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(54) **CRYSTALLINE FORMS OF NIRAPARIB FREEBASE**

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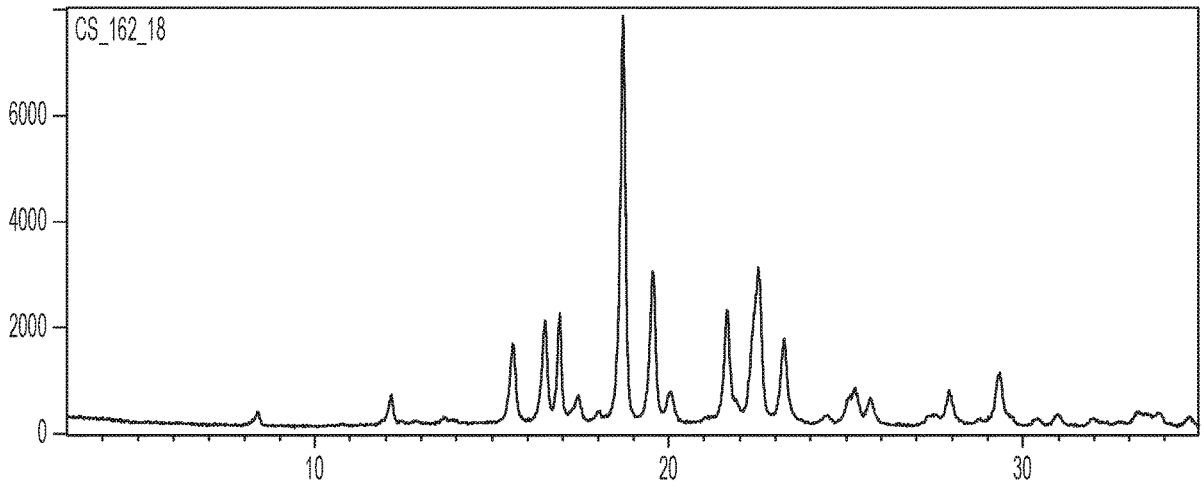
(57) **ABSTRACT**

Crystalline niraparib freebase is provided. Also provided are pharmaceutical compositions comprising crystalline niraparib freebase, and methods and uses pertaining to the same.



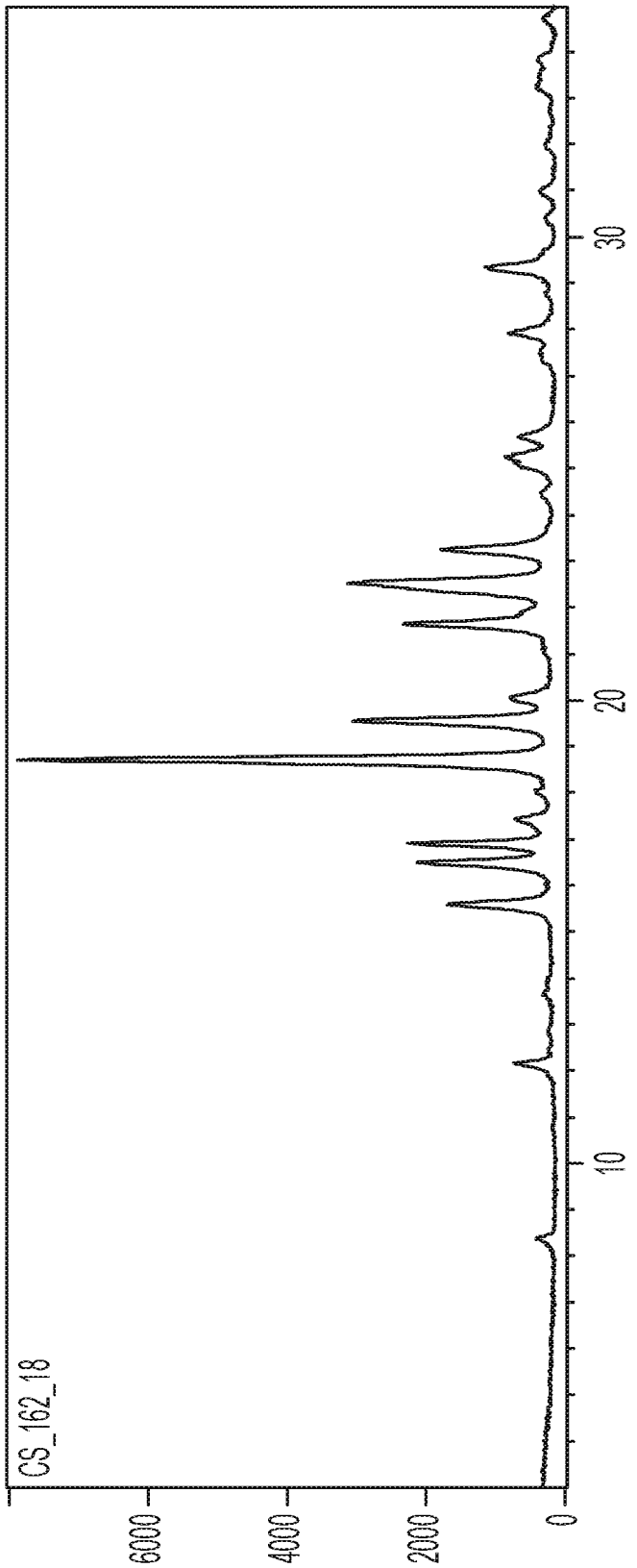


FIG. 1

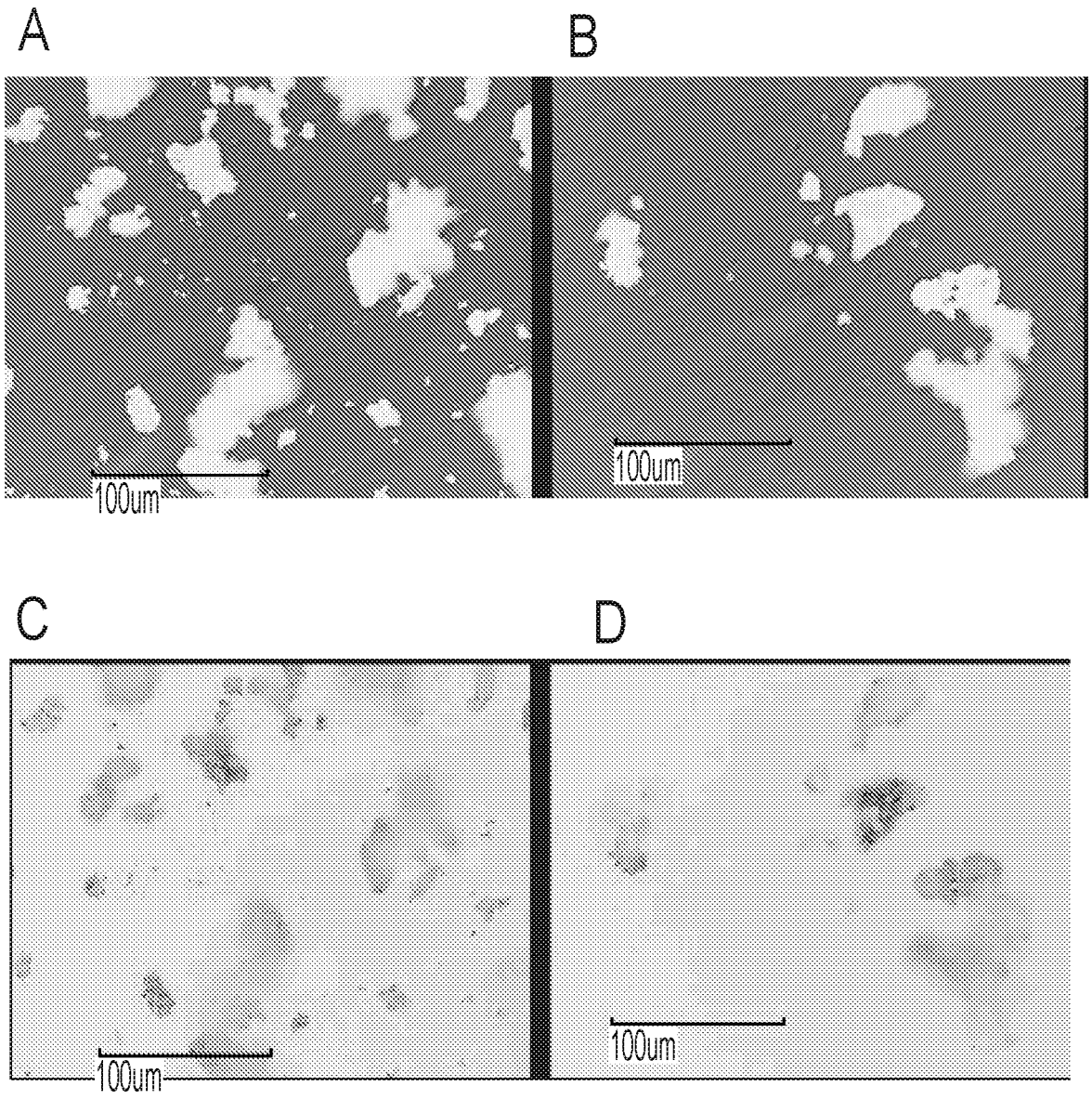


FIG. 2

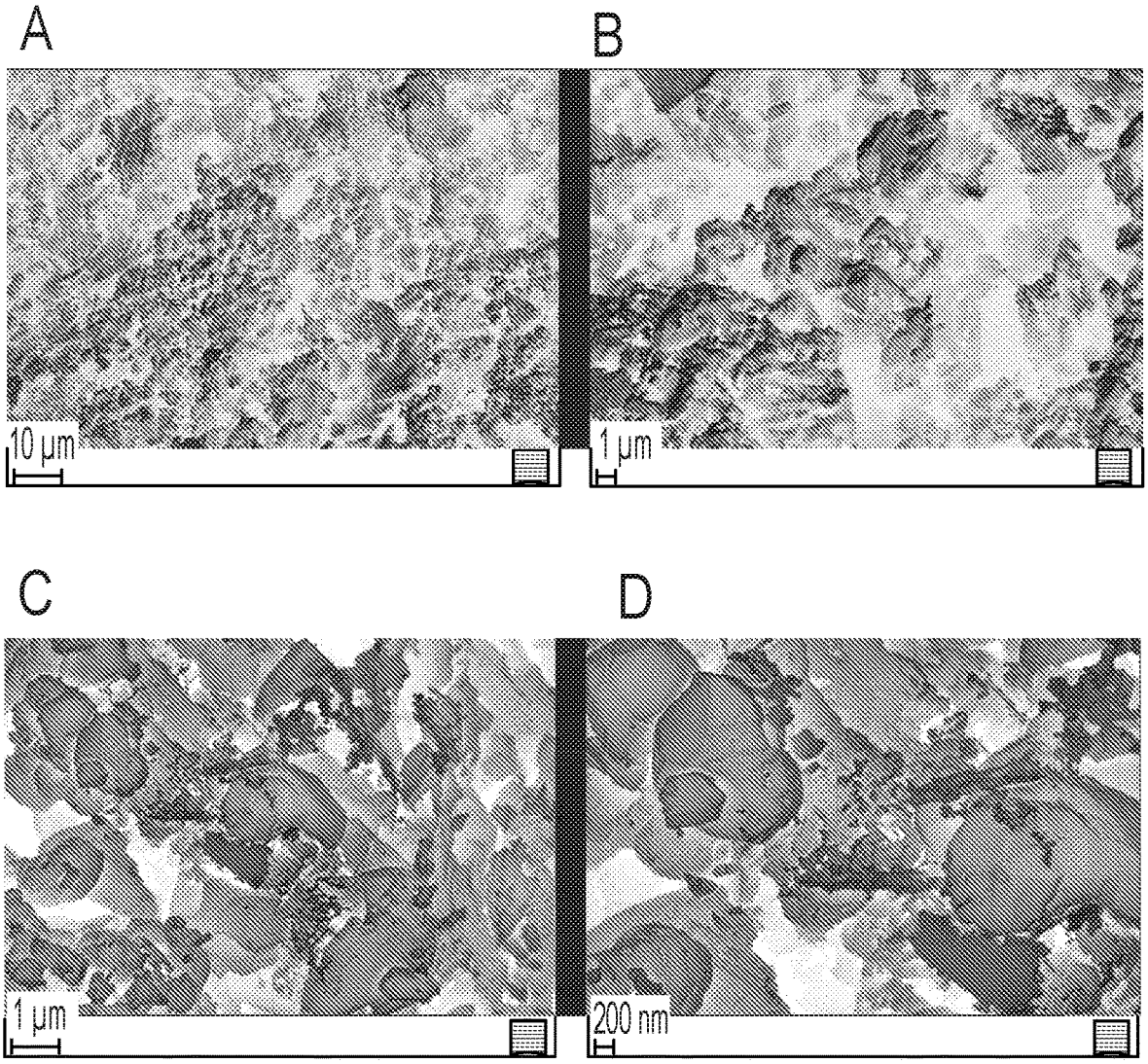


FIG. 3

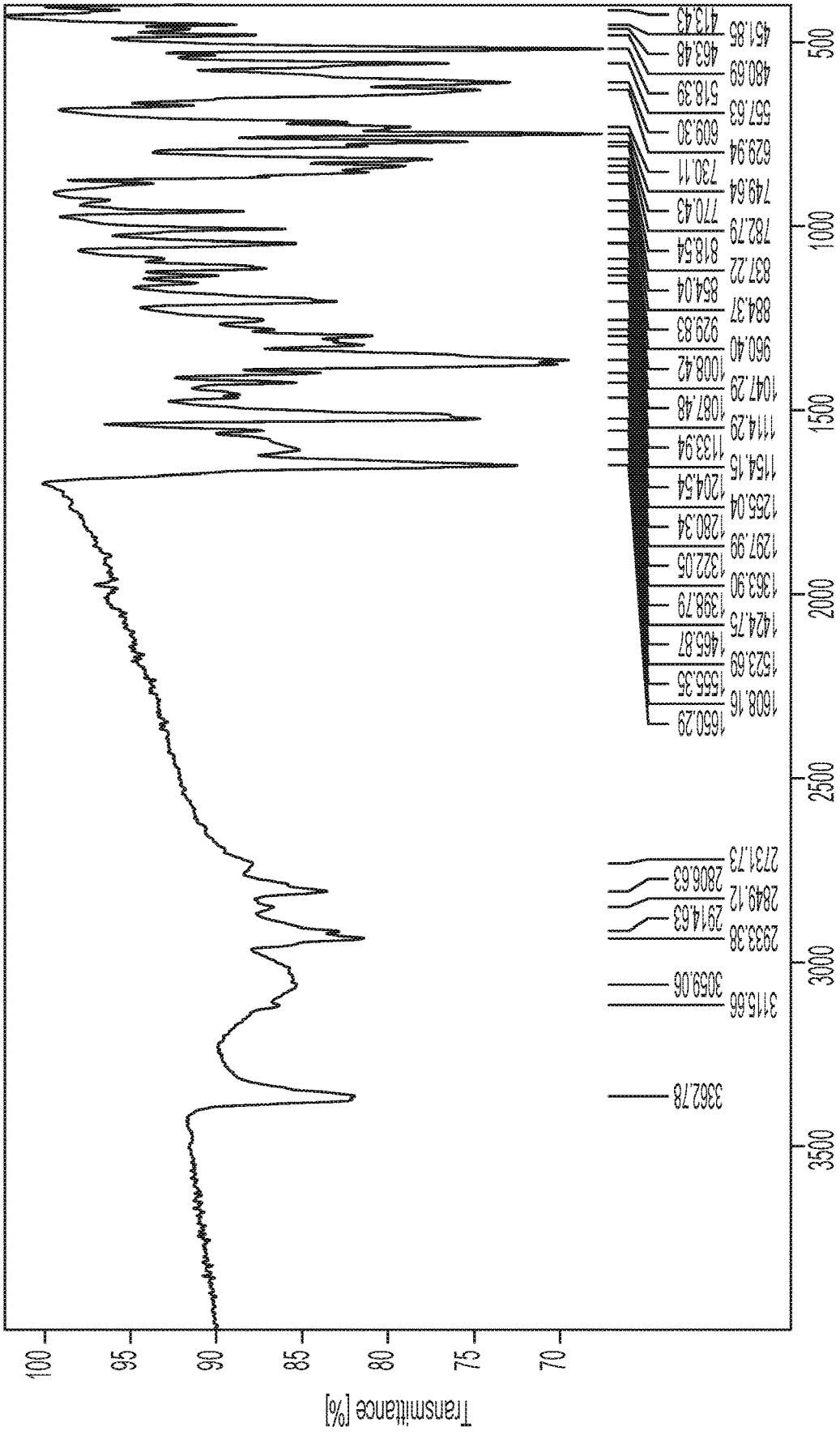

Transmittance [%]
100
95
90
85
80
75
70
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1
3362.78
3115.66
3059.06
2933.38
2914.63
2849.12
2806.63
2731.73
1650.29
1608.16
1555.35
1523.69
1466.87
1424.75
1398.79
1363.90
1322.05
1297.99
1280.34
1255.04
1204.54
1154.15
1133.94
1114.29
1087.48
1047.29
1008.42
960.40
929.83
884.37
854.04
837.22
818.54
782.79
770.43
749.64
730.11
629.94
609.30
557.63
518.39
480.69
463.48
451.85
413.43

