

CRYSTALLINE FORMS OF MRTX0902

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 63/545,142, filed, October 20, 2023, the entire content of which is hereby incorporated herein by reference.

FIELD OF THE INVENTION

[001] The present invention relates to crystalline forms of the SOS1 inhibitor (*R*)-2-methyl-3-(1-((4-methyl-7-morpholinopyrido[3,4-*d*]pyridazin-1-yl)amino)ethyl)benzonitrile (aka “MRTX0902”), pharmaceutical compositions comprising the crystalline forms, processes for preparing the crystalline forms and methods of use thereof.

BACKGROUND OF THE INVENTION

[002] The Ras family comprises v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS), neuroblastoma RAS viral oncogene homolog (NRAS), and Harvey murine sarcoma virus oncogene (HRAS) and critically regulates cellular division, growth and function in normal and altered states including cancer (see e.g., Simanshu et al. Cell, 2017. 170(1): p. 17-33; Matikas et al., Crit Rev Oncol Hematol, 2017. 110: p. 1-12). RAS proteins are activated by upstream signals, including receptor tyrosine kinases (RTKs), and transduce signals to several downstream signaling pathways such as the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinases (ERK) pathway. Hyperactivation of RAS signaling is frequently observed in cancer as a result of mutations or alterations in RAS genes or other genes in the RAS pathway. The identification of strategies to inhibit RAS and RAS signaling are predicted to be useful for the treatment of cancer and RAS-regulated disease states.

[003] RAS proteins are guanosine triphosphatases (GTPases) that cycle between an inactive, guanosine diphosphate (GDP)-bound state and an active guanosine triphosphate (GTP)-bound state. Son of sevenless homolog 1 (SOS1) is a guanine nucleotide exchange factor (GEF) that mediates the exchange of GDP for GTP, thereby activating RAS proteins. RAS proteins hydrolyze GTP to GDP through their intrinsic GTPase activity which is greatly enhanced by GTPase-activating proteins (GAPs). This regulation through GAPs and GEFs is the mechanism whereby activation and deactivation are tightly regulated under normal

conditions. Mutations at several residues in all three RAS proteins are frequently observed in cancer and result in RAS remaining predominantly in the activated state (Sanchez-Vega et al., Cell, 2018. 173: p. 321-337 Li et al., Nature Reviews Cancer, 2018. 18: p. 767-777). Mutations at codon 12 and 13 are the most frequently mutated RAS residues and prevent GAP-stimulated GTP hydrolysis by blocking the interaction of GAP proteins and RAS. Recent biochemical analyses however, demonstrated these mutated proteins still require nucleotide cycling for activation based on their intrinsic GTPase activity and/or partial sensitivity to extrinsic GTPases. As such, mutant RAS proteins are sensitive to inhibition of upstream factors such as SOS1 or SHP2, another upstream signaling molecule required for RAS activation (Hillig, 2019; Patricelli, 2016; Lito, 2016; Nichols, 2018).

[004] The three main RAS-GEF families that have been identified in mammalian cells are SOS, RAS-GRF and RAS-GRP (Rojas, 2011). RAS-GRF and RAS-GRP are expressed in the cells of the central nervous system and hematopoietic cells, respectively, while the SOS family is ubiquitously expressed and is responsible for transducing RTK signaling. The SOS family comprises SOS1 and SOS2 and these proteins share approximately 70% sequence identity. SOS1 appears to be much more active than SOS2 due to the rapid degradation of SOS2. The mouse SOS2 knockout is viable whereas the SOS1 knockout is embryonic lethal. A tamoxifen-inducible SOS1 knockout mouse model was used to interrogate the role of SOS1 and SOS2 in adult mice and demonstrated the SOS1 knockout was viable but the SOS1/2 double knockout was not viable (Baltanas, 2013) suggesting functional redundancy and that selective inhibition of SOS1 may have a sufficient therapeutic index for the treatment of SOS1 – RAS activated diseases.

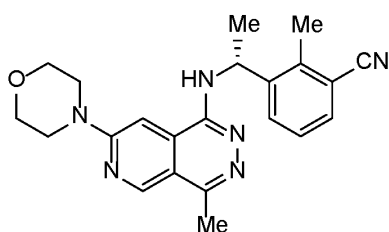
[005] SOS proteins are recruited to phosphorylated RTKs through an interaction with growth factor receptor bound protein 2 (GRB2). Recruitment to the plasma membrane places SOS in close proximity to RAS and enables SOS-mediated RAS activation. SOS proteins bind to RAS through a binding site that promotes nucleotide exchange as well as through an allosteric site that binds GTP-bound RAS-family proteins and increases the function of SOS (Freedman et al., Proc. Natl. Acad. Sci, USA 2006. 103(45): p. 16692-97). Binding to the allosteric site relieves steric occlusion of the RAS substrate binding site and is therefore required for nucleotide exchange. Retention of the active conformation at the catalytic site following interaction with the allosteric site is maintained in isolation due to strengthened interactions of key domains in the activated state. SOS1 mutations are found in Noonan syndrome and several cancers including lung adenocarcinoma, embryonal

rhabdomyosarcoma, Sertoli cell testis tumor and granular cell tumors of the skin (see e.g., Denayer, E., et al, Genes Chromosomes Cancer, 2010. 49(3): p. 242-52).

[006] GTPase-activating proteins (GAPs) are proteins that stimulate the low intrinsic GTPase activity of RAS family members and therefore converts active GTP-bound RAS proteins into inactive, GDP-bound RAS proteins (e.g., see Simanshu, D.K., Cell, 2017, Ras Proteins and their Regulators in Human Disease). While activating alterations in the GEF SOS1 occur in cancers, inactivating mutations and loss-of-function alterations in the GAPs neurofibromin 1 (NF-1) or neurofibromin 2 (NF-2) also occur creating a state where SOS1 activity is unopposed and activity downstream of the pathway through RAS proteins is elevated.

[007] Thus, the compounds of the present invention that block the interaction between SOS1 and Ras-family members prevent the recycling of KRas into the active GTP-bound form and, therefore, may provide therapeutic benefit for a wide range of cancers, particularly Ras family member-associated cancers. The compounds of the present invention offer potential therapeutic benefit as inhibitors of SOS1-KRas interaction that may be useful for negatively modulating the activity of KRas through blocking SOS1-KRas interaction in a cell for treating various forms of cancer, including Ras-associated cancer, SOS1-associated cancer and NF1/NF2-associated cancer.

[008] SOS1 inhibitor compound (R)-2-methyl-3-(1-((4-methyl-7-morpholinopyrido[3,4-d]pyridazin-1-yl)amino)ethyl)benzonitrile (also known as MRTX0902) has the following structure:



[009]

[0010] MRTX0902 is described, for example, in Example 12-10 of PCT Application WO 2021/127429.

[0011] For all the foregoing reasons, there is a need to produce a solid, crystalline form of MRTX0902, that would ideally provide enhanced dissolution rate, solubility, bioavailability,

manufacturing improvements and/or storage shelf life of the pharmaceutical composition. The present invention advantageously addresses one or more of those needs.

SUMMARY OF THE INVENTION

[0012] In one aspect of the invention, provided herein are crystalline forms of salts of the SOS1 inhibitor (*R*)-2-methyl-3-(1-((4-methyl-7-morpholinopyrido[3,4-*d*]pyridazin-1-yl)amino)ethyl)benzonitrile (“MRTX0902”).

[0013] In one embodiment, the crystalline form is crystalline Form F. In one embodiment, crystalline Form F has an X-ray powder diffraction pattern (“XRPD”) comprising at least one characteristic peak at $^{\circ}2\theta$ values selected from 9.2 ± 0.2 , 11.2 ± 0.2 , 18.5 ± 0.2 , 18.9 ± 0.2 , 19.4 ± 0.2 , 22.3 ± 0.2 , 22.5 ± 0.2 and 24.5 ± 0.2 . In some embodiments only a single characteristic peak is present. In some embodiments two characteristic peaks are present. In some embodiments three characteristic peaks are present. In some embodiments four characteristic peaks are present. In some embodiments five characteristic peaks are present. In some embodiments six characteristic peaks are present. In some embodiments seven characteristic peaks are present. In some embodiments eight characteristic peaks are present.

[0014] In one embodiment, crystalline Form F has an X-ray powder diffraction pattern comprising peaks at $^{\circ}2\theta$ values of 9.2 ± 0.2 , 11.2 ± 0.2 , 18.5 ± 0.2 , 18.9 ± 0.2 , and 24.5 ± 0.2 .

[0015] In another embodiment, crystalline Form F has an X-ray powder diffraction pattern comprising peaks at $^{\circ}2\theta$ values of 9.2 ± 0.2 , 11.2 ± 0.2 , 18.5 ± 0.2 , 18.9 ± 0.2 , 19.4 ± 0.2 , 22.3 ± 0.2 , 22.5 ± 0.2 and 24.5 ± 0.2 .

[0016] In another embodiment, crystalline Form F has an X-ray powder diffraction pattern comprising two or more peaks at $^{\circ}2\theta$ at 9.2 ± 0.2 , 11.2 ± 0.2 , 18.5 ± 0.2 , 18.9 ± 0.2 , 19.4 ± 0.2 , 22.3 ± 0.2 , 22.5 ± 0.2 and 24.5 ± 0.2 .

[0017] In another embodiment, crystalline Form F has an X-ray powder diffraction pattern comprising three or more peaks at $^{\circ}2\theta$ at 9.2 ± 0.2 , 11.2 ± 0.2 , 18.5 ± 0.2 , 18.9 ± 0.2 , 19.4 ± 0.2 , 22.3 ± 0.2 , 22.5 ± 0.2 and 24.5 ± 0.2 .

[0018] In other embodiments, crystalline Form F has an XRPD pattern substantially as shown in FIG. 1.

[0019] In one embodiment, crystalline Form F is characterized by having an endothermic peak onset at about 122.3°C as measured by differential scanning calorimetry (“DSC”). In another embodiment, crystalline Form F has a DSC thermogram substantially as shown in FIG. 2.

[0020] In another embodiment, crystalline Form F has both: 1) one or more DSC characteristics described above; and 2) an X-ray powder diffraction pattern comprising at least one peak at 2θ selected from 9.2 ± 0.2 , 11.2 ± 0.2 , 18.5 ± 0.2 , 18.9 ± 0.2 , 19.4 ± 0.2 , 22.3 ± 0.2 , 22.5 ± 0.2 and 24.5 ± 0.2 .

[0021] In another embodiment, crystalline Form F has both: 1) one or more DSC characteristics described above; and 2) an X-ray powder diffraction pattern comprising peaks at 2θ values of 9.2 ± 0.2 , 11.2 ± 0.2 , 18.5 ± 0.2 , 18.9 ± 0.2 , and 24.5 ± 0.2 .

[0022] In one embodiment, crystalline Form F is characterized by having about 8.5% weight loss until the onset of degradation at about 150°C as estimated by thermogravimetric analysis (“TGA”). In another embodiment, crystalline Form F has a TGA profile substantially as shown in FIG. 2.

[0023] In another embodiment, crystalline Form F has both: 1) one or more TGA characteristics described above; and 2) an X-ray powder diffraction pattern comprising at least one peak at 2θ selected from 9.2 ± 0.2 , 11.2 ± 0.2 , 18.5 ± 0.2 , 18.9 ± 0.2 , 19.4 ± 0.2 , 22.3 ± 0.2 , 22.5 ± 0.2 and 24.5 ± 0.2 . In another embodiment, crystalline Form F has both: 1) one or more TGA characteristics described above; and 2) an X-ray powder diffraction pattern comprising peaks at 2θ values of 9.2 ± 0.2 , 11.2 ± 0.2 , 18.5 ± 0.2 , 18.9 ± 0.2 , and 24.5 ± 0.2 .

[0024] In one embodiment, crystalline Form F is characterized by having an observed water uptake of about 0.07% at 25 °C/80% Relative Humidity (RH), as measured by dynamic vapor sorption (“DVS”).

[0025] In another embodiment, crystalline Form F has a DVS isotherm substantially as shown in FIG. 3.

[0026] In another embodiment, crystalline Form F has both: 1) one or more DVS characteristics described above; and 2) an X-ray powder diffraction pattern comprising at least one peak at 2θ selected from 9.2 ± 0.2 , 11.2 ± 0.2 , 18.5 ± 0.2 , 18.9 ± 0.2 , 19.4 ± 0.2 , 22.3 ± 0.2 , 22.5 ± 0.2 and 24.5 ± 0.2 .

[0027] In another embodiment, crystalline Form F has both: 1) one or more DVS characteristics described above; and 2) an X-ray powder diffraction pattern comprising peaks at $^{\circ}2\theta$ values of 9.2 ± 0.2 , 11.2 ± 0.2 , 18.5 ± 0.2 , 18.9 ± 0.2 , and 24.5 ± 0.2 .

[0028] In one embodiment, crystalline Form F is substantially free of residual organic solvents.

[0029] In one embodiment, the crystalline form is designated crystalline Form J.

[0030] In one embodiment, crystalline Form J has an XRPD pattern comprising at least one characteristic peak at $^{\circ}2\theta$ values selected from 9.7 ± 0.2 , 10.5 ± 0.2 , 10.8 ± 0.2 , 12.4 ± 0.2 , 15.1 ± 0.2 , 18.1 ± 0.2 , 18.6 ± 0.2 , 21.6 ± 0.2 , 22.4 ± 0.2 , and 25.9 ± 0.2 . In some embodiments only a single characteristic peak is present. In some embodiments two characteristic peaks are present. In some embodiments three characteristic peaks are present. In some embodiments four characteristic peaks are present. In some embodiments five characteristic peaks are present. In some embodiments six characteristic peaks are present. In some embodiments seven characteristic peaks are present. In some embodiments eight characteristic peaks are present. In some embodiments nine characteristic peaks are present. In some embodiments ten characteristic peaks are present.

[0031] In one embodiment, crystalline Form J has an XRPD pattern comprising peaks at $^{\circ}2\theta$ values of 9.7 ± 0.2 , 10.5 ± 0.2 , 10.8 ± 0.2 , 12.4 ± 0.2 , 15.1 ± 0.2 , 18.1 ± 0.2 , 18.6 ± 0.2 , 21.6 ± 0.2 , 22.4 ± 0.2 , and 25.9 ± 0.2 .

[0032] In another embodiment, crystalline Form J has an XRPD pattern comprising peaks at $^{\circ}2\theta$ values of 9.7 ± 0.2 , 10.5 ± 0.2 , 10.8 ± 0.2 , 12.4 ± 0.2 , 15.1 ± 0.2 , and 18.1 ± 0.2 .

[0033] In another embodiment, crystalline Form J has an XRPD pattern comprising two or more peaks at $^{\circ}2\theta$ at 9.7 ± 0.2 , 10.5 ± 0.2 , 10.8 ± 0.2 , 12.4 ± 0.2 , 15.1 ± 0.2 , 18.1 ± 0.2 , 18.6 ± 0.2 , 21.6 ± 0.2 , 22.4 ± 0.2 , and 25.9 ± 0.2 .

[0034] In another embodiment, crystalline Form J has an XRPD pattern comprising three or more peaks at $^{\circ}2\theta$ at 9.7 ± 0.2 , 10.5 ± 0.2 , 10.8 ± 0.2 , 12.4 ± 0.2 , 15.1 ± 0.2 , 18.1 ± 0.2 , 18.6 ± 0.2 , 21.6 ± 0.2 , 22.4 ± 0.2 , and 25.9 ± 0.2 .

[0035] In other embodiments, crystalline Form J has an XRPD pattern substantially as shown in FIG. 5.

[0036] In one embodiment, crystalline Form J is characterized by having an endothermic peak onset at about 271.5°C as measured by DSC. In another embodiment, crystalline Form J has a DSC thermogram substantially as shown in FIG. 6.

[0037] In another embodiment, crystalline Form J has both: 1) one or more DSC characteristics described above; and 2) an X-ray powder diffraction pattern comprising at least one peak at 2θ selected from 9.7 ± 0.2 , 10.5 ± 0.2 , 10.8 ± 0.2 , 12.4 ± 0.2 , 15.1 ± 0.2 , 18.1 ± 0.2 , 18.6 ± 0.2 , 21.6 ± 0.2 , 22.4 ± 0.2 , and 25.9 ± 0.2 .

[0038] In another embodiment, crystalline Form J has both: 1) one or more DSC characteristics described above; and 2) an XRPD pattern comprising peaks at 2θ values of 9.7 ± 0.2 , 10.5 ± 0.2 , 10.8 ± 0.2 , 12.4 ± 0.2 , 15.1 ± 0.2 , and 18.1 ± 0.2 .

[0039] In one embodiment, crystalline Form J is characterized by having about 1.0% weight loss until the onset of degradation at about 150°C as estimated by TGA. In another embodiment, crystalline Form J has a TGA profile substantially as shown in FIG. 6.

[0040] In another embodiment, crystalline Form J has both: 1) one or more TGA characteristics described above; and 2) an XRPD pattern comprising at least one peak at 2θ selected from 9.7 ± 0.2 , 10.5 ± 0.2 , 10.8 ± 0.2 , 12.4 ± 0.2 , 15.1 ± 0.2 , 18.1 ± 0.2 , 18.6 ± 0.2 , 21.6 ± 0.2 , 22.4 ± 0.2 , and 25.9 ± 0.2 . In another embodiment, crystalline Form J has both: 1) one or more TGA characteristics described above; and 2) an XRPD pattern comprising peaks at 2θ values of 9.7 ± 0.2 , 10.5 ± 0.2 , 10.8 ± 0.2 , 12.4 ± 0.2 , 15.1 ± 0.2 , and 18.1 ± 0.2 .

[0041] In one embodiment, crystalline Form J is characterized by having an observed water uptake of about 0.31% at 25 °C/80% RH, as measured by DVS.

[0042] In another embodiment, crystalline Form J has a DVS isotherm substantially as shown in FIG. 7.

[0043] In another embodiment, crystalline Form J has both: 1) one or more DVS characteristics described above; and 2) an XRPD pattern comprising at least one peak at 2θ selected from 9.7 ± 0.2 , 10.5 ± 0.2 , 10.8 ± 0.2 , 12.4 ± 0.2 , 15.1 ± 0.2 , 18.1 ± 0.2 , 18.6 ± 0.2 , 21.6 ± 0.2 , 22.4 ± 0.2 , and 25.9 ± 0.2 .

[0044] In another embodiment, crystalline Form J has both: 1) one or more DVS characteristics described above; and 2) an XRPD pattern comprising peaks at 2θ values of 9.7 ± 0.2 , 10.5 ± 0.2 , 10.8 ± 0.2 , 12.4 ± 0.2 , 15.1 ± 0.2 , and 18.1 ± 0.2 .

[0045] In one embodiment, crystalline Form J is substantially free of residual organic solvents.

[0046] In one embodiment, the crystalline forms of the present invention are at least 40%, 50%, 60%, 70%, 80%, 90% or 95% crystalline.

[0047] In another aspect of the invention, pharmaceutical compositions are provided for use in the methods comprising a therapeutically effective amount of at least one of the following: crystalline Form F and crystalline Form J, and/or a pharmaceutically acceptable excipient. The invention also encompasses pharmaceutical compositions comprising any of other crystalline forms described in the application.

[0048] The invention also encompassed any mixtures of any of the described crystalline forms with the amorphous form of MRTX0902.

[0049] In some embodiments, the pharmaceutical compositions of the present invention comprise at least 95%, or at least 80%, or at least 70%, or at least 60%, or at least 50% of crystalline Form F of MRTX0902 or salts thereof.

[0050] In some embodiments, the pharmaceutical compositions of the present invention comprise at least 95%, or at least 80%, or at least 70%, or at least 60%, or at least 50% of crystalline Form J of MRTX0902 or salts thereof.

[0051] In one aspect of the invention, provided herein are methods for inhibiting SOS1 activity in a cell, comprising contacting the cell in which inhibition of SOS1 activity is desired with a therapeutically effective amount of a crystalline form of the present invention, alone or in combination with one or more pharmaceutically acceptable excipients and/or diluents. In one embodiment, the crystalline form is crystalline Form F. In another embodiment, the crystalline form is crystalline Form J. In other embodiments, the crystalline form is any of the other forms described in this application.

[0052] In one embodiment, the crystalline form is a mixture of crystalline Form F and crystalline Form J. In another embodiment, the crystalline form is a mixture of any of the described crystalline forms with the amorphous form.

[0053] In one aspect of the invention, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective

amount of a crystalline form of MRTX0902. In one embodiment, the cancer is a SOS1-associated cancer. In one embodiment, the SOS1-associated cancer is lung cancer.

[0054] In one embodiment, the crystalline form is crystalline Form F. In another embodiment, the crystalline form is crystalline Form J. In other embodiments, the crystalline form is any of the other forms described in this application.

[0055] In one embodiment, the crystalline form is a mixture of crystalline Form F and crystalline Form J. In another embodiment, the crystalline form is a mixture of any of the described crystalline forms with the amorphous form.

[0056] Also provided herein are methods for treating cancer in a subject in need thereof, the method comprising (a) determining that cancer is associated with a SOS1 mutation (e.g., a SOS1-associated cancer) (e.g., as determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit); and (b) administering to the patient a therapeutically effective amount of a crystalline form of MRTX0902, alone or in combination with one or more pharmaceutically acceptable excipients and/or diluent.

[0057] In one embodiment, the subject is an adult patient. In one embodiment, the subject is a pediatric patient.

[0058] In some embodiments of any of the methods described herein, before treatment with the compositions or methods of the invention, the patient was treated with one or more of a chemotherapy, a targeted anticancer agent, radiation therapy, and surgery, and optionally, the prior treatment was unsuccessful; and/or the patient has been administered surgery and optionally, the surgery was unsuccessful; and/or the patient has been treated with a platinum-based chemotherapeutic agent, and optionally, the patient has been previously determined to be non-responsive to treatment with the platinum-based chemotherapeutic agent; and/or the patient has been treated with a kinase inhibitor, and optionally, the prior treatment with the kinase inhibitor was unsuccessful; and/or the patient was treated with one or more other therapeutic agent(s).

[0059] In another aspect of the invention, provided herein are process for the preparation of crystalline forms of MRTX0902. In one embodiment, the process describes the preparation of crystalline Form F. In one embodiment, the process describes the preparation of crystalline Form J. In other embodiments, the process describes the preparation of other crystalline forms of MRTX0902.

BRIEF DESCRIPTION OF THE FIGURES

[0060] FIG. 1 illustrates X-ray powder diffraction (XRPD) pattern of crystalline Form F of MRTX0902, prepared according to the methods described in the application.

[0061] FIG. 2 illustrates a combined thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) profile of crystalline Form F prepared according to the methods described in the application.

[0062] FIG. 3 illustrates a dynamic vapor sorption (DVS) isotherm profile of crystalline Form F prepared according to the methods described in the application.

[0063] FIG. 4 illustrates a ¹H-NMR profile of crystalline Form F prepared according to the methods described in the application.

[0064] FIG. 5 illustrates an XRPD pattern of crystalline Form J prepared according to the methods described in the application before and after DVS evaluation.

[0065] FIG. 6 illustrates a combined DSC and TGA profile of crystalline Form J prepared according to the methods described in the application.

[0066] FIG. 7 illustrates a DVS isotherm profile of crystalline Form J prepared according to the methods described in the application.

[0067] FIG. 8 illustrates a ¹H-NMR profile of crystalline Form J prepared according to the methods described in the application.

[0068] FIG. 9 is a compactability profile of MTRX0902 freebase crystalline Form F, freebase crystalline Form J, and fumarate crystalline Form A.

[0069] FIG. 10 is a tabletability profile of MTRX0902 freebase crystalline Form F, freebase crystalline Form J, and fumarate crystalline Form A.

[0070] FIG. 11 is a compressibility profile of MTRX0902 freebase crystalline Form F, freebase crystalline Form J, and fumarate crystalline Form A.

DETAILED DESCRIPTION OF THE INVENTION

[0071] The present invention relates to crystalline forms of the SOS1 inhibitor MRTX0902 ((*R*)-2-methyl-3-(1-((4-methyl-7-morpholinopyrido[3,4-*d*]pyridazin-1-yl)amino)ethyl)benzonitrile). In particular, the present invention relates to crystalline Form F and crystalline Form J, pharmaceutical compositions comprising the crystalline forms, processes for preparing the crystalline forms and methods of use thereof.

DEFINITIONS

[0072] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. All patents, patent applications, and publications referred to herein are incorporated by reference.

[0073] As used herein, “SOS1” refers to a mammalian Son of sevenless homolog 1 (SOS1) enzyme.

[0074] A “SOS1-associated disease or disorder” as used herein refers to diseases or disorders associated with or mediated by or having an activating SOS1 mutation. Examples of activating SOS1 mutations include SOS1 N233S and SOS1 N233Y mutations.

[0075] As used herein, “SOS1 N233S” refers to a mutant form of a mammalian SOS1 protein that contains an amino acid substitution of a serine for a glutamine at amino acid position 233. The assignment of amino acid codon and residue positions for human SOS1 is based on the amino acid sequence identified by UniProtKB/Swiss-Prot Q07889: Variant p.Gln233Ser.

[0076] As used herein, “SOS1 N233Y” refers to a mutant form of a mammalian SOS1 protein that contains an amino acid substitution of a tyrosine for a glutamine at amino acid position 233. The assignment of amino acid codon and residue positions for human SOS1 is based on the amino acid sequence identified by UniProtKB/Swiss-Prot Q07889: Variant p.Gln233Tyr.

[0077] As used herein, an “SOS1 inhibitor” refers to compounds of the present invention that are represented by Formula (I) as described herein. These compounds are capable of negatively inhibiting all or a portion of the interaction of SOS1 with Ras family mutant or

SOS1 activating mutation thereby reducing and/or modulating the nucleotide exchange activity of Ras family member - SOS1 complex.

[0078] As used herein, a "NF-1/NF-2 -associated disease or disorder" refers to diseases or disorders associated with or mediated by or having a loss-of-function mutation in the neurofibromin (NF-1) gene or neurofibromin 2 (NF-2) gene.

[0079] As used herein, a "loss-of-function mutation" refers to any point mutation(s), splice site mutation(s), fusions, nonsense mutations (an amino acid is mutated to a stop codon), in-frame or frame-shifting mutations, including insertions and deletions, and a homozygous deletion of the genes encoding the protein in a target cell or cancer cell that results in a partial or complete loss of the presence, activity and/or function of the encoded protein.

[0080] As used herein, the term "solvate" refers to a crystalline form of MRTX0902 which contains solvent.

[0081] As used herein, the term "hydrate" refers to a solvate wherein the solvent comprises water.

[0082] As used herein, the term "residual organic solvents" refers to organic volatile chemicals used or produced during the crystallization/manufacturing processes that are not completely removed during the manufacturing technique.

[0083] As used herein, the term "substantially free of residual organic solvents" means that the manufactured pharmaceutical preparation, e.g., a pharmaceutical preparation comprising a crystalline form of MRTX0902, contains less than 1.0% by weight of residual organic solvents, contains less than 0.5% by weight of residual organic solvents, contains less than 0.4% by weight of residual organic solvents, contains less than 0.3% by weight of residual organic solvents, contains less than 0.2% by weight of residual organic solvents, or contains less than 0.1% by weight of residual organic solvents.

[0084] A "SOS1-associated disease or disorder" as used herein refers to diseases or disorders associated with or mediated by or having a SOS1 mutation. A non-limiting example of a SOS1-associated disease or disorder is a SOS1-associated cancer.

[0085] As used herein, the term "subject," "individual," or "patient," used interchangeably, refers to any animal, including mammals such as mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, primates, and humans. In some embodiments, the patient is a

human. In some embodiments, the subject has experienced and/or exhibited at least one symptom of the disease or disorder to be treated and/or prevented. In some embodiments, the subject has been identified or diagnosed as having a cancer having a SOS1 mutation (e.g., as determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit). In some embodiments, the subject has a tumor that is positive for a SOS1 mutation (e.g., as determined using a regulatory agency-approved assay or kit). The subject can be a subject with a tumor(s) that is positive for a SOS1 mutation (e.g., identified as positive using a regulatory agency-approved, e.g., FDA-approved, assay or kit). The subject can be a subject whose tumors have a SOS1 mutation (e.g., where the tumor is identified as such using a regulatory agency-approved, e.g., FDA-approved, kit or assay). In some embodiments, the subject is suspected of having a SOS1 gene-associated cancer. In some embodiments, the subject has a clinical record indicating that the subject has a tumor that has a SOS1 mutation (and optionally the clinical record indicates that the subject should be treated with any of the compositions provided herein).

[0086] The term “pediatric patient” as used herein refers to a patient under the age of 16 years at the time of diagnosis or treatment. The term “pediatric” can be further be divided into various subpopulations including: neonates (from birth through the first month of life); infants (1 month up to two years of age); children (two years of age up to 12 years of age); and adolescents (12 years of age through 21 years of age (up to, but not including, the twenty-second birthday)). Berhman RE, Kliegman R, Arvin AM, Nelson WE. Nelson Textbook of Pediatrics, 15th Ed. Philadelphia: W.B. Saunders Company, 1996; Rudolph AM, et al. Rudolph’s Pediatrics, 21st Ed. New York: McGraw-Hill, 2002; and Avery MD, First LR. Pediatric Medicine, 2nd Ed. Baltimore: Williams & Wilkins; 1994.

[0087] In some embodiments of any of the methods or uses described herein, an assay is used to determine whether the patient has SOS1 mutation using a sample (e.g., a biological sample or a biopsy sample such as a paraffin-embedded biopsy sample) from a patient (e.g., a patient suspected of having a SOS1-associated cancer, a patient having one or more symptoms of a SOS1-associated cancer, and/or a patient that has an increased risk of developing a SOS1-associated cancer) can include, for example, next generation sequencing, immunohistochemistry, fluorescence microscopy, break apart FISH analysis, Southern blotting, Western blotting, FACS analysis, Northern blotting, and PCR-based amplification (e.g., RT-PCR, quantitative real-time RT-PCR, allele-specific genotyping or ddPCR). As is

well-known in the art, the assays are typically performed, e.g., with at least one labelled nucleic acid probe or at least one labelled antibody or antigen-binding fragment thereof.

[0088] The term “regulatory agency” is a country’s agency for the approval of the medical use of pharmaceutical agents with the country. For example, a non-limiting example of a regulatory agency is the U.S. Food and Drug Administration (FDA).

[0089] As used herein, a “therapeutically effective amount” of a crystalline form of MRTX0902 is an amount that is sufficient to ameliorate, or in some manner reduce a symptom or stop or reverse progression of a condition, or negatively modulate or inhibit the activity of SOS1. Such amount may be administered as a single dosage or may be administered according to a regimen, whereby it is effective.

[0090] As used herein, treatment means any manner in which the symptoms or pathology of a condition, disorder or disease are ameliorated or otherwise beneficially altered. Treatment also encompasses any pharmaceutical use of the compositions herein.

[0091] As used herein, amelioration of the symptoms of a particular disorder by administration of a particular pharmaceutical composition refers to any lessening, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the composition.

[0092] As used herein, the term “about” when used to modify a numerically defined parameter (e.g., the dose of a crystalline form of MRTX0902, or the length of treatment time described herein) means that the parameter may vary by as much as 10% below or above the stated numerical value for that parameter. For example, a dose of about 5 mg/kg may vary between 4.5 mg/kg and 5.5 mg/kg. “About” when used at the beginning of a listing of parameters is meant to modify each parameter. For example, about 0.5 mg, 0.75 mg or 1.0 mg means about 0.5 mg, about 0.75 mg or about 1.0 mg. Likewise, about 5% or more, 10% or more, 15% or more, 20% or more, and 25% or more means about 5% or more, about 10% or more, about 15% or more, about 20% or more, and about 25% or more.

[0093] As used herein, the term “about” when used in reference to XRPD peak positions refers to the inherent variability of peaks depending on the calibration of the instrument, processes used to prepare the crystalline forms of the present invention, age of the crystalline forms and the type of instrument used in the analysis. The variability of the instrumentation used for XRPD analysis was about $\pm 0.2^\circ 2\theta$.

GENERAL METHODS AND INSTRUMENTATION

[0094] The general methods outlined below were used in the exemplified Examples, unless otherwise noted.

[0095] Crystalline forms may be analyzed using any suitable analytical method or assay procedure including, but not limited to, X-Ray Powder Diffraction, NMR, differential scanning calorimetry, thermo-gravimetric analysis, and gravimetric vapor sorption to assure formation of the preferred crystalline form of MRTX0902. The crystalline form is typically produced in an amount of greater than 50% by weight isolated yield, greater than 60% by weight isolated yield, greater than 70% by weight isolated yield, greater than 80% by weight isolated yield, greater than 90% by weight isolated yield or greater than 95% by weight isolated yield.

[0096] In one embodiment, the crystalline forms of the present invention are at least 40%, 50%, 60%, 70%, 80%, 90% or 95% crystalline.

[0097] Instruments and Methods

[0098] X-ray Powder Diffraction (XRPD)

Instrument: Panalytical Empyrean

Parameters: X-Ray tube Cu ($K\alpha$ radiation); tube voltage 45 kV; tube current 40 mA

Scanning range: 2 to 40 2θ (degree)

Step size: 0.01 degree

Scanning speed: 1.31 degree (2θ) per minute

[0099] Thermogravimetric Analysis (TGA)

Instrument: TA Instruments Discovery TGA

Parameters: Ramp 10 °C per minute, 25 to 300 °C, 50 mL/min N₂ sweep

[00100] Differential Scanning Calorimetry (DSC)

Instrument: TA Instruments Discovery DSC

Parameters: Ramp 10 °C per minute, up to 300 °C

[00101] Dynamic Vapor Sorption (DVS)

[00102] Dynamic vapor sorption was performed with a TA Instruments Q5000SA DVS at 25 °C under nitrogen blow. Approximately 10-15 mg of material was used. Samples were analyzed using methods below:

[00103] For anhydrate:

0% RH to 90% RH at 10% RH

90% RH to 0% RH at 10% RH

[00104] For hydrate:

30% RH to 90% RH at 10% RH

90% RH to 0% RH at 10% RH

[00105] **Equilibrium Solubility studies**

[00106] Weigh about 10 mg material in a 4 mL vial. Gradually add the solubility medium up to 1mL. Keep the vial stirred at 25C. (If the solution became clear, add 10 more mg of material)

[00107] Sample 0.5 to 1.0 mL suspension at 24 h timepoint.

[00108] Filter each solubility sample using centrifuge at > 5000 rpm for 5 min.

[00109] Dilute the sample, as needed, and submit it for HPLC assay and analyze the residual solids via XRPD for any form change.

[00110] **Competitive Slurry Experiments**

[00111] For anhydrate:

The solvent was added to the vial containing 8-10 mg of Type J to obtain suspension, which was allowed to equilibrate for 2 h.

~5 mg of other anhydrates (Type D, G, K, and L) was added correspondingly to the same vial and stirred.

[00112] For critical water activity:

The suspension of Type F at each condition was made and allowed to equilibrate for 2 h.

~5 mg of Type J and Type A was added correspondingly to the vial and stirred.

[00113] **Polymorph Screening Experiments**

1. Slurry at RT - ~30 mg Free Base Type F was suspended in different solvents in 4 mL vials at RT. The solids in slurry were characterized by XRPD after 14 days.
2. Slurry at 50 °C - ~30 mg Free Base Type F was suspended in different solvents in 4 mL vials at 50 °C. The solids in slurry were characterized by XRPD after 6 days.
3. Anti-solvent addition - ~30 mg Free Base Type F was dissolved in different solvents to obtain saturated solutions and anti-solvents were added up to 20 time in volume. The obtained solids were characterized by XRPD.
4. Solid vapor diffusion - ~30 mg Free Base Type F was kept in 4 mL vials which were placed in 20 mL glass vials containing different solvents. The solids were characterized by XRPD after 14 days.
5. Liquid vapor diffusion - ~30 mg Free Base Type F was dissolved in different solvents to obtain saturated solutions in 4 mL vials which were placed in 20 mL glass vials containing anti-solvents. The obtained solids were characterized by XRPD after 12 days.
6. Slow evaporation at RT and 50 °C - ~30 mg Free Base Type F was dissolved in different solvents to obtain saturated solutions in 4 mL vials. The vials were covered with paraffin film with 3-5 holes and placed at RT or 50 °C for evaporation. The obtained solids were characterized by XRPD.
7. Slow cooling - ~30 mg Free Base Type F was dissolved in different solvents to obtain saturated solutions in 4 mL vials at 55 °C. The solutions were slowly cooled down to 5°C at 0.5 °C/min. The obtained solids were characterized by XRPD.
8. Polymer induced crystallization - ~30 mg Free Base Type F was dissolved in different solvents to create saturated solutions. PVP, PEO, PVA, or HPMC was added to the saturated solutions to induce heteronucleation. The obtained solids were characterized by XRPD after 12 days.

a. Solvent Abbreviation

The abbreviation of solvents used is listed in Table below

Table Solvent abbreviation list			
Abbreviation	Solvent	Abbreviation	Solvent
MTBE	Methyl tert-butyl ether	H ₂ O	Water
CPME	Cyclopentyl methyl ether	ACN	Acetonitrile
MeOH	Methanol	EtOH	Ethanol
EtOAc	Ethyl acetate	MEK	Methyl ethyl ketone
IPAc	Isopropyl acetate	MIBK	Methyl isobutyl ketone
DCM	Dichloromethane	DME	Dimethoxyethane
IPA	Isopropyl alcohol	CHCl ₃	Chloroform
2-MeTHF	2-Methyl tetrahydrofuran	THF	Tetrahydrofuran
DMSO	Dimethyl sulfoxide	--	--

b. Buffer Preparation

Buffer	Preparation Procedure
FaSSIF	1. Weigh 832.9 mg of FaSSIF Buffer Concentrate into a flask.
	2. Weigh 19.222 g of water into the flask to produce buffer.
	3. Weigh 44.8 mg of FaSSIF powder into weighing boat and then add to the flask. Rinse weighing boat with buffer to ensure all powder has been transferred.
	4. Place container on stirrer plate with PTFE. Leave to stir until fully dissolved.
FeSSIF	1. Weigh 1.628 g of FeSSIF Buffer Concentrate into a flask.
	2. Weigh 18.389 g of water into the flask to produce buffer.
	3. Weigh 224.0 mg of FeSSIF powder into weighing boat and then add to the flask. Rinse weighing boat with buffer to ensure all powder has been transferred.
	4. Place the flask on stirrer plate with PTFE. Leave to stir until fully dissolved.
SGF	1. Weigh 735.6 mg of FaSSGF Buffer Concentrate into a flask.
	2. Weigh 19.238 g of water into the flask to produce buffer.
	3. Weigh 1.2 mg of FaSSGF powder into weighing boat and then add to the flask. Rinse weighing boat with buffer to ensure all powder has been transferred.
	4. Place the flask on stirrer plate with PTFE. Leave to stir until fully dissolved.

Buffer	Preparation Procedure
0.2% Tween80 in water	1. Weigh 20 mg 0.2 % Tween 80 in 10 mL DI 2. Stir until fully dissolved
PBS buffers	1. Weigh 5.33 g PBS solid into a volumetric flask and add 196 mL H₂O 2. Add 0.2 M NaOH solution to a total volume of 250 mL 3. Split the solution into 4 portions and adjust the pH to 3.0, 4.5, 6.0, and 7.5 individually with 0.2 M NaOH and 0.2 M HCl.

V. Nuclear Magnetic Resonance

[00114] Solution proton NMR spectra were acquired using a Bruker Advance 300 MHz NMR spectrometer according to the manufacturer's instructions. Samples were prepared by dissolving about 5-10 mg of sample in DMSO-d₆ or CD₃OD containing TMS.

SOS1 INHIBITOR

[00115] In one aspect of the invention, provided herein are crystalline forms of MRTX0902, also known as (R)-2-methyl-3-(1-((4-methyl-7-morpholinopyrido[3,4-d]pyridazin-1-yl)amino)ethyl)benzonitrile.

[00116] Methods for manufacturing MRTX0902 are known. For example, MRTX0902 is described in Example 12-10 of PCT Application WO 2021/127429.

[00117] CRYSTALLINE FORMS OF MRTX0902

[00118] In one embodiment, the crystalline form is crystalline Form F. In one embodiment, crystalline Form F has an X-ray powder diffraction pattern ("XRPD") comprising at least one characteristic peak at 2θ values selected from 9.2 ± 0.2 , 11.2 ± 0.2 , 18.5 ± 0.2 , 18.9 ± 0.2 , 19.4 ± 0.2 , 22.3 ± 0.2 , 22.5 ± 0.2 and 24.5 ± 0.2 . In some embodiments only a single characteristic peak is present. In some embodiments two characteristic peaks are present. In some embodiments three characteristic peaks are present. In some embodiments four characteristic peaks are present. In some embodiments five characteristic peaks are present. In some embodiments six characteristic peaks are present. In some embodiments seven characteristic peaks are present. In some embodiments eight characteristic peaks are present.

[00119] In one embodiment, crystalline Form F has an X-ray powder diffraction pattern comprising peaks at 2θ values of 9.2 ± 0.2 , 11.2 ± 0.2 , 18.5 ± 0.2 , 18.9 ± 0.2 , and 24.5 ± 0.2 .

[00120] In another embodiment, crystalline Form F has an X-ray powder diffraction pattern comprising peaks at 2θ values of 9.2 ± 0.2 , 11.2 ± 0.2 , 18.5 ± 0.2 , 18.9 ± 0.2 , 19.4 ± 0.2 , 22.3 ± 0.2 , 22.5 ± 0.2 and 24.5 ± 0.2 .

[00121] In another embodiment, crystalline Form F has an X-ray powder diffraction pattern comprising two or more peaks at 2θ at 9.2 ± 0.2 , 11.2 ± 0.2 , 18.5 ± 0.2 , 18.9 ± 0.2 , 19.4 ± 0.2 , 22.3 ± 0.2 , 22.5 ± 0.2 and 24.5 ± 0.2 .

[00122] In another embodiment, crystalline Form F has an X-ray powder diffraction pattern comprising three or more peaks at 2θ at 9.2 ± 0.2 , 11.2 ± 0.2 , 18.5 ± 0.2 , 18.9 ± 0.2 , 19.4 ± 0.2 , 22.3 ± 0.2 , 22.5 ± 0.2 and 24.5 ± 0.2 .

[00123] In other embodiments, crystalline Form F has an XRPD pattern substantially as shown in FIG. 1.

[00124] In one embodiment, crystalline Form F is characterized by having an endothermic peak onset at about 122.3°C as measured by differential scanning calorimetry ("DSC"). In another embodiment, crystalline Form F has a DSC thermogram substantially as shown in FIG. 2.

[00125] In another embodiment, crystalline Form F has both: 1) one or more DSC characteristics described above; and 2) an X-ray powder diffraction pattern comprising at least one peak at 2θ selected from 9.2 ± 0.2 , 11.2 ± 0.2 , 18.5 ± 0.2 , 18.9 ± 0.2 , 19.4 ± 0.2 , 22.3 ± 0.2 , 22.5 ± 0.2 and 24.5 ± 0.2 .

[00126] In another embodiment, crystalline Form F has both: 1) one or more DSC characteristics described above; and 2) an X-ray powder diffraction pattern comprising peaks at 2θ values of 9.2 ± 0.2 , 11.2 ± 0.2 , 18.5 ± 0.2 , 18.9 ± 0.2 , and 24.5 ± 0.2 .

[00127] In one embodiment, crystalline Form F is characterized by having about 8.5% weight loss until the onset of degradation at about 150°C as estimated by thermogravimetric analysis ("TGA"). In another embodiment, crystalline Form F has a TGA profile substantially as shown in FIG. 2.

[00128] In another embodiment, crystalline Form F has both: 1) one or more TGA characteristics described above; and 2) an X-ray powder diffraction pattern comprising at least one peak at 2θ selected from 9.2 ± 0.2 , 11.2 ± 0.2 , 18.5 ± 0.2 , 18.9 ± 0.2 , 19.4 ± 0.2 , 22.3 ± 0.2 , 22.5 ± 0.2 and 24.5 ± 0.2 . In another embodiment, crystalline Form F has both: 1) one or more TGA characteristics described above; and 2) an X-ray powder diffraction pattern comprising peaks at 2θ values of 9.2 ± 0.2 , 11.2 ± 0.2 , 18.5 ± 0.2 , 18.9 ± 0.2 , and 24.5 ± 0.2 .

[00129] In one embodiment, crystalline Form F is characterized by having an observed water uptake of about 0.07% at 25 °C/80% Relative Humidity (RH), as measured by dynamic vapor sorption (“DVS”).

[00130] In another embodiment, crystalline Form F has a DVS isotherm substantially as shown in FIG. 3.

[00131] In another embodiment, crystalline Form F has both: 1) one or more DVS characteristics described above; and 2) an X-ray powder diffraction pattern comprising at least one peak at 2θ selected from 9.2 ± 0.2 , 11.2 ± 0.2 , 18.5 ± 0.2 , 18.9 ± 0.2 , 19.4 ± 0.2 , 22.3 ± 0.2 , 22.5 ± 0.2 and 24.5 ± 0.2 .

[00132] In another embodiment, crystalline Form F has both: 1) one or more DVS characteristics described above; and 2) an X-ray powder diffraction pattern comprising peaks at 2θ values of 9.2 ± 0.2 , 11.2 ± 0.2 , 18.5 ± 0.2 , 18.9 ± 0.2 , and 24.5 ± 0.2 .

[00133] In one embodiment, crystalline Form F is substantially free of residual organic solvents.

[00134] In one embodiment, the crystalline form is designated crystalline Form J.

[00135] In one embodiment, crystalline Form J has an XRPD pattern comprising at least one characteristic peak at 2θ values selected from 9.7 ± 0.2 , 10.5 ± 0.2 , 10.8 ± 0.2 , 12.4 ± 0.2 , 15.1 ± 0.2 , 18.1 ± 0.2 , 18.6 ± 0.2 , 21.6 ± 0.2 , 22.4 ± 0.2 , and 25.9 ± 0.2 . In some embodiments only a single characteristic peak is present. In some embodiments two characteristic peaks are present. In some embodiments three characteristic peaks are present. In some embodiments four characteristic peaks are present. In some embodiments five characteristic peaks are present. In some embodiments six characteristic peaks are present. In some embodiments seven characteristic peaks are present. In some embodiments eight characteristic peaks are

present. In some embodiments nine characteristic peaks are present. In some embodiments ten characteristic peaks are present.

[00136] In one embodiment, crystalline Form J has an XRPD pattern comprising peaks at 2θ values of 9.7 ± 0.2 , 10.5 ± 0.2 , 10.8 ± 0.2 , 12.4 ± 0.2 , 15.1 ± 0.2 , 18.1 ± 0.2 , 18.6 ± 0.2 , 21.6 ± 0.2 , 22.4 ± 0.2 , and 25.9 ± 0.2 .

[00137] In another embodiment, crystalline Form J has an XRPD pattern comprising peaks at 2θ values of 9.7 ± 0.2 , 10.5 ± 0.2 , 10.8 ± 0.2 , 12.4 ± 0.2 , 15.1 ± 0.2 , and 18.1 ± 0.2 .

[00138] In another embodiment, crystalline Form J has an XRPD pattern comprising two or more peaks at 2θ at 9.7 ± 0.2 , 10.5 ± 0.2 , 10.8 ± 0.2 , 12.4 ± 0.2 , 15.1 ± 0.2 , 18.1 ± 0.2 , 18.6 ± 0.2 , 21.6 ± 0.2 , 22.4 ± 0.2 , and 25.9 ± 0.2 .

[00139] In another embodiment, crystalline Form J has an XRPD pattern comprising three or more peaks at 2θ at 9.7 ± 0.2 , 10.5 ± 0.2 , 10.8 ± 0.2 , 12.4 ± 0.2 , 15.1 ± 0.2 , 18.1 ± 0.2 , 18.6 ± 0.2 , 21.6 ± 0.2 , 22.4 ± 0.2 , and 25.9 ± 0.2 .

[00140] In other embodiments, crystalline Form J has an XRPD pattern substantially as shown in FIG. 5.

[00141] In one embodiment, crystalline Form J is characterized by having an endothermic peak onset at about 271.5°C as measured by DSC. In another embodiment, crystalline Form J has a DSC thermogram substantially as shown in FIG. 6.

[00142] In another embodiment, crystalline Form J has both: 1) one or more DSC characteristics described above; and 2) an X-ray powder diffraction pattern comprising at least one peak at 2θ selected from 9.7 ± 0.2 , 10.5 ± 0.2 , 10.8 ± 0.2 , 12.4 ± 0.2 , 15.1 ± 0.2 , 18.1 ± 0.2 , 18.6 ± 0.2 , 21.6 ± 0.2 , 22.4 ± 0.2 , and 25.9 ± 0.2 .

[00143] In another embodiment, crystalline Form J has both: 1) one or more DSC characteristics described above; and 2) an XRPD pattern comprising peaks at 2θ values of 9.7 ± 0.2 , 10.5 ± 0.2 , 10.8 ± 0.2 , 12.4 ± 0.2 , 15.1 ± 0.2 , and 18.1 ± 0.2 .

[00144] In one embodiment, crystalline Form J is characterized by having about 1.0% weight loss until the onset of degradation at about 150°C as estimated by TGA. In another embodiment, crystalline Form J has a TGA profile substantially as shown in FIG. 6.

[00145] In another embodiment, crystalline Form J has both: 1) one or more TGA characteristics described above; and 2) an XRPD pattern comprising at least one peak at 2θ selected from 9.7 ± 0.2 , 10.5 ± 0.2 , 10.8 ± 0.2 , 12.4 ± 0.2 , 15.1 ± 0.2 , 18.1 ± 0.2 , 18.6 ± 0.2 , 21.6 ± 0.2 , 22.4 ± 0.2 , and 25.9 ± 0.2 . In another embodiment, crystalline Form J has both: 1) one or more TGA characteristics described above; and 2) an XRPD pattern comprising peaks at 2θ values of 9.7 ± 0.2 , 10.5 ± 0.2 , 10.8 ± 0.2 , 12.4 ± 0.2 , 15.1 ± 0.2 , and 18.1 ± 0.2 .

[00146] In one embodiment, crystalline Form J is characterized by having an observed water uptake of about 0.31% at 25 °C/80% RH, as measured by DVS.

[00147] In another embodiment, crystalline Form J has a DVS isotherm substantially as shown in FIG. 7.

[00148] In another embodiment, crystalline Form J has both: 1) one or more DVS characteristics described above; and 2) an XRPD pattern comprising at least one peak at 2θ selected from 9.7 ± 0.2 , 10.5 ± 0.2 , 10.8 ± 0.2 , 12.4 ± 0.2 , 15.1 ± 0.2 , 18.1 ± 0.2 , 18.6 ± 0.2 , 21.6 ± 0.2 , 22.4 ± 0.2 , and 25.9 ± 0.2 .

[00149] In another embodiment, crystalline Form J has both: 1) one or more DVS characteristics described above; and 2) an XRPD pattern comprising peaks at 2θ values of 9.7 ± 0.2 , 10.5 ± 0.2 , 10.8 ± 0.2 , 12.4 ± 0.2 , 15.1 ± 0.2 , and 18.1 ± 0.2 .

[00150] In one embodiment, crystalline Form J is substantially free of residual organic solvents.

[00151] In other embodiments, the invention provides seven more crystalline forms which are designated: Type G (anhydrate), Type I (MTBE solvate), Type K (anhydrate), Type L (anhydrate), Type M (EtOH solvate), Type N (1-BuOH solvate), and Type O (acetic acid solvate). Additionally, the invention provides five more forms (Free Base Type A-E). Four of them were also identified and fully characterized as a part of this work except Type C. Type A was a likely sesquihydrate, Type B was an IPA solvate, Type E was an isomorphic solvate (obtained from ACN and low water activity experiments (< 0.6 aw)) and Type D was identified as anhydrate.

[00152] Based on the screening results, Type J was selected as lead anhydrate and successfully reproduced at the 300 mg scale.

[00153] Hygroscopicity evaluation was conducted using DVS for hydrate form Type F and anhydrate form Type J. Based on the % weight gain between 30 % relative humidity (RH) and 80%RH, Type F was concluded as non-hygroscopic; whereas, up to 80 %RH, Type J was determined to be slightly hygroscopic. After DVS evaluation, Type F showed drop in crystallinity along with extra peaks in addition to Type F (major), suggesting a mixture of Type F (major) and a new form, but Type J showed no form change.

[00154] To determine the most stable anhydrous form among the five anhydrides (Type D, G, J, K, and L), competitive slurry experiments were conducted using two solvents (MIBK and IPAc) at two different temperatures (RT or 60 °C). The results suggested that Type J is the most stable anhydrate in methyl isobutyl ketone (MIBK) system. However, a potential intermediate solvate formation may have occurred in IPAc at 60 °C, which eventually converted to anhydrate Type G. Furthermore, competitive slurry experiments at different water activities were performed to determine the relative stability of anhydrate (Type J) and hydrate forms (Type A and F) at RT. At low water activity (< 0.6 aw), the isomorphic solvate Type E was observed. At 0.6 aw and 0.8 aw, Type A was found. When aw is 1.0, Type F was obtained.

[00155] Free Base Type F and J were subjected to solid state stability study under three stability conditions (25 °C/ 60%RH, 40 °C/75 %RH and 60 °C, open). Both forms were chemically and physically stable in the three conditions for at least two weeks. No crystallinity change was observed, except slight decrease for Type F in the 60 °C open condition after two weeks. Additionally, 24 h equilibrium solubility of Type F and Type J were measured in eight media. Both forms showed a relatively higher solubility in pH 4.5 compared to all other media tested. Type F underwent form change to a mixture of Type A + Type F in pH 6.0 buffer and FeSSIF, whereas in most cases Type J converted to Type F except in FaSSIF.

[00156] Considering the solvate propensity of this molecule, Type J was not reproducible using EtOAc, IPAc and other solvents as it resulted in solvates. Therefore, additional attempts were carried out to be able to successfully reproduce Type J. Type J was successfully reproduced twice via antisolvent addition technique by using DCM as solvent and heptane as anti-solvent.

[00157] In one embodiment, the crystalline forms of the present invention are at least 40%, 50%, 60%, 70%, 80%, 90% or 95% crystalline.

[00158] In another aspect of the invention, pharmaceutical compositions are provided for use in the methods comprising a therapeutically effective amount of at least one of the following: crystalline Form F and crystalline Form J, and/or a pharmaceutically acceptable excipient. The invention also encompasses pharmaceutical compositions comprising any of other crystalline forms described in the application.

[00159] The invention also encompassed any mixtures of any of the described crystalline forms with the amorphous form of MRTX0902.

[00160] In some embodiments, the pharmaceutical compositions of the present invention comprise at least 95%, or at least 80%, or at least 70%, or at least 60%, or at least 50% of crystalline Form F of MRTX0902 or salts thereof.

[00161] In some embodiments, the pharmaceutical compositions of the present invention comprise at least 95%, or at least 80%, or at least 70%, or at least 60%, or at least 50% of crystalline Form J of MRTX0902 or salts thereof.

[00162] In one aspect of the invention, provided herein are methods for inhibiting SOS1 activity in a cell, comprising contacting the cell in which inhibition of SOS1 activity is desired with a therapeutically effective amount of a crystalline form of the present invention, alone or in combination with one or more pharmaceutically acceptable excipients and/or diluents. In one embodiment, the crystalline form is crystalline Form F. In another embodiment, the crystalline form is crystalline Form J. In other embodiments, the crystalline form is any of the other forms described in this application.

[00163] In one embodiment, the crystalline form is a mixture of crystalline Form F and crystalline Form J. In another embodiment, the crystalline form is a mixture of any of the described crystalline forms with the amorphous form.

[00164] In one aspect of the invention, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a crystalline form of MRTX0902. In one embodiment, the cancer is a SOS1-associated cancer. In one embodiment, the SOS1-associated cancer is lung cancer.

[00165] In one embodiment, the crystalline form is crystalline Form F. In another embodiment, the crystalline form is crystalline Form J. In other embodiments, the crystalline form is any of the other forms described in this application.

[00166] In one embodiment, the crystalline form is a mixture of crystalline Form F and crystalline Form J. In another embodiment, the crystalline form is a mixture of any of the described crystalline forms with the amorphous form.

[00167] Also provided herein are methods for treating cancer in a subject in need thereof, the method comprising (a) determining that cancer is associated with a SOS1 mutation (e.g., a SOS1-associated cancer) (e.g., as determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit); and (b) administering to the patient a therapeutically effective amount of a crystalline form of MRTX0902, alone or in combination with one or more pharmaceutically acceptable excipients and/or diluent.

[00168] In one embodiment, the subject is an adult patient. In one embodiment, the subject is a pediatric patient.

[00169] In some embodiments of any of the methods described herein, before treatment with the compositions or methods of the invention, the patient was treated with one or more of a chemotherapy, a targeted anticancer agent, radiation therapy, and surgery, and optionally, the prior treatment was unsuccessful; and/or the patient has been administered surgery and optionally, the surgery was unsuccessful; and/or the patient has been treated with a platinum-based chemotherapeutic agent, and optionally, the patient has been previously determined to be non-responsive to treatment with the platinum-based chemotherapeutic agent; and/or the patient has been treated with a kinase inhibitor, and optionally, the prior treatment with the kinase inhibitor was unsuccessful; and/or the patient was treated with one or more other therapeutic agent(s).

[00170] In another aspect of the invention, provided herein are process for the preparation of crystalline forms of MRTX0902. In one embodiment, the process describes the preparation of crystalline Form F. In one embodiment, the process describes the preparation of crystalline Form J. In other embodiments, the process describes the preparation of other crystalline forms of MRTX0902.

[00171] PHARMACEUTICAL COMPOSITIONS

[00172] In another aspect, the invention provides pharmaceutical compositions comprising crystalline forms of MRTX0902 and a pharmaceutically acceptable carrier, excipient, or

diluent that may be used in the methods disclosed herein. The crystalline forms of MRTX0902 may be formulated by any method well known in the art and may be prepared for administration by any route, including, without limitation, parenteral, oral, sublingual, transdermal, topical, intranasal, intratracheal, or intrarectal. In certain embodiments, the crystalline forms of MRTX0902 are administered intravenously in a hospital setting. In one embodiment, administration may be by the oral route.

[00173] In one aspect of the invention, pharmaceutical compositions are provided for use in the methods comprising a therapeutically effective amount of at least one of the following: crystalline Form F and crystalline Form J, and/or a pharmaceutically acceptable excipient. The invention also encompasses pharmaceutical compositions comprising any of other crystalline forms described in the application.

[00174] The invention also encompassed any mixtures of any of the described crystalline forms with the amorphous form of MRTX0902.

[00175] In some embodiments, the pharmaceutical compositions of the present invention comprise at least 95%, or at least 80%, or at least 70%, or at least 60%, or at least 50% of crystalline Form F of MRTX0902 or salts thereof.

[00176] In some embodiments, the pharmaceutical compositions of the present invention comprise at least 95%, or at least 80%, or at least 70%, or at least 60%, or at least 50% of crystalline Form J of MRTX0902 or salts thereof.

[00177] The characteristics of the carrier will depend on the route of administration. As used herein, the term "pharmaceutically acceptable" means a non-toxic material that is compatible with a biological system such as a cell, cell culture, tissue, or organism, and that does not interfere with the effectiveness of the biological activity of the active ingredient(s). Thus, compositions may contain, in addition to the inhibitor, diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The preparation of pharmaceutically acceptable formulations is described in, e.g., Remington's Pharmaceutical Sciences, 18th Edition, ed. A. Gennaro, Mack Publishing Co., Easton, Pa., 1990.

[00178] The active compound is included in the pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver to a patient a therapeutically effective amount without causing serious toxic effects in the patient treated. In one embodiment, a dose of the active compound for all of the above-mentioned conditions is in the range from about 0.01 to

about 300 mg/kg, from about 0.1 to about 100 mg/kg per day, from about 0.5 to about 50 mg/kg per day, or from about 1 to about 25 mg/kg per day. A typical topical dosage will range from 0.01-3% wt/wt in a suitable carrier. The effective dosage range of the pharmaceutically acceptable derivatives can be calculated based on the weight of the parent compound to be delivered. If the derivative exhibits activity in itself, the effective dosage can be estimated as above using the weight of the derivative, or by other means known to those skilled in the art.

[00179] The pharmaceutical compositions comprising the crystalline forms of MRTX0902 or salt thereof may be used in the methods of use described herein.

[00180] METHODS OF USE

[00181] The compositions and methods provided herein may be used for the treatment of a wide variety of cancers including tumors such as lung, colorectal, pancreas, prostate, breast, brain, skin, cervical carcinomas, testicular carcinomas, etc. More particularly, cancers that may be treated by the compositions and methods of the invention include, but are not limited to, tumor types such as astrocytic, breast, cervical, colorectal, endometrial, esophageal, gastric, head and neck, hepatocellular, laryngeal, lung, oral, ovarian, prostate and thyroid carcinomas and sarcomas. More specifically, these compounds can be used to treat: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular

carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Biliary tract: gall bladder carcinoma, ampullary carcinoma, cholangiocarcinoma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochondroma (osteochondrogenous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma); Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma. In certain embodiments, the cancer is non-small cell lung cancer.

[00182] Also provided herein are methods for treating cancer in a subject in need thereof, the method comprising (a) determining that cancer is associated with a SOS1 mutation (e.g., a SOS1-associated cancer) (e.g., as determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit); and (b) administering to the patient a therapeutically effective amount of a crystalline form of MRTX0902, alone or in combination with one or more pharmaceutically acceptable excipients and/or diluent.

[00183] In one embodiment, the subject is an adult patient. In one embodiment, the subject is a pediatric patient.

[00184] In one embodiment, a crystalline form of MRTX0902 is administered as a capsule during the period of time. In embodiments of the invention, a tablet or capsule comprises about 10 mg to about 1500 mg, for instance about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1100 mg, about 1200 mg, about 1300 mg, about 1400 mg and about 1500 mg.

[00185] In one embodiment, the method comprises oral administration of a crystalline form once or twice a day on a daily basis (during a period of time), e.g., in an amount of about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1100 mg, about 1200 mg, about 1300 mg, about 1400 mg and about 1500 mg. Oral administration of a crystalline form of MRTX0902 occurs, for example, once a day on a daily basis (during a period of time). In one embodiment, MRTX0902 is orally administered once daily. In one embodiment, the crystalline form of MRTX0902 is orally administered twice daily.

[00186] One skilled in the art will recognize that, both in vivo and in vitro trials using suitable, known and generally accepted cell and/or animal models are predictive of the ability of a test compound of the combination or the combination to treat or prevent a given disorder.

[00187] One skilled in the art will further recognize that human clinical trials including first-in-human, dose ranging and efficacy trials, in healthy patients and/or those suffering from a given disorder, may be completed according to methods well known in the clinical and medical arts.

[00188] In some embodiments, the methods provided herein can result in a 1% to 99% (e.g., 1% to 98%, 1% to 95%, 1% to 90%, 1 to 85%, 1 to 80%, 1% to 75%, 1% to 70%, 1% to 65%, 1% to 60%, 1% to 55%, 1% to 50%, 1% to 45%, 1% to 40%, 1% to 35%, 1% to 30%, 1% to 25%, 1% to 20%, 1% to 15%, 1% to 10%, 1% to 5%, 2% to 99%, 2% to 90%, 2% to 85%, 2% to 80%, 2% to 75%, 2% to 70%, 2% to 65%, 2% to 60%, 2% to 55%, 2% to 50%, 2% to 45%, 2% to 40%, 2% to 35%, 2% to 30%, 2% to 25%, 2% to 20%, 2% to 15%, 2% to 10%, 2% to 5%, 4% to 99%, 4% to 95%, 4% to 90%, 4% to 85%, 4% to 80%, 4% to 75%,

4% to 70%, 4% to 65%, 4% to 60%, 4% to 55%, 4% to 50%, 4% to 45%, 4% to 40%, 4% to 35%, 4% to 30%, 4% to 25%, 4% to 20%, 4% to 15%, 4% to 10%, 6% to 99%, 6% to 95%, 6% to 90%, 6% to 85%, 6% to 80%, 6% to 75%, 6% to 70%, 6% to 65%, 6% to 60%, 6% to 55%, 6% to 50%, 6% to 45%, 6% to 40%, 6% to 35%, 6% to 30%, 6% to 25%, 6% to 20%, 6% to 15%, 6% to 10%, 8% to 99%, 8% to 95%, 8% to 90%, 8% to 85%, 8% to 80%, 8% to 75%, 8% to 70%, 8% to 65%, 8% to 60%, 8% to 55%, 8% to 50%, 8% to 45%, 8% to 40%, 8% to 35%, 8% to 30%, 8% to 25%, 8% to 20%, 8% to 15%, 10% to 99%, 10% to 95%, 10% to 90%, 10% to 85%, 10% to 80%, 10% to 75%, 10% to 70%, 10% to 65%, 10% to 60%, 10% to 55%, 10% to 50%, 10% to 45%, 10% to 40%, 10% to 35%, 10% to 30%, 10% to 25%, 10% to 20%, 10% to 15%, 15% to 99%, 15% to 95%, 15% to 90%, 15% to 85%, 15% to 80%, 15% to 75%, 15% to 70%, 15% to 65%, 15% to 60%, 15% to 55%, 15% to 50%, 15% to 45%, 15% to 40%, 15% to 35%, 15% to 30%, 15% to 25%, 15% to 20%, 20% to 99%, 20% to 95%, 20% to 90%, 20% to 85%, 20% to 80%, 20% to 75%, 20% to 70%, 20% to 65%, 20% to 60%, 20% to 55%, 20% to 50%, 20% to 45%, 20% to 40%, 20% to 35%, 20% to 30%, 20% to 25%, 25% to 99%, 25% to 95%, 25% to 90%, 25% to 85%, 25% to 80%, 25% to 75%, 25% to 70%, 25% to 65%, 25% to 60%, 25% to 55%, 25% to 50%, 25% to 45%, 25% to 40%, 25% to 35%, 25% to 30%, 30% to 99%, 30% to 95%, 30% to 90%, 30% to 85%, 30% to 80%, 30% to 75%, 30% to 70%, 30% to 65%, 30% to 60%, 30% to 55%, 30% to 50%, 30% to 45%, 30% to 40%, 30% to 35%, 35% to 99%, 35% to 95%, 35% to 90%, 35% to 85%, 35% to 80%, 35% to 75%, 35% to 70%, 35% to 65%, 35% to 60%, 35% to 55%, 35% to 50%, 35% to 45%, 35% to 40%, 40% to 99%, 40% to 95%, 40% to 90%, 40% to 85%, 40% to 80%, 40% to 75%, 40% to 70%, 40% to 65%, 40% to 60%, 40% to 55%, 40% to 50%, 40% to 45%, 45% to 99%, 45% to 95%, 45% to 90%, 45% to 85%, 45% to 80%, 45% to 75%, 45% to 70%, 45% to 65%, 45% to 60%, 45% to 55%, 45% to 50%, 50% to 99%, 50% to 95%, 50% to 90%, 50% to 85%, 50% to 80%, 50% to 75%, 50% to 70%, 50% to 65%, 50% to 60%, 50% to 55%, 55% to 99%, 55% to 95%, 55% to 90%, 55% to 85%, 55% to 80%, 55% to 75%, 55% to 70%, 55% to 65%, 55% to 60%, 60% to 99%, 60% to 95%, 60% to 90%, 60% to 85%, 60% to 80%, 60% to 75%, 60% to 70%, 60% to 65%, 65% to 99%, 65% to 95%, 65% to 90%, 65% to 85%, 65% to 80%, 65% to 75%, 65% to 70%, 65% to 60%, 70% to 99%, 70% to 95%, 70% to 90%, 70% to 85%, 70% to 80%, 70% to 75%, 75% to 99%, 75% to 95%, 75% to 90%, 75% to 85%, 75% to 80%, 80% to 99%, 80% to 95%, 80% to 90%, 80% to 85%, 85% to 99%, 85% to 95%, 85% to 90%, 90% to 99%, 90% to 95%, or 95% to 100%) reduction in the volume of one or more solid tumors in a patient

following treatment with the combination therapy for a period of time between 1 day and 2 years (e.g., between 1 day and 22 months, between 1 day and 20 months, between 1 day and 18 months, between 1 day and 16 months, between 1 day and 14 months, between 1 day and 12 months, between 1 day and 10 months, between 1 day and 9 months, between 1 day and 8 months, between 1 day and 7 months, between 1 day and 6 months, between 1 day and 5 months, between 1 day and 4 months, between 1 day and 3 months, between 1 day and 2 months, between 1 day and 1 month, between one week and 2 years, between 1 week and 22 months, between 1 week and 20 months, between 1 week and 18 months, between 1 week and 16 months, between 1 week and 14 months, between 1 week and 12 months, between 1 week and 10 months, between 1 week and 9 months, between 1 week and 8 months, between 1 week and 7 months, between 1 week and 6 months, between 1 week and 5 months, between 1 week and 4 months, between 1 week and 3 months, between 1 week and 2 months, between 1 week and 1 month, between 2 weeks and 2 years, between 2 weeks and 22 months, between 2 weeks and 20 months, between 2 weeks and 18 months, between 2 weeks and 16 months, between 2 weeks and 14 months, between 2 weeks and 12 months, between 2 weeks and 10 months, between 2 weeks and 9 months, between 2 weeks and 8 months, between 2 weeks and 7 months, between 2 weeks and 6 months, between 2 weeks and 5 months, between 2 weeks and 4 months, between 2 weeks and 3 months, between 2 weeks and 2 months, between 2 weeks and 1 month, between 1 month and 2 years, between 1 month and 22 months, between 1 month and 20 months, between 1 month and 18 months, between 1 month and 16 months, between 1 month and 14 months, between 1 month and 12 months, between 1 month and 10 months, between 1 month and 9 months, between 1 month and 8 months, between 1 month and 7 months, between 1 month and 6 months, between 1 month and 5 months, between 1 month and 4 months, between 1 month and 3 months, between 1 month and 2 months, between 2 months and 2 years, between 2 months and 22 months, between 2 months and 20 months, between 2 months and 18 months, between 2 months and 16 months, between 2 months and 14 months, between 2 months and 12 months, between 2 months and 10 months, between 2 months and 9 months, between 2 months and 8 months, between 2 months and 7 months, between 2 months and 6 months, or between 2 months and 5 months, between 2 months and 4 months, between 3 months and 2 years, between 3 months and 22 months, between 3 months and 20 months, between 3 months and 18 months, between 3 months and 16 months, between 3 months and 14 months, between 3 months and 12 months, between 3 months and 10 months, between 3 months and 8 months, between 3 months and 6 months, between 4 months and 2 years, between 4 months

and 22 months, between 4 months and 20 months, between 4 months and 18 months, between 4 months and 16 months, between 4 months and 14 months, between 4 months and 12 months, between 4 months and 10 months, between 4 months and 8 months, between 4 months and 6 months, between 6 months and 2 years, between 6 months and 22 months, between 6 months and 20 months, between 6 months and 18 months, between 6 months and 16 months, between 6 months and 14 months, between 6 months and 12 months, between 6 months and 10 months, or between 6 months and 8 months) (e.g., as compared to the size of the one or more solid tumors in the patient prior to treatment).

[00189] The phrase “time of survival” means the length of time between the identification or diagnosis of cancer (e.g., any of the cancers described herein) in a mammal by a medical professional and the time of death of the mammal (caused by the cancer). Methods of increasing the time of survival in a mammal having a cancer are described herein.

[00190] In some embodiments, any of the methods described herein can result in an increase (e.g., a 1% to 400%, 1% to 380%, 1% to 360%, 1% to 340%, 1% to 320%, 1% to 300%, 1% to 280%, 1% to 260%, 1% to 240%, 1% to 220%, 1% to 200%, 1% to 180%, 1% to 160%, 1% to 140%, 1% to 120%, 1% to 100%, 1% to 95%, 1% to 90%, 1% to 85%, 1% to 80%, 1% to 75%, 1% to 70%, 1% to 65%, 1% to 60%, 1% to 55%, 1% to 50%, 1% to 45%, 1% to 40%, 1% to 35%, 1% to 30%, 1% to 25%, 1% to 20%, 1% to 15%, 1% to 10%, 1% to 5%, 5% to 400%, 5% to 380%, 5% to 360%, 5% to 340%, 5% to 320%, 5% to 300%, 5% to 280%, 5% to 260%, 5% to 240%, 5% to 220%, 5% to 200%, 5% to 180%, 5% to 160%, 5% to 140%, 5% to 120%, 5% to 100%, 5% to 90%, 5% to 80%, 5% to 70%, 5% to 60%, 5% to 50%, 5% to 40%, 5% to 30%, 5% to 20%, 5% to 10%, 10% to 400%, 10% to 380%, 10% to 360%, 10% to 340%, 10% to 320%, 10% to 300%, 10% to 280%, 10% to 260%, 10% to 240%, 10% to 220%, 10% to 200%, 10% to 180%, 10% to 160%, 10% to 140%, 10% to 120%, 10% to 100%, 10% to 90%, 10% to 80%, 10% to 70%, 10% to 60%, 10% to 50%, 10% to 40%, 10% to 30%, 10% to 20%, 20% to 400%, 20% to 380%, 20% to 360%, 20% to 340%, 20% to 320%, 20% to 300%, 20% to 280%, 20% to 260%, 20% to 240%, 20% to 220%, 20% to 200%, 20% to 180%, 20% to 160%, 20% to 140%, 20% to 120%, 20% to 100%, 20% to 90%, 20% to 80%, 20% to 70%, 20% to 60%, 20% to 50%, 20% to 40%, 20% to 30%, 30% to 400%, 30% to 380%, 30% to 360%, 30% to 340%, 30% to 320%, 30% to 300%, 30% to 280%, 30% to 260%, 30% to 240%, 30% to 220%, 30% to 200%, 30% to 180%, 30% to 160%, 30% to 140%, 30% to 120%, 30% to 100%, 30% to 90%, 30% to 80%, 30% to 70%, 30% to 60%, 30% to 50%, 30% to 40%, 40% to 400%, 40% to 380%, 40% to

360%, 40% to 340%, 40% to 320%, 40% to 300%, 40% to 280%, 40% to 260%, 40% to 240%, 40% to 220%, 40% to 200%, 40% to 180%, 40% to 160%, 40% to 140%, 40% to 120%, 40% to 100%, 40% to 90%, 40% to 80%, 40% to 70%, 40% to 60%, 40% to 50%, 50% to 400%, 50% to 380%, 50% to 360%, 50% to 340%, 50% to 320%, 50% to 300%, 50% to 280%, 50% to 260%, 50% to 240%, 50% to 220%, 50% to 200%, 50% to 180%, 50% to 160%, 50% to 140%, 50% to 120%, 50% to 100%, 50% to 90%, 50% to 80%, 50% to 70%, 50% to 60%, 60% to 400%, 60% to 380%, 60% to 360%, 60% to 340%, 60% to 320%, 60% to 300%, 60% to 280%, 60% to 260%, 60% to 240%, 60% to 220%, 60% to 200%, 60% to 180%, 60% to 160%, 60% to 140%, 60% to 120%, 60% to 100%, 60% to 90%, 60% to 80%, 60% to 70%, 70% to 400%, 70% to 380%, 70% to 360%, 70% to 340%, 70% to 320%, 70% to 300%, 70% to 280%, 70% to 260%, 70% to 240%, 70% to 220%, 70% to 200%, 70% to 180%, 70% to 160%, 70% to 140%, 70% to 120%, 70% to 100%, 70% to 90%, 70% to 80%, 80% to 400%, 80% to 380%, 80% to 360%, 80% to 340%, 80% to 320%, 80% to 300%, 80% to 280%, 80% to 260%, 80% to 240%, 80% to 220%, 80% to 200%, 80% to 180%, 80% to 160%, 80% to 140%, 80% to 120%, 80% to 100%, 80% to 90%, 90% to 400%, 90% to 380%, 90% to 360%, 90% to 340%, 90% to 320%, 90% to 300%, 90% to 280%, 90% to 260%, 90% to 240%, 90% to 220%, 90% to 200%, 90% to 180%, 90% to 160%, 90% to 140%, 90% to 120%, 90% to 100%, 100% to 400%, 100% to 380%, 100% to 360%, 100% to 340%, 100% to 320%, 100% to 300%, 100% to 280%, 100% to 260%, 100% to 240%, 100% to 220%, 100% to 200%, 100% to 180%, 100% to 160%, 100% to 140%, 100% to 120%, 120% to 400%, 120% to 380%, 120% to 360%, 120% to 340%, 120% to 320%, 120% to 300%, 120% to 280%, 120% to 260%, 120% to 240%, 120% to 220%, 120% to 200%, 120% to 180%, 120% to 160%, 120% to 140%, 140% to 400%, 140% to 380%, 140% to 360%, 140% to 340%, 140% to 320%, 140% to 300%, 140% to 280%, 140% to 260%, 140% to 240%, 140% to 220%, 140% to 200%, 140% to 180%, 140% to 160%, 160% to 400%, 160% to 380%, 160% to 360%, 160% to 340%, 160% to 320%, 160% to 300%, 160% to 280%, 160% to 260%, 160% to 240%, 160% to 220%, 160% to 200%, 160% to 180%, 180% to 400%, 180% to 380%, 180% to 360%, 180% to 340%, 180% to 320%, 180% to 300%, 180% to 280%, 180% to 260%, 180% to 240%, 180% to 220%, 180% to 200%, 200% to 400%, 200% to 380%, 200% to 360%, 200% to 340%, 200% to 320%, 200% to 300%, 200% to 280%, 200% to 260%, 200% to 240%, 200% to 220%, 220% to 400%, 220% to 380%, 220% to 360%, 220% to 340%, 220% to 320%, 220% to 300%, 220% to 280%, 220% to 260%, 220% to 240%, 240% to 400%, 240% to 380%, 240% to 360%, 240% to 340%, 240% to 320%, 240% to 300%, 240% to 280%, 240% to 260%, 260% to 400%, 260%

to 380%, 260% to 360%, 260% to 340%, 260% to 320%, 260% to 300%, 260% to 280%, 280% to 400%, 280% to 380%, 280% to 360%, 280% to 340%, 280% to 320%, 280% to 300%, 300% to 400%, 300% to 380%, 300% to 360%, 300% to 340%, or 300% to 320%) in the time of survival of the patient (e.g., as compared to a patient having a similar cancer and administered a different treatment or not receiving a treatment).

[00191] The following Examples are intended to illustrate further certain embodiments of the invention and are not intended to limit the scope of the invention.

EXAMPLE 1

Preparation of crystalline Form F of MRTX0902

[00192] This Example illustrates the preparation of crystalline Form F of MRTX0902.

[00193] (*R*)-2-methyl-3-(1-((4-methyl-7-morpholinopyrido[3,4-*d*]pyridazin-1-yl)amino)ethyl)benzonitrile - MRTX0902 free base Type F dihydrate. To a 100 L reactor was added 4-(1-chloro-4-methylpyrido[3,4-*d*]pyridazin-7-yl)morpholine [6.12 kg, 23.1 mol, 1.0 equiv.] and *t*AmOH [61.2 L]. Then (*R*)-3-(1-aminoethyl)-2-methylbenzonitrile hydrochloride [5.02 kg, 25.5 mol, 1.1 equiv.] was added followed by MgCl₂ [3.30 kg, 34.7 mol, 1.5 equiv.] and DIPEA [9.04 kg, 69.9 mol, 3.0 equiv.]. At the end of the addition the temperature was increased to 75 °C for 1 h. The reaction was then heated to 100 °C and allowed to react until the starting material was ≤3.0 area% by HPLC analysis (typically 36 - 48 h). The reaction mixture was cooled to 25 °C and ethyl acetate [55.2 L] was added to the reaction mixture. Water [61.2 L] was added to the mixture at the controlled temperature 20 to 30 °C. The aqueous phase was discarded, and volatiles were removed under reduced pressure. Acetonitrile [36.7 L] were added to the obtained mixture and the precipitate was filtered. The filtrate was concentrated under reduced pressure. Acetonitrile [18.4 L] was added and the mixture was heated to 50 °C. Upon addition of water, seeding with Type F dihydrate and cooling to 20 °C, crystallization was observed. The crystalline material was filtered, washed once with a pre-mixed solution of water [6.1 L] and acetonitrile [3.0 L]. The wet cake was then dried at 50 °C under vacuum to afford 7.85 kg of (*R*)-2-methyl-3-(1-((4-methyl-7-morpholinopyrido[3,4-*d*]pyridazin-1-yl)amino)ethyl)benzonitrile in 87% yield (dihydrate obtained - 78% anhydrous potency adjusted yield).

[00194] M.p. 122.3 – 122.4 °C.

[00195] ¹H NMR (400 MHz, DMSO-d₆) δ 8.99 (s, 1H), 7.71 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.61 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.53 (d, *J* = 6.8 Hz, 1H), 7.40 (s, 1H), 7.31 (m, 1H), 5.52 (p, *J* = 6.9 Hz, 1H), 3.78 (dd, *J* = 5.8, 3.8 Hz, 4H), 3.68 (dd, *J* = 5.8, 3.8 Hz, 4H), 2.65 (s, 3H), 2.55 (s, 3H), 1.54 (d, *J* = 6.9 Hz, 3H).

[00196] ¹³C NMR (101 MHz, DMSO-d₆) δ 159.8, 151.2, 149.4, 147.6, 146.4, 139.2, 131.3, 129.7, 127.4, 125.1, 119.0, 114.5, 112.7, 93.6, 66.3, 47.1, 45.5, 21.9, 18.5, 17.2.

[00197] HRMS (ESI) calculated for C₂₂H₂₅N₆O: 389.2085 [M+H]⁺, Found: 389.2085.

EXAMPLE 2

Preparation of crystalline Form J of MRTX0902

[00198] (*R*)-2-methyl-3-(1-((4-methyl-7-morpholinopyrido[3,4-*d*]pyridazin-1-yl)amino)ethyl)benzonitrile - MRTX0902 free base Type J anhydrate. To a 500 mL reactor was added (*R*)-2-methyl-3-(1-((4-methyl-7-morpholinopyrido[3,4-*d*]pyridazin-1-yl)amino)ethyl)benzonitrile MRTX0902 free base Type F dihydrate [50 g, 118.0 mol, 1.0 equiv.] and EtOAc [250 mL]. The suspension was concentrated under reduced pressure at 40 °C to 3V [150 mL]. Then seed of crystalline MRTX0902 free base Type J anhydrate [0.75 g, 1.5% w/w] was added. EtOAc [200 mL] were added and the suspension was concentrated under reduced pressure at 40 °C to 3V [150 mL]. An aliquot of crystalline material in the reactor was taken for XPRD analysis. In case the polymorph change was not complete, EtOAc [200 mL] were added and concentrated under reduced pressure at 40 °C to 3V [150 mL] until XRPD analysis on aliquot confirmed complete polymorph change. The reaction mixture was then cooled to 20 °C and the crystalline material was then filtered, washed with EtOAc [100 mL] and dried at 40 °C under vacuum to afford 45.1 g of (*R*)-2-methyl-3-(1-((4-methyl-7-morpholinopyrido[3,4-*d*]pyridazin-1-yl)amino)ethyl)benzonitrile MRTX0902 free base Type J anhydrate in 98% yield.

[00199] M.p. 270.5 – 270.6 °C.

[00200] ¹H NMR (400 MHz, DMSO-d₆) δ 8.99 (s, 1H), 7.71 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.61 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.53 (d, *J* = 6.8 Hz, 1H), 7.40 (s, 1H), 7.31 (m, 1H), 5.52 (p, *J* = 6.9

Hz, 1H), 3.78 (dd, $J = 5.8, 3.8$ Hz, 4H), 3.68 (dd, $J = 5.8, 3.8$ Hz, 4H), 2.65 (s, 3H), 2.55 (s, 3H), 1.54 (d, $J = 6.9$ Hz, 3H).

[00201] ^{13}C NMR (101 MHz, DMSO- d_6) δ 159.8, 151.2, 149.4, 147.6, 146.4, 139.2, 131.3, 129.7, 127.4, 125.1, 119.0, 114.5, 112.7, 93.6, 66.3, 47.1, 45.5, 21.9, 18.5, 17.2.

[00202] HRMS (ESI) calculated for $\text{C}_{22}\text{H}_{25}\text{N}_6\text{O}$: 389.2085 $[\text{M}+\text{H}]^+$, Found: 389.2085.

EXAMPLE 3

Combined Results of Solid-State Properties, Solubility Studies, and Stability Studies of Crystalline Form F and Crystalline Form J

[00203] Table 1 summarizes the combined results of solid-state properties, solubility studies, and stability studies of Crystalline Form F and Crystalline Form J.

Table 1

Characterization summary of lead forms (Free Base Crystalline Type F and J)

Crystal Form	Free Base Type F	Free Base Type J
Batch No.	1024-18-1	1024-29-1
Form Identity	Dihydrate	Anhydrate
Crystallinity	High	High
Crystal Morphology	Crystals of irregular shape	Tiny particles
Wt. Loss by TGA (wt % loss, °C)	8.5%, 150 °C	~1.0%, 150 °C
Endo. by DSC (°C, peak temp)	122.34 and 269.80 180.10 (exo)	271.47
Water Uptake at 25 °C/80%RH*	0.07%	0.31%
Crystal Form post DVS	Type F + Type A	Type J
Equilibrium Solubility studies (mg/mL)		
0.2% Tween 80 in Water	0.10	0.06
pH 3.0	0.01	0.01
pH 4.5	0.25	0.24
pH 6.0	<0.01	<0.01
pH 7.5	<0.01	<0.01
SGF	0.08	0.07

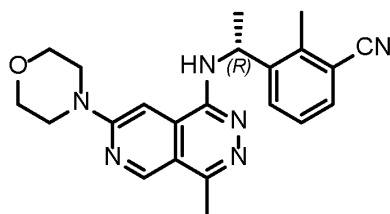
FeSSIF	0.09	0.09
FaSSIF	0.01	0.04
Stability studies (open conditions)		
25 °C / 60 %RH	Stable both physically and chemically	Stable both physically and chemically
40 °C / 75 %RH	Stable both physically and chemically	Stable both physically and chemically
60 °C	Stable both physically and chemically	Stable both physically and chemically

* % wt gained is provided between 30 % RH and 80 % RH for Type F and the ambient humidity was found to be 30% at the time of testing

EXAMPLE 4

Characterization of MRTX0902 free base starting material

[00204] The starting material MRTX0902 (Free Base, Lot#PB1700617-012-01) was received as yellow solid. The chemical structure is shown below:



[00205]

[00206] A polymorph screening of free base was performed to identify potential crystalline form with good solid-state properties suitable for further development.

[00207] The starting material was characterized by XRPD, PLM, DSC, TGA, and ¹H-NMR. The results are summarized in Table 2.

Table 2

Characterization summary of MRTX0902 Free Base starting material

Sample	Technique	Data	Results
MRTX0902 Free Base Lot #PB1700617-012-01	XRPD	Figure 1	Highly crystalline, Type F
	PLM		Crystals of irregular shape

	DSC	Figure 2	Endo peak at 122.34°C and 269.80 °C, exo peak at 180.10 °C
	TGA	Figure 2	8.5% weight loss observed before 150 °C
	NMR	Figure 4	Consistent with chemical structure in DMSO-D ₆

EXAMPLE 5

Polymorph Screen Experiments of MRTX0902

[00208] Based on the approximate solubility of MRTX0902 Free Base Type F, a total of 102 polymorph screening experiments were designed using different screening techniques that include slurry at RT, slurry at 50 °C, anti-solvent addition, solid vapor diffusion, liquid vapor diffusion, slow evaporation at RT and 50 °C, slow cooling and polymer-induced crystallization.

[00209] In total, 15 forms were discovered for this free base. The previously reported forms (Free Base Type A, B, D, and E) were reproduced in a few cases, but Type C was not observed during the screening experiments. By NMR, Type B was confirmed to be an IPA solvate, while Type E obtained from ACN and other solvents was confirmed to be isomorphic solvate. In an attempt to dehydrate Type F using DSC, Free Base Type G was obtained by heating the starting material (Type F) to 200 °C and keeping isotherm at 200 °C for 5 min followed by cooling to RT.

[00210] During the polymorph screening experiments, seven new forms (Type I-O) were identified and confirmed by distinct XRPD patterns. Type I (MTBE solvate) was obtained from antisolvent addition involving MTBE. Type J, K, and L are likely anhydrate, obtained from multiple conditions. Type M (EtOH solvate) was discovered from solid vapor diffusion in EtOH. Type N (1-BuOH solvate) was obtained from solid vapor diffusion in 1-BuOH. Type O (acetic acid solvate) was obtained from slurry at RT as well as polymer induced crystallization which used acetic acid. The solvate forms were confirmed by solution NMR.

[00211] The characterization summary of all forms (Type A to Type O) is presented in Table 3.

Table 3

Characterization summary of different forms of MRTX0902 Free Base

Crystal Form		Crystallinity by XRPD	Wt. Loss in TGA (% , °C)	Endo. in DSC (peak, °C)	Speculated Form
Free Base	Type A	High	5.97 (150)	83.0 179.7 (exo) 266.8	Likely sesquihydrate
	Type B	High	3.59 (150)	64.4 180.8 (exo) 268.3	IPA Solvate
	Type C	High	5.79 (150)	98.6 188.1 (exo) 269.2	Hydrate/Solvate
	Type D	High	Negligible weight loss	266.4	Anhydrate
	Type E	High	2.64 (150)	156.4 (exo) 271.0	ACN Solvate/ Isomorphic solvate
	Type F	High	8.55 (150)	122.3 180.1 (exo) 269.8	Dihydrate
	Type G	Moderate	0.24 (120)	269.0	Anhydrate
	Type H*	High	--	--	DCM Solvate
	Type I	Moderate	2.98 (150)	95.5 269.5	MTBE Solvate
	Type J	High	0.44 (120)	269.6	Anhydrate
	Type K	High	0.21 (120)	272.2	Likely anhydrate
	Type L	High	0.93 (150)	148.0 271.2	Likely anhydrate with solvent occlusion
	Type M	High	5.01 (150)	86.5 188.5 (exo) 271.3	EtOH Solvate
	Type N	High	6.34 (150)	115.8 175.6 (exo) 271.7	1-BuOH Solvate
	Type O	High	23.99 (200)	135.2 184.9 270.8	Acetic acid solvate

* Type H was simulated from the single crystal data.

EXAMPLE 6**Scale-up of Crystalline Form J**

[00212] The scale-up of Crystalline Form J (also referred to as Type J) was conducted via slurry method (procedure described in Table 4), wherein ~300 mg of the starting material MRTX0902 (Free Base Type F) was slurried in 3mL IPAc at RT. At the end of day 2, the

XRPD pattern suggested a mixture of Type J (major) and Type F. The sample was isolated and vacuum dried for competitive slurry experiments. The remaining isolated solids were re-slurried in mother liquor and continued the slurry conversion for additional 3 days to obtain pure Type J. The slurry was filtered, and the wet cake was vacuumed dried at 40 °C overnight and characterized using XRPD, DSC, TGA, PLM, and ¹H NMR (Table 5).

Table 4

Procedure of Free Base Type J (XD-1024-29-1, scale up batch)

Form	Procedure
Free Base Type J (XD-1024-29-1)	1. Weigh 300 mg MRTX0902 starting material in a 20 mL vial and then add 3 mL IPAc manually. 2. Stir (@300 rpm) at RT for 2 days and thick slurry was obtained. 3. Sample XRPD test, which was confirmed to be a mixture of Type J (major) and Type F. 4. Isolate the solid using a funnel filter (pore size 20 μ, polypropylene) with vacuum pull. A part of solid was used for competitive slurry experiments. 5. Put the remaining solid back to the mother liquor and stir for additional 3 days. 6. Sample XRPD test, which was confirmed to be Type J. 7. Isolate solid using a funnel filter (pore size 20 μ, polypropylene) with vacuum pull. 8. Vacuum dry the sample at 40 °C overnight

Table 5

Characterization summary of Free Base Type J (XD-1024-29-1, scale up batch)

Sample	Technique	Results
Free Base Type J (XD-1024-29-1)	XRPD	Highly crystalline
	PLM	Tiny particles
	DSC	Endo peak at 271.47 °C
	TGA	1.0% weight loss observed before 150 °C
	NMR	Consistent with chemical structure in DMSO-D ₆

EXAMPLE 7

Additional Scale-up of Crystalline Form J

[00213] To improve the reproducibility of scaling up Free Base Type J, additional trials were conducted. Crystalline Form J was reproduced at 100 mg scale, as well as successfully scaled up at 260 mg scale via anti-solvent addition method. The detailed procedure for both experiments is listed in Table 6.

Table 6

Detailed procedure for FB Type J reproduction

Form (Batch No.)	Procedure
FB Type J (XD-1024-84-2)	1. Weigh ~100 mg MRTX0902 starting material (FB Type F) in a 4 mL vial. 2. Add 0.4 mL DCM to dissolve the solid by heating. 3. Add 0.8 mL antisolvent heptane was added slowly at once. 4. The sample turned turbid during the addition of heptane and yellow gel formed on the bottom of vial. 5. Stir at RT for overnight and thin slurry was obtained. 6. Sample for XRPD test, which was confirmed to be FB Type J. 7. Vacuum dry the sample at 40 °C for 2h.
FB Type J (XD-1024-87-1)	1. Weigh ~260 mg MRTX0902 starting material (FB Type F) in a 20 mL vial. 2. Add 2.5 mL DCM to dissolve the solid by heating. 3. Add 5 mL antisolvent heptane dropwise (approximately 3.3 mL/min speed). 4. The sample turned turbid during the addition of heptane and yellow gel formed on the bottom of vial. 5. Stir at RT for 4 days and thin slurry was obtained. 6. Sample for XRPD test, which was confirmed to be FB Type J. 7. Isolate solid using a funnel filter (pore size 20 μ, polypropylene) with vacuum pull. 8. Vacuum dry the sample at 40 °C for 2h. 144 mg sample was obtained. % yield – ~61 %

EXAMPLE 8**Hygroscopicity of Crystalline Form F and Crystalline Form J**

[00214] Free Base Type F (XD-1024-18-1) showed a water uptake of ~0.07 % between 25 °C/30%RH and 25 °C/80%RH, suggesting it to be non-hygroscopic. After DVS evaluation, the XRPD pattern showed a mixture of Type F (major) and a new form due to additional peaks observed.

[00215] Free Base Type J (XD-1024-29-1) showed a water uptake of ~0.31 % between 25 °C/0%RH and 25 °C/80%RH, suggesting it to be slightly hygroscopic. No form change was observed for sample after DVS evaluation.

EXAMPLE 9**Competitive Slurry Experiments**

[00216] To determine the most stable anhydrous form among the five anhydrates (Type D, G, J, K, and L), the competitive slurry experiments were conducted using two solvents (MIBK and IPAc) at two different temperatures (RT or 60 °C). The solids were characterized by XRPD at interval of 2 days until full conversion was observed. The results were listed in Table 7.

[00217] Type J was obtained in both solvent systems at RT and MIBK at 60 °C, while Type G was observed in IPAc at 60 °C. Extra Type J seeds were added to IPAc at 60 °C experiments, which further yielded Type G at day 5. The results are suggestive of Type J as the most stable anhydrate as observed from MIBK system; however, a potential intermediate solvate formation may have occurred in IPAc at 60 °C, which eventually converted to anhydrate Type G.

Table 7

Competitive Slurry experiments with anhydrates

Exp.ID	Condition	Duration	Crystal Form
XD-1024-28-1	MIBK, RT	2 days	Type J
XD-1024-28-2	IPAc, RT	2 days	Type J
XD-1024-28-3	MIBK, 60 °C	2 days	Type J
XD-1024-28-4	IPAc, 60 °C	2 days	Type G
		4 days	Type G

[00218] To determine the critical water activity between the most stable anhydrate Type J and hydrates (Type A and F), a series of competitive slurry experiments were carried out at different water activity in acetone water system. The results were shown in Table 8. At low water activity ($< 0.6 a_w$), Type E (an isomorphic solvate) was observed. At $0.6 a_w$ and $0.8 a_w$, Type A was observed. At $1.0 a_w$, Type F was obtained.

Table 8Competitive Slurry a_w experiments with Type J and hydrates

Exp.ID	Solvent	Duration	Crystal Form
XD-1024-31-1	Acetone	1 day	Type E
		4 days	Type E
XD-1024-31-2	Acetone/H ₂ O ($a_w=0.2$)	1 day	Type E
		4 days	Type E
XD-1024-31-3	Acetone/H ₂ O ($a_w=0.4$)	1 day	Type E
		4 days	Type E
XD-1024-31-4	Acetone/H ₂ O ($a_w=0.6$)	1 day	Type A
		4 days	Type A
XD-1024-31-5	Acetone/H ₂ O ($a_w=0.8$)	1 day	Type A
		4 days	Type A
XD-1024-31-6	H ₂ O	1 day	Type F (Majorly) + Type A
		4 days	Type F (Majorly) + Type A

EXAMPLE 10**Stability Study of Crystalline Form F and Form J**

[00219] Solid state stability studies were performed to assess the physicochemical stability of Free Base Type F (XD-1024-32-1) and Type J (XD-1024-32-2) under three stability conditions (25 °C/ 60%RH, 40 °C/75 %RH and 60 °C, open). Both forms were chemically and physically stable in the three conditions for at least two weeks. No crystallinity change was observed for Type F, except slight decrease in XRPD peak intensity was observed at 60 °C open condition after two weeks.

EXAMPLE 11**Equilibrium Solubility Study of Crystalline Form F and Form J**

[00220] 24 h Equilibrium solubility studies of Free base Type F (XD-1024-35-1) and Type J (XD-1024-35-2) were performed in eight media. In pH 4.5 buffer, Type F and J showed a relatively higher solubility compared to all other media tested. The solubility results in all

media tested are reported in Table 9. Type F showed form change in pH 6.0 buffer and FeSSIF, while Type J showed form change in most cases except in the FaSSIF (Table 9).

Table 9

24 h Equilibrium solubility results of Free Base Type F and Type J

24h Equilibrium Solubility (mg/mL) in 0.2% Tween80 in Water at 25 °C (A)			
Sample	Solubility (mg/mL)	pH	FC*
Free Base Type F	0.10	5.55	No
Free Base Type J	0.06	5.42	Yes (Type F)
24h Equilibrium Solubility (mg/mL) in PB (pH 3.0) at 25 °C (B)			
Sample	Solubility (mg/mL)	pH	FC
Free Base Type F	0.01	4.18	No
Free Base Type J	0.01	4.24	Yes (Type F)
24h Equilibrium Solubility (mg/mL) in PB (pH 4.5) at 25 °C (C)			
Sample	Solubility (mg/mL)	pH	FC
Free Base Type F	0.25	4.55	No
Free Base Type J	0.24	4.63	Yes (Type F + A)
24h Equilibrium Solubility (mg/mL) in PB (pH 6.0) at 25 °C (D)			
Sample	Solubility (mg/mL)	pH	FC
Free Base Type F	<0.01	5.97	Yes (Type F + A)
Free Base Type J	<0.01	6.02	Yes (Type F + A)
24h Equilibrium Solubility (mg/mL) in PB (pH 7.5) at 25 °C (E)			
Sample	Solubility (mg/mL)	pH	FC
Free Base Type F	<0.01	7.28	No
Free Base Type J	<0.01	7.31	Yes (Type F + A)
24h Equilibrium Solubility (mg/mL) in SGF at 25 °C (F)			
Sample	Solubility (mg/mL)	pH	FC
Free Base Type F	0.08	2.53	No
Free Base Type J	0.07	2.38	Yes (Type F)
24h Equilibrium Solubility (mg/mL) in FeSSIF at 25 °C (G)			
Sample	Solubility (mg/mL)	pH	FC
Free Base Type F	0.09	4.98	Yes (Type F + A)
Free Base Type J	0.09	5.02	Yes (Type F + A)
24h Equilibrium Solubility (mg/mL) in FaSSIF at 25 °C (H)			
Sample	Solubility (mg/mL)	pH	FC
Free Base Type F	0.01	6.30	No
Free Base Type J	0.04	6.35	No

*FC: form change.

[00221]

EXAMPLE 12**Compactability, Tableability and Compressibility (CTC) profile of MRTX0902
Crystalline Forms F and J, and Fumarate Salt Form A.**

[00222] Different freebase polymorphic forms (Type F and Type J) and fumarate salt of MRTX0902 were compressed on a compaction simulator (Styl'One Evolution, MedelPharm, France) simulating a Korsch XL100 compression cycle. The main compaction pressure ranged from 0.5-30kN and powder was compressed using 8mm round flat-faced punches (Natoli Engineering). External lubrication in the form of magnesium stearate spray (Styl'One MIST) was used on the die wall and punch tips before each compression cycle. Tablet hardness and dimensions were analyzed using Sotax ST50. True density was measured using Accupyc II (Micromeritics®). Flow Function coefficient (FFc) and flowability was analyzed using Ring Shear Tester RST-XS (Dietmar Schultze). Single crystal diffraction studies were carried out on a Bruker SMART Pt135 CCD diffractometer equipped with Cu Ka radiation. The structure was solved using direct methods (SHELXT). Morphological assessment of the API forms was carried using Phenom SEM (NanoScience). Particle size determination was carried using Mastersizer 3000 (Malvern Pananalytical). The following equations were used to determine tensile strength and solid fraction of the compressed API.

Fell Newton equation [2]:

$$\text{Tensile Strength} = \frac{2F}{\pi dh}$$

where F = breaking strength (in N),

d = diameter of tablet (in mm),

h = height of tablet (in mm)

$$\text{Solid Fraction} = \frac{\text{Tablet Density}}{\text{True Density}}$$

[00223] **Results**

[00224] Significant differences were observed between the mechanical properties of the fumarate salt and free base of MRTX0902. The two freebase forms Type F and Type J also exhibit changes in crystal packing. Compressibility, Tabletability and Compactability (CTC) of Type F, Type J and Fumarate Salt Form A (two lots) of MRTX0902 reveals significant differences in the mechanical properties of free base Type J and Type F, and fumarate salt Form A. As Figures 9, 10, and 11 demonstrate, Freebase Type J and Type F both exhibited lower tabletability and compactability as compared to Fumarate Salt Form A (both lots), while Type J exhibits better tabletability and higher tensile strength at 100-200MPa tablet compression than Type F. Low compactability of Type F in comparison to Type J and fumarate salt Form A was identified as a critical factor in form selection.

[00225] In addition, Fumarate Salt Form A (lot 1) exhibited sticking to the punch tips which was significantly reduced with Fumarate Salt Form A (lot 2). Fumarate Salt Form A (lot 2) exhibited significant improvement in CTC, sticking and flowability parameters. Due to the different advantages of Freebase Type J and Fumarate Salt Form A, both were recommended for further evaluation to identify scalable processes.

[00226] While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth, and as follows in the scope of the appended claims.

WE CLAIM:

1. A crystalline form of (*R*)-2-methyl-3-(1-((4-methyl-7-morpholinopyrido[3,4-*d*]pyridazin-1-yl)amino)ethyl)benzonitrile.
2. The crystalline form according to claim 1, wherein the crystalline form is Form F having an X-ray powder diffraction pattern comprising at least one peak at $^{\circ}2\theta$ selected from 9.2 ± 0.2 , 11.2 ± 0.2 , 18.5 ± 0.2 , 18.9 ± 0.2 , 19.4 ± 0.2 , 22.3 ± 0.2 , 22.5 ± 0.2 and 24.5 ± 0.2 .
3. The crystalline form according to claim 1, wherein the crystalline form is Form F having an X-ray powder diffraction pattern comprising peaks at $^{\circ}2\theta$ values of 9.2 ± 0.2 , 11.2 ± 0.2 , 18.5 ± 0.2 , 18.9 ± 0.2 , and 24.5 ± 0.2 .
4. The crystalline form according to claim 1, wherein the crystalline form is Form F having an X-ray powder diffraction pattern comprising two or more peaks at $^{\circ}2\theta$ at 9.2 ± 0.2 , 11.2 ± 0.2 , 18.5 ± 0.2 , 18.9 ± 0.2 , 19.4 ± 0.2 , 22.3 ± 0.2 , 22.5 ± 0.2 and 24.5 ± 0.2 .
5. The crystalline form according to claim 1, wherein the crystalline form is Form F having an X-ray powder diffraction pattern comprising three or more peaks at $^{\circ}2\theta$ at 9.2 ± 0.2 , 11.2 ± 0.2 , 18.5 ± 0.2 , 18.9 ± 0.2 , 19.4 ± 0.2 , 22.3 ± 0.2 , 22.5 ± 0.2 and 24.5 ± 0.2 .
6. The crystalline form according to claim 1, wherein the crystalline form is Form F having an XRPD pattern substantially as shown in FIG. 1.
7. The crystalline form according to claim 1, wherein the crystalline form is Form F characterized by having an endothermic peak with an onset at about 122.3°C by differential scanning calorimetry (DSC).
8. The crystalline form according to any one of claims 1-7, wherein the crystalline form is Form F having a DSC thermogram substantially as shown in FIG. 2.
9. The crystalline form according to any one of claims 1-8, wherein the crystalline form is Form F having a thermogravimetric analysis ("TGA") profile substantially as shown in FIG. 2.

10. The crystalline form according to any one of claims 1-9, wherein the crystalline form is Form F and which has about 8.5% weight loss until the onset of degradation at about 150°C as estimated by TGA.
11. The crystalline form according to any one of claims 1-10, wherein the crystalline form is Form F having dynamic vapor sorption (“DVS”) isotherm substantially as shown in FIG. 3.
12. The crystalline form according to any one of claims 1-11, wherein the crystalline form is Form F which has an observed water uptake of about 0.07% at 25 °C/80% Relative Humidity (RH), as measured by dynamic vapor sorption (“DVS”).
13. The crystalline form according to claim 1, wherein the crystalline form is Form J having an X-ray powder diffraction pattern comprising at least one peak at 2θ selected from 9.7 ± 0.2 , 10.5 ± 0.2 , 10.8 ± 0.2 , 12.4 ± 0.2 , 15.1 ± 0.2 , 18.1 ± 0.2 , 18.6 ± 0.2 , 21.6 ± 0.2 , 22.4 ± 0.2 , and 25.9 ± 0.2 .
14. The crystalline form according to claim 1, wherein the crystalline form is Form J having an X-ray powder diffraction pattern comprising peaks at 2θ values of 9.7 ± 0.2 , 10.5 ± 0.2 , 10.8 ± 0.2 , 12.4 ± 0.2 , 15.1 ± 0.2 , 18.1 ± 0.2 , 18.6 ± 0.2 , 21.6 ± 0.2 , 22.4 ± 0.2 , and 25.9 ± 0.2 .
15. The crystalline form according to claim 1, wherein the crystalline form is Form J having an X-ray powder diffraction pattern comprising two or more peaks at 9.7 ± 0.2 , 10.5 ± 0.2 , 10.8 ± 0.2 , 12.4 ± 0.2 , 15.1 ± 0.2 , 18.1 ± 0.2 , 18.6 ± 0.2 , 21.6 ± 0.2 , 22.4 ± 0.2 , and 25.9 ± 0.2 .
16. The crystalline form according to claim 1, wherein the crystalline form is Form J having an X-ray powder diffraction pattern comprising three or more peaks at 9.7 ± 0.2 , 10.5 ± 0.2 , 10.8 ± 0.2 , 12.4 ± 0.2 , 15.1 ± 0.2 , 18.1 ± 0.2 , 18.6 ± 0.2 , 21.6 ± 0.2 , 22.4 ± 0.2 , and 25.9 ± 0.2 .
17. The crystalline form according to claim 1, wherein the crystalline form is Form J having an X-ray powder diffraction pattern comprising peaks at 2θ at 9.7 ± 0.2 , 10.5 ± 0.2 , 10.8 ± 0.2 , 12.4 ± 0.2 , 15.1 ± 0.2 , and 18.1 ± 0.2 .

18. The crystalline form according to claim 1, wherein the crystalline form is Form J having an XRPD pattern substantially as shown in FIG. 5.
19. The crystalline form according to any one of claims 1 or 13-18, wherein the crystalline form is Form J characterized by having an endothermic peak with an onset at about 271.5°C by differential scanning calorimetry.
20. The crystalline form according to any one of claims 1 or 13-19, wherein the crystalline form is Form J characterized by having a DSC thermogram substantially as shown in FIG. 6.
21. The crystalline form according to any one of claims 1 or 13-20, wherein the crystalline form is Form J which has a thermogravimetric analysis (“TGA”) profile substantially as shown in FIG. 6.
22. The crystalline form according to any one of claims 1 or 13-21, wherein the crystalline form is Form J and which has about 1.0% weight loss until the onset of degradation at about 150°C as estimated by TGA.
23. The crystalline form according to any one of claims 1 or 13-22, wherein the crystalline form is Form J having dynamic vapor sorption (“DVS”) isotherm substantially as shown in FIG. 7.
24. The crystalline form according to any one of claims 1 or 13-23, wherein the crystalline form is Form J which has an observed water uptake of about 0.31% at 25 °C/80% RH, as measured by DVS.
25. The crystalline form according to any one of claims 1-24, wherein the crystalline form is substantially free of residual organic solvents.
26. The crystalline form according to any one of claims 1-25, wherein the crystalline form is a hydrate or a dihydrate.
27. The crystalline form according to any one of claims 1-25, wherein the crystalline form is anhydrous.

28. A pharmaceutical composition, comprising a therapeutically effective amount of a crystalline form of (*R*)-2-methyl-3-(1-((4-methyl-7-morpholinopyrido[3,4-*d*]pyridazin-1-yl)amino)ethyl)benzonitrile according to any one of claims 1-27.
29. The pharmaceutical composition according to claim 28, further comprising at least one pharmaceutically acceptable excipient and/or diluent.
30. A method for inhibiting SOS1 activity in a cell, comprising contacting the cell in which inhibition of SOS1 activity is desired with a therapeutically effective amount of a crystalline form according to any one of claims 1-27, alone or in combination with one or more pharmaceutically acceptable excipient and/or diluent.
31. A method for treating cancer in a subject in need thereof comprising administering to the subject with a therapeutically effective amount of the crystalline form of (*R*)-2-methyl-3-(1-((4-methyl-7-morpholinopyrido[3,4-*d*]pyridazin-1-yl)amino)ethyl)benzonitrile according to any one of claims 1-27, alone or in combination with one or more pharmaceutically acceptable excipient and/or diluent.
32. The method according to claim 31, wherein the therapeutically effective amount of the crystalline form of (*R*)-2-methyl-3-(1-((4-methyl-7-morpholinopyrido[3,4-*d*]pyridazin-1-yl)amino)ethyl)benzonitrile is between about 0.01 to 100 mg/kg per day.
33. The method according to claim 31, wherein the therapeutically effective amount of (*R*)-2-methyl-3-(1-((4-methyl-7-morpholinopyrido[3,4-*d*]pyridazin-1-yl)amino)ethyl)benzonitrile is between about 0.1 to 50 mg/kg per day.
34. The method of claim 31, wherein the cancer is selected from the group consisting of Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel

(adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Biliary tract: gall bladder carcinoma, ampullary carcinoma, cholangiocarcinoma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochondroma (osteochondrogenous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma); Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma.

35. The method according to claim 31, wherein the cancer is a SOS1-associated cancer.

- 36. The method according to claim 31, wherein the cancer is non-small cell lung cancer.
- 37. The method according to claim 31, wherein the subject is an adult patient.
- 38. The method according to claim 31, wherein the subject is a pediatric patient.