

## CRYSTALLINE FORMS OF FUMARATE SALT OF MRTX0902

### CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 63/545,133, 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 fumarate salt of 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.

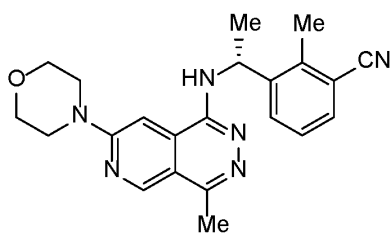
[005] SOS proteins are recruited to phosphorylated RTKs through an interaction with growth factor receptor bound protein 2 (GRB2). Recruitment to the plasma membrane places SOS in close proximity to RAS and enables SOS-mediated RAS activation. SOS proteins bind to RAS through a binding site that promotes 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] Process development for pharmaceutical compositions plays an important role for solid pharmaceutical compounds in balancing the desired pharmacological properties of the therapeutic agent. For example, identifying an appropriate crystalline forms and salt forms of the solid therapeutic agent can beneficially influence the dissolution rate, solubility, bioavailability, manufacturing, packaging and/or storage shelf life of the pharmaceutical composition. In addition, crystalline forms may be pressed into tablets for oral delivery as opposed to the need to use a capsule or spray-dry form for amorphous compounds.

[0012] For all the foregoing reasons, there is a need to produce a solid, crystalline salt 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

[0013] In one aspect of the invention, provided herein are crystalline forms of fumarate salt of the SOS1 inhibitor (*R*)-2-methyl-3-(1-((4-methyl-7-morpholinopyrido[3,4-*d*]pyridazin-1-yl)amino)ethyl)benzonitrile (“MRTX0902”).

[0014] In one embodiment, the crystalline form is fumarate crystalline Form A. In one embodiment, fumarate crystalline Form A has an X-ray powder diffraction pattern (“XRPD”) comprising at least one characteristic peak at  $2\theta$  values selected from  $6.9\pm 0.2$ ,  $13.8\pm 0.2$ ,  $14.2\pm 0.2$ ,  $15.7\pm 0.2$ ,  $18.4\pm 0.2$ ,  $23.0\pm 0.2$ ,  $23.8\pm 0.2$ ,  $26.6\pm 0.2$ ,  $27.3\pm 0.2$  and  $28.6\pm 0.2$ . 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.

[0015] In one embodiment, fumarate crystalline Form A has an X-ray powder diffraction pattern comprising peaks at  $2\theta$  values of  $6.9\pm 0.2$ ,  $13.8\pm 0.2$ ,  $14.2\pm 0.2$ ,  $18.4\pm 0.2$ , and  $23.8\pm 0.2$ .

[0016] In another embodiment, fumarate crystalline Form A has an X-ray powder diffraction pattern comprising peaks at  $^{\circ}2\theta$  values of  $6.9\pm0.2$ ,  $13.8\pm0.2$ ,  $14.2\pm0.2$ ,  $15.7\pm0.2$ ,  $18.4\pm0.2$ ,  $23.0\pm0.2$ ,  $23.8\pm0.2$ ,  $26.6\pm0.2$ ,  $27.3\pm0.2$  and  $28.6\pm0.2$ .

[0017] In another embodiment, fumarate crystalline Form A has an X-ray powder diffraction pattern comprising two or more peaks at  $^{\circ}2\theta$  at  $6.9\pm0.2$ ,  $13.8\pm0.2$ ,  $14.2\pm0.2$ ,  $15.7\pm0.2$ ,  $18.4\pm0.2$ ,  $23.0\pm0.2$ ,  $23.8\pm0.2$ ,  $26.6\pm0.2$ ,  $27.3\pm0.2$  and  $28.6\pm0.2$ .

[0018] In another embodiment, fumarate crystalline Form A has an X-ray powder diffraction pattern comprising three or more peaks at  $^{\circ}2\theta$  at  $6.9\pm0.2$ ,  $13.8\pm0.2$ ,  $14.2\pm0.2$ ,  $15.7\pm0.2$ ,  $18.4\pm0.2$ ,  $23.0\pm0.2$ ,  $23.8\pm0.2$ ,  $26.6\pm0.2$ ,  $27.3\pm0.2$  and  $28.6\pm0.2$ .

[0019] In other embodiments, fumarate crystalline Form A has an XRPD pattern substantially as shown in FIG. 1.

[0020] In one embodiment, fumarate crystalline Form A is characterized by having an endothermic peak onset at about  $248^{\circ}\text{C}$  as measured by differential scanning calorimetry ("DSC"). In another embodiment, fumarate crystalline Form A has a DSC thermogram substantially as shown in FIG. 2.

[0021] In another embodiment, fumarate crystalline Form A has both: 1) one or more DSC characteristics described above; and 2) an X-ray powder diffraction pattern comprising at least one peak at  $^{\circ}2\theta$  selected from  $6.9\pm0.2$ ,  $13.8\pm0.2$ ,  $14.2\pm0.2$ ,  $15.7\pm0.2$ ,  $18.4\pm0.2$ ,  $23.0\pm0.2$ ,  $23.8\pm0.2$ ,  $26.6\pm0.2$ ,  $27.3\pm0.2$  and  $28.6\pm0.2$ .

[0022] In another embodiment, fumarate crystalline Form A has both: 1) one or more DSC characteristics described above; and 2) an X-ray powder diffraction pattern comprising peaks at  $^{\circ}2\theta$  values of  $6.9\pm0.2$ ,  $13.8\pm0.2$ ,  $14.2\pm0.2$ ,  $18.4\pm0.2$ , and  $23.8\pm0.2$ .

[0023] In one embodiment, fumarate crystalline Form A is characterized by having about 0.02-0.25% weight loss until the onset of degradation at about  $150^{\circ}\text{C}$  as estimated by thermogravimetric analysis ("TGA"). In another embodiment, fumarate crystalline Form A has a TGA profile substantially as shown in FIG. 2.

[0024] In another embodiment, fumarate crystalline Form A has both: 1) one or more TGA characteristics described above; and 2) an X-ray powder diffraction pattern comprising at least one peak at  $^{\circ}2\theta$  selected from  $6.9\pm0.2$ ,  $13.8\pm0.2$ ,  $14.2\pm0.2$ ,  $15.7\pm0.2$ ,  $18.4\pm0.2$ ,  $23.0\pm0.2$ ,  $23.8\pm0.2$ ,  $26.6\pm0.2$ ,  $27.3\pm0.2$  and  $28.6\pm0.2$ . In another embodiment, fumarate

crystalline Form A has both: 1) one or more TGA characteristics described above; and 2) an X-ray powder diffraction pattern comprising peaks at  $2\theta$  values of  $6.9\pm0.2$ ,  $13.8\pm0.2$ ,  $14.2\pm0.2$ ,  $18.4\pm0.2$ , and  $23.8\pm0.2$ .

[0025] In one embodiment, fumarate crystalline Form A is characterized by having an observed water uptake of about 0.13-0.16 % at 25 °C/80% Relative Humidity (RH), as measured by dynamic vapor sorption (“DVS”).

[0026] In another embodiment, fumarate crystalline Form A has a DVS isotherm substantially as shown in FIG. 3.

[0027] In another embodiment, fumarate crystalline Form A has both: 1) one or more DVS characteristics described above; and 2) an X-ray powder diffraction pattern comprising at least one peak at  $2\theta$  selected from  $6.9\pm0.2$ ,  $13.8\pm0.2$ ,  $14.2\pm0.2$ ,  $15.7\pm0.2$ ,  $18.4\pm0.2$ ,  $23.0\pm0.2$ ,  $23.8\pm0.2$ ,  $26.6\pm0.2$ ,  $27.3\pm0.2$  and  $28.6\pm0.2$ .

[0028] In another embodiment, fumarate crystalline Form A has both: 1) one or more DVS characteristics described above; and 2) an X-ray powder diffraction pattern comprising peaks at  $2\theta$  values of  $6.9\pm0.2$ ,  $13.8\pm0.2$ ,  $14.2\pm0.2$ ,  $18.4\pm0.2$ , and  $23.8\pm0.2$ .

[0029] In one embodiment, fumarate crystalline Form A is substantially free of residual organic solvents.

[0030] In one embodiment, the fumarate crystalline forms of the present invention are at least 40%, 50%, 60%, 70%, 80%, 90% or 95% crystalline.

[0031] 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: fumarate crystalline Form A and a pharmaceutically acceptable excipient. The invention also encompasses pharmaceutical compositions comprising any of other fumarate crystalline forms described in the application.

[0032] The invention also encompassed any mixtures of any of the described fumarate crystalline forms with the amorphous form of MRTX0902.

[0033] In one embodiment, the fumarate crystalline form is a mixture of fumarate crystalline Form A with any of the described fumarate crystalline forms and/or with the amorphous form of fumarate MRTX0902.

[0034] 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 fumarate crystalline Form A of MRTX0902.

[0035] 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 fumarate crystalline form is fumarate crystalline Form A. In other embodiments, the fumarate crystalline form is any of the other forms described in this application.

[0036] 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 fumarate crystalline form of MRTX0902. In one embodiment, the cancer is a SOS1-associated cancer. In one embodiment, the SOS1-associated cancer is lung cancer.

[0037] In one embodiment, the fumarate crystalline form is fumarate crystalline Form A. In other embodiments, the fumarate crystalline form is any of the other forms described in this application.

[0038] 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 fumarate crystalline form of MRTX0902, alone or in combination with one or more pharmaceutically acceptable excipients and/or diluent.

[0039] In one embodiment, the subject is an adult patient. In one embodiment, the subject is a pediatric patient.

[0040] 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).

[0041] In another aspect of the invention, provided herein are process for the preparation of fumarate crystalline forms of MRTX0902. In one embodiment, the process describes the preparation of fumarate crystalline Form A. In other embodiments, the process describes the preparation of other crystalline forms of MRTX0902.

#### **BRIEF DESCRIPTION OF THE FIGURES**

[0042] FIG. 1 illustrates X-ray powder diffraction (XRPD) patterns of fumarate crystalline Form A of MRTX0902 prepared from 95% EtOH solvent system, THF/95% EtOH solvent system and fumarate salt reference.

[0043] FIG. 2A illustrates a combined thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) profile of fumarate crystalline Form A prepared from 95% EtOH solvent system.

[0044] FIG. 2B illustrates a combined TGA and DSC profile of fumarate crystalline Form A prepared from THF/95% EtOH solvent system.

[0045] FIG. 3A illustrates a dynamic vapor sorption (DVS) isotherm profile of fumarate crystalline Form A prepared from 95% EtOH solvent system.

[0046] FIG. 3B illustrates a DVS isotherm profile of fumarate crystalline Form A prepared from THF/95% EtOH solvent system.

[0047] FIG. 4 illustrates <sup>1</sup>H-NMR profiles of fumarate crystalline Form A prepared from 95% EtOH solvent system, THF/95% EtOH solvent system and fumarate salt reference.

[0048] FIG. 5 is a compactability profile of MTRX0902 freebase crystalline Form F, freebase crystalline Form J, and fumarate crystalline Form A.

[0049] FIG. 6 is a tabletability profile of MTRX0902 freebase crystalline Form F, freebase crystalline Form J, and fumarate crystalline Form A.

[0050] FIG. 7 is a compressibility profile of MTRX0902 freebase crystalline Form F, freebase crystalline Form J, and fumarate crystalline Form A.

## DETAILED DESCRIPTION OF THE INVENTION

[0051] The present invention relates to fumarate 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 fumarate crystalline Form A, pharmaceutical compositions comprising the crystalline forms, processes for preparing the crystalline forms and methods of use thereof.

## DEFINITIONS

[0052] 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.

[0053] As used herein, “SOS1” refers to a mammalian Son of sevenless homolog 1 (SOS1) enzyme.

[0054] 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.

[0055] 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.

[0056] 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.

[0057] 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.

[0058] 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.

[0059] 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.

[0060] As used herein, the term “fumarate salt” includes, but is not limited to, compositions wherein the stoichiometry of acid to base is approximately 1:1.

[0061] As used herein, the term “solvate” refers to a fumarate crystalline form of MRTX0902 which contains solvent.

[0062] As used herein, the term “hydrate” refers to a solvate wherein the solvent comprises water.

[0063] 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.

[0064] As used herein, the term “substantially free of residual organic solvents” means that the manufactured pharmaceutical preparation, e.g., a pharmaceutical preparation comprising a fumarate 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.

[0065] 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.

[0066] 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).

[0067] 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.

[0068] 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.

[0069] 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).

[0070] As used herein, a "therapeutically effective amount" of a fumarate 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.

[0071] 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.

[0072] 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.

[0073] As used herein, the term “about” when used to modify a numerically defined parameter (e.g., the dose of a fumarate 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.

[0074] 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

[0075] The general methods outlined below were used in the exemplified Examples, unless otherwise noted.

[0076] 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 fumarate 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.

[0077] In one embodiment, the crystalline forms of the present invention are at least 40%, 50%, 60%, 70%, 80%, 90% or 95% crystalline.

#### [0078] Instruments and Methods

[0079] 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  $2\theta$  (degree)

Step size: 0.01 degree

Scanning speed: 1.31 degree ( $2\theta$ ) per minute

[0080] Thermogravimetric Analysis (TGA)

Instrument: TA Instruments Discovery TGA

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

[0081] Differential Scanning Calorimetry (DSC)

Instrument: TA Instruments Discovery DSC

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

[0082] **Dynamic Vapor Sorption (DVS)**

[0083] 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:

[0084] **For anhydrate:**

0% RH to 90% RH at 10% RH

90% RH to 0% RH at 10% RH

[0085] **Nuclear Magnetic Resonance (NMR)**

Instrument: Bruker 400 MHz UltraShield

Software: Topspin 3.2

[0086] **Polymorph Screening Experiments**

1. Anti-solvent addition - ~30 mg solids were dissolved in solvent to create a saturated solution and anti-solvent was added up to 20 volume ratio, the obtained solids were characterized by XRPD.
2. Solid vapor diffusion - ~30 mg solids were kept in a 4 mL HPLC vial, the vial was placed in 20 mL glass vial containing solvent. The solids were characterized by XRPD after 14 days.

3. Liquid vapor diffusion - ~30 mg solids were dissolved in solvent to create a saturated solution in a 4 mL HPLC vial, the vial was placed in 20 mL glass vial containing anti-solvent. The obtained solids were characterized by XRPD after 10 days.
4. Slurry at RT - ~30 mg solids were slurried in different solvents in a 4 mL HPLC vial using magnetic stirrer at RT. The solids in slurry were characterized by XRPD after 7 days.
5. Slurry at 50 °C - ~30 mg solids were slurried in different solvents in a 4 mL HPLC vial using mechanical at 50 °C. The solids in slurry were characterized by XRPD after 3-5 days.
6. Slow evaporation at 50 °C - ~30 mg solids were dissolved in solvent to create a saturated solution in 4 mL HPLC vial. The vial was covered with paraffin film and 3-5 holes were created. The obtained solids were characterized by XRPD.
7. Temperature cycling - ~30 mg solids were slurried in solvent to create a suspension in 4 mL glass vial at RT. The vial was placed in a mechanical shaker with a starting temperature of 50 °C and cool it down to 5 °C for 3 cycles. The obtained solids were characterized by XRPD.
8. Slow cooling - ~30 mg solids were dissolved in solvent to create a saturated solution in 4 mL glass vial. The vial was placed in a mechanical shaker and the five temperature steps were ran, 50 °C for 3 hours, 40 °C for 4 hours, 25 °C for 4 hours, 10 °C for 5 hours and 5 °C for 5 hours . The obtained solids were characterized by XRPD.
9. Polymer induced crystallization - ~30 mg solids were dissolved in solvent to create a saturated solution. PVP, PVA, or PVC was added to saturated solution to induce heteronucleation.

***Solvent Abbreviation***

The abbreviation of solvents used is listed in Table below:

Table  
Solvent abbreviation list

| Abbreviation     | Solvent       | Abbreviation | Solvent         |
|------------------|---------------|--------------|-----------------|
| MeOH             | Methanol      | EtOH         | Ethanol         |
| EtOAc            | Ethyl acetate | THF          | Tetrahydrofuran |
| H <sub>2</sub> O | Water         | --           | --              |

*Polymorph Screening experiments and results**Table**Anti-solvent addition*

| <i>Exp.ID</i>   | <i>Solvent</i> | <i>Anti-solvent</i> | <i>Observation</i> | <i>Crystal Form</i> |
|-----------------|----------------|---------------------|--------------------|---------------------|
| NW-919-58-AS-1  | DMSO           | H2O                 | Yellow solids      | Type A              |
| NW-919-58-AS-2  |                | IPA                 | Yellow solids      | Type A              |
| NW-919-58-AS-3  |                | MEK                 | Yellow solids      | Type A              |
| NW-919-58-AS-4  | MeOH           | H2O                 | Yellow solids      | Type A              |
| NW-919-58-AS-5  |                | MTBE                | Yellow solids      | Type A              |
| NW-919-58-AS-6  |                | IPAc                | Yellow solids      | Type A              |
| NW-919-58-AS-7  | NMP            | IPAc                | Yellow solids      | Type A              |
| NW-919-58-AS-8  |                | anisole             | Off white solids   | Type B              |
| NW-919-58-AS-9  |                | H2O                 | Yellow solids      | Type A              |
| NW-919-58-AS-10 | DMA            | H2O                 | Yellow solids      | Type A              |
| NW-919-58-AS-11 |                | MTBE                | Yellow solids      | Type A              |
| NW-919-58-AS-12 |                | EtOAc               | Yellow solids      | Type A              |

*Table*

*Solid Vapor Diffusion*

| <i>Exp.ID</i>    | <i>Solvent</i>    | <i>Observation</i> | <i>Crystal Form</i> |
|------------------|-------------------|--------------------|---------------------|
| NW-919-58-SVD-1  | ACN               | Yellow solids      | Type A              |
| NW-919-58-SVD-2  | 1-Butanol         | Yellow solids      | Type A              |
| NW-919-58-SVD-3  | CHCl <sub>3</sub> | Yellow solids      | Type A              |
| NW-919-58-SVD-4  | MEK               | Yellow solids      | Type A              |
| NW-919-58-SVD-5  | Dimethoxyethane   | Yellow solids      | Type A              |
| NW-919-58-SVD-6  | 1,4-dioxane       | Yellow solids      | Type A              |
| NW-919-58-SVD-7  | EtOAc             | Yellow solids      | Type A              |
| NW-919-58-SVD-8  | THF               | Yellow solids      | Type A              |
| NW-919-58-SVD-9  | Toluene           | Yellow solids      | Type A              |
| NW-919-58-SVD-10 | water             | Yellow solids      | Type A              |
| NW-919-58-SVD-11 | MeOH              | Yellow solids      | Type A              |
| NW-919-58-SVD-12 | DMSO              | Yellow solids      | Type A              |
| NW-919-58-SVD-13 | acetic acid       | Yellow solids      | Type A              |

*Table**Liquid Vapor Diffusion*

| <i>Exp.ID</i>   | <i>Solvent</i> | <i>Anti-solvent</i> | <i>Observation</i> | <i>Crystal Form</i> |
|-----------------|----------------|---------------------|--------------------|---------------------|
| NW-919-59-LVD-1 | DMSO           | IPAc                | Yellow solids      | Type A              |
| NW-919-59-LVD-2 |                | water               | Yellow solids      | Type A              |
| NW-919-59-LVD-3 |                | MTBE                | Yellow solids      | Type A              |
| NW-919-59-LVD-4 | MeOH           | EtOAc               | Yellow solids      | Type A              |
| NW-919-59-LVD-5 |                | CPME                | Yellow solids      | Type A              |
| NW-919-59-LVD-6 |                | H <sub>2</sub> O    | Yellow solids      | Type A              |
| NW-919-59-LVD-7 | NMP            | H <sub>2</sub> O    | Yellow solids      | Type A              |
| NW-919-59-LVD-8 |                | MTBE                | Yellow solids      | Type A              |
| NW-919-59-LVD-9 |                | Acetone             | Yellow solids      | Type A              |

**Table****Slurry experiments at RT**

| <i>Exp.ID</i>    | <i>Solvent (v:v)</i> | <i>Observation</i> | <i>Crystal Form</i>                 |
|------------------|----------------------|--------------------|-------------------------------------|
| NW-919-59-S25-1  | MeOH                 | Yellow slurry      | Type A                              |
| NW-919-59-S25-2  | IPA                  | Yellow slurry      | Type A                              |
| NW-919-59-S25-3  | EtOH                 | Yellow slurry      | Type A                              |
| NW-919-59-S25-4  | Acetone              | Yellow slurry      | Type A                              |
| NW-919-59-S25-5  | Acetic acid          | Off white slurry   | Fumaric acid (substitution product) |
| NW-919-59-S25-6  | Anisole              | Off white slurry   | Type B                              |
| NW-919-59-S25-7  | CPME                 | Yellows slurry     | Type A                              |
| NW-919-59-S25-8  | DCM                  | Yellow slurry      | Type A                              |
| NW-919-59-S25-9  | DMSO/water (1:2)     | Yellow slurry      | Type A                              |
| NW-919-59-S25-10 | DMSO/MTBE (1:2)      | Yellow slurry      | Type A                              |
| NW-919-59-S25-11 | DMSO/IPAc (1:2)      | Yellow slurry      | Type A                              |
| NW-919-59-S25-12 | EtOAc                | Yellow slurry      | Type A                              |
| NW-919-59-S25-13 | IPAc                 | Yellow slurry      | Type A                              |
| NW-919-59-S25-14 | MTBE                 | Yellow slurry      | Type A                              |

|                  |                                             |               |        |
|------------------|---------------------------------------------|---------------|--------|
| NW-919-59-S25-15 | MIBK                                        | Yellow slurry | Type A |
| NW-919-59-S25-16 | MEK                                         | Yellow slurry | Type A |
| NW-919-59-S25-17 | NMP/IPA (1:2)                               | Yellow slurry | Type A |
| NW-919-59-S25-18 | NMP/H <sub>2</sub> O (1:2)                  | Yellow slurry | Type A |
| NW-919-59-S25-19 | Toluene                                     | Yellow slurry | Type A |
| NW-919-59-S25-20 | MeOH                                        | Yellow slurry | Type A |
| NW-919-59-S25-21 | MeOH/H <sub>2</sub> O (a <sub>w</sub> =0.2) | Yellow slurry | Type A |
| NW-919-59-S25-22 | MeOH/H <sub>2</sub> O (a <sub>w</sub> =0.4) | Yellow slurry | Type A |
| NW-919-59-S25-23 | MeOHH <sub>2</sub> O (a <sub>w</sub> =0.6)  | Yellow slurry | Type A |
| NW-919-59-S25-24 | MeOH/H <sub>2</sub> O (a <sub>w</sub> =0.8) | Yellow slurry | Type A |
| NW-919-59-S25-25 | H <sub>2</sub> O                            | Yellow slurry | Type A |

**Table****Slurry experiments at 50 °C**

| <i>Exp.ID</i>    | <i>Solvent (v:v)</i> | <i>Observation</i> | <i>Crystal Form</i> |
|------------------|----------------------|--------------------|---------------------|
| NW-919-60-S50-1  | ACN                  | Yellow slurry      | Type A              |
| NW-919-60-S50-2  | DMA/water (1:5)      | Yellow slurry      | Type A              |
| NW-919-60-S50-3  | DMSO/water (1:5)     | Yellow slurry      | Type A              |
| NW-919-60-S50-4  | Dimethoxyethane      | Yellow slurry      | Type A              |
| NW-919-60-S50-5  | 1,4 -dioxane         | Yellow slurry      | Type A              |
| NW-919-60-S50-6  | NPA                  | Yellow slurry      | Type A              |
| NW-919-60-S50-7  | IPAc                 | Yellow slurry      | Type A              |
| NW-919-60-S50-8  | 2-MeTHF              | Yellow slurry      | Type A              |
| NW-919-60-S50-9  | MTBE                 | Yellow slurry      | Type A              |
| NW-919-60-S50-10 | MEK                  | Yellow slurry      | Type A              |
| NW-919-60-S50-11 | MeOH                 | Yellow slurry      | Type A              |
| NW-919-60-S50-12 | NMP/CPME (1:5)       | Yellow slurry      | Type A              |
| NW-919-60-S50-13 | THF                  | Yellow slurry      | Type A              |
| NW-919-60-S50-14 | Toluene              | Yellow slurry      | Type A              |
| NW-919-60-S50-15 | H2O                  | Yellow slurry      | Type A              |

Table

Slow Evaporation at 50 °C

| <i>Exp.ID</i>  | <i>Solvent</i> | <i>Observation</i>  | <i>Crystal Form</i> |
|----------------|----------------|---------------------|---------------------|
| NW-919-60-SE-1 | DMA            | Yellow solids       | Type A              |
| NW-919-60-SE-2 | MeOH           | Yellow solids       | Type A              |
| NW-919-60-SE-3 | NMP            | Yellow solids       | Type A              |
| NW-919-60-SE-4 | DMF            | Yellow solids       | Type A              |
| NW-919-60-SE-5 | DMA/MTBE (1:2) | Yellow solids       | Type A              |
| NW-919-60-SE-6 | DMSO           | Clear needle shaped | Type C              |

Table

*Temperature cycling (5-50 °C)*

| <i>Exp.ID</i>  | <i>Solvent (v/v)</i> | <i>Observation</i> | <i>Crystal Form</i>                 |
|----------------|----------------------|--------------------|-------------------------------------|
| NW-919-60-TC-1 | Acetic acid          | Off white solids   | Fumaric acid (substitution product) |
| NW-919-60-TC-2 | MeOH                 | Yellow solids      | Type A                              |
| NW-919-60-TC-3 | DMA/MTBE (1:2)       | Yellow solids*     | Type A                              |
| NW-919-60-TC-4 | DMSO/IPAc (1:2)      | Yellow solids*     | Type A                              |
| NW-919-60-TC-5 | DMF/IPA (1:2)        | Yellow solids      | Type A                              |
| NW-919-60-TC-6 | DMA/THF (1:2)        | Yellow solids*     | Type A                              |
| NW-919-60-TC-7 | NMP/MEK              | Yellow solids      | Type A                              |

*\* clear solution after temperature cycling was subjected to evaporation at 5 °C*

*Table**Slow Cooling*

| <i>Exp.ID</i>  | <i>Solvent (v:v)</i>       | <i>Observation</i> | <i>Crystal Form</i> |
|----------------|----------------------------|--------------------|---------------------|
| NW-919-61-SC-1 | MeOH                       | Yellow solids      | Type A              |
| NW-919-61-SC-2 | DMSO:MTBE (1:2)            | Yellow solids*     | Type A              |
| NW-919-61-SC-3 | DMSO:Dimethoxyethane (1:2) | Yellow solids*     | Type A              |
| NW-919-61-SC-4 | DMA/toluene (1:2)          | Yellow solids      | Type A              |
| NW-919-61-SC-5 | NMP                        | Yellos solids*     | Type A              |
| NW-919-61-SC-6 | NMP/MTBE (1:2)             | Yellow solids      | Type A              |

*\* clear solution after slow cooling was subjected to evaporation at 5 °C*

*Table**Polymer induced crystallizaiton*

| <i>Exp.ID</i>   | <i>Solvent</i> | <i>Polymer</i> | <i>Observation</i> | <i>Crystal Form</i>                 |
|-----------------|----------------|----------------|--------------------|-------------------------------------|
| NW-919-61-PIC-1 | MeOH           | PVC            | Yellow solids      | Type A                              |
| NW-919-61-PIC-2 | acetic acid    | PVC            | Off white solids   | Fumaric acid (substitution product) |
| NW-919-61-PIC-3 | DMA/DME (1:1)  | PVP            | Yellow solids      | Type A                              |
| NW-919-61-PIC-4 | DMA            | PVP            | Yellow solids      | Type A                              |
| NW-919-61-PIC-5 | NMP            | PVP            | Yellow solids      | Type A                              |
| NW-919-61-PIC-6 | MeOH           | PVP            | Yellow solids      | Type A                              |
| NW-919-61-PIC-7 | DMSO           | PVA            | Needle/rod shaped  | Type C                              |

***Approximate Solubility (MRTX0902 Fumarate salt)***

***Table***

***Approximate solubility of MRTX0902 Fumarate at RT***

| Exp ID       | Solvent (ICH Class)        | b.p (°C) | Solubility (mg/mL) |
|--------------|----------------------------|----------|--------------------|
| NW-919-56-1  | Acetone (III)              | 56.5     | S<1.4              |
| NW-919-56-2  | Acetonitrile (ACN) (II)    | 82.0     | S<1.4              |
| NW-919-56-3  | 1-Butanol (III)            | 117.7    | S<1.7              |
| NW-919-56-4  | DCM (II)                   | 39.6     | S<1.5              |
| NW-919-56-5  | Dimethoxyethane (DME) (II) | 85.0     | S<1.6              |
| NW-919-56-6  | DMSO (III)                 | 189.0    | 44.0<S<88.0        |
| NW-919-56-7  | Ethanol (EtOH) (III)       | 78.4     | S<1.4              |
| NW-919-56-8  | EtOAc (III)                | 77.1     | S<1.4              |
| NW-919-56-9  | Anisole (III)              | 153.8    | S<1.5              |
| NW-919-56-10 | n-Heptane (III)            | 98.5     | S<1.9              |
| NW-919-56-11 | IPA (III)                  | 82.5     | S<1.9              |

| Exp ID       | Solvent (ICH Class)                | b.p (°C) | Solubility (mg/mL) |
|--------------|------------------------------------|----------|--------------------|
| NW-919-56-12 | Isopropyl acetate (IPAC) (III)     | 88.4     | S<1.6              |
| NW-919-56-13 | Methanol (MeOH) (II)               | 64.7     | 2.9<S<4.3          |
| NW-919-56-14 | Methylisobutyl Ketone (MIBK) (III) | 106.0    | S<1.6              |
| NW-919-56-15 | 2-Methyl THF                       | 80.2     | S<1.6              |
| NW-919-56-16 | MTBE (III)                         | 55.2     | S<2.0              |
| NW-919-56-17 | THF (II)                           | 66.0     | S<1.4              |
| NW-919-56-18 | Toluene (II)                       | 110.6    | S<1.6              |
| NW-919-56-19 | N-Methyl Pyrrolidone (NMP) (II)    | 202      | 43.0<S<86.0        |
| NW-919-56-20 | Water (III)                        | 100      | S<1.8              |

SOS1 INHIBITOR

[0087] In one aspect of the invention, provided herein are fumarate 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.

[0088] Methods for manufacturing MRTX0902 are known. For example, MRTX0902 is described in Example 12-10 of PCT Application WO 2021/127429.

[0089] FUMARATE CRYSTALLINE FORMS OF MRTX0902

[0090] In one embodiment, the crystalline form is fumarate crystalline Form A. In one embodiment, fumarate crystalline Form A has an X-ray powder diffraction pattern ("XRPD") comprising at least one characteristic peak at  $2\theta$  values selected from  $6.9 \pm 0.2$ ,  $13.8 \pm 0.2$ ,  $14.2 \pm 0.2$ ,  $15.7 \pm 0.2$ ,  $18.4 \pm 0.2$ ,  $23.0 \pm 0.2$ ,  $23.8 \pm 0.2$ ,  $26.6 \pm 0.2$ ,  $27.3 \pm 0.2$  and  $28.6 \pm 0.2$ . 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.

[0091] In one embodiment, fumarate crystalline Form A has an X-ray powder diffraction pattern comprising peaks at  $2\theta$  values of  $6.9 \pm 0.2$ ,  $13.8 \pm 0.2$ ,  $14.2 \pm 0.2$ ,  $18.4 \pm 0.2$ , and  $23.8 \pm 0.2$ .

[0092] In another embodiment, fumarate crystalline Form A has an X-ray powder diffraction pattern comprising peaks at  $2\theta$  values of  $6.9 \pm 0.2$ ,  $13.8 \pm 0.2$ ,  $14.2 \pm 0.2$ ,  $15.7 \pm 0.2$ ,  $18.4 \pm 0.2$ ,  $23.0 \pm 0.2$ ,  $23.8 \pm 0.2$ ,  $26.6 \pm 0.2$ ,  $27.3 \pm 0.2$  and  $28.6 \pm 0.2$ .

[0093] In another embodiment, fumarate crystalline Form A has an X-ray powder diffraction pattern comprising two or more peaks at  $2\theta$  at  $6.9 \pm 0.2$ ,  $13.8 \pm 0.2$ ,  $14.2 \pm 0.2$ ,  $15.7 \pm 0.2$ ,  $18.4 \pm 0.2$ ,  $23.0 \pm 0.2$ ,  $23.8 \pm 0.2$ ,  $26.6 \pm 0.2$ ,  $27.3 \pm 0.2$  and  $28.6 \pm 0.2$ .

[0094] In another embodiment, fumarate crystalline Form A has an X-ray powder diffraction pattern comprising three or more peaks at  $2\theta$  at  $6.9 \pm 0.2$ ,  $13.8 \pm 0.2$ ,  $14.2 \pm 0.2$ ,  $15.7 \pm 0.2$ ,  $18.4 \pm 0.2$ ,  $23.0 \pm 0.2$ ,  $23.8 \pm 0.2$ ,  $26.6 \pm 0.2$ ,  $27.3 \pm 0.2$  and  $28.6 \pm 0.2$ .

[0095] In other embodiments, fumarate crystalline Form A has an XRPD pattern substantially as shown in FIG. 1.

[0096] In one embodiment, fumarate crystalline Form A is characterized by having an endothermic peak onset at about 248°C as measured by differential scanning calorimetry (“DSC”). In another embodiment, fumarate crystalline Form A has a DSC thermogram substantially as shown in FIG. 2.

[0097] In another embodiment, fumarate crystalline Form A has both: 1) one or more DSC characteristics described above; and 2) an X-ray powder diffraction pattern comprising at least one peak at  $2\theta$  selected from  $6.9\pm0.2$ ,  $13.8\pm0.2$ ,  $14.2\pm0.2$ ,  $15.7\pm0.2$ ,  $18.4\pm0.2$ ,  $23.0\pm0.2$ ,  $23.8\pm0.2$ ,  $26.6\pm0.2$ ,  $27.3\pm0.2$  and  $28.6\pm0.2$ .

[0098] In another embodiment, fumarate crystalline Form A has both: 1) one or more DSC characteristics described above; and 2) an X-ray powder diffraction pattern comprising peaks at  $2\theta$  values of  $6.9\pm0.2$ ,  $13.8\pm0.2$ ,  $14.2\pm0.2$ ,  $18.4\pm0.2$ , and  $23.8\pm0.2$ .

[0099] In one embodiment, fumarate crystalline Form A is characterized by having about 0.02-0.25% weight loss until the onset of degradation at about 150°C as estimated by thermogravimetric analysis (“TGA”). In another embodiment, fumarate crystalline Form A has a TGA profile substantially as shown in FIG. 2.

[00100] In another embodiment, fumarate crystalline Form A has both: 1) one or more TGA characteristics described above; and 2) an X-ray powder diffraction pattern comprising at least one peak at  $2\theta$  selected from  $6.9\pm0.2$ ,  $13.8\pm0.2$ ,  $14.2\pm0.2$ ,  $15.7\pm0.2$ ,  $18.4\pm0.2$ ,  $23.0\pm0.2$ ,  $23.8\pm0.2$ ,  $26.6\pm0.2$ ,  $27.3\pm0.2$  and  $28.6\pm0.2$ . In another embodiment, fumarate crystalline Form A has both: 1) one or more TGA characteristics described above; and 2) an X-ray powder diffraction pattern comprising peaks at  $2\theta$  values of  $6.9\pm0.2$ ,  $13.8\pm0.2$ ,  $14.2\pm0.2$ ,  $18.4\pm0.2$ , and  $23.8\pm0.2$ .

[00101] In one embodiment, fumarate crystalline Form A is characterized by having an observed water uptake of about 0.13-0.16 % at 25 °C/80% Relative Humidity (RH), as measured by dynamic vapor sorption (“DVS”).

[00102] In another embodiment, fumarate crystalline Form A has a DVS isotherm substantially as shown in FIG. 3.

[00103] In another embodiment, fumarate crystalline Form A has both: 1) one or more DVS characteristics described above; and 2) an X-ray powder diffraction pattern comprising at least one peak at  $^{\circ}2\theta$  selected from  $6.9\pm0.2$ ,  $13.8\pm0.2$ ,  $14.2\pm0.2$ ,  $15.7\pm0.2$ ,  $18.4\pm0.2$ ,  $23.0\pm0.2$ ,  $23.8\pm0.2$ ,  $26.6\pm0.2$ ,  $27.3\pm0.2$  and  $28.6\pm0.2$ .

[00104] In another embodiment, fumarate crystalline Form A 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  $6.9\pm0.2$ ,  $13.8\pm0.2$ ,  $14.2\pm0.2$ ,  $18.4\pm0.2$ , and  $23.8\pm0.2$ .

[00105] In one embodiment, fumarate crystalline Form A is substantially free of residual organic solvents.

[00106] In one embodiment, the fumarate crystalline forms of the present invention are at least 40%, 50%, 60%, 70%, 80%, 90% or 95% crystalline.

[00107] 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: fumarate crystalline Form A and a pharmaceutically acceptable excipient. The invention also encompasses pharmaceutical compositions comprising any of other fumarate crystalline forms described in the application.

[00108] The invention also encompassed any mixtures of any of the described fumarate crystalline forms with the amorphous form of MRTX0902.

[00109] In one embodiment, the fumarate crystalline form is a mixture of fumarate crystalline Form A with any of the described fumarate crystalline forms and/or with the amorphous form of fumarate MRTX0902.

[00110] 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 fumarate crystalline Form A of MRTX0902.

[00111] 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 fumarate crystalline form is fumarate crystalline Form A.

In other embodiments, the fumarate crystalline form is any of the other forms described in this application.

[00112] 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 fumarate crystalline form of MRTX0902. In one embodiment, the cancer is a SOS1-associated cancer. In one embodiment, the SOS1-associated cancer is lung cancer.

[00113] In one embodiment, the fumarate crystalline form is fumarate crystalline Form A. In other embodiments, the fumarate crystalline form is any of the other forms described in this application.

[00114] 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 fumarate crystalline form of MRTX0902, alone or in combination with one or more pharmaceutically acceptable excipients and/or diluent.

[00115] In one embodiment, the subject is an adult patient. In one embodiment, the subject is a pediatric patient.

[00116] 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).

[00117] In another aspect of the invention, provided herein are process for the preparation of fumarate crystalline forms of MRTX0902. In one embodiment, the process describes the preparation of fumarate crystalline Form A. In other embodiments, the process describes the preparation of other crystalline forms of MRTX0902.

[00118] PHARMACEUTICAL COMPOSITIONS

[00119] In another aspect, the invention provides pharmaceutical compositions comprising fumarate crystalline forms of MRTX0902 and a pharmaceutically acceptable carrier, excipient, or diluent that may be used in the methods disclosed herein. The fumarate 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 fumarate crystalline forms of MRTX0902 are administered intravenously in a hospital setting. In one embodiment, administration may be by the oral route.

[00120] 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: fumarate crystalline Form A and a pharmaceutically acceptable excipient. The invention also encompasses pharmaceutical compositions comprising any of other crystalline forms described in the application.

[00121] The invention also encompassed any mixtures of any of the described fumarate crystalline forms with the amorphous form of MRTX0902.

[00122] 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 fumarate crystalline Form A of MRTX0902.

[00123] 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.

[00124] 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.

[00125] The pharmaceutical compositions comprising the fumarate crystalline forms of MRTX0902 may be used in the methods of use described herein.

#### [00126] METHODS OF USE

[00127] 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.

[00128] 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 fumarate crystalline form of MRTX0902, alone or in combination with one or more pharmaceutically acceptable excipients and/or diluent.

[00129] In one embodiment, the subject is an adult patient. In one embodiment, the subject is a pediatric patient.

[00130] In one embodiment, a fumarate 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.

[00131] 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.

[00132] 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.

[00133] 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.

[00134] 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 65%, 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).

[00135] 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.

[00136] 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%, 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).

[00137] 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 Fumarate Crystalline Form A of MRTX0902

[00138] This Example illustrates the preparation of fumarate crystalline Form A of MRTX0902.

[00139] (R)-2-methyl-3-(1-((4-methyl-7-morpholinopyrido[3,4-d]pyridazin-1-yl)amino)ethyl)benzonitrile fumarate – MRTX0902 fumarate Form A. To a 400 mL reactor was added (R)-2-methyl-3-(1-((4-methyl-7-morpholinopyrido[3,4-d]pyridazin-1-yl)amino)ethyl)benzonitrile dihydrate [40 g, 94.7 mmol, 1.0 equiv.] and EtOH [200 mL]. The suspension was heated to 70 °C to obtain a solution. Then solid fumaric acid [12.1 g, 104 mmol, 1.1 equiv.] was added in one portion. Crystallization was observed within minutes and stirring was continued at 70 °C for 1 h. The reaction mixture was cooled to 20 °C over 0.25 h and then stirring was continued for 1 h at the same temperature. The suspension was filtered and the collected solid was rinsed with EtOH [80 mL]. The wet cake was then dried at 40 °C under vacuum to afford 47.4 g of (R)-2-methyl-3-(1-((4-methyl-7-morpholinopyrido[3,4-d]pyridazin-1-yl)amino)ethyl)benzonitrile fumarate Type A in 99% yield.

[00140] M.p. 253.2 – 253.3 °C.

[00141] <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 9.01 (s, 1H), 7.71 (dd, J = 7.9, 1.4 Hz, 1H), 7.64 – 7.55 (m, 2H), 7.42 (s, 1H), 7.32 (t, J = 7.8 Hz, 1H), 6.61 (s, 2H), 5.51 (s, 1H), 3.80 – 3.74 (m, 4H), 3.73 – 3.66 (m, 4H), 2.65 (s, 3H), 2.56 (s, 3H), 1.54 (d, J = 7.0 Hz, 3H).

[00142]  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  166.6, 159.9, 151.3, 149.7, 147.7, 146.3, 139.2, 134.6, 131.3, 129.7, 127.4, 125.3, 119.0, 114.3, 112.7, 93.7, 66.3, 47.1, 45.5, 21.8, 18.2, 17.2.

[00143] 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 2

### Characterization Summary of Crystalline Form A From Crystallization

[00144] The starting material (WX-80355 free base, Batch # PCS 0437, also referred to as MRTX0902) as received was characterized by X-ray powder diffraction (XRPD), polarized light microscopy (PLM), thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), proton nuclear magnetic resonance ( $^1\text{H}$ -NMR) spectroscopy and high performance liquid chromatography (HPLC). The starting material had a purity of 90.5 % by qNMR.

[00145] As a first step, the WX-80355 fumarate salt was successfully scaled-up in two different solvent systems THF/95% EtOH and 95%EtOH at 5 g scale using a systematic crystallization approach in Easymax 102. A summary of WX-80355 fumarate Type A salt from both crystallization solvent systems is presented in Table 1. The same crystal form was prepared in both approaches.

[00146] Based on the approximate solubility of the starting material in 20 different solvent systems, 100 polymorph screening experiments were set up using techniques such as anti-solvent addition, solid vapor diffusion, liquid vapor diffusion, slurry at RT and 50 °C, slow evaporation at RT and 50 °C, slow cooling and polymer induced crystallization. A total of three crystal forms were identified, namely Type A (anhydrate), Type B (anisole solvate) and Type C (DMSO solvate).

[00147] Hygroscopicity evaluation was conducted using Dynamic Vapor Sorption (DVS) as part of salt screening project under Q-3438. Based on the % weight gain up to 80% relative humidity (RH), Fumarate Type A was identified to be non-hygroscopic with no form change after DVS evaluation.

[00148] Based on the characterization results, Fumarate Type A (anhydrate) with good solid-state properties was recommended for further development.

[00149] Table 1 summarizes the combined results of solid-state properties, solubility studies, and stability studies of two lots of Fumarate Type A.

Table 1

| Crystal Form                        | Fumarate Type A                                                       | Fumarate Type A                  |
|-------------------------------------|-----------------------------------------------------------------------|----------------------------------|
| Solid-State Properties              |                                                                       |                                  |
| Batch No.                           | Lot # JO-906-63-01 (lot 1)                                            | Lot # JO-906-66-01 (lot 2)       |
| Crystallization Solvents            | 95 % EtOH                                                             | THF / 95 % ETOH                  |
| Form Identity                       | Anhydrate                                                             | Anhydrate                        |
| Crystallinity                       | High                                                                  | High                             |
| Wt. Loss by TGA (%)                 | 0.25                                                                  | 0.02                             |
| Endo. by DSC (°C, onset)            | 248.4                                                                 | 249.2                            |
| Morphology                          | Thin-rod shaped particles                                             | Thin-rod shaped particles        |
| Stoichiometry (acid/base)           | 1:1                                                                   | 1:1                              |
| Water Uptake at 25 °C/80% RH by DVS | 0.13 %                                                                | 0.16 %                           |
| Hygroscopicity#                     | Non hygroscopic                                                       | Non hygroscopic                  |
| Crystal Form post DVS               | Fumarate Type A                                                       | Fumarate Type A                  |
| Residual Solvents                   | EtOH – 1764 ppm                                                       | EtOH – 859 ppm<br>THF – 1881 ppm |
| Stability Studies (Open Conditions) |                                                                       |                                  |
| 25 °C / 60 %RH                      | Stable both physically and chemically in all conditions for two weeks |                                  |
| 40 °C / 75 %RH                      |                                                                       |                                  |
| 60 °C                               |                                                                       |                                  |

<sup>#</sup> "Pharmeuropa, Vol. 4 (3), pp. 228-230, 1992" and "Callahan, J.C., Cleary, G.W., Elefant, M., Kaplan, G., Kensler, T., and Nash, R.A. 1982. Equilibrium moisture content of pharmaceutical excipients. Drug Development and Industrial Pharmacy, 8: 355-69."

### EXAMPLE 3

#### Preparation And Characterization of MRTX0902 Fumarate at 5 g scale

[00150] MRTX0902 Fumarate Form A was prepared using Easymax 102 procedures. The preparation procedure is detailed in Tables 2 and 3, from 95% EtOH and THF/95% EtOH solvent system, respectively. The material was confirmed to be MRTX0902 Fumarate Form

A by XRPD and further characterized by DSC, TGA, DVS and NMR. The solid-state characterization summary of solids obtained from both experiments is provided in Table 4.

**Table 2****Procedure from 95% EtOH and Summary of Results**

| Material and Equipment |                                                                                                        | NB#906-63                                                                                                                                               |
|------------------------|--------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|
| API                    | MRTX0902 FB (90.5 % purity by qNMR)                                                                    | 5 g                                                                                                                                                     |
| Solvents               | 12.5 volumes of EtOH (95%)                                                                             | 80 mg/mL                                                                                                                                                |
| Seeds                  | MRTX0902 Fumarate Salt                                                                                 | 1 wt.% (50 mg)                                                                                                                                          |
| Crystallizers          | EasyMax 102 (100 mL)                                                                                   |                                                                                                                                                         |
| Procedure NB#906-63    |                                                                                                        |                                                                                                                                                         |
| 1                      | Transfer 5 g of SM and 62.5 mL 95%EtOH to reactor with 500 rpm agitation                               | Some API became very hard and stuck to the bottom of the glass vessel, so a sonication probe was used to break up agglomeration and resuspend particles |
| 2                      | Heat the batch to 77 °C in 40 minutes                                                                  | Clear, dark reddish/brown solution observed                                                                                                             |
| 3                      | Add 1 wt.% fumarate salt seeds                                                                         | Seeds held                                                                                                                                              |
| 4                      | Add 10 mL of fumaric acid/95%EtOH solution (0.36 M) quickly and add remaining 26 mL dropwise over 2 hr | Solution delivered via syringe (60 mL) and syringe pump. Some secondary nucleation observed after initial addition                                      |
| 5                      | Age the batch at 77 °C for 1 hr                                                                        |                                                                                                                                                         |
| 6                      | Cool batch to 20 °C over 2 hr                                                                          |                                                                                                                                                         |
| 7                      | Age batch at 20 °C overnight                                                                           | Aged ~14 hr at 20 °C. Thick slurry with yellow solids observed                                                                                          |
| 8                      | Sample the batch for PLM, XRPD                                                                         | Confirmed to be Fumarate Salt Type A, plate shaped crystals                                                                                             |
| 9                      | Filter the batch; wash with 2 x 3 vol of EtOH                                                          | Fast filtration and wash observed                                                                                                                       |
| 10                     | Dry at rt with vacuum pull (~1 hr) followed by drying at 60°C in vacuum oven for 2h                    | Confirmed to be Fumarate Salt Type A, ~96.9% yield                                                                                                      |

**Table 3****Procedure from THF/95% EtOH and Summary of Results**

| Material and Equipment |                                                                            | NB#906-66                                   |
|------------------------|----------------------------------------------------------------------------|---------------------------------------------|
| API                    | MRTX0902 FB (90.5 % purity by qNMR)                                        | 5 g                                         |
| Solvents               | 12 volumes of THF                                                          | 80 mg/mL                                    |
| Seeds                  | MRTX0902 Fumarate Salt                                                     | 1 wt.% (50 mg)                              |
| Crystallizers          | EasyMax 102 (100 mL)                                                       |                                             |
| Procedure NB#906-66    |                                                                            |                                             |
| 1                      | Add 5 g of SM and 60 mL THF to 100 mL conical flask and stirred at 500 rpm | Clear, dark reddish/brown solution observed |
| 2                      | Polish filtration using 0.45 µ filter                                      | Gravity filtered through a fritted funnel   |
| 3                      | Transfer API solution to reactor with 500 rpm agitation                    |                                             |
| 4                      | Add 1 wt.% fumarate salt seeds                                             | Seeds held                                  |

|    |                                                                                       |                                                          |
|----|---------------------------------------------------------------------------------------|----------------------------------------------------------|
| 5  | Add 36.75 mL of fumaric acid/95%EtOH solution (0.36 M) dropwise over 2 hr             | Solution delivered via syringe (60 mL) and syringe pump. |
| 6  | Age the batch at 20 °C for 1 hr                                                       | 3 hr total at 20 °C (2 hr solution addition, 1 hr aging) |
| 7  | Heat the batch to 60 °C in 1 hr                                                       |                                                          |
| 8  | Age the batch at 60 °C for 15 hr                                                      |                                                          |
| 9  | Cool batch to 20 °C over 3 hr                                                         |                                                          |
| 10 | Age batch at 20 °C for 3 hr                                                           | Thick slurry with yellow solids observed                 |
| 10 | Sample the batch for PLM, XRPD                                                        |                                                          |
| 11 | Filter the batch; wash with 2 x 3 vol of THF                                          | Fast filtration and wash observed                        |
| 12 | Dry at RT with vacuum pull (~1 hr) followed by drying at 60°C in vacuum oven for 2 hr | Confirmed to be Fumarate Salt Form A, ~99% yield         |

Table 4

### Characterization Summary of MRTX0902 Fumarate

| Technique                                         | 95%EtOH Scaleup                                                          | THF/95%EtOH scaleup                                                      |
|---------------------------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Batch No.                                         | JO-906-63-01                                                             | JO-906-66-01                                                             |
| Form Identity                                     | Anhydrate, Fumarate Form A                                               | Anhydrate, Fumarate Form A                                               |
| Crystallinity                                     | Highly crystalline                                                       | Highly crystalline                                                       |
| Morphology                                        | Thin rod-plate like (~50 μ)                                              | Thin rod-plate like (~25 μ)                                              |
| Endo by DSC                                       | Endotherm at 254.81 °C (peak temp), 172.21 J/g (enthalpy)                | Endotherm at 255.10 °C (peak temp) , 172.25 J/g (enthalpy)               |
| % wt loss by TGA (%)                              | 0.25 % (150 °C)                                                          | 0.02 % (150 °C)                                                          |
| NMR                                               | Consistent with chemical structure, API:fumaric acid (stoichiometry) 1:1 | Consistent with chemical structure, API:fumaric acid (stoichiometry) 1:1 |
| Water Uptake from 0% RH to 80% RH at 25 °C by DVS | 0.13 %                                                                   | 0.16 %                                                                   |
| Hygroscopicity                                    | Non-hygroscopic                                                          | Non-hygroscopic                                                          |
| Crystal form after DVS                            | Fumarate Type A                                                          | Fumarate Type A                                                          |

### EXAMPLE 4

#### Polymorph Screen Experiments of MRTX0902

[00151] A total of 100 polymorph screening experiments were completed. Three crystal forms were identified, namely Fumarate Form A, Form B, and Form C. The characterization summary of all solid forms is provided in Table 5. Form A, which is the form of the starting

fumarate, was identified as an anhydrate. Form B was discovered in solvent systems involving anisole, and was identified as an anisole solvate. Form C was discovered in DMSO system by slow evaporation or polymer induced crystallization. The NMR data suggested that Form C is a DMSO solvate. When heated up to ~160°C, dissociation of Form C to free base was observed after desolvation, suggesting concurrent desolvation and salt disproportionation.

[00152] The characterization summary of all forms (Forms A, B and C) is presented in Table 5.

**Table 5**

Characterization summary of different fumarate crystalline forms of MRTX0902

| Crystal Form | Sample ID                         | Crystallinity by XRPD | Wt. Loss in TGA (% , °C) | Endo. in DSC (peak, °C) | Speculated Form      |
|--------------|-----------------------------------|-----------------------|--------------------------|-------------------------|----------------------|
| Form A       | JO-906-63-01                      | High                  | 0.25 (150)               | 254.8                   | Anhydrate            |
| Form B       | NW-919-58-AS-8                    | High                  | 18.51 (200)              | 132.7, 177.1, 253.0     | Mono-Anisole solvate |
| Form C       | NW-919-60-SE-6<br>NW-919-61-PIC-7 | High                  | 16.71 (200)              | 154.8, 169.2, 271.2     | Mono-DMSO solvate    |

## EXAMPLE 5

### Solid State Stability Study of Fumarate Crystalline Form A

[00153] Solid-state stability of Fumarate Salt Form A (scale up batch) under three open dish conditions (i) 25 °C/60% RH, (ii) 40 °C/75% RH and (iii) 60 °C were evaluated for 2 weeks. The study design is provided in Table 6. After storing under those conditions for one/two weeks, samples were collected and analyzed for its appearance, form and crystallinity by XRPD and % purity by HPLC (Table 7).

[00154] Fumarate Form A showed no substantial change in crystal form and chemical purity, suggesting good physical and chemical stabilities for at least 2 weeks.

**Table 6**

Stability Study Design for Fumarate Form A

| Crystal Forms   | Packaging | Storage Condition | Timepoints | Tests                        |
|-----------------|-----------|-------------------|------------|------------------------------|
| Fumarate Form A | Open dish | 25°C /60% RH      | Initial    | Appearance                   |
|                 |           |                   | 1 Week     | Assay/impurities by HPLC     |
|                 |           |                   | 2 weeks    | XRD (Form and Crystallinity) |
|                 | Open dish | 40°C/75% RH       | Initial    | Appearance                   |
|                 |           |                   | 1 Week     | Assay/impurities by HPLC     |
|                 |           |                   | 2 weeks    | XRD (Form and Crystallinity) |
|                 | Open dish | 60°C              | Initial    | Appearance                   |
|                 |           |                   | 1 Week     | Assay/impurities by HPLC     |
|                 |           |                   | 2 weeks    | XRD (Form and Crystallinity) |

Table 7

## Results of Accelerated Stability Tests

| Storage Condition | Timepoint<br>(Date)<br>NB # 919-# | Test*        | Fumarate Form A<br>(Lot # JO-906-63-01) (lot 1) |
|-------------------|-----------------------------------|--------------|-------------------------------------------------|
| N/A               | Initial                           | Appearance   | Yellow solids                                   |
|                   |                                   | Assay Purity | 99.1%                                           |
|                   |                                   | XRPD         | Fumarate Form A                                 |
| 25°C / 60% RH     | 1 wk                              | Lab NB #     | NW-919-62-A1-1w                                 |
|                   |                                   | Appearance   | Yellow solids                                   |
|                   |                                   | Assay Purity | 99.1%                                           |
|                   |                                   | XRPD         | Fumarate Form A                                 |
|                   | 2 wk                              | Lab NB #     | NW-919-62-A1-2w                                 |
|                   |                                   | Appearance   | Yellow solids                                   |
|                   |                                   | Assay Purity | 99.1%                                           |
|                   |                                   | XRPD         | Fumarate Form A                                 |
| 40°C/75% RH       | 1 wk                              | Lab NB #     | NW-919-62-B1-1w                                 |
|                   |                                   | Appearance   | Yellow solids                                   |
|                   |                                   | Assay Purity | 99.0%                                           |
|                   |                                   | XRPD         | Fumarate Form A                                 |
|                   | 2 wk                              | Lab NB #     | NW-919-62-B1-2w                                 |
|                   |                                   | Appearance   | Yellow solids                                   |
|                   |                                   | Assay Purity | 99.1%                                           |
|                   |                                   | XRPD         | Fumarate Form A                                 |

| Storage Condition | Timepoint<br>(Date)<br>NB # 919-# | Test*        | Fumarate Form A<br>(Lot # JO-906-63-01) (lot 1) |
|-------------------|-----------------------------------|--------------|-------------------------------------------------|
|                   |                                   | XRPD         | Fumarate Form A                                 |
|                   |                                   | Lab NB #     | NW-919-62-C1-1w                                 |
|                   | 1 wk                              | Appearance   | Yellow solids                                   |
|                   |                                   | Assay Purity | 99.1%                                           |
|                   |                                   | XRPD         | Fumarate Form A                                 |
| 60°C              | 2 wk                              | Lab NB #     | NW-919-62-C1-2w                                 |
|                   |                                   | Appearance   | Yellow solids                                   |
|                   |                                   | Assay Purity | 99.1%                                           |
|                   |                                   | XRPD         | Fumarate Form A                                 |

### EXAMPLE 6

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

[00155] 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)

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

[00156] **Results**

[00157] 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 5, 6, and 7 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.

[00158] In addition, Fumarate Salt Form A (lot 1 in Table 1) exhibited sticking to the punch tips which was significantly reduced with Fumarate Salt Form A (lot 2 in Table 1). Fumarate Salt Form A (lot 2 in Table 1) 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.

[00159] 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 fumarate crystalline form of (*R*)-2-methyl-3-(1-((4-methyl-7-morpholinopyrido[3,4-*d*]pyridazin-1-yl)amino)ethyl)benzonitrile.
2. The fumarate crystalline form according to claim 1, wherein the crystalline form is Form A having an X-ray powder diffraction pattern comprising at least one peak at  $^{\circ}2\theta$  selected from  $6.9\pm0.2$ ,  $13.8\pm0.2$ ,  $14.2\pm0.2$ ,  $15.7\pm0.2$ ,  $18.4\pm0.2$ ,  $23.0\pm0.2$ ,  $23.8\pm0.2$ ,  $26.6\pm0.2$ ,  $27.3\pm0.2$  and  $28.6\pm0.2$ .
3. The fumarate crystalline form according to claim 1, wherein the crystalline form is Form A having an X-ray powder diffraction pattern comprising peaks at  $^{\circ}2\theta$  values of  $6.9\pm0.2$ ,  $13.8\pm0.2$ ,  $14.2\pm0.2$ ,  $18.4\pm0.2$ , and  $23.8\pm0.2$ .
4. The fumarate crystalline form according to claim 1, wherein the crystalline form is Form A having an X-ray powder diffraction pattern comprising two or more peaks at  $^{\circ}2\theta$  at  $6.9\pm0.2$ ,  $13.8\pm0.2$ ,  $14.2\pm0.2$ ,  $15.7\pm0.2$ ,  $18.4\pm0.2$ ,  $23.0\pm0.2$ ,  $23.8\pm0.2$ ,  $26.6\pm0.2$ ,  $27.3\pm0.2$  and  $28.6\pm0.2$ .
5. The fumarate crystalline form according to claim 1, wherein the crystalline form is Form A having an X-ray powder diffraction pattern comprising three or more peaks at  $^{\circ}2\theta$  at  $6.9\pm0.2$ ,  $13.8\pm0.2$ ,  $14.2\pm0.2$ ,  $15.7\pm0.2$ ,  $18.4\pm0.2$ ,  $23.0\pm0.2$ ,  $23.8\pm0.2$ ,  $26.6\pm0.2$ ,  $27.3\pm0.2$  and  $28.6\pm0.2$ .
6. The fumarate crystalline form according to claim 1, wherein the crystalline form is Form A having an XRPD pattern substantially as shown in FIG. 1.
7. The fumarate crystalline form according to claim 1, wherein the crystalline form is Form A characterized by having an endothermic peak with an onset at about  $248^{\circ}\text{C}$  by differential scanning calorimetry (DSC).
8. The fumarate crystalline form according to any one of claims 1-7, wherein the crystalline form is Form A having a DSC thermogram substantially as shown in FIG. 2.
9. The fumarate crystalline form according to any one of claims 1-8, wherein the crystalline form is Form A having a thermogravimetric analysis ("TGA") profile substantially as shown in FIG. 2.

10. The fumarate crystalline form according to any one of claims 1-9, wherein the crystalline form is Form A and which has about 0.02-0.25% weight loss until the onset of degradation at about 150°C as estimated by TGA.
11. The fumarate crystalline form according to any one of claims 1-10, wherein the crystalline form is Form A having dynamic vapor sorption (“DVS”) isotherm substantially as shown in FIG. 3.
12. The fumarate crystalline form according to any one of claims 1-11, wherein the crystalline form is Form A which has an observed water uptake of about 0.13-0.16% at 25 °C/80% Relative Humidity (RH), as measured by dynamic vapor sorption (“DVS”).
13. The fumarate crystalline form according to any one of claims 1-12, wherein the crystalline form is substantially free of residual organic solvents.
14. The crystalline form according to any one of claims 1-13, wherein the crystalline form is a hydrate or a dihydrate.
15. The crystalline form according to any one of claims 1-13, wherein the crystalline form is anhydrous.
16. A pharmaceutical composition, comprising a therapeutically effective amount of a fumarate 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 1-15.
17. The pharmaceutical composition according to claim 16, further comprising at least one pharmaceutically acceptable excipient and/or diluent.
18. 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 fumarate crystalline form according to any one of claims 1-18, alone or in combination with one or more pharmaceutically acceptable excipient and/or diluent.
19. 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 1-15, alone or in combination with one or more pharmaceutically acceptable excipient and/or diluent.

20. The method according to claim 19, wherein the therapeutically effective amount of the fumarate 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.
21. The method according to claim 19, 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.
22. The method of claim 19, 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 (osteochondrosarcoma)

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.

23. The method according to claim 19, wherein the cancer is a SOS1-associated cancer.
24. The method according to claim 19, wherein the cancer is non-small cell lung cancer.
25. The method according to claim 19, wherein the subject is an adult patient.
26. The method according to claim 19, wherein the subject is a pediatric patient.