FIG. 4

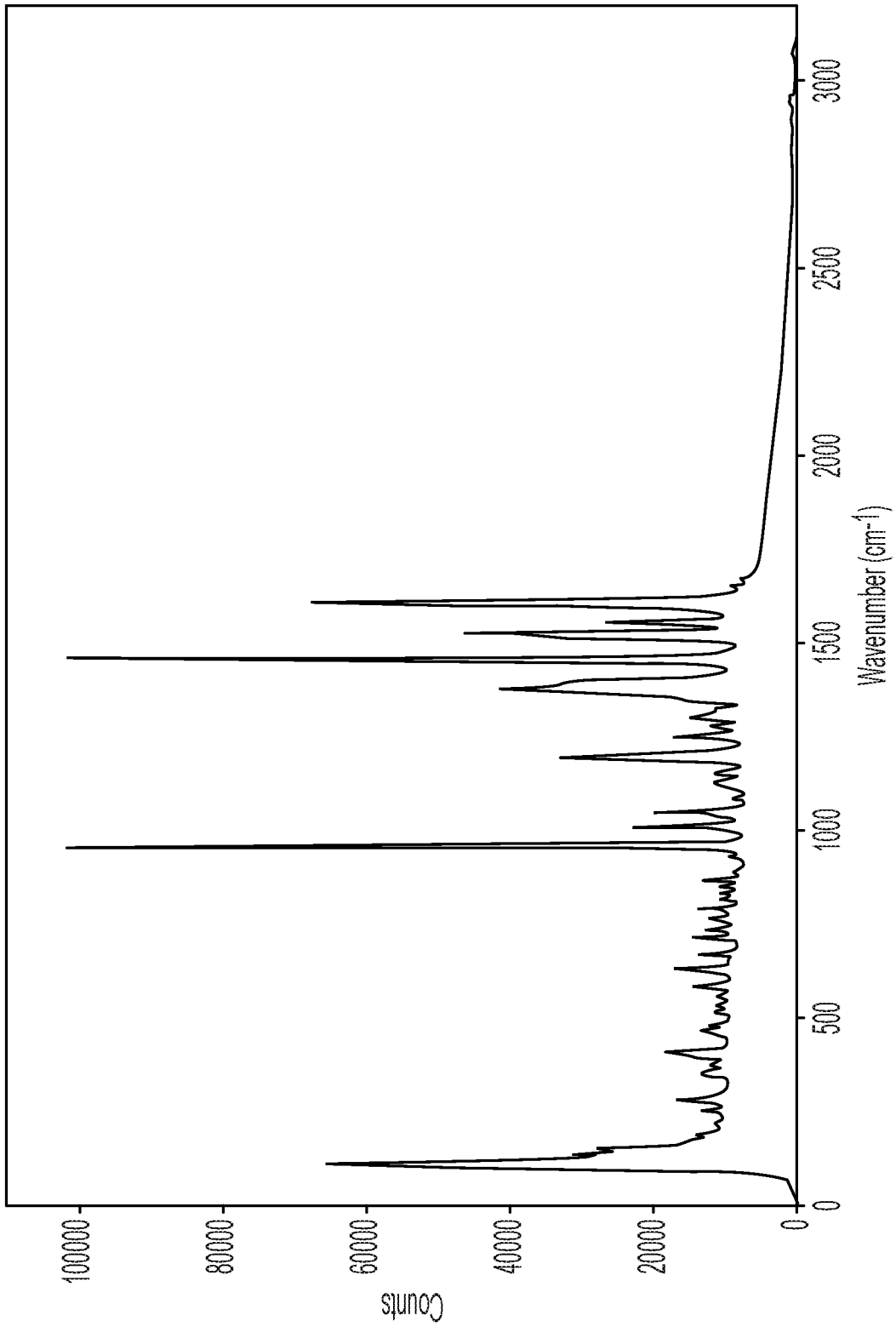

Counts
100000
80000
60000
40000
20000
0
0
500
1000
1500
2000
2500
3000
Wavenumber (cm-1)

FIG. 5

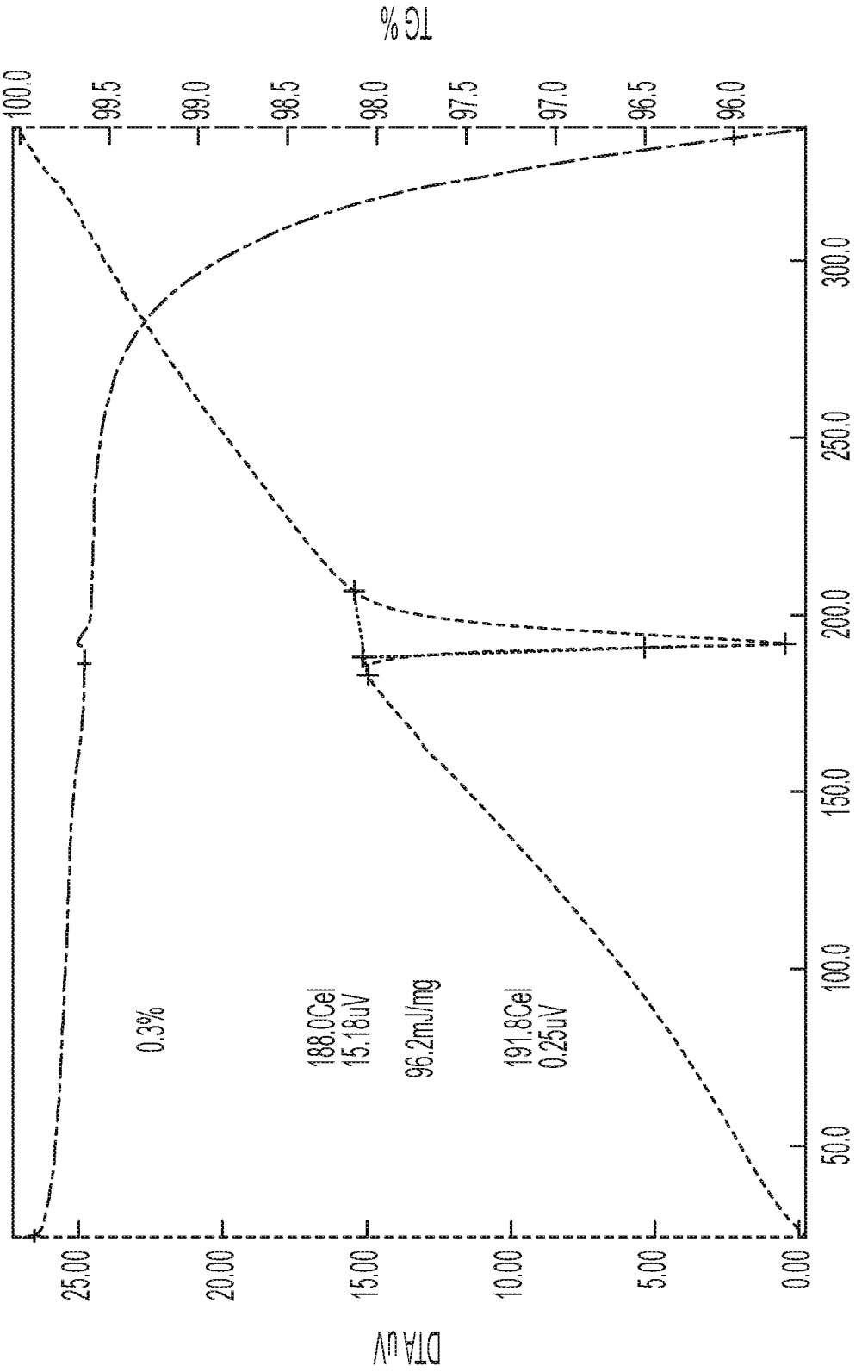

TG %
100.0
99.5
99.0
98.5
98.0
97.5
97.0
96.5
96.0
DTA uV
25.00
20.00
15.00
10.00
5.00
0.00
50.0
100.0
150.0
200.0
250.0
300.0
Temp Cel
0.3%
188.0Cel
15.18uV
96.2mJ/mg
191.8Cel
0.25uV

FIG. 6

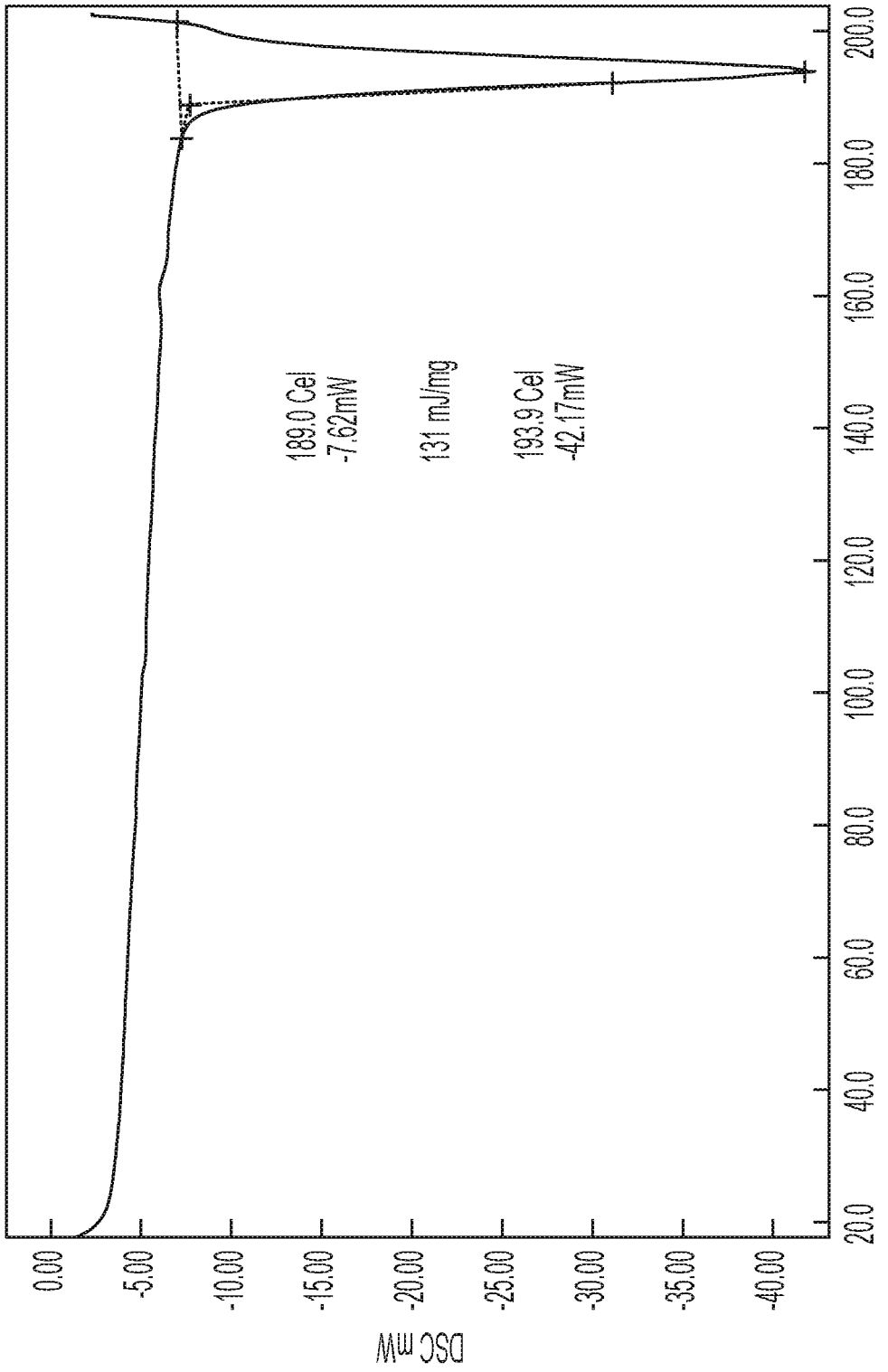

189.0 Cel
-7.62mW
131 mJ/mg
193.9 Cel
-42.17mW
DSC mW
0.00
-5.00
-10.00
-15.00
-20.00
-25.00
-30.00
-35.00
-40.00
20.0
40.0
60.0
80.0
100.0
120.0
140.0
160.0
180.0
200.0
Temp Cel

FIG. 7

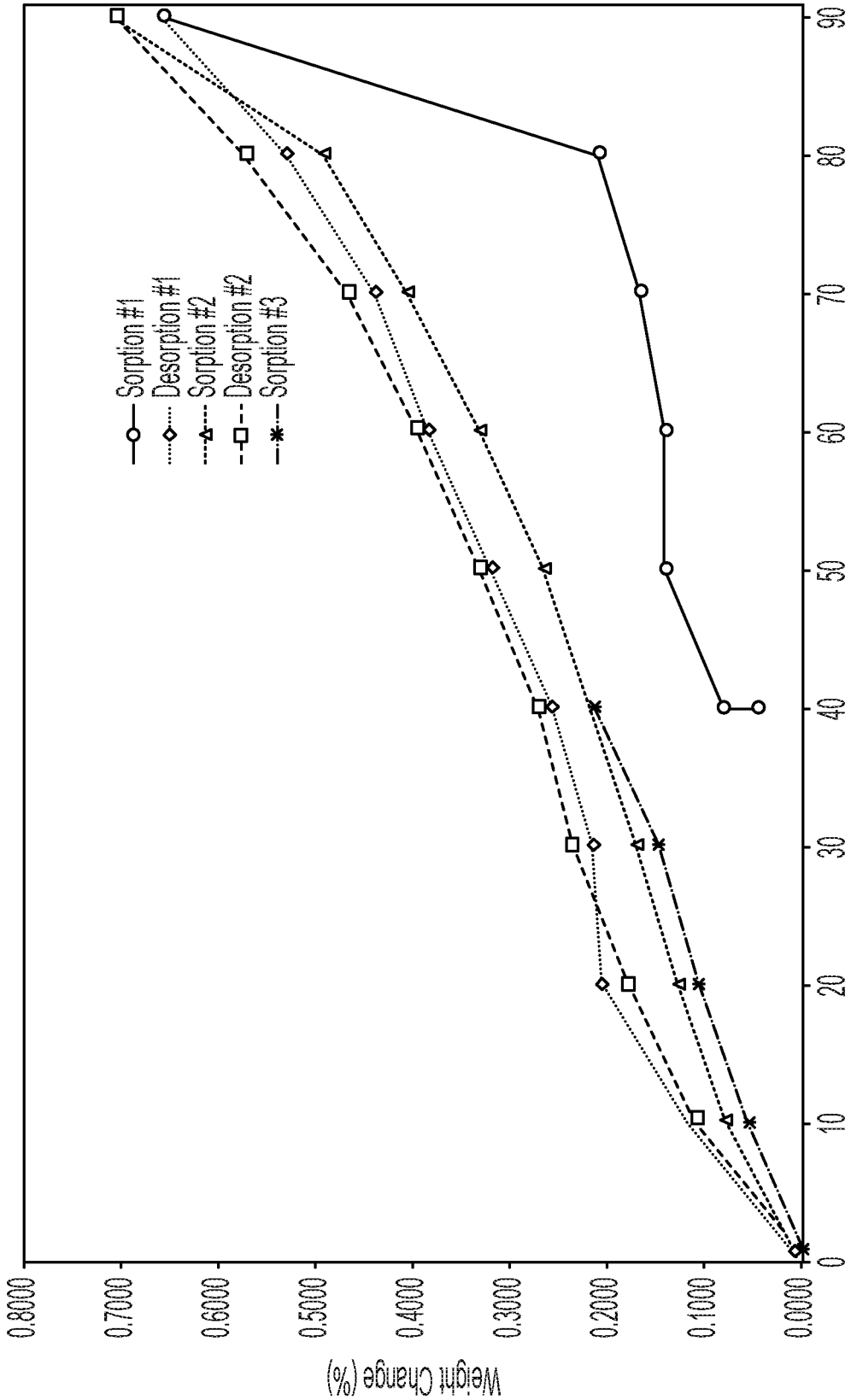

Weight Change (%)
0.8000
0.7000
0.6000
0.5000
0.4000
0.3000
0.2000
0.1000
0.0000
Relative Humidity (%)
0
10
20
30
40
50
60
70
80
90
Sorption #1
Desorption #1
Sorption #2
Desorption #2
Sorption #3

