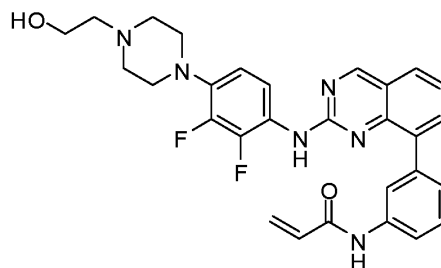


CLAIMS

What is claimed is:

1. A composition comprising a crystalline form of a compound of Formula I:



Formula I.

2. The composition of claim 1, wherein the composition comprises a crystalline form of the compound of Formula I.
3. The composition of claim 1 or 2, wherein the composition can be stored at about 40 °C, 75% relative humidity, for a time period of about 30 days or more without significant degradation or change in the crystalline form.
4. The composition of claim 1 or 2, wherein the composition can be stored at about 60 °C for a time period of about 30 days or more without significant degradation or change in the crystalline form.
5. The composition of any one of claims 1-4, wherein the crystalline form is a polymorph Form I of the compound of Formula I.
6. The composition of claim 5, wherein the polymorph Form I is characterized by an X-ray powder diffraction pattern comprising peaks at 21.4 ± 0.2 degrees, 18.3 ± 0.2 degrees and 22.7 ± 0.2 degrees two theta.
7. The composition of claim 6, wherein the X-ray powder diffraction pattern further comprises at least one peak selected from 13.5 ± 0.2 degrees, 17.2 ± 0.2 degrees, and 5.0 ± 0.2 degrees two theta.
8. The composition of claim 6 or 7, wherein the X-ray powder diffraction pattern further comprises at least one peak selected from 25.8 ± 0.2 degrees and 23.6 ± 0.2 degrees two theta.

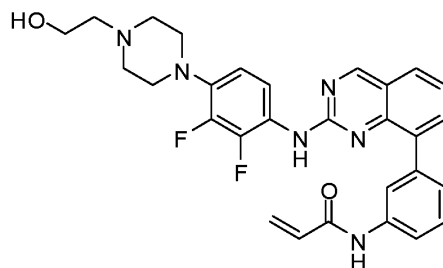
9. The composition of any one of claims 6-8, wherein the X-ray powder diffraction pattern comprises peaks at 21.4 ± 0.2 degrees, 18.3 ± 0.2 degrees, 22.7 ± 0.2 degrees, 13.5 ± 0.2 degrees, 17.2 ± 0.2 degrees, 5.0 ± 0.2 degrees, 25.8 ± 0.2 degrees, and 23.6 ± 0.2 degrees two theta.
10. The composition of any one of claims 5 to 9, wherein the polymorph Form I is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm in the range of about 160-180 °C.
11. The composition of any one of claims 5-10, wherein the polymorph Form I has a melting point of about 173 °C.
12. The composition of any one of claims 5 to 11, wherein greater than about 90%, 95%, or 99% by weight of the compound of Formula I in the composition is the polymorph Form I.
13. The composition of any one of claims 5 to 12, wherein the polymorph Form I comprises (i) rod like crystals or (ii) rod and column crystals.
14. The composition of any one of claims 5-13 wherein the polymorph Form I is dry, non-solvated, non-hydrated, and/or non-hygroscopic.
15. The composition of any one of claims 1-4, wherein the crystalline form is a polymorph Form II of the compound of Formula I.
16. The composition of claim 15, wherein the polymorph Form II is characterized by an X-ray powder diffraction pattern comprising peaks at 7.5 ± 0.2 degrees, 19.5 ± 0.2 degrees, and 23.5 ± 0.2 degrees two theta.
17. The composition of claim 15 or 16, wherein the polymorph Form II is characterized by a DSC thermogram comprising endotherms in the range of about 120-150 °C and about 175-200 °C, for example endotherms at about 124 °C and about 183 °C.
18. The composition of any one of claims 1-4, wherein the crystalline form is a polymorph Form III of the compound of Formula I.
19. The composition of claim 18, wherein the polymorph Form III is characterized by an X-ray powder diffraction pattern comprising a peak at 6.5 ± 0.2 degrees two theta.

20. The composition of claim 19, wherein the X-ray powder diffraction pattern further comprises at least one peak selected from 19.6 ± 0.2 degrees, 22.4 ± 0.2 degrees, 13.0 ± 0.2 degrees and 20.3 ± 0.2 degrees two theta.
21. The composition of claim 19 or 20, wherein the X-ray powder diffraction pattern further comprises at least one peak selected from 14.0 ± 0.2 degrees, 26.2 ± 0.2 degrees, 16.6 ± 0.2 degrees, and 23.3 ± 0.2 degrees two theta.
22. The composition of any one of claims 19-21, wherein the X-ray powder diffraction pattern comprises peaks at 6.5 ± 0.2 degrees, 19.6 ± 0.2 degrees, 22.4 ± 0.2 degrees, 13.0 ± 0.2 degrees, 20.3 ± 0.2 degrees, 14.0 ± 0.2 degrees, 26.2 ± 0.2 degrees, 16.6 ± 0.2 degrees, and 23.3 ± 0.2 degrees two theta.
23. The composition of any one of claims 18-22, wherein the polymorph Form III is characterized by a DSC thermogram comprising endotherms in the range of about 116-136 °C and about 184-194 °C, for example endotherms at about 120 °C and about 188 °C.
24. The composition of any one of claims 18-23, wherein the polymorph Form III has a melting point of about 188 °C.
25. The composition of any one of claims 18-24, wherein greater than about 90%, 95%, or 99% of the compound of Formula I in the composition is the polymorph Form III.
26. The composition of any one of claims 18-25, wherein the polymorph Form III is dry, or wherein the polymorph Form III is non-solvated, or wherein the polymorph Form III is solvated.
27. The composition of any one of claims 1-4, wherein the crystalline form is a polymorph Form IV of the compound of Formula I.
28. The composition of claim 27, wherein the polymorph Form IV is characterized by an X-ray powder diffraction pattern comprising peaks at 24.5 ± 0.2 degrees and 20.7 ± 0.2 degrees two theta.
29. The composition of claim 28, wherein the X-ray powder diffraction pattern further comprises at least one peak selected from 19.6 ± 0.2 degrees, 18.0 ± 0.2 degrees, 23.2 ± 0.2 degrees, 7.4 ± 0.2 degrees, 8.0 ± 0.2 degrees, 16.1 ± 0.2 degrees and 17.8 ± 0.2 degrees two theta.

30. The composition of claim 28 or 29, wherein the X-ray powder diffraction pattern comprises peaks at 24.5 ± 0.2 degrees, 20.7 ± 0.2 degrees, 19.6 ± 0.2 degrees, 18.0 ± 0.2 degrees, 23.2 ± 0.2 degrees, 7.4 ± 0.2 degrees, 8.0 ± 0.2 degrees, 16.1 ± 0.2 degrees, and 17.8 ± 0.2 degrees two theta.
31. The composition of any one of claims 27-30, wherein the polymorph Form IV is characterized by a DSC thermogram comprising endotherms in the range of about 115-135 °C, about 168-178 °C and about 184-194 °C, for example endotherms at about 119 °C, about 170 °C and about 187 °C.
32. The composition of claim 31, wherein the DSC thermogram further comprises an exotherm at about 137-147 °C, for example at about 140 °C .
33. The composition of any one of claims 27-32, wherein greater than about 90%, 95%, or 99% of the compound of Formula I in the composition is the polymorph Form IV.
34. The composition of any one of claims 27-33, wherein the polymorph Form IV is dry or wherein the polymorph Form IV is solvated.
35. The composition of any one of claims 1-4, wherein the crystalline form is a polymorph Form V of the compound of Formula I.
36. The composition of claim 35, wherein the polymorph Form V is characterized by an X-ray powder diffraction pattern comprising peaks at 5.7 ± 0.2 degrees, 21.6 ± 0.2 degrees, and 14.6 ± 0.2 degrees two theta.
37. The composition of claim 36, wherein the X-ray powder diffraction pattern further comprises at least one peak selected from 19.5 ± 0.2 degrees, 20.0 ± 0.2 degrees, 25.1 ± 0.2 degrees, 7.2 ± 0.2 degrees, 21.4 ± 0.2 degrees, and 12.2 ± 0.2 degrees two theta.
38. The composition of claim 36 or 37, wherein the X-ray powder diffraction pattern comprises peaks at 5.7 ± 0.2 degrees, 21.6 ± 0.2 degrees, 14.6 ± 0.2 degrees, 19.5 ± 0.2 degrees, 20.0 ± 0.2 degrees, 25.1 ± 0.2 degrees, 7.2 ± 0.2 degrees, 21.4 ± 0.2 degrees, and 12.2 ± 0.2 degrees two theta.
39. The composition of any one of claims 35-38, wherein the polymorph Form V is characterized by a DSC thermogram comprising endotherms in the range of about 152-162 °C and about 183-193 °C, for example endotherms at about 156 °C and about 187 °C.

40. The composition of claim 39, wherein the DSC thermogram further comprises an exotherm at about 159 °C.
41. The composition of any one of claims 35-40, wherein greater than about 90%, 95%, or 99% of the compound of Formula I in the composition is the polymorph Form V.
42. The composition of any one of claims 35-41, wherein the polymorph Form V is dry or wherein the polymorph Form V is solvated.
43. The composition of any one of claims 1-4, wherein the crystalline form is a polymorph Form VI of the compound of Formula I.
44. The composition of claim 43, wherein the polymorph Form VI is characterized by an X-ray powder diffraction pattern comprising a peak at 6.6 ± 0.2 degrees two theta.
45. The composition of claim 44, wherein the X-ray powder diffraction pattern further comprises at least one peak selected from 20.5 ± 0.2 degrees, 22.6 ± 0.2 degrees, and 14.1 ± 0.2 degrees two theta.
46. The composition of claim 44 or 45, wherein the X-ray powder diffraction pattern further comprises peak at least one peak selected from 26.0 ± 0.2 degrees, 19.7 ± 0.2 degrees, 12.4 ± 0.2 degrees, 17.6 ± 0.2 degrees and 23.3 ± 0.2 degrees two theta.
47. The composition of any one of claims 44-46, wherein the X-ray powder diffraction pattern comprises peaks at 6.6 ± 0.2 degrees, 20.5 ± 0.2 degrees, 22.6 ± 0.2 degrees, 14.1 ± 0.2 degrees, 26.0 ± 0.2 degrees, 19.7 ± 0.2 degrees, 12.4 ± 0.2 degrees, 17.6 ± 0.2 degrees, and 23.3 ± 0.2 degrees two theta.
48. The composition of any one of claims 43-47, wherein the polymorph Form VI is characterized by a DSC thermogram comprising endotherms in the range of about 120-140 °C and about 185-195 °C, for example endotherms at about 123 °C and at about 188 °C.
49. The composition of any one of claims 43-49, wherein the polymorph Form VI has a melting point of about 188 °C.
50. The composition of any one of claims 43-49, wherein greater than about 90%, 95%, or 99% of the compound of Formula I in the composition is the polymorph Form VI.

51. The composition of any one of claims 43-50, wherein the polymorph Form VI is dry, or wherein the polymorph Form VI is non-solvated, or wherein the polymorph Form VI is solvated.
52. The composition of any one of claims 1-4, wherein the crystalline form is a polymorph Form VIII of the compound of Formula I.
53. The composition of claim 52, wherein the polymorph Form VIII is characterized by an X-ray powder diffraction pattern comprising a peak at 20.7 ± 0.2 degrees two theta.
54. The composition of claim 53, wherein the X-ray powder diffraction pattern further comprises at least one peak selected from 22.7 ± 0.2 degrees, 6.7 ± 0.2 degrees, 7.4 ± 0.2 degrees, and 14.1 ± 0.2 degrees two theta.
55. The composition of claim 53 or 54, wherein the X-ray powder diffraction pattern further comprises at least one peak selected from 15.7 ± 0.2 degrees, 26.1 ± 0.2 degrees, 19.7 ± 0.2 degrees, and 12.5 ± 0.2 degrees two theta.
56. The composition of any one of claims 53-55, wherein the X-ray powder diffraction pattern comprises peaks at 20.7 ± 0.2 degrees, 22.7 ± 0.2 degrees, 6.7 ± 0.2 degrees, 7.4 ± 0.2 degrees, 14.1 ± 0.2 degrees, 15.7 ± 0.2 degrees, 26.1 ± 0.2 degrees, 19.7 ± 0.2 degrees, and 12.5 ± 0.2 degrees two theta.
57. The composition of any one of claims 52-56, wherein the polymorph Form VIII is characterized by a DSC thermogram comprising endotherm in the range of about 182-192 °C, for example endotherm at about 187 °C.
58. The composition of claim 57, wherein the DSC thermogram further comprises endotherm at about 110-135 °C for example at about 114 °C.
59. A composition comprising one or more crystalline forms of a compound of Formula I:



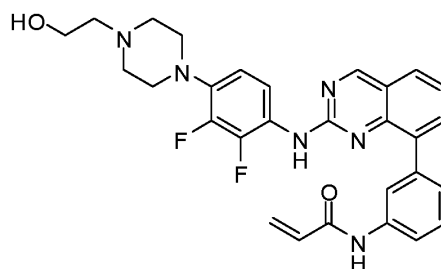
Formula I.

wherein the one or more crystalline forms are selected from the group consisting of:

- (i) a crystalline form characterized by an X-ray powder diffraction pattern comprising peaks at 21.4 ± 0.2 degrees, 18.3 ± 0.2 degrees and 22.7 ± 0.2 degrees two theta;
 - (ii) a crystalline form characterized by an X-ray powder diffraction pattern comprising peaks at 7.5 ± 0.2 degrees, 19.5 ± 0.2 degrees and 23.5 ± 0.2 degrees two theta;
 - (iii) a crystalline form characterized by an X-ray powder diffraction pattern comprising peaks at 6.5 ± 0.2 degrees, 19.6 ± 0.2 degrees, 22.4 ± 0.2 degrees, 13.0 ± 0.2 degrees and 20.3 ± 0.2 degrees two theta;
 - (iv) a crystalline form characterized by an X-ray powder diffraction pattern comprising peaks at 24.5 ± 0.2 degrees, 20.7 ± 0.2 degrees, 19.6 ± 0.2 degrees, 18.0 ± 0.2 degrees, 23.2 ± 0.2 degrees, 7.4 ± 0.2 degrees, and 8.0 ± 0.2 degrees two theta;
 - (v) a crystalline form characterized by an X-ray powder diffraction pattern comprising peaks at 5.7 ± 0.2 degrees, 21.6 ± 0.2 degrees, 14.6 ± 0.2 degrees two theta;
 - (vi) a crystalline form characterized by an X-ray powder diffraction pattern comprising peaks at 6.6 ± 0.2 degrees, 20.5 ± 0.2 degrees, 22.6 ± 0.2 degrees, and 14.1 ± 0.2 degrees two theta; and
 - (vii) a crystalline form characterized by an X-ray powder diffraction pattern comprising peaks at 20.7 ± 0.2 degrees, 22.7 ± 0.2 degrees, 6.7 ± 0.2 degrees, 7.4 ± 0.2 degrees, and 14.1 ± 0.2 degrees two theta.
60. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the composition of any one of the preceding claims.
61. A method of treating a cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the composition of any one of claims 1 to 59 or the pharmaceutical composition of claim 60.
62. A method of treating a disorder mediated by EGFR in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the composition of any one of claims 1 to 59 or the pharmaceutical composition of claim 60.
63. A method of treating a disorder in a subject in need thereof, comprising:
- a) determining the presence or absence of an EGFR mutation in a biological sample isolated from the subject; and
 - b) if an EGFR mutation or double mutation is determined to be present in the subject, administering to the subject a therapeutically effective amount of the composition of any one of claims 1 to 59 or the pharmaceutical composition of claim 60.

64. The method of claim 63, wherein the EGFR mutation is a mutation in codon 790, del E746-A750, del E747-E749/A750P, del E747-S752/P753S, del E747-T751/Sins/A750P, del S752-I759, G719S, G719C, L861Q, L858R, T790M, or L858R/T790M.
65. The method of claim 63, wherein determining the presence or absence of the EGFR mutation comprises (i) amplifying EGFR nucleic acid from the biological sample and sequencing the amplified nucleic acid or (ii) detecting a mutant EGFR polypeptide in the biological sample using a binding agent to a mutant EGFR polypeptide.
66. The method of any one of claims 62 to 65, wherein the disorder is cancer.
67. The method of claim 61 or 66, wherein the cancer is colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, thyroid cancer, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chondroma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, non-small cell lung cancer, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, leukemia, acute lymphocytic leukemia and acute myelocytic leukemia (myeloblastic, promyelocytic, myelomonocytic, monocytic and erythroleukemia); chronic leukemia (chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia); and polycythemia vera, lymphoma (Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, or heavy chain disease.
68. The method of claim 61 or 66, wherein the cancer is non-small cell lung cancer, colon cancer, thyroid cancer, or ovarian cancer.
69. The method of any one of claims 61 to 68, further comprising administering an additional anti-cancer and/or cytotoxic agent.

70. A method of preparing a crystalline form of a compound of Formula I:

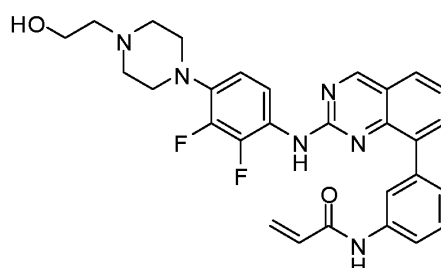


Formula I,

wherein the method comprises:

- (i) dissolving the compound of Formula I in a first solvent to obtain a mixture; and
 - (ii) crystallizing the mixture to obtain the crystalline form of the compound of Formula I.
71. The method of claim 70, wherein the first solvent comprises ethyl acetate, DCM, ethyl alcohol, or isopropyl alcohol.
72. The method of claim 70 or 71, wherein the dissolving of the compound of Formula I is performed at a temperature of about 50-90 °C, for example at a temperature of about 55-65 °C or about 75-85 °C.
73. The method of any one of claims 70-72, further comprising adding a second solvent to the mixture before crystallizing.
74. The method of claim 73, wherein the second solvent is an alkane, for example heptane.
75. The method of any one of claims 70-74, wherein crystallizing the mixture comprises heating the mixture to a temperature of about 75-85 °C and maintaining the mixture at this temperature for about 30 mins-2 hours, e.g. about 1 hour.
76. The method of claim 75, wherein crystallizing further comprises cooling the heated mixture to a temperature of about 50-60 °C and maintaining the mixture at this temperature for about 1-3 hours, e.g. about 2 hours.
77. The method of any one of claims 75-76, wherein the heating followed by the cooling is repeated at least 2 times.
78. The method of claim 77, wherein the mixture is further cooled down to about 20-30 °C and is maintained at this temperature for about 1-4 hours, e.g. about 3 hours.

79. The method of any one of claims 70-78, wherein the method comprises treating the mixture with a drying agent, decolorizing agent, and/or a silica metal scavenger.
80. The method of claim 79, wherein the drying agent is anhydrous Na_2SO_4 and/or the decolorizing agent is activated charcoal.
81. The method of claim 79 or 80, wherein the method further comprises filtering the mixture treated with the drying agent, decolorizing agent, and/or a silica metal scavenger and concentrating the filtrate.
82. The method of claim 81, wherein the concentration is performed under vacuum at a temperature of about 20-30 °C.
83. The method of claim 82, wherein the method further comprises dissolving the concentrated product in another solvent, for example in DCM.
84. The process of claim 83, wherein the mixture is further cooled down to about 20-30 °C.
85. The process of any one of claims 70-84, further comprising filtering the mixture after crystallization and/or drying the obtained crystalline form.
86. A method of making a second crystalline form of a compound of Formula I:



Formula I,

wherein the method comprises drying a first crystalline form of the compound of Formula I at a temperature of about 70-90 °C.

87. The method of claim 86, wherein the first form is Form III and the second form is Form V or wherein the first form is Form VI and the second form is Form VIII.