at least one point mutation in a NTRK2 gene, and/or the at least one point mutation in a NTRK3 gene, has an increased likelihood of having a cancer.

21. The method of any one of claims 19-20, wherein the subject or cell is identified as having been exposed to a significant level of carcinogen(s).

22. The method of any one of claims 19-20, wherein the subject or cell is suspected of having a cancer.

23. The methods of any one of claims 19-20, wherein the subject or cell has one or more symptoms of cancer.

24. The method of any one of claims 19-23, 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, esophagus and stomach carcinoma, 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, kidney carcinoma, leukemia lymphocytic, leukemia lymphocytic chronic, liver cholangiocarcinoma, liver hepatocellular carcinoma, liver 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, upper aerodigestive tract squamous cell carcinoma, upper aerodigestive tract 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, lymphoma, non-Hodgkins, 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), large intestine/colon carcinoma, large intestine adenocarcinoma, 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, lymphoid 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.

25. The method of claim 20 or 21, wherein the step of determining whether a cell in a sample obtained from the subject has the at least one point mutation in a NTRK1 gene, the at least one point mutation in a NTRK2 gene, and/or the at least one point mutation in a

NTRK3 gene, comprises performing an assay to determine the presence of the at least one point mutation in a NTRK1 gene, the presence of the at least one point mutation in a NTRK2 gene, and/or the presence of the at least one point mutation in a NTRK3 gene, in a cell in the sample.

26. The method of claim 25, wherein 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.

27. The method of claim 25, wherein the assay comprises sequencing a segment of the NTRK1 gene comprising the at least one point mutation, a segment of the NTRK2 gene comprising the at least one point mutation, and/or a segment of the NTRK3 gene comprising the at least one point mutation.

28. The use or method of any one of claims 1-27, wherein:

the TrkA protein comprises a mutation at one or more amino acid positions selected from the group consisting of S241F, S241H, S241Y, R314G, R314H, R314L, R314P, N318S, G319S, S320F, V321M, I510T, V511M, L512F, L512R, S552R, A553T, R554P, R554Q, R554W, A636E, A636T, A636V, G637E, G637W, M638V, R649L, R649W, R654C, R654H, N655Y, D679N, D679Y, Y680H, T687I, M688I, L689M, P690H, R692C, R692H, P695S, P696L, E697K, E747K, R748L, R748Q, R748W, P749Q, R750C, R750H, and R750L;

the TrkB protein comprises a mutation at one or more amino acid position(s) selected from the group consisting of M240I, N241D, E242K, R251G, R251K, I252V, S256L, S257F, D258N, I264M, A314E, A314G, A314V, L315F, G401A, G401E, G401R, T426I, G427S, R428Q, A440S, A440T, A440V, R598C, R598S, K599M, D600H, H602N, R603S, L664M, T665M, T665S, Q666L, A677T, A678T, A678V, G679D, M680I, V689M, D692N, F746I, T747M, T748M, E749K, Q784H, G785V, R786Q, V787F, L788M, Q789E, G804E, C805R, and C805Y; and/or

the TrkC protein comprises a mutation at one or more amino acid position(s) selected from the group consisting of V221I, R222Q, E223D, D242N, W243C, I244T, T269A, T269M, T270M, T270Q, T270V, V271L, V271M, E276D, D277E, D277G, D277N,

T281I, T281P, T282M, T283A, T283K, T283M, S296I, S296R, V297I, V325M, R326C, R326G, R326H, R326L, R326P, N328S, P329N, P329S, P330Q, E344G, E344V, S345F, K346N, H349Y, V350E, E351D, Y353F, Q354K, D537E, D537Y, I538N, V539M, L540M, G545C, G545D, G550R, K551E, L560V, P562L, P562Q, P562R, P562T, K575E, D576N, P577S, P582Q, P582W, K583%, D584E, D584N, V601A, V601I, K602R, F603L, Y604F, Y604H, Y604N, C607F, G608C, G608E, D609G, D609H, D609N, D609V, G610R, P612A, P612L, P612S, P612T, D624Y, L625M, N626K, K627N, K627R, F628L, L629F, L629I, P634L, P634T, D635H, A636E, A636V, M637I, M637K, M637V, E650V, L651P, G652R, G652V, L653F, L653P, H677Y, R678Q, D679G, D679N, V687A, V687I, G688R, A689E, A689V, Y705N, S706I, T707M, D708N, P715L, P715S, S716Y, G717R, T730N, M731I, M731L, L732I, P738H, P738S, Y744F, R745P, R745W, K746R, K746T, G786C, G786S, R787C, R787H, R787S, P796L, P796S, D801N, Q808H, R809W, and E810K.

29. 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 241, 314, 318, 319, 320, 321, 510, 511, 512, 552, 553, 554, 636, 637, 638, 649, 654, 655, 679, 680, 687, 688, 689, 690, 692, 695, 696, 697, 747, 748, 749, and 750 in a TrkA protein;

a segment of a NTRK2 gene that encodes a mutation at one of amino acid positions 240, 241, 242, 251, 252, 256, 257, 258, 264, 314, 315, 401, 426, 427, 428, 440, 598, 599, 600, 602, 603, 664, 665, 677, 678, 679, 680, 689, 692, 746, 747, 748, 749, 784, 785, 786, 787, 788, 789, 804, and 805, or an amino acid substitution of Q666L in TrkB protein; or

a segment of a NTRK3 gene that encodes a mutation at one of amino acid positions 221, 222, 223, 242, 243, 244, 269, 270, 271, 276, 277, 281, 282, 283, 296, 297, 325, 326, 328, 329, 344, 345, 346, 349, 350, 351, 353, 354, 537, 538, 539, 540, 545, 550, 551, 560, 562, 575, 576, 577, 582, 583, 584, 601, 602, 603, 604, 607, 609, 610, 612, 624, 625, 626, 627, 628, 629, 634, 635, 636, 637, 650, 651, 652, 653, 678, 679, 687, 688, 689, 705, 706, 707, 708, 715, 716, 717, 732, 738, 744, 745, 746, 786, 787, 796, 801, 808, 809, and 810, or an amino acid substitution of G608C, G608E, M731I, M731L, or L732I in a TrkC protein.

30. The kit of claim 29, wherein the kit comprises 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 S241F, S241H, S241Y, R314G, R314H, R314L, R314P, N318S, G319S,

S320F, V321M, I510T, V511M, L512F, L512R, S552R, A553T, R554P, R554Q, R554W, A636E, A636T, A636V, G637E, G637W, M638V, R649L, R649W, R654C, R654H, N655Y, D679N, D679Y, Y680H, T687I, M688I, L689M, P690H, R692C, R692H, P695S, P696L, E697K, E747K, R748L, R748Q, R748W, P749Q, R750C, R750H, and R750L in a TrkA protein;

a segment of a NTRK2 gene that encodes a mutation selected from the group consisting of M240I, N241D, E242K, R251G, R251K, I252V, S256L, S257F, D258N, I264M, A314E, A314G, A314V, L315F, G401A, G401E, G401R, T426I, G427S, R428Q, A440S, A440T, A440V, R598C, R598S, K599M, D600H, H602N, R603S, L664M, T665M, T665S, Q666L, A677T, A678T, A678V, G679D, M680I, V689M, D692N, F746I, T747M, T748M, E749K, Q784H, G785V, R786Q, V787F, L788M, Q789E, G804E, C805R, and C805Y in TrkB protein; or

a segment of a NTRK3 gene that encodes a mutation selected from the group consisting of V221I, R222Q, E223D, D242N, W243C, I244T, T269A, T269M, T270M, T270Q, T270V, V271L, V271M, E276D, D277E, D277G, D277N, T281I, T281P, T282M, T283A, T283K, T283M, S296I, S296R, V297I, V325M, R326C, R326G, R326H, R326L, R326P, N328S, P329N, P329S, P330Q, E344G, E344V, S345F, K346N, H349Y, V350E, E351D, Y353F, Q354K, D537E, D537Y, I538N, V539M, L540M, G545C, G545D, G550R, K551E, L560V, P562L, P562Q, P562R, P562T, K575E, D576N, P577S, P582Q, P582W, K583%, D584E, D584N, V601A, V601I, K602R, F603L, Y604F, Y604H, Y604N, C607F, G608C, G608E, D609G, D609H, D609N, D609V, G610R, P612A, P612L, P612S, P612T, D624Y, L625M, N626K, K627N, K627R, F628L, L629F, L629I, P634L, P634T, D635H, A636E, A636V, M637I, M637K, M637V, E650V, L651P, G652R, G652V, L653F, L653P, H677Y, R678Q, D679G, D679N, V687A, V687I, G688R, A689E, A689V, Y705N, S706I, T707M, D708N, P715L, P715S, S716Y, G717R, T730N, M731I, M731L, L732I, P738H, P738S, Y744F, R745P, R745W, K746R, K746T, G786C, G786S, R787C, R787H, R787S, P796L, P796S, D801N, Q808H, R809W, and E810K in a TrkC protein.

31. The kit of claim 29 or 30, wherein the one or more probes are labeled with a detectable probe.

32. The kit of claims 29-31, wherein the one or more probes are covalently attached to a substrate.

33. The kit of claim 32, wherein the substrate is a film, a plate, or a bead.