FIG. 8

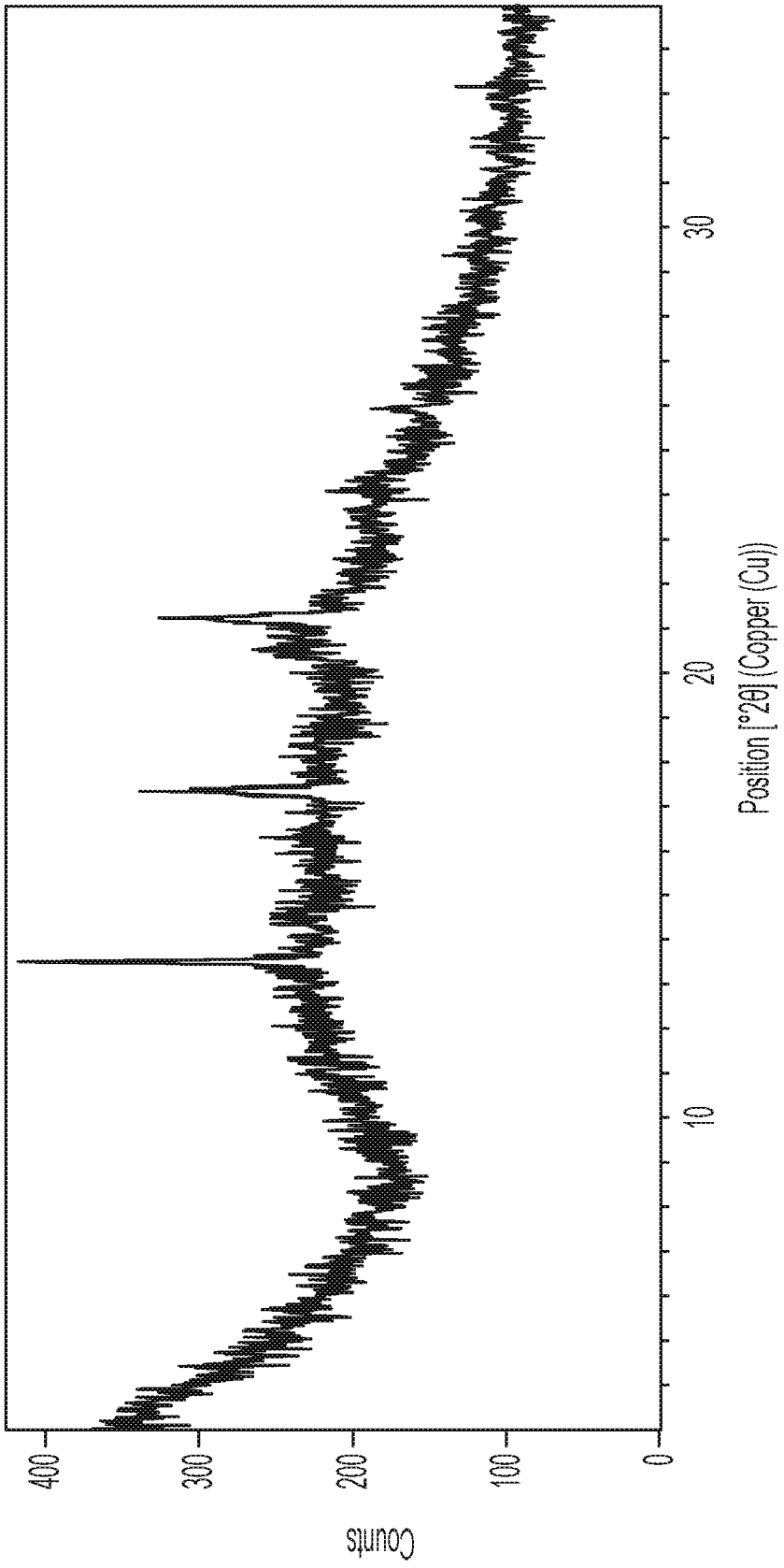


FIG. 9

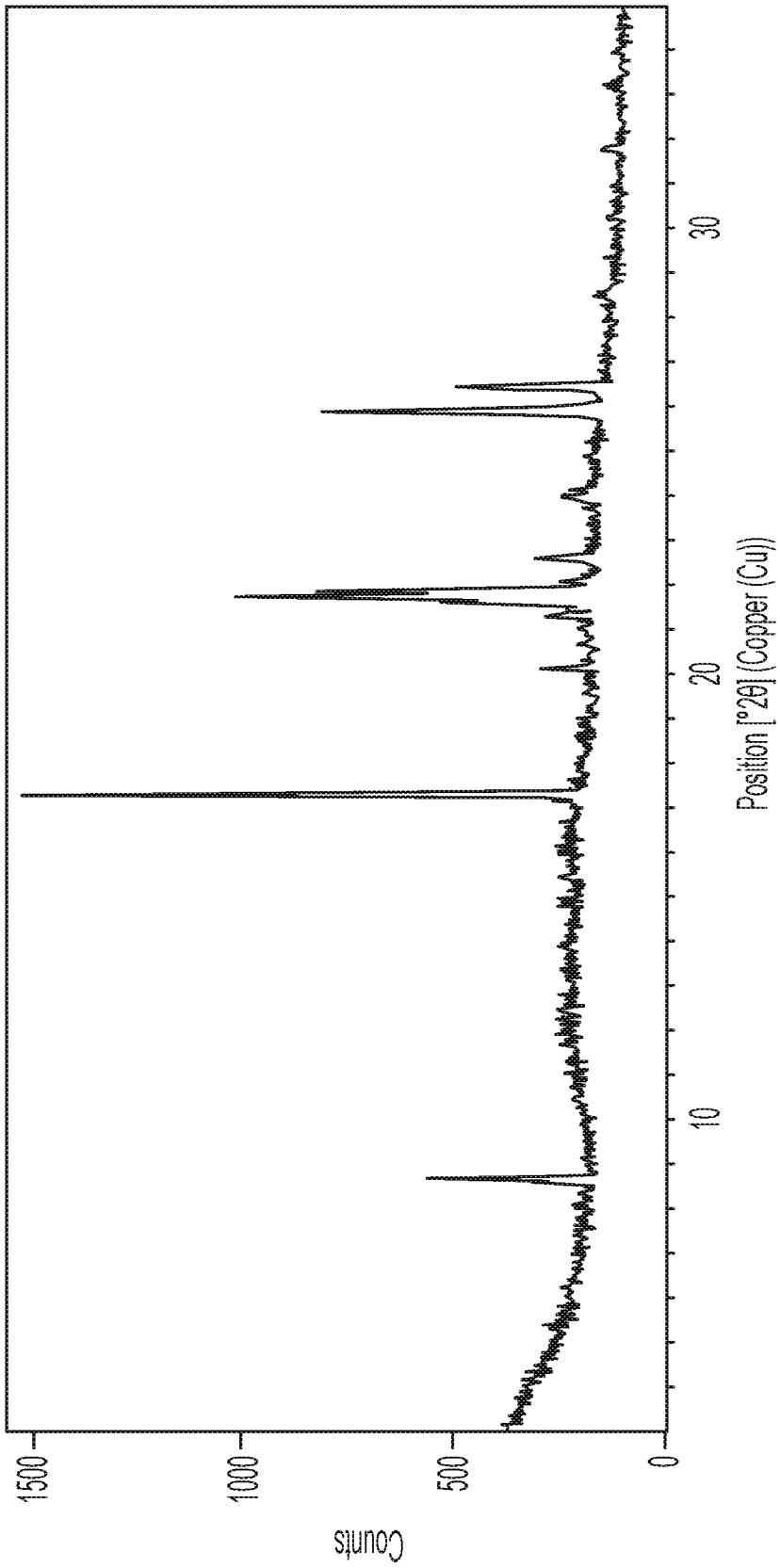


FIG. 10

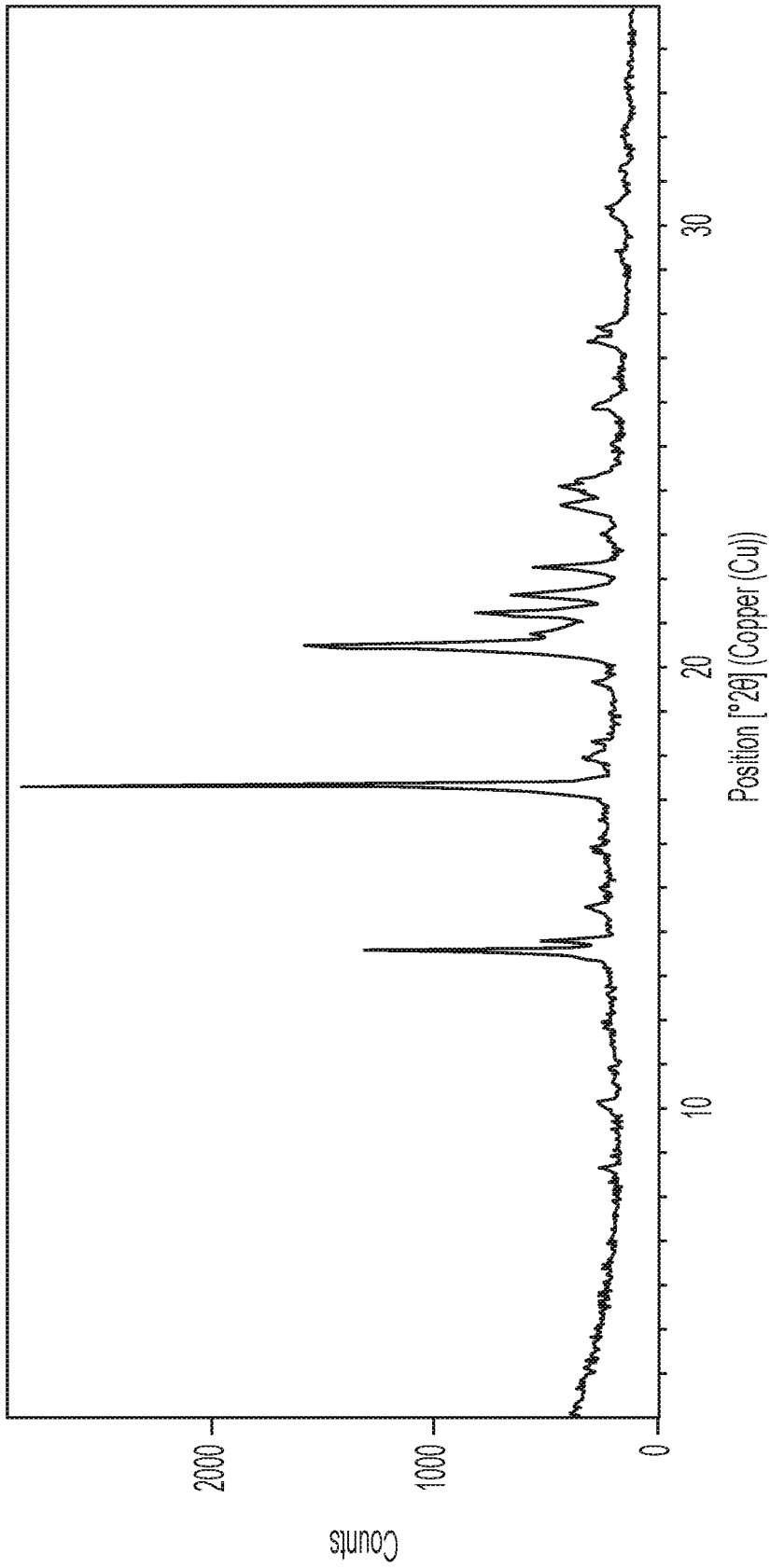


FIG. 11

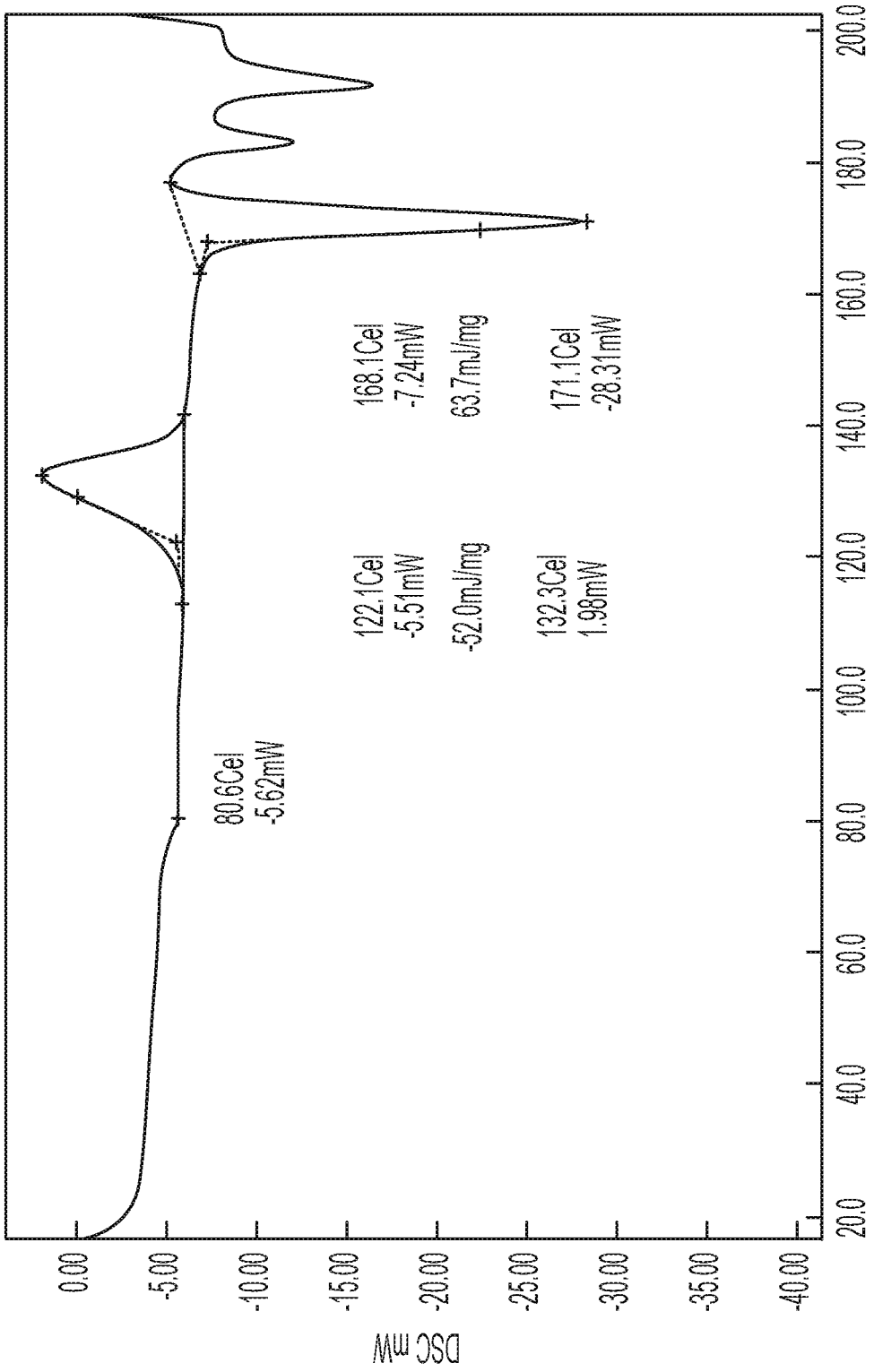

80.6Cel
-5.62mW
122.1Cel
-5.51mW
-52.0mJ/mg
132.3Cel
1.98mW
168.1Cel
-7.24mW
63.7mJ/mg
171.1Cel
-28.31mW
DSC mW
0.00
-5.00
-10.00
-15.00
-20.00
-25.00
-30.00
-35.00
-40.00
20.0
40.0
60.0
80.0
100.0
120.0
140.0
160.0
180.0
200.0
Temp Cel

FIG. 12

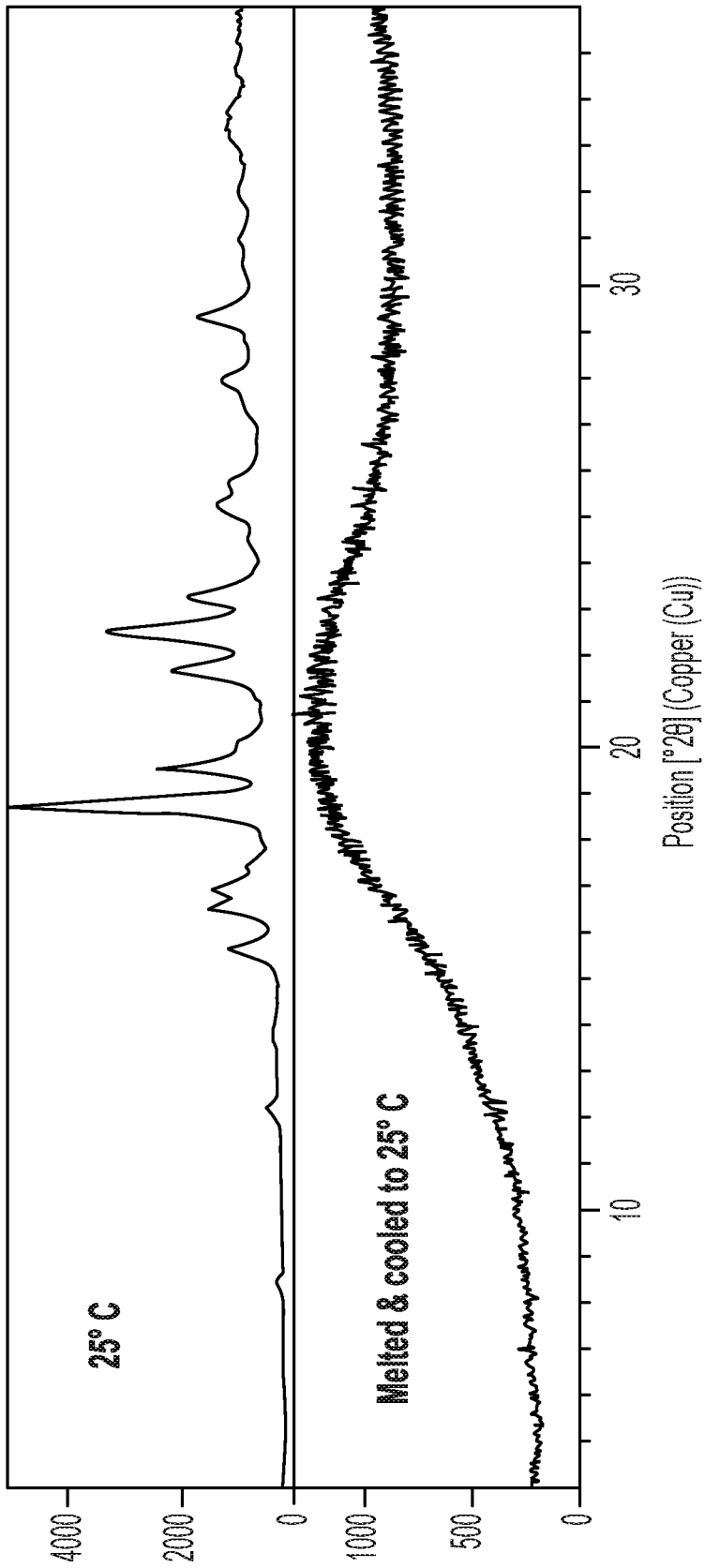

25° C
Melted & cooled to 25° C
4000
2000
0
1000
500
0
10
20
30
Position [°2θ] (Copper (Cu))

FIG. 13

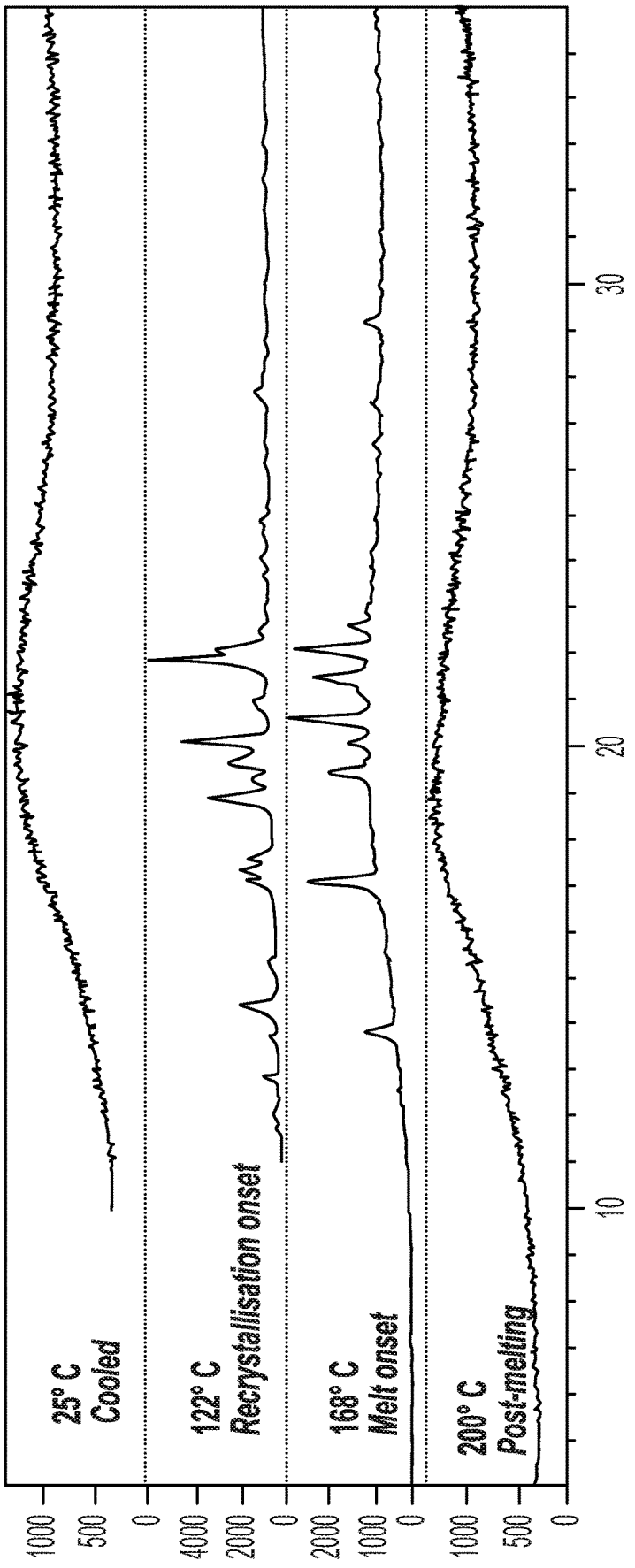

25° C
Cooled
122° C
Recrystallisation onset
168° C
Melt onset
200° C
Post-melting
1000
500
0
4000
2000
0
2000
1000
0
1000
500
0
10
20
30
Position [°2θ] (Copper (Cu))

FIG. 14

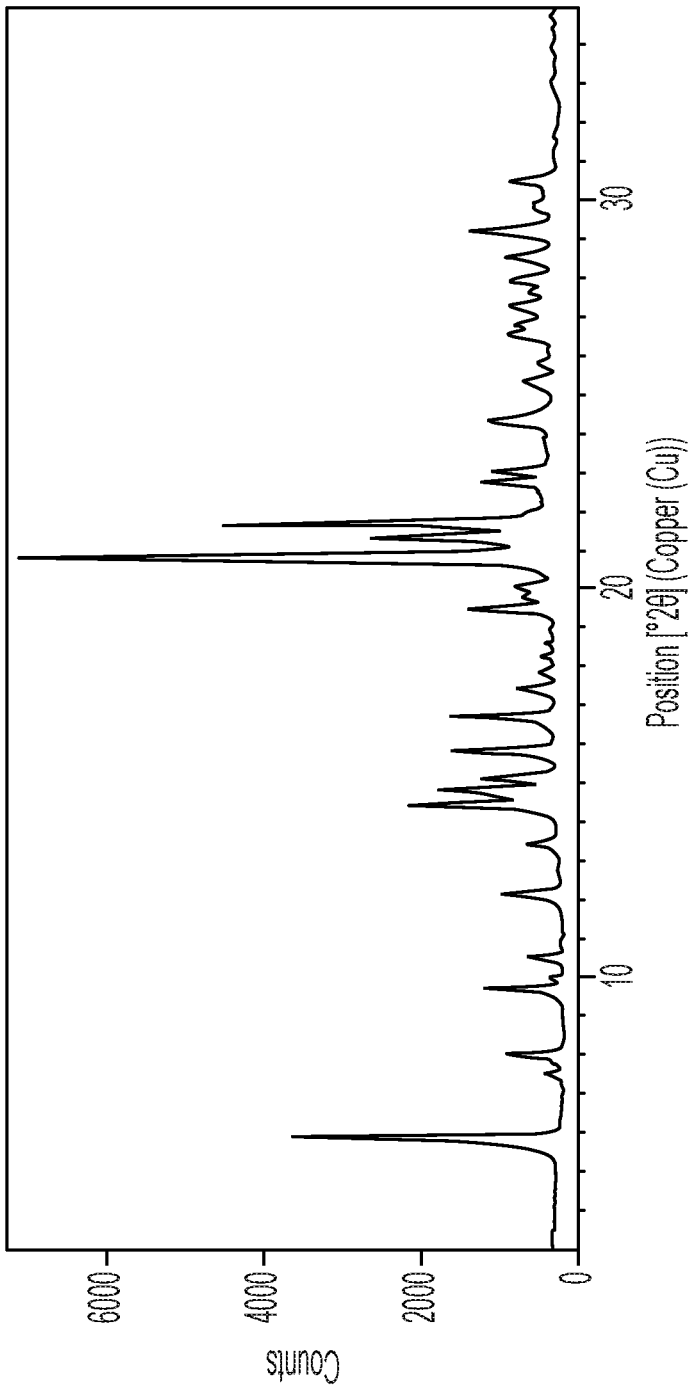


FIG. 15

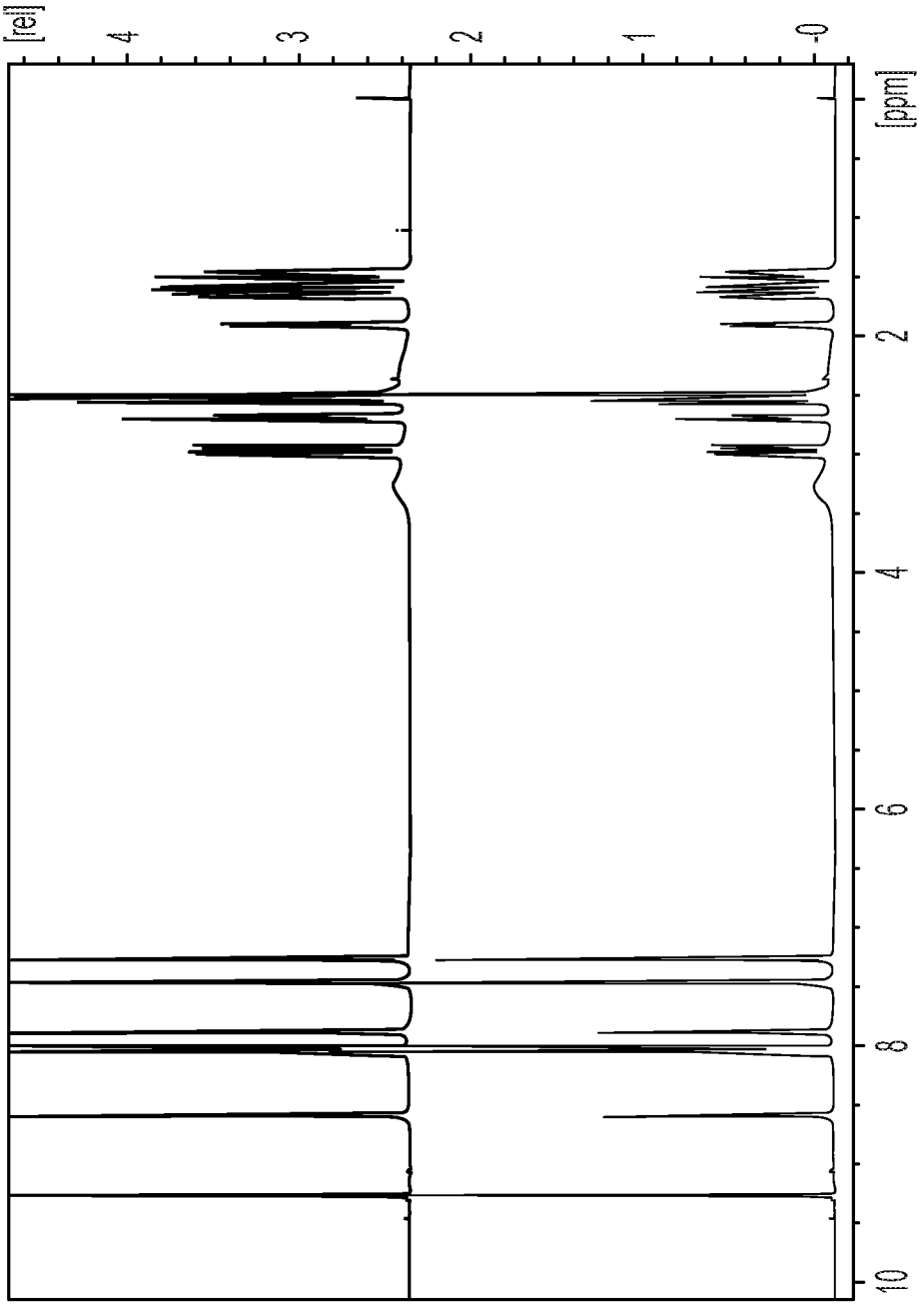


FIG. 16

CRYSTALLINE FORMS OF NIRAPARIB FREEBASE

CROSS-REFERENCE TO RELATED APPLICATIONS

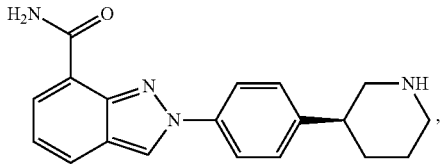
[0001] The present application claims benefit of U.S. Provisional Application No. 62/740,869, filed Oct. 3, 2018, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] This disclosure relates to crystalline niraparib, to compositions comprising crystalline niraparib, and to uses of the same.

SUMMARY OF THE INVENTION

[0003] Niraparib is the international nonproprietory name for 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide. The compound has the structure



("niraparib")

and it is a potent inhibitor of poly (ADP-ribose) polymerase ("PARP") proteins, in particular being selective for PARP-1 and PARP-2 (see e.g. Thorsell et al., *J. Med. Chem.* (2017) 60:1262-1271).

[0004] Niraparib inhibits the proliferation of BRCA1- and BRCA2-deficient cell lines in vitro. Niraparib decreases tumor growth in mouse xenograft models of human cancers with deficiencies in BRCA1 and BRCA2 or with homologous recombination deficiency (HRD) that have either mutated or wild-type BRCA1/2. Niraparib also can be useful in treating cancers characterized a deficiency in certain genes involved in the homologous recombination repair (HRR) pathway, including non-BRCA1/2 HRR genes. Niraparib can form PARP-DNA complexes resulting in DNA damage, apoptosis, and cell death (Murai et al., *Cancer Res.* (2012) 72:5588-99). Niraparib also has pharmacologic activity on dopamine, norepinephrine and serotonin transporters at concentrations similar to those which are effective for PARP inhibition (see e.g. Ison et al., *Clinical Cancer Research* (2018) 24(17):4066-4071). Niraparib therefore has the potential to treat conditions including cancers (especially cancers which are refractory to platinum-based chemotherapy), as well as conditions such as stroke, autoimmune diabetes, neurological diseases, inflammatory diseases, metabolic diseases and cardiovascular diseases.

[0005] The discovery of niraparib and its activity as a PARP inhibitor is reported by Jones et al. (*J. Med. Chem.*, 2009, 52:7170-7185). Jones et al. describe a synthesis of niraparib in which the freebase form of the compound is obtained as a lyophilised powder.

[0006] Amorphous niraparib freebase is poorly soluble in water (around 1 mg/mL) and its solubility does not improve greatly at lower pH values. Typically, organic compounds are more readily soluble when in an amorphous state than when in a crystalline state. Surprisingly, however, the present inventors have discovered that niraparib freebase can be obtained in crystalline form, wherein the crystalline form has a similar or an increased solubility relative to the amorphous form. Crystalline niraparib freebase has other desirable properties, including a good stability and a lack of hygroscopicity.

[0007] Accordingly, the present invention relates to crystalline niraparib freebase, and to compositions and uses of the same. The present invention meets a need for new forms of niraparib having desirable properties for pharmaceutical formulation (e.g. into oral dosage forms), such as e.g. improved physicochemical and/or pharmacokinetic properties.

[0008] In a first aspect, the invention provides a crystalline form of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase.

[0009] In other aspects and embodiments, the invention provides a crystalline Form I of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase.

[0010] In embodiments, a crystalline form of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase has an X-ray powder diffraction (XRPD) pattern comprising at least three diffraction angles, when measured using Cu K radiation, selected from a group consisting of about 12.2, 15.6, 16.5, 16.9, 18.7, 19.6, 21.6, 22.4, 22.5, 23.2, 25.2, 27.9, and 29.3 degrees 2θ.

[0011] In embodiments, a crystalline form of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase has an X-ray powder diffraction (XRPD) pattern comprising at least three diffraction angles, when measured using Cu K radiation, selected from a group consisting of about 15.6, 16.5, 16.9, 18.7, 19.6, 21.6, 22.4, 22.5, 23.2, and 29.3 degrees 2θ.

[0012] In embodiments, a crystalline form of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase has an X-ray powder diffraction (XRPD) pattern comprising at least three diffraction angles, when measured using Cu K radiation, selected from a group consisting of about 15.6, 16.5, 18.7, 19.6, 21.6, 22.4, 22.5, and 23.2 degrees 2θ.

[0013] In embodiments, a crystalline form of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase has an XRPD pattern, when measured using Cu K radiation, comprising diffraction angles of about 15.6, 16.5, 16.9, 18.7, 19.6, 21.6, and 22.5 degrees 2θ.

[0014] In embodiments, a crystalline form of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase has an X-ray powder diffraction (XRPD) pattern, when measured using Cu K radiation, comprising diffraction angles of about 18.7, 19.6, 21.6, and 22.5 degrees 2θ.

[0015] In embodiments, a crystalline form (crystalline Form I) of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase has an X-ray powder diffraction (XRPD) pattern comprising a diffraction angle at 18.7±0.2° 2θ.

[0016] In embodiments, a crystalline form (crystalline Form I) of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase has an XRPD pattern comprising diffraction angles at 18.7 and 22.5±0.2° 2θ.

[0017] In embodiments, a crystalline form (crystalline Form I) of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-

7-carboxamide (niraparib) freebase has an XRPD pattern comprising diffraction angles at 18.7 and 19.6±0.2° 2θ.

[0018] In embodiments, a crystalline form (crystalline Form I) of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase has an XRPD pattern comprising diffraction angles at 18.7, 19.6 and 22.5±0.2° 2θ.

[0019] In embodiments, a crystalline form (crystalline Form I) of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase has an XRPD pattern comprising one or more diffraction angles at 16.9, 18.7, 19.6, 21.6 and 22.5±0.2° 2θ.

[0020] In embodiments a crystalline form (crystalline Form I) of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase has an XRPD pattern comprising at least two diffraction angles at 16.9, 18.7, 19.6, 21.6 and 22.5±0.2° 2θ.

[0021] In embodiments, a crystalline form (crystalline Form I) of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase has an XRPD pattern comprising at least three diffraction angles at 16.9, 18.7, 19.6, 21.6 and 22.5±0.2° 2θ.

[0022] In embodiments, a crystalline form (crystalline Form I) of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase has an XRPD pattern comprising at least four diffraction angles at 16.9, 18.7, 19.6, 21.6 and 22.5±0.2° 2θ.

[0023] In embodiments, a crystalline form (crystalline Form I) of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase has an XRPD pattern comprising diffraction angles at 16.9, 18.7, 19.6, 21.6 and 22.5±0.2° 2θ.

[0024] In embodiments, a crystalline form (crystalline Form I) of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase has an XRPD pattern comprising one or more diffraction angles at 15.6, 16.5, 22.4, 23.2, and 29.3±0.2° 2θ.

[0025] In embodiments, a crystalline form (crystalline Form I) of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase has an XRPD pattern comprising at least two diffraction angles at 15.6, 16.5, 22.4, 23.2, and 29.3±0.2° 2θ.

[0026] In embodiments, a crystalline form (crystalline Form I) of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase has an XRPD pattern comprising at least three diffraction angles at 15.6, 16.5, 22.4, 23.2, and 29.3±0.2° 2θ.

[0027] In embodiments, a crystalline form (crystalline Form I) of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase has an XRPD pattern comprising at least four diffraction angles at 15.6, 16.5, 22.4, 23.2, and/or 29.3±0.2° 2θ.

[0028] In embodiments, a crystalline form (crystalline Form I) of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase has an XRPD pattern comprising diffraction angles at 15.6, 16.5, 22.4, 23.2, and 29.3±0.2° 2θ.

[0029] In embodiments, a crystalline form (crystalline Form I) of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase has an XRPD pattern comprising diffraction angles at 15.6, 16.5, 16.9, 18.7, 19.6, 21.6, 22.4, 22.5, 23.2 and 29.3±0.2° 2θ.

[0030] In embodiments, a crystalline form (crystalline Form I) of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase has an XRPD pattern comprising diffraction angles with the 2θ values, and optionally also relative intensities, according to the following table:

Pos. [°2θ]	Rel. Int. [%]
8.4	3
12.2	8
12.8	1
13.7	1
15.6	19
16.5	25
16.9	27
17.4	7
18.0	2
18.7	100
19.6	37
20.0	7
21.6	28
22.4	23
22.5	38
23.2	21
24.4	2
25.0	6
25.2	9
25.7	6
27.3	2
27.9	8
29.3	13
30.4	2
31.0	3
32.0	2
32.7	1
33.2	3
33.8	3
34.7	2

[0031] In embodiments, a crystalline form (crystalline Form I) of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase is characterised by an XRPD pattern substantially as shown in FIG. **1**.

[0032] In embodiments, a crystalline form (crystalline Form I) of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase is characterised by an infrared (IR) spectrum comprising a peak at about 1652 cm^{-1} and a peak at about 1608 cm^{1}.

[0033] In embodiments, a crystalline form (crystalline Form I) of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase is characterised by an infrared (IR) spectrum substantially as shown in FIG. **4**.

[0034] In embodiments, a crystalline form (crystalline Form I) of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase is characterised by a Raman spectrum comprising peaks at about 960.3, 1457.5 and 1607.0 cm^{-1}.

[0035] In embodiments, a crystalline form (crystalline Form I) of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase is characterised by a Raman spectrum substantially as shown in FIG. **5**.

[0036] In embodiments, a crystalline form (crystalline Form I) of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase is characterised by a melting point of about 185-195° C.

[0037] In embodiments, a crystalline form (crystalline Form I) of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase is characterised by a DTA thermogram substantially as shown in FIG. **6**.

[0038] In embodiments, a crystalline form (crystalline Form I) of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-

7-carboxamide (niraparib) freebase is characterised by a DSC thermogram substantially as shown in FIG. **7**.

[0039] In embodiments, a crystalline form (crystalline Form I) of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase is characterised by adsorbing less than about 1% by weight of water up to about 90% relative humidity at about 25° C.

[0040] In other aspects and embodiments, the invention provides a crystalline Form II, III, IV, or V of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase.

[0041] In other aspects, the invention provides a composition comprising a crystalline niraparib freebase defined hereinbefore, wherein the composition is substantially free of amorphous niraparib, a pharmaceutically acceptable salt of niraparib, and/or any other solid form of niraparib or niraparib salt.

[0042] In embodiments, less than about 10% or less than about 5% of the total niraparib in the composition is in the form of said amorphous niraparib, said pharmaceutically acceptable salt of niraparib, and/or any other solid form of niraparib or niraparib salt.

[0043] In other aspects, the invention provides a pharmaceutical composition comprising a crystalline niraparib freebase defined hereinbefore, and at least one pharmaceutically acceptable excipient.

[0044] In other aspects, the invention provides the crystalline niraparib freebase, the composition, or the pharmaceutical composition defined hereinbefore, for use in therapy.

[0045] In other aspects, the invention provides use of the crystalline niraparib freebase, or the pharmaceutical composition defined hereinbefore, in the manufacture of a medicament.

[0046] In other aspects, the invention provides a method of treating cancer, stroke, autoimmune diabetes, a neurological disease, an inflammatory disease, a metabolic disease or a cardiovascular disease in a subject, the method comprising administering to the subject an effective amount of the crystalline niraparib freebase, or the composition, or the pharmaceutical composition defined hereinbefore.

[0047] In embodiments, the method is a method of treating cancer.

[0048] In embodiments, said cancer is associated with BRCA1 and/or BRCA2 mutations.

[0049] In embodiments, said cancer is association with a mutation in ATM, ATR, BAP1, BARD1, BLM, BRIP1, MRE11A, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, or XRCC2, or any combination thereof.

[0050] In embodiments, said cancer is epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer.

[0051] In other aspects, the invention provides the crystalline niraparib freebase, or the composition, or the pharmaceutical composition defined hereinbefore, for use in a method as defined hereinbefore.

[0052] In other aspects, the invention provides use of the crystalline niraparib freebase, or the composition, or the pharmaceutical composition defined hereinbefore, in the manufacture of a medicament for use in a method as defined hereinbefore.

BRIEF DESCRIPTION OF THE FIGURES

[0053] FIG. **1** shows an XRPD pattern of niraparib freebase Form I prepared according to the present Examples.

[0054] FIG. **2** shows photomicrographs of niraparib freebase Form I prepared according to the present Examples. These are obtained under standard (FIGS. **2**A and **2**B) and polarised light (FIGS. **2**C and **2**D) conditions.

[0055] FIG. **3** shows SEM images of niraparib freebase Form I crystals prepared according to the present Examples at various levels of magnification.

[0056] FIG. **4** shows an FT-IR spectrum of niraparib freebase Form I prepared according to the present Examples.

[0057] FIG. **5** shows a Raman spectrum of niraparib freebase Form I (λ_{ex}=785 nm) prepared according to the present Examples.

[0058] FIG. **6** shows TG/DTA thermograms of niraparib freebase Form I prepared according to the present Examples.

[0059] FIG. **7** shows a DSC thermogram of niraparib freebase Form I prepared according to the present Examples.

[0060] FIG. **8** shows a GVS isotherm plot of niraparib freebase Form I prepared according to the present Examples. The figure overlays two full sorption/desorption cycles. The solid line with empty circular markers shows sorption #1 (40% to 90% RH) and the dashed line with filled diamond markers shows desorption #1 (90% to 0% RH). The solid line with empty triangular markers shows sorption #2 (0% to 90% RH) and the dashed line with filled square markers shows desorption #2 (90% to 0% RH). The solid line with asterisk markers shows sorption #3 (0% to 40% RH).

[0061] FIG. **9** shows the XRPD pattern of amorphous niraparib freebase prepared according to the present Examples.

[0062] FIG. **10** shows an XRPD pattern of niraparib freebase Form II prepared according to the present Examples.

[0063] FIG. **11** shows an XRPD pattern of niraparib freebase Form III prepared according to the present Examples.

[0064] FIG. **12** shows a DSC thermogram in which a previously-heated and cooled sample of niraparib freebase is re-heated.

[0065] FIG. **13** shows an overlay of XRPD patterns of niraparib freebase Form I (top) versus amorphous niraparib freebase (bottom) obtained by melting and cooling (VT-XRPD).

[0066] FIG. **14** shows an overlay of XRPD patterns obtained by reheating a cooled sample of niraparib freebase (VT-XRPD). The top scan shows the XRPD pattern of the initial, cool material. The second scan shows the onset of recrystallization to Form IV at ~122° C. The third scan shows the change in XRPD pattern at the onset of melting at ~168° C. The bottom scan shows the pattern at 200° C., after melting.

[0067] FIG. **15** shows the XRPD pattern of niraparib freebase Form V prepared according to the present Examples.

[0068] FIG. **16** shows an overlay of the ^{1}H-NMR spectra of crystalline niraparib Form I (upper trace) and Form IV (lower trace) prepared according to the present Examples.

DETAILED DESCRIPTION

[0069] Although specific embodiments of the present disclosure will now be described with reference to the description and examples, it should be understood that such

embodiments are by way of example only and merely illustrative of but a small number of the many possible specific embodiments which can represent applications of the principles of the present disclosure. Various changes and modifications will be obvious to those of skill in the art given the benefit of the present disclosure and are deemed to be within the spirit and scope of the present disclosure as further defined in the appended claims.

Definitions

[0070] Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, exemplary methods, devices, and materials are now described. All technical and patent publications cited herein are incorporated herein by reference in their entirety. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

[0071] The practice of the present disclosure will employ, unless otherwise indicated, conventional techniques of chemical synthesis, tissue culture, immunology, molecular biology, microbiology, cell biology and recombinant DNA, which are within the skill of the art. See, e.g., Michael R. Green and Joseph Sambrook, Molecular Cloning (4^{th} ed., Cold Spring Harbor Laboratory Press 2012.

[0072] Numerical designations, e.g. pH, temperature, time, concentration, molecular weight, etc., including ranges, are approximations which are varied (+) or (−) by increments of 0.1 or 1.0, where appropriate. It is to be understood, although not always explicitly stated that all numerical designations are preceded by the term "about". It also is to be understood, although not always explicitly stated, that the reagents described herein are merely exemplary and that equivalents of such may be known in the art.

[0073] As used in the specification and claims, the singular forms "a", "an" and "the" include plural references unless the context clearly dictates otherwise. For example, the term "a cell" includes a plurality of cells, including mixtures thereof. Unless specifically stated or obvious from context, as used herein, the term "or" is understood to be inclusive. The term "including" is used herein to mean, and is used interchangeably with, the phrase "including but not limited to".

[0074] As used herein, and unless otherwise specified, the terms "about" and "approximately", when used in connection with doses, amounts, or weight percent of ingredients of a composition or a dosage form, mean a dose, amount, or weight percent that is recognized by those of ordinary skill in the art to provide a pharmacological effect equivalent to that obtained from the specified dose, amount, or weight percent. Specifically, the terms "about" and "approximately", when used in this context, contemplate a dose, amount, or weight percent within 15%, more specifically within 10%, more specifically within 5%, of the specified dose, amount, or weight percent. As used herein, and unless otherwise specified, the terms "about" and "approximately", when used in connection with a numeric value or range of values which is provided to characterize a particular solid form, e.g., a specific temperature or temperature range, such as, for example, that describing a melting, dehydration, desolvation or glass transition temperature; a mass change, such as, for example, a mass change as a function of temperature or humidity; a solvent or water content, in terms of, for example, mass or a percentage; or a peak position or diffraction angle, such as, for example, in analysis by IR or Raman spectroscopy or XRPD; indicate that the value or range of values may deviate to an extent deemed reasonable to one of ordinary skill in the art while still describing the particular solid form. Specifically, the terms "about" and "approximately", when used in this context, indicate that the numeric value or range of values may vary, in particular embodiments, within 20%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1.5%, 1%, 0.5%, or 0.25% of the recited value or range of values. With respect to XRPD, values given are ±0.2 degrees 2θ if not expressly specified as such.

[0075] As used herein, the term "comprising" or "comprises" is intended to mean that the compositions and methods include the recited elements, but not excluding others. "Consisting essentially of" when used to define compositions and methods, shall mean excluding other elements of any essential significance to the combination for the stated purpose. Thus, a composition consisting essentially of the elements as defined herein would not exclude contaminants from the isolation and purification method and pharmaceutically acceptable carriers, such as phosphate buffered saline, preservatives and the like. "Consisting of" shall mean excluding more than trace elements of other ingredients and substantial method steps for administering the compositions of this disclosure or process steps to produce a composition or achieve an intended result. Embodiments defined by each of these transition terms are within the scope of this invention. Use of the term "comprising" herein is intended to encompass, and to disclose, the corresponding statements in which the term "comprising" is replaced by "consisting essentially of" or "consisting of".

[0076] A "subject", "individual" or "patient" is used interchangeably herein, and refers to a vertebrate, such as a mammal. Mammals include, but are not limited to, rodents, farm animals, sport animals, pets and primates; for example murines, rats, rabbit, simians, bovines, ovines, porcines, canines, felines, equines, and humans. In one embodiment, the mammals include horses, dogs, and cats. In a preferred embodiment, the mammal is a human.

[0077] "Administering" is defined herein as a means of providing an agent or a composition containing the agent to a subject in a manner that results in the agent being inside the subject's body. Such an administration can be by any route including, without limitation, oral, transdermal (e.g. by the vagina, rectum, or oral mucosa), by injection (e.g. subcutaneous, intravenous, parenteral, intraperitoneal, or into the central nervous system), or by inhalation (e.g. oral or nasal). Pharmaceutical preparations are, of course, given by forms suitable for each administration route.

[0078] "Treating" or "treatment" of a disease includes: (1) preventing the disease, i.e. causing the clinical symptoms of the disease not to develop in a patient that may be predisposed to the disease but does not yet experience or display symptoms of the disease; (2) inhibiting the disease, i.e. arresting or reducing the development of the disease or its clinical symptoms; and/or (3) relieving the disease, i.e. causing regression of the disease or its clinical symptoms.

[0079] The term "suffering" as it relates to the term "treatment" refers to a patient or individual who has been diagnosed with or is predisposed to the disease. A patient

may also be referred to being "at risk of suffering" from a disease because of a history of disease in their family lineage or because of the presence of genetic mutations associated with the disease. A patient at risk of a disease has not yet developed all or some of the characteristic pathologies of the disease.

[0080] An "effective amount" or "therapeutically effective amount" is an amount sufficient to effect beneficial or desired results. An effective amount can be administered in one or more administrations, applications or dosages. Such delivery is dependent on a number of variables including the time period for which the individual dosage unit is to be used, the bioavailability of the therapeutic agent, the route of administration, etc. It is understood, however, that specific dose levels of the therapeutic agents of the present invention for any particular subject depends upon a variety of factors including, for example, the activity of the specific compound employed, the age, body weight, general health, sex, and diet of the subject, the time of administration, the rate of excretion, the drug combination, and the severity of the particular disorder being treated and form of administration. Treatment dosages generally may be titrated to optimize safety and efficacy. Typically, dosage-effect relationships from in vitro and/or in vivo tests initially can provide useful guidance on the proper doses for patient administration. In general, one will desire to administer an amount of the compound that is effective to achieve a serum level commensurate with the concentrations found to be effective in vitro. Determination of these parameters is well within the skill of the art. These considerations, as well as effective formulations and administration procedures are well known in the art and are described in standard textbooks.

[0081] As used herein, the term "pharmaceutically acceptable excipient" encompasses any of the standard pharmaceutical excipients, including carriers such as a phosphate buffered saline solution, water, and emulsions, such as an oil/water or water/oil emulsion, and various types of wetting agents. Pharmaceutical compositions also can include other components such as stabilizers and preservatives. For examples of carriers, stabilizers and adjuvants, see Remington's Pharmaceutical Sciences (20th ed., Mack Publishing Co. 2000).

[0082] The term "freebase" is generally used herein to mean niraparib (when in a solid, e.g. crystalline, state) which is substantially free of counter-ionic species. Thus, in solid niraparib freebase, the niraparib is substantially in a non-ionized, i.e. neutral, form. The niraparib freebase of the present disclosure is typically at least 90% in a non-ionized form, preferably at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% in a non-ionized form, e.g. essentially 100% in a non-ionized form.

[0083] The term "amorphous", "amorphous form", and related terms used herein mean that the substance, component or product in question is not substantially crystalline as determined by X-ray diffraction. In certain embodiments, a sample comprising an amorphous form of a substance may be substantially free of other amorphous forms and/or crystal forms.

[0084] The term "crystalline" and related terms used herein, when used to describe a substance, component, product, or form, means that the substance, component or product is substantially crystalline as determined by X-ray diffraction (see e.g. Remington's Pharmaceutical Sciences, 22nd ed., Pharmaceutical Press, 2012; and The United States Pharmacopoeia, 30th ed., 2011).

[0085] The term "crystal form", "crystalline form" and related terms herein refer to a crystalline solid form comprising a chemical compound, and may refer to a particular single-component or multiple-component crystal form, including, but not limited to, a polymorph, a solvate, a hydrate or other molecular complex.

[0086] The terms "polymorphs", "polymorphic forms" and related terms herein refer to two or more crystal forms that comprise the same molecule, molecules or ions. Different polymorphs may have different physical properties such as, for example, melting temperatures, heats of fusion, solubilities, dissolution rates and/or vibrational spectra as a result of the arrangement or conformation of the molecules or ions in the crystal lattice. The differences in physical properties exhibited by polymorphs may affect pharmaceutical parameters such as storage stability, compressibility and density (which can be important in formulation and product manufacturing), and dissolution rate (which can be an important factor in bioavailability). Differences in stability can result from changes in chemical reactivity (e.g. differential oxidation, such that a dosage form discolors more rapidly when comprised of one polymorph than when comprised of another polymorph) or mechanical changes (e.g. tablets crumble on storage as a kinetically favored polymorph converts to thermodynamically more stable polymorph) or both (e.g. tablets of one polymorph are more susceptible to breakdown at high humidity). As a result of solubility/dissolution differences, in the extreme case, some polymorphic transitions may result in variations in potency or lack of potency, or variations in toxicity, which may result in higher or lower incidence of unwanted side effects or a change in severity of an unwanted side effect. In addition, the physical properties of the crystal may be important in processing; for example, one polymorph might be more likely to form solvates or might be difficult to filter and wash free of impurities (e.g. particle shape and size distribution might be different between polymorphs).

[0087] Techniques for characterizing crystal forms and amorphous forms include, but are not limited to, thermal gravimetric analysis (TGA), melting point, differential scanning calorimetry (DSC), X-ray powder diffractometry (XRPD), single-crystal X-ray diffractometry, vibrational spectroscopy, e.g. infrared (IR) and Raman spectroscopy, solid-state and solution nuclear magnetic resonance (NMR) spectroscopy, optical microscopy (e.g. polaraized light microscopy), hot stage optical microscopy, scanning electron microscopy (SEM), electron crystallography, dynamic vapor sorption (DVS), and quantitative analysis, particle size analysis (PSA), surface area analysis, solubility studies and dissolution studies. Exemplary experimental values described herein may be variable according to the standard measures of the field, such as the exemplary variation described herein.

[0088] Where a crystalline form is characterized by one or more XRPD diffraction angles, and unless otherwise indicated, it is to be understood that the XRPD pattern is obtained under standard conditions (e.g. as described herein) and that the 2θ values may be variable according to the standard measures in the field. For example, 2θ values recited herein may be variable by ±0.2°. Furthermore, where a crystalline form is characterized by one or more specified XRPD diffraction angles, those diffraction angles will typi-

cally represent diffraction angles having a relative intensity within the diffractogram of at least 1%, e.g. of at least 2%, 5% or 10% relative intensity.

[0089] The recitation of an embodiment for a variable or aspect herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

[0090] Compositions and methods provided herein may be combined with one or more of any of the other compositions and methods provided herein.

[0091] The following abbreviations are used herein:

[0092] ° C.=Celsius

[0093] DMSO=dimethyl sulfoxide

[0094] DTA=differential thermal analysis

[0095] DSC=differential scanning calorimetry

[0096] GC=gas chromatography

[0097] h=hour

[0098] HPLC=high pressure liquid chromatography

[0099] HRD=homologous recombination deficiency

[0100] Hz=hertz

[0101] MEK=methyl ethyl ketone

[0102] 2-MeTHF=2-methyltetrahydrofuran

[0103] MHz=megahertz;

[0104] min=minute

[0105] MS=mass spectrometry

[0106] NMR=nuclear magnetic resonance

[0107] PARP=poly (ADP-ribose) polymerase

[0108] rt/RT=room temperature

[0109] TBME=tert-butyl methyl ether

[0110] TGA=thermogravimetric analysis

[0111] (VT-)XRPD=(variable temperature) X-ray power diffraction

Crystalline Niraparib Freebase

[0112] The present invention relates to the drug niraparib in a new physical form (crystalline freebase) having desirable properties for pharmaceutical formulation, such as e.g. improved physicochemical and/or pharmacokinetic properties. The use of niraparib in its freebase form also allows for increased drug loading possibilities relative to other forms. For example, relative to a salt form of niraparib, the drug loading of a niraparib freebase dosage form could be increased by at least around 40%. Such an increased drug loading could translate into a reduced unit dosage size and/or a reduced pill burden for a subject who receives the dosage form, both of which are desirable outcomes from a pharmaceutical perspective.

[0113] In a first aspect, therefore, the present invention provides a crystalline form of 2-{4-[(3S)-piperidin-3-yl] phenyl}-2H-indazole-7-carboxamide (niraparib)freebase.

[0114] In one embodiment, the crystalline 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase comprises Form I, Form II, Form III, Form IV and/or Form V crystalline niraparib freebase, e.g. as characterised herein. In another embodiment, the crystalline niraparib freebase is substantially free from Form II, Form III, Form IV and/or Form V crystalline niraparib freebase, e.g. as characterised herein.

[0115] Exemplary crystalline forms are described herein. Exemplary X-ray powder diffraction (XRPD) patterns are also described herein. In embodiments, an XRPD pattern is measured using Cu K radiation. In embodiments, an XRPD pattern is characterized by certain diffraction angles (peaks) as described herein.

Form I Crystalline Niraparib Freebase

[0116] In one embodiment, the crystalline 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib)freebase comprises Form I crystalline niraparib freebase, e.g. as characterised herein. Viewed from this aspect, the invention provides a crystalline Form I of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase.

[0117] The crystalline niraparib freebase may be characterised by one or more (e.g. one, two, three, four or five) XRPD diffraction angles at 2θ values of 16.9°, 18.7°, 19.6°, 21.6° and 22.5°. In embodiments, the crystalline niraparib freebase is characterised by at least two XRPD diffraction angles at 2θ values of 16.9°, 18.7°, 19.6°, 21.6° and 22.5°. In embodiments, the crystalline niraparib freebase is characterised by at least three XRPD diffraction angles at 2θ values of 16.9°, 18.7°, 19.6°, 21.6° and 22.5°. In embodiments, the crystalline niraparib freebase is characterised by at least four XRPD diffraction angles at 2θ values of 16.9°, 18.7°, 19.6°, 21.6° and 22.5°. In embodiments, the crystalline niraparib freebase is characterised by XRPD diffraction angles at 2θ values of 16.9°, 18.7°, 19.6°, 21.6° and 22.5°. In embodiments, the crystalline niraparib freebase is characterised by (e.g. further characterised by) one or more (e.g. one, two, three, four or five) XRPD diffraction angles at 2θ values of 15.6°, 16.5°, 22.4°, 23.2°, and 29.3°. In embodiments, the crystalline niraparib freebase is characterised by at least two XRPD diffraction angles at 2θ values of 15.6°, 16.5°, 22.4°, 23.2°, and 29.3°. In embodiments, the crystalline niraparib freebase is characterised by at least three XRPD diffraction angles at 2θ values of 15.6°, 16.5°, 22.4°, 23.2°, and 29.3°. In embodiments, the crystalline niraparib freebase is characterised by at least four XRPD diffraction angles at 2θ values of 15.6°, 16.5°, 22.4°, 23.2°, and 29.3°. In embodiments, the crystalline niraparib freebase is characterised by XRPD diffraction angles at 2θ values of 15.6°, 16.5°, 22.4°, 23.2°, and 29.3°.

[0118] In one embodiment, the crystalline niraparib freebase is characterised by an XRPD diffraction angle at a 2θ value of 18.7°, and is optionally further characterised by one or more XRPD diffraction angles e.g. at 2θ values of 22.5°, 19.6°, 21.6°, 16.9°, 16.5°, 22.4°, 23.2°, 15.6° and 29.32°. Thus, the crystalline niraparib freebase may be characterised by one, two, three, four, five, six, seven, eight, nine or ten diffraction angles at 2θ values of 18.7°, 22.5°, 19.6°, 21.6°, 16.9°, 16.5°, 22.4°, 23.2°, 15.6° and 29.3°. In embodiments, the crystalline niraparib freebase is characterised by XRPD diffraction angles at 2θ values of 15.6°, 16.5°, 16.9°, 18.7°, 19.6°, 21.6°, 22.4°, 22.5°, 23.2° and 29.3°.

[0119] In one embodiment, the crystalline niraparib freebase is characterised by XRPD diffraction angles at 2θ values of 18.7° and 22.5°. In another embodiment, the crystalline niraparib freebase is characterised by XRPD diffraction angles at 2θ values of 18.7° and 19.6°. In yet another embodiment, the crystalline niraparib freebase is characterised by XRPD diffraction angles at 2θ values of 18.7°, 22.5°, and 19.6°. In a further embodiment, the crystalline niraparib freebase is characterised by XRPD diffraction angles at 18.7° and 22.50, as well as one, two, three, four, five, six or seven of 19.6°, 21.6°, 16.9°, 16.5°, 22.4°, 23.3° and 15.6°. In a further embodiment, the crystalline niraparib freebase is characterised by XRPD diffraction angles at 18.7° and 19.6°, as well as one, two, three, four, five, six or seven of 22.5°, 21.6°, 16.9°, 16.5°, 22.4°, 23.2°

and 15.6°. In a further embodiment, the crystalline niraparib freebase is characterised by XRPD diffraction angles at 18.7°, 22.5°, and 19.6°, as well as one, two, three, four, five or six of 21.6°, 16.9°, 16.5°, 22.4°, 23.2° and 15.6°. In a further embodiment, the crystalline niraparib freebase is characterised by XRPD diffraction angles at 2θ values of 16.9°, 18.7°, 19.6°, 21.6° and 22.5°. In a yet further embodiment, the crystalline niraparib freebase is characterised by XRPD diffraction angles at 2θ values of 15.6°, 16.5°, 16.9°, 18.7°, 19.6°, 21.6°, 22.4°, 22.5°, 23.2° and 29.3°.

[0120] In one embodiment, the crystalline niraparib freebase is characterised by one or more (e.g. one, two, three, four or five) XRPD diffraction angles at 2θ values of 15.6°, 16.5°, 23.2°, 25.2° and 27.9°. In embodiments, the crystalline niraparib freebase is characterised by at least two XRPD diffraction angles at 2θ values of 15.6°, 16.5°, 23.2°, 25.2° and 27.9°. In embodiments, the crystalline niraparib freebase is characterised by at least three XRPD diffraction angles at 2θ values of 15.6°, 16.5°, 23.2°, 25.2° and 27.9°. In embodiments, the crystalline niraparib freebase is characterised by at least four XRPD diffraction angles at 2θ values of 15.6°, 16.5°, 23.2°, 25.2° and 27.9°. In embodiments, the crystalline niraparib freebase is characterised by XRPD diffraction angles at 2θ values of 15.6°, 16.5°, 23.2°, 25.2° and 27.9°. In embodiments, the crystalline niraparib freebase is characterised by an XRPD diffraction angle at a 2θ value of 18.7°, and is further characterised by one or more (e.g. one, two, three, four or five) XRPD diffraction angles at 2θ values of 15.6°, 16.5°, 23.2°, 25.2° and 27.9°.

[0121] In embodiments, a crystalline form of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase has an X-ray powder diffraction (XRPD) pattern comprising at least three diffraction angles, when measured using Cu K radiation, selected from a group consisting of about 12.2, 15.6, 16.5, 16.9, 18.7, 19.6, 21.6, 22.4, 22.5, 23.2, 25.2, 27.9, and 29.3 degrees 2θ.

[0122] In embodiments, a crystalline form of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase has an X-ray powder diffraction (XRPD) pattern comprising at least three diffraction angles, when measured using Cu K radiation, selected from a group consisting of about 15.6, 16.5, 16.9, 18.7, 19.6, 21.6, 22.4, 22.5, 23.2, and 29.3 degrees 2θ.

[0123] In embodiments, a crystalline form of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase has an X-ray powder diffraction (XRPD) pattern comprising at least three diffraction angles, when measured using Cu K radiation, selected from a group consisting of about 15.6, 16.5, 18.7, 19.6, 21.6, 22.4, 22.5, and 23.2 degrees 2θ.

[0124] In embodiments, a crystalline form of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase has an XRPD pattern, when measured using Cu K radiation, comprising diffraction angles of about 15.6, 16.5, 16.9, 18.7, 19.6, 21.6, and 22.5 degrees 2θ.

[0125] In embodiments, a crystalline form of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase has an X-ray powder diffraction (XRPD) pattern, when measured using Cu K radiation, comprising diffraction angles of about 18.7, 19.6, 21.6, and 22.5 degrees 2θ.

[0126] In one embodiment, the crystalline niraparib freebase is characterised by XRPD diffraction angles having 2θ values (and, optionally, relative intensity values) as recited in the table below:

Pos. [°2θ]	Rel. Int. [%]
8.4	3
12.2	8
12.8	1
13.7	1
15.6	19
16.5	25
16.9	27
17.4	7
18.0	2
18.7	100
19.6	37
20.0	7
21.6	28
22.4	23
22.5	38
23.2	21
24.4	2
25.0	6
25.2	9
25.7	6
27.3	2
27.9	8
29.3	13
30.4	2
31.0	3
32.0	2
32.7	1
33.2	3
33.8	3
34.7	2

[0127] In one embodiment, the crystalline niraparib freebase is characterised by an XRPD pattern substantially according to Table 1 of Example 1. In embodiments, the position of an XRPD diffraction angle is within ±0.2000° 2θ of the value specified in Table 1; the d-spacing is within ±0.2000 Å or ±0.1000 Å of the value specified in Table 1; and/or the relative intensity is within ±10% or ±5% of the value specified in Table 1. In one embodiment, the crystalline niraparib freebase is characterised by an XRPD pattern as shown (or substantially as shown) in FIG. **1**.

[0128] In embodiments, the crystalline niraparib freebase is characterised by having an infra-red spectrum which includes a peak at about 1652 cm^{-1} and a peak at about 1608 cm^{-1}, e.g. when measured using a FT-IR method as described herein. In embodiments, the crystalline niraparib freebase is characterised by infra-red peaks substantially according to Table 2 of Example 1. In embodiments, an absorption peak is within ±1.00, 0.50, or 0.20 cm^{-1} of the value specified in Table 2. In embodiments, a transmittance value is within ±10% or ±5% of the value specified in Table 2. In embodiments, the crystalline niraparib freebase is characterised by having an infra-red spectrum as shown (or substantially as shown) in FIG. **4**.

[0129] In embodiments, the crystalline niraparib freebase is characterised by having a Raman spectrum which includes peaks at shift values of about 960.3, about 1457.5 and about 1607.0 cm^{-1}. In embodiments, the crystalline niraparib freebase is characterised by Raman peaks substantially according to Table 3 of Example 1. In embodiments, an absorption peak is within ±1.00, 0.50, or 0.20 cm^{-1} of the value specified in Table 3. In embodiments, a transmittance

value is within ±10% or ±5% of the value specified in Table 3. In embodiments, the crystalline niraparib freebase is characterised by having a Raman spectrum as shown (or substantially as shown) in FIG. **5**.

[0130] In embodiments, the crystalline niraparib freebase is characterised by having a melting point in the range of about 185-195° C., such as e.g. a melting point of about 190° C.

[0131] The melting point may be determined, for example, by DTA (e.g. as described in the following Examples). Thus, in embodiments, the crystalline niraparib freebase is characterised by a DTA thermogram in which the onset of melting (endothermic peak) is about 188.0° C. and/or wherein the peak minimum is about 191.8° C. In embodiments, the crystalline niraparib freebase is characterised by having a DTA thermogram as shown (or substantially as shown) in FIG. **6** (lower trace).

[0132] The melting point may also be determined, for example, by DSC (e.g. as described in the following Examples). Thus, in embodiments, the crystalline niraparib freebase is characterised by a DSC thermogram in which the onset of melting (endothermic peak) is about 189.0° C. and/or wherein the peak minimum is about 193.9° C. In embodiments, the crystalline niraparib freebase is characterised by a DSC thermogram as shown (or substantially as shown) in FIG. **7**.

[0133] In embodiments, the crystalline niraparib freebase is characterised by not being hygroscopic. Hygroscopicity may be determined, for example, by GVS (e.g. as described in the following Examples). Thus, in embodiments, the crystalline niraparib freebase is characterised by adsorbing less than about 1% by weight of water up to about 90% relative humidity (e.g. at about 25° C.). In embodiments, the crystalline niraparib freebase is characterised by adsorbing about 0.7% by weight of water up to about 90% relative humidity (e.g. at about 25° C.).

[0134] In embodiments, the crystalline niraparib freebase is characterised by being stable under conditions of elevated humidity and/or when in aqueous suspension.

[0135] In embodiments, substantially all (e.g. at least about 90%, at least about 95%, at least about 99% or about 100%) of the crystalline niraparib freebase retains the same form (e.g. polymorphic form as assessed by XRPD) when exposed to about 90% relative humidity at room temperature (e.g. at about 25° C.). In other embodiments, substantially all (e.g. at least about 90%, at least about 95%, at least about 99% or about 100%) of the crystalline niraparib freebase retains the same form (e.g. polymorphic form as assessed by XRPD) when exposed to about 90% relative humidity at elevated temperature (e.g. at about 30° C., 40° C., 50° C., 60° C. or 75° C.).

[0136] In embodiments, substantially all (e.g. at least about 90%, at least about 95%, at least about 99% or about 100%) of the crystalline niraparib freebase retains the same form (e.g. polymorphic form as assessed by XRPD) when suspended in, or slurried with, water. In other embodiments, substantially all (e.g. at least about 90%, at least about 95%, at least about 99% or about 100%) of the crystalline niraparib freebase retains the same form (e.g. polymorphic form as assessed by XRPD) when suspended in, or slurried with, an aqueous buffer having a pH between about 1 and about 7 (e.g. a buffer as in the present Examples).

[0137] In embodiments, the crystalline niraparib freebase is characterised by being free of water or organic solvents, e.g. as assessed by Karl Fisher analysis or gas chromatography.

[0138] In embodiments, the crystalline niraparib freebase is substantially free of water, e.g. as assessed by Karl Fisher analysis. In these embodiments, the water content is preferably less than about 1%, such as e.g. less than about 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2% or 0.1%. The water content may be, for example, between about 0.25% and about 0.35%, such as e.g. about 0.30%.

[0139] In embodiments, the crystalline niraparib freebase is substantially free of organic solvents such as 2-MeTHF, e.g. as assessed by GC. In these embodiments, the content of each (and every) organic solvent is preferably less than about 1%, such as e.g. less than about 0.5%, 0.4%, 0.3%, 0.2%, 0.1% or 0.05%. The content of 2-MeTHF may be, for example, less than about 0.1%, such as e.g. about 0.07%.

[0140] In a further aspect, the present disclosure provides a crystalline Form II, III, IV, and/or V niraparib freebase. The crystalline niraparib freebase may comprise Form II crystalline niraparib freebase, e.g. as characterised herein. The crystalline niraparib freebase may comprise Form III crystalline niraparib freebase, e.g. as characterised herein. The crystalline niraparib freebase may comprise Form IV crystalline niraparib freebase, e.g. as characterised herein. The crystalline niraparib freebase may comprise Form V crystalline niraparib freebase, e.g. as characterised herein.

Form II Crystalline Niraparib Freebase

[0141] In one embodiment, the crystalline 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase comprises Form II crystalline niraparib freebase, e.g. as characterised herein. Viewed from this aspect, the invention provides a crystalline Form II of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase.

[0142] In embodiments, the crystalline Form II is characterised by one or more (e.g. one, two, three, four or five) XRPD diffraction angles at 2θ values of 17.3°, 21.7°, 21.8°, 25.8°, and 21.6°. In embodiments, the crystalline Form II is characterised by one or more (e.g. one, two, three, four or five) XRPD diffraction angles at 2θ values of 8.6°, 26.4°, 22.6°, 20.10, and 21.3°. In embodiments, the crystalline Form II is characterised by XRPD diffraction angles at 2θ values of 8.6°, 17.3°, 20.10, 21.3°, 21.6°, 21.7°, 21.8°, 22.6°, 25.8° and 26.4°. In embodiments, the crystalline Form II is characterised by an XRPD diffraction angle at a 2θ value of 3.2°.

[0143] In embodiments, the crystalline Form II is characterised by XRPD diffraction angles having 2θ values (and, optionally, relative intensity values) substantially as recited in Table 4 in Example 3. In embodiments, the position of an XRPD diffraction angle is within ±0.2000° 2θ of the value specified in Table 4; the d-spacing is within ±0.20000 Å or ±0.10000 Å of the value specified in Table 4; and/or the relative intensity is within ±10% or ±5% of the value specified in Table 4. In embodiments, the crystalline Form II is characterised by an XRPD pattern as shown (or substantially as shown) in FIG. **10**.

Form III Crystalline Niraparib Freebase

[0144] In one embodiment, the crystalline 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (nira-

parib) freebase comprises Form III crystalline niraparib freebase, e.g. as characterised herein. Viewed from this aspect, the invention provides a crystalline Form III of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase.

[0145] In embodiments, the crystalline Form III is characterised by one or more (e.g. one, two, three, four or five) XRPD diffraction angles at 2θ values of 17.3°, 20.5°, 13.6°, 21.3° and 21.7°. In embodiments, the crystalline Form III is characterised by one or more (e.g. one, two, three, four or five) XRPD diffraction angles at 2θ values of 22.3°, 13.8°, 24.10, 23.7° and 14.6°. In embodiments, the crystalline Form III is characterised by XRPD diffraction angles at 2θ values of 13.6°, 13.8°, 14.6°, 17.3°, 20.5°, 21.3°, 21.7°, 22.3°, 23.7° and 24.1°. In embodiments, the crystalline Form III is characterised by an XRPD diffraction angle at a 2θ value of 20.5°. In embodiments, the crystalline Form III is characterised by XRPD diffraction angles at 2θ values of 20.5° and 23.7°. In embodiments, the crystalline Form III is characterised by XRPD diffraction angles at 2θ values of 20.5°, 23.7° and 10.1°.

[0146] In embodiments, the crystalline Form III is characterised by XRPD diffraction angles having 2θ values (and, optionally, relative intensity values) substantially as recited in Table 5 in Example 3. In embodiments, the position of an XRPD diffraction angle is within ±0.2000° 2θ of the value specified in Table 5; the d-spacing is within ±0.20000 Å or ±0.10000 Å of the value specified in Table 5; and/or the relative intensity is within ±10% or ±5% of the value specified in Table 5. In embodiments, the crystalline Form III is characterised by an XRPD pattern as shown (or substantially as shown) in FIG. **11**.

Form IV Crystalline Niraparib Freebase

[0147] In one embodiment, the crystalline 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase comprises Form IV crystalline niraparib freebase, e.g. as characterised herein. Viewed from this aspect, the invention provides a crystalline Form IV of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase.

[0148] In embodiments, the crystalline Form IV is characterised by one or more (e.g. one, two, three, four or five) XRPD diffraction angles at 2θ values of 21.9°, 20.1°, 18.9°, 22.1° and 19.7°. In embodiments, the crystalline Form IV is characterised by one or more (e.g. one, two, three, four or five) XRPD diffraction angles at 2θ values of 14.4°, 17.3°, 17.10, 19.8° and 17.6°. In embodiments, the crystalline Form IV is characterised by XRPD diffraction angles at 2θ values of 14.4°, 17.10, 17.3°, 17.6°, 18.9°, 19.7°, 19.8°, 20.10, 21.9° and 22.1°. In embodiments, the crystalline Form IV is characterised by an XRPD diffraction angle at a 2θ value of 27.6°. In embodiments, the crystalline Form IV is characterised by XRPD diffraction angles at 2θ values of 27.6° and 24.8°. In embodiments, the crystalline Form IV is characterised by XRPD diffraction angles at 2θ values of 27.6°, 24.8° and 7.3°.

[0149] In embodiments, the crystalline Form IV is characterised by XRPD diffraction angles having 2θ values (and, optionally, relative intensity values) substantially as recited in Table 6 in Example 4. In embodiments, the position of an XRPD diffraction angle is within ±0.2000° 2θ of the value specified in Table 6; the d-spacing is within ±0.20000 Å or ±0.10000 Å of the value specified in Table 6; and/or the relative intensity is within ±10% or ±5% of the value specified in Table 6. In embodiments, the crystalline Form IV is characterised by an XRPD pattern as shown (or substantially as shown) in FIG. **14** (the 122° C. trace).

Form V Crystalline Niraparib Freebase

[0150] In one embodiment, the crystalline 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase comprises Form V crystalline niraparib freebase, e.g. as characterised herein. Viewed from this aspect, the invention provides a crystalline Form V of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase.

[0151] In embodiments, the crystalline Form V is characterised by one or more (e.g. one, two, three, four or five) XRPD diffraction angles at 2θ values of 20.8°, 21.6°, 5.9°, 21.3° and 14.4°. In embodiments, the crystalline Form V is characterised by one or more (e.g. one, two, three, four or five) XRPD diffraction angles at 2θ values of 14.8°, 16.7°, 15.8°, 19.5° and 29.2°. In embodiments, the crystalline Form V is characterised by XRPD diffraction angles at 2θ values of 5.9°, 14.4°, 14.8°, 15.8°, 16.7°, 19.5°, 20.8°, 21.3°, 21.6° and 29.2°. In embodiments, the crystalline Form V is characterised by an XRPD diffraction angle at a 2θ value of 5.9°. In embodiments, the crystalline Form V is characterised by an XRPD diffraction angle at a 2θ value of 5.9° and further characterised by XRPD diffraction angles at 2θ values of 15.10 and/or 9.7°. In embodiments, the crystalline Form V is characterised by XRPD diffraction angles at 2θ values of 5.9°, 15.1°, 9.7° and 8.0°.

[0152] In embodiments, the crystalline Form V is characterised by XRPD diffraction angles having 2θ values (and, optionally, relative intensity values) substantially as recited in Table 8 in Example 5. In embodiments, the position of an XRPD diffraction angle is within ±0.2000° 2θ of the value specified in Table 8; the d-spacing is within ±0.20000 Å or ±0.10000 Å of the value specified in Table 8; and/or the relative intensity is within ±10% or ±5% of the value specified in Table 8. In embodiments, the crystalline Form V is characterised by an XRPD pattern as shown (or substantially as shown) in FIG. **15**.

Compositions

[0153] The present disclosure provides a composition (e.g. a pharmaceutical composition) comprising crystalline 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase. In embodiments, the composition is substantially free of amorphous niraparib. In embodiments, the composition is substantially free of a (e.g. any) pharmaceutically acceptable salt of niraparib. In embodiments, the composition is substantially free of any other solid form of niraparib freebase or niraparib salt (besides a crystalline niraparib freebase as described herein). In embodiments, less than about 10% (e.g. less than about 5%, less than about 4%, less than about 3%, less than about 2% or less than about 1%) of the total niraparib in the composition is in the form of said amorphous niraparib, said pharmaceutically acceptable salt of niraparib, and/or said other solid form of niraparib freebase or niraparib salt.

[0154] The present disclosure provides a pharmaceutical composition comprising crystalline niraparib freebase as described herein and at least one pharmaceutically accept-

able excipient. The pharmaceutical compositions may be used according to the methods disclosed herein.

[0155] In one embodiment, the pharmaceutical composition comprises crystalline niraparib freebase Form I as described herein. In embodiments, the pharmaceutical composition is substantially free from (e.g. as assessed by XRPD) Form II, Form III, Form IV and/or Form V crystalline niraparib freebase. In embodiments, the pharmaceutical composition is substantially free from (e.g. as assessed by XRPD) Form II, Form III, Form IV and Form V crystalline niraparib freebase. In embodiments, the pharmaceutical composition is substantially free from (e.g. as assessed by XRPD) amorphous niraparib freebase.

[0156] In embodiments, the pharmaceutical composition comprises about 20-80 wt % of crystalline niraparib freebase, such as e.g. about 45-70 wt %, about 40-50 wt %, about 45-55 wt %, about 50-60 wt %, about 55-65 wt %, about 60-70 wt %, about 65-75 wt %, about 70-80 wt %, or about 40-60 wt % of crystalline niraparib freebase.

[0157] The pharmaceutically acceptable excipient can be any such excipient known in the art including those described in, for example, Remington's Pharmaceutical Sciences, Mack Publishing Co. (A. R. Gennaro edit. 1985). Pharmaceutical compositions of the compounds presently disclosed may be prepared by conventional means known in the art including, for example, mixing at least one presently disclosed compound with a pharmaceutically acceptable excipient.

[0158] Exemplary pharmaceutically acceptable excipients for the purposes of pharmaceutical compositions disclosed herein include, but are not limited to, binders, disintegrants, superdisintegrants, lubricants, diluents, fillers, flavors, glidants, sorbents, solubilizers, chelating agents, emulsifiers, thickening agents, dispersants, stabilizers, suspending agents, adsorbents, granulating agents, preservatives, buffers, coloring agents and sweeteners or combinations thereof. In embodiments, the pharmaceutically acceptable excipient comprises hydroxypropyl methylcellulose, e.g. low substituted hydroxypropyl cellulose. In embodiments, the pharmaceutically acceptable excipient comprises lactose, e.g. lactose monohydrate. In embodiments, the pharmaceutically acceptable excipient comprises magnesium stearate. In some embodiments, the pharmaceutically acceptable excipient is lactose monohydrate and magnesium stearate.

[0159] Various useful fillers or diluents include, but are not limited to, calcium carbonate (Barcroft™, MagGran™, Millicarb™, Pharma-Carb™, Precarb™, Sturcal™, Vivapres Ca™), calcium phosphate, dibasic anhydrous (Emcompress Anhydrous™, Fujicalin™) calcium phosphate, dibasic dihydrate (Calstar™, Di-Cafos™, Emcompress™), calcium phosphate tribasic (Tri-Cafos™, TRI-TAB™), calcium sulphate (Destab™, Drierite™, Snow White™, Cal-Tab™, Compactrol™), cellulose powdered (Arbocel™, Elcema™, Sanacet™), silicified microcrystailine cellulose, cellulose acetate, compressible sugar (Di-Pac™), confectioner's sugar, dextrates (Candex™, Emdex™), dextrin (Avedex™, Caloreen™, Primogran W™), dextrose (Caridex™, Dextrofin™, Tab fine D-IOO™) fructose (Fructofin™, Krystar™), kaolin (Lion™, Sim 90™), lactitol (Finlac DC™, Finlac MCX™), lactose (Anhydrox™, CapsuLac™, Fast-Flo™, FlowLac™, GranuLac™, InhaLac™, Lactochem™, Lactohaie™, Lactopress™, Microfme™, Microtose™, Pharmatose™, Prisma Lac™, Respitose™, SacheLac™, SorboLac™, Super-Tab™, Tablettose™, Wyndale™, Zeparox™), lactose monohydrate, magnesium carbonate, magnesium oxide (MagGran MO™), maltodextrin (C*Dry MD™, Lycatab DSH™, Maldex™, Maitagran™, Maltrin™, Maltrin QD™, Paselli MD 10 PH™, Star-Dri™) maltose (Advantose 100™), mannitol (Mannogem™, Pearlitol™), microcrystalline cellulose (Avicel PH™, Celex™, Celphere™, Ceolus KG™, Emcocel™, Pharmacel™, Tabulose™ Vivapur™), polydextrose (Litesse™), simethicone (Dow Corning Q7-2243 LVA™, Cow Coming Q7-2587™, Sentry Simethicone™), sodium alginate (Keltone™, Protanal™) sodium chloride (Alberger™), sorbitol (Liponec 70-NC™, Liponic 76-NCv, Meritol™, Neosorb™, Sorbitol Instant™, Sorbogem™), starch (Flufiex W™, Instant Pure-Cote™, Melojei™, Meritena Paygel 55™, Perfectamyl D6PH™, Pure-Cote™, Pure-Dent™, Pure-Gel™, Pure-Set™, Purity 21™, Purity 826™, Tablet White™), pregelatinized starch, sucrose, trehalose and xylitol, or mixtures thereof. In embodiments, the filler comprises lactose monohydrate.

[0160] In embodiments, the composition comprises about 5-90% by weight of filler, e.g. the filler is present in an amount of about 10-80%, about 15-70%, about 20-60% or about 25-50% by weight. For example, the composition may comprise about 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or 80% by weight of filler. In embodiments, the composition comprises from about 25 mg to about 1000 mg of filler, e.g. the filler is present in an amount of from about 50 mg to about 750 mg, from about 100 mg to about 600 mg, from about 150 mg to about 500 mg or from about 200 mg to about 450 mg. For example, the composition may comprise about 250, 275, 300, 325, 350, 375, 400, 425, 450, 475 or 500 mg of filler.

[0161] Various useful lubricants include, but are not limited to, calcium stearate (HyQual™), glycerine monostearate (Imwitor™ 191 and 900, Kessco GMS5™, 450 and 600, Myvaplex 600P™, Myvatex™, Rita GMS™, Stepan GMS™, Tegin™, Tegin™ 503 and 515, Tegin 4100™, Tegin M™, Unimate GMS™), glyceryl behenate (Compritol 888 ATO™), glyceryl palmitostearate (Precirol ATO 5™), hydrogenated castor oil (Castorwax MP 80™, Croduret™, Cutina HR™, Fancol™, Simulsol 1293™), hydrogenated vegetable oil 0 type I (Sterotex™, Dynasan P60™, Hydrocote™, Lipovol HS-K™, Sterotex HM™) magnesium lauryl sulphate, magnesium stearate, medium-chain triglycerides (Captex 300™, Labrafac CC™, Miglyol 810™, Neobee MS™, Nesatol™, Waglinol 3/9280™), poloxamer (Pluronic™, Synperonic™), polyethylene 5 glycol (Carbowax Sentry™, Lipo™, Lipoxol™, Lutrol E™, Pluriol E™), sodium benzoate (Antimol™), sodium chloride, sodium lauryl sulphate (Elfan 240™, Texapon Kl 2P™), sodium stearyl fumarate (Pruv™), stearic acid (Hystrene™, Industrene™, Kortacid 1895™, Pristerene™), talc (Altaic™, Luzenac™, Luzenac Pharma™, Magsil Osmanthus™, 0 Magsil Star™, Superiore™), sucrose stearate (Surfhope SE Pharma D-1803 F™) and zinc stearate (HyQual™) or mixtures thereof. Examples of suitable lubricants include, but are not limited to, magnesium stearate, calcium stearate, zinc stearate, stearic acid, talc, glyceryl behenate, polyethylene glycol, polyethylene oxide polymers, sodium lauryl sulfate, magnesium lauryl sulfate, sodium oleate, sodium stearyl fumarate, DL-leucine, colloidal silica. In embodiments, the lubricant comprises magnesium stearate.

[0162] In embodiments, the composition comprises about 0.1-5% by weight of lubricant, e.g. the lubricant is present in an amount of about 0.2-2%, about 0.3-1%, about 0.4-0.75% or about 0.5-0.7% by weight. For example, the composition may comprise about 0.3%, 0.4%, 0.5%, 0.6%, 0.7% or 0.8% by weight of lubricant. In embodiments, the composition comprises from about 0.01 mg to about 10 mg of lubricant, e.g. the lubricant is present in an amount of from about 0.01 mg to 0.05 mg, 0.05 mg to 0.1 mg, 0.1 mg to 0.2 mg, 0.2 mg to 0.25 mg, 0.25 mg to 0.5 mg, 0.5 mg to 0.75 mg, 0.7 mg to 0.95 mg, 0.9 mg to 1.15 mg, 1.1 mg to 1.35 mg, 1.3 mg to 1.5 mg, 1.5 mg to 1.75 mg, 1.75 to 1.95 mg, 1.9 mg to 2.15 mg, 2.1 mg to 2.35 mg, 2.3 mg to 2.55 mg, 2.5 mg to 2.75 mg, 2.7 mg to 3.0 mg, 2.9 mg to 3.15 mg, 3.1 mg to 3.35 mg, 3.3 mg to 3.5 mg, 3.5 mg to 3.75 mg, 3.7 mg to 4.0 mg, 4.0 mg to 4.5 mg, 4.5 mg to 5.0 mg, 5.0 mg to 5.5 mg, 5.5 mg to 6.0 mg, 6.0 mg to 6.5 mg, 6.5 mg to 7.0 mg, 7.0 mg to 7.5 mg, 7.5 mg to 8.0 mg, 8.0 mg to 8.5 mg, 8.5 mg to 9.0 mg, 9.0 mg to 9.5 mg, or 9.5 mg to 10.0 mg. For example, the composition may comprise about 0.01 mg, 0.05 mg, 0.1 mg, 0.2 mg, 0.25 mg, 0.5 mg, 0.7 mg, 0.9 mg, 1.1 mg, 1.3 mg, 1.5 mg, 1.7 mg, 1.9 mg, 2. mg, 2.3 mg, 2.5 mg, 2.75 mg, 3.0 mg, 3.1 mg, 3.3 mg, 3.5 mg, 3.7 mg, 4.0 mg, 4.5 mg, 5.0 mg, 5.5 mg, 6.0 mg, 6.5 mg, 7.0 mg, 7.5 mg, 8.0 mg, 8.5 mg, 9.0 mg, 9.5 mg or 10.0 mg by weight of lubricant.

[0163] Various useful disintegrants include, but are not limited to, alginic acid (Protacid™, Satialgine H8™), calcium phosphate, tribasic (TRI-TAB™) carboxymethylcellulose calcium (ECG 505™), carboxymethylcellulose sodium (Akucell™, Finnfix™, Nymcel Tylose CB™), colloidal silicon dioxide (Aerosil™, Cab-O-Sil™, Wacker HDK™), croscarmellose sodium (Ac-Di-Sol™, Pharmacel XL™, Primellose™, Solutab™, Vivasol™), crospovidone (Collison CL™, Collison CL-M™, Polyplasdone XL™), docusate sodium, guar gum (Meyprodor™, Meyprofm™, Meyproguar™), low substituted hydroxypropyl cellulose, magnesium aluminum silicate (Magnabite™, Neusilin™, Pharmsorb™, Veegum™), methylcellulose (Methocel™, Metolose™), microcrystalline cellulose (Avicel PH™, Ceoius KG™, Emcoel™, Ethispheres™, Fibrocel™, Pharmacel™, Vivapur™), povidone (Collison™, Plasdone™) sodium alginate (Kelcosol™, Ketone™, Protanal™), sodium starch glycolate, polacrilin potassium (Amberlite IRP88™), silicified microcrystalline cellulose (ProSotv™), starch (Aytex P™, Fluftex W™, Melojel™, Meritena™, Paygel 55™, Perfectamyl D6PH™, Pure-Bind™, Pure-Cote™, Pure-Dent™, Purity 21™, Purity 826™, Tablet White™) or pre-gelatinized starch (Lycatab PGS™, Merigel™, National 78-1551™, Pharma-Gel™, Prejel™, Sepistab ST 200™, Spress B820™, Starch 1500 G™, Tablitz™, Unipure LD™), or mixtures thereof. In embodiments, the composition comprises about 0 to about 10% by weight of disintegrant.

[0164] Various useful glidants include, but are not limited to, tribasic calcium phosphate (TRI-TAB™), calcium silicate, cellulose powdered (Sanacel™, Solka-Floe™), colloidal silicon dioxide (Aerosil™, Cab-O-Sil M-5P™, Wacker HDK™), magnesium silicate, magnesium trisilicate, starch (Melojel™, Meritena™, Paygel 55™, Perfectamyl D6PH™, Pure-Bind™, Pure-Cote™, Pure-Dent™, Pure-Gel™, Pure-Set™, Purity 21™, Purity 826™, Tablet White™) and talc (Luzenac Pharma™, Magsil Osmanthus™, Magsil Star™, Superiore™), or mixtures thereof. In embodiments, the composition comprises about 0 to about 15% by weight of glidant.

[0165] Pharmaceutically acceptable surfactants include, but are limited to, both non-ionic and ionic surfactants suitable for use in pharmaceutical dosage forms. Ionic surfactants may include one or more of anionic, cationic or zwitterionic surfactants. Various useful surfactants include, but are not limited to, sodium lauryl sulfate, monooleate, monolaurate, monopalmitate, monostearate or another ester of olyoxyethylene sorbitane, sodium dioctylsulfosuccinate, lecithin, stearyic alcohol, cetostearylic alcohol, cholesterol, polyoxyethylene ricin oil, polyoxyethylene fatty acid glycerides, poloxamer, or any other commercially available co-processed surfactant like SEPITRAP® 80 or SEPITRAP® 4000 and mixtures thereof. In embodiments, the composition comprises about 0 to about 5% by weight of surfactant.

[0166] In embodiments, a solid pharmaceutical composition of the disclosure comprises crystalline niraparib freebase as described herein, a diluent and a lubricant. In embodiments, the solid pharmaceutical composition comprises crystalline niraparib freebase as described herein (e.g. crystalline niraparib freebase Form I), lactose monohydrate and magnesium stearate.

[0167] In embodiments, a solid pharmaceutical composition of the disclosure comprises (by weight of the composition) about 20-60% crystalline niraparib freebase, about 20-80% diluent and about 0.1-5% lubricant. In embodiments, the pharmaceutical composition comprises (by weight of the composition) about 40-60% crystalline niraparib freebase, about 40-70% diluent (e.g. lactose monohydrate) and about 0.2-2% lubricant (e.g. magnesium stearate).

[0168] The pharmaceutical compositions can be formulated so as to provide slow, extended, or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. The pharmaceutical compositions can also optionally contain opacifying agents and may be of a composition that releases the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner, e.g. by using an enteric coating. Examples of embedding compositions include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more pharmaceutically acceptable carriers, excipients, or diluents well known in the art (see, e.g. Remington's). The compounds presently disclosed may be formulated for sustained delivery according to methods well known to those of ordinary skill in the art. Examples of such formulations can be found in U.S. Pat. Nos. 3,119,742; 3,492,397; 3,538,214; 4,060,598; and 4,173,626.

Synthesis

[0169] Crystalline niraparib freebase may be prepared from amorphous niraparib freebase, e.g. by dissolution/recrystallisation, by slurrying with solvent such as water, or by heating/cooling. It may also be prepared from a niraparib acid addition salt (such as e.g. niraparib tosylate monohydrate) by conversion with a base such as dilute NaOH. Methods for the preparation of crystalline niraparib freebase are illustrated in the following Examples.

[0170] In particular, crystalline niraparib freebase may be prepared by recrystallization from, or by slurrying with, an organic solvent, such as e.g. 2-MeTHF.

[0171] Alternative methods for the preparation of crystalline niraparib freebase would be apparent to the skilled person on the basis of their common general knowledge and the teaching of the present application.

Medical Indications

[0172] The crystalline 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase and pharmaceutical compositions described herein are useful in therapy, in particular in the therapeutic treatment of PARP-1 and PARP-2 mediated conditions in a subject. Methods for treating PARP-1 and PARP-2 mediated conditions are described in WO 2018/005818.

[0173] In certain embodiments, crystalline niraparib freebase may provide improved therapeutic benefits as compared to administration of a different form of niraparib (e.g. a crystalline niraparib tosylate monohydrate). In embodiments, an improved therapeutic benefit may be a change (e.g. a reduction) in the incidence and/or severity of an unwanted side-effect observed with a different form of niraparib. In embodiments, an unwanted side effect is thrombocytopenia, anemia, neutropenia, leukopenia, palpitations, nausea, constipation, vomiting, abdominal pain/distention, mucositis/stomatitis, diarrhea, dyspepsia, dry mouth, fatigue/asthenia, decreased appetite, urinary tract infection, AST/ALT elevation, myalgia, back pain, arthralgia, headache, dizziness, dysgeusia, insomnia, anxiety, nasopharyngitis, dyspnea, cough, rash, or hypertension. In embodiments, an unwanted side-effect is a hematological side-effect (e.g. thrombocytopenia, anemia, neutropenia, or leukopenia). In embodiments, an unwanted side-effect is a non-hematological side effect. In embodiments, an unwanted side-effect is a cardiovascular effect (e.g. palpitations). In embodiments, an unwanted side-effect is a gastrointestinal disorder (e.g. nausea, constipation, vomiting, abdominal pain/distension, mucositis/stomatitis, diarrhea, dyspepsia, or dry mouth). In embodiments, an unwanted side-effect is fatigue or asthenia. In embodiments, an unwanted side-effect is a metabolism or nutrition disorder (e.g. decreased appetite). In embodiments, an unwanted side-effect is an infection or infestation (e.g. urinary tract infection). In embodiments, an unwanted side-effect is elevation in AST/ALT. In embodiments, an unwanted side-effect is a musculoskeletal or connective tissue disorder (e.g. myalgia, back pain, or arthralgia). In embodiments, an unwanted side-effect is a nervous system disorder (e.g. headache, dizziness, or dysgeusia). In embodiments, an unwanted side-effect is a psychiatric disorder (e.g. insomnia or anxiety). In embodiments, an unwanted side-effect is a respiratory, thoracic, or mediastinal disorder (e.g. nasopharyngitis, dyspnea, or cough). In embodiments, an unwanted side-effect is a skin or subcutaneous tissue disorder (e.g. rash). In embodiments, an unwanted side-effect is a vascular disorder (e.g. hypertension).

[0174] In embodiments, an unwanted side-effect is myelodysplastic syndrome/acute myeloid leukemia. In embodiments, an unwanted side-effect is bone marrow suppression.

[0175] Subjects to be treated according to the methods described herein include vertebrates, such as mammals. In preferred embodiments the mammal is a human patient.

[0176] In one aspect, the present disclosure provides crystalline niraparib freebase as described herein, e.g. crystalline niraparib freebase Form I, for use in therapy. Also provided is the use of crystalline niraparib freebase as described herein, e.g. crystalline niraparib freebase Form I, in the manufacture of a medicament.

[0177] In another aspect, the present disclosure provides a method of treating cancer, stroke, autoimmune diabetes, a neurological disease, an inflammatory disease, a metabolic disease or a cardiovascular disease in a subject, the method comprising administering to the subject an effective amount of niraparib freebase as described herein, e.g. crystalline niraparib freebase Form I. Also provided is crystalline niraparib freebase as described herein, e.g. crystalline niraparib freebase Form I, for use in a method of treating cancer, stroke, autoimmune diabetes, a neurological disease, an inflammatory disease, a metabolic disease or a cardiovascular disease. Further provided is the use of crystalline niraparib freebase as described herein, e.g. crystalline niraparib freebase Form I, in the manufacture of a medicament for use in a method of treating cancer, stroke, autoimmune diabetes, a neurological disease, an inflammatory disease, a metabolic disease or a cardiovascular disease.

[0178] In a further aspect, the disclosure provides a method of treating a PARP-1 and/or PARP-2 mediated condition in a subject, the method administering to the subject an effective amount of niraparib freebase as described herein, e.g. crystalline niraparib freebase Form I. Also provided is crystalline niraparib freebase as described herein, e.g. crystalline niraparib freebase Form I, for use in a method of treating a PARP-1 and/or PARP-2 mediated condition. Further provided is the use of crystalline niraparib freebase as described herein, e.g. crystalline niraparib freebase Form I, in the manufacture of a medicament for use in a method of treating a PARP-1 and/or PARP-2 mediated condition.

Oncological Conditions (Cancers)

[0179] PARP inhibitors have shown activity as a monotherapy against tumors with existing DNA repair defects, such as BRCA1 and BRCA2, and as a combination therapy when administered together with anti-cancer agents that induce DNA damage. Despite several advances in treatment of ovarian cancer, most patients eventually relapse, and subsequent responses to additional treatment are often limited in duration. Women with germline BRCA1 or BRCA2 mutations have an increased risk for developing high grade serous ovarian cancer (HGSOC), and their tumors appear to be particularly sensitive to treatment with a PARP inhibitor. In addition, published scientific literature indicates that patients with platinum sensitive HGSOC who do not have germline BRCA1 or BRCA2 mutations may also experience clinical benefit from treatment with a PARP inhibitor. Since PARP inhibitors block DNA repair, in the context of cancer cells with the BRCA mutation, PARP inhibition results in synthetic lethality. For this reason, patients with germline mutations in a BRCA gene show marked clinical benefit following treatment with a PARP inhibitor.

[0180] In one embodiment, the condition to be treated is a cancer, especially a cancer which is associated with DNA repair defects, such as BRCA1 and/or BRCA2 mutations.

[0181] In embodiments, the cancer is a recurrent cancer.

[0182] In embodiments, a cancer is breast cancer, ovarian cancer, cervical cancer, epithelial ovarian cancer, fallopian

tube cancer, primary peritoneal cancer, endometrial cancer, prostate cancer, testicular cancer, pancreatic cancer, esophageal cancer, head and neck cancer, gastric cancer, bladder cancer, lung cancer (e.g. adenocarcinoma, NSCLC and SCLC), bone cancer (e.g. osteosarcoma), colon cancer, rectal cancer, thyroid cancer, brain and central nervous system cancers, glioblastoma, neuroblastoma, neuroendocrine cancer, rhabdoid cancer, keratoacanthoma, epidermoid carcinoma, seminoma, melanoma, sarcoma (e.g. liposarcoma), bladder cancer, liver cancer (e.g. hepatocellular carcinoma), kidney cancer (e.g. renal cell carcinoma), myeloid disorders (e.g. AML, CML, myelodysplastic syndrome and promyelocytic leukemia), and lymphoid disorders (e.g. leukemia, multiple myeloma, mantle cell lymphoma, ALL, CLL, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma) may be treated with compounds and methods described herein.

[0183] The cancer may be selected from head and neck cancer, breast cancer (e.g. metastatic breast cancer), prostate cancer (e.g. metastatic prostate cancer), testicular cancer, ovarian cancer, endometrial cancer, colon cancer, rectal cancer, lung cancer (e.g. non-small cell lung cancer), bladder cancer, pancreatic cancer (e.g. metastatic pancreatic cancer), brain and central nervous system cancers (e.g. primary malignant brain tumour), neuroendocrine cancer, rhabdoid cancer, gynaecological cancer, peritoneal cancer, skin cancer, thyroid cancer, oesophageal cancer, cervical cancer, gastric cancer, liver cancer, stomach cancer, renal cell cancer, biliary tract cancer, hematologic cancer, bone cancer, and blood cancer.

[0184] In embodiments, the cancer is selected from colorectal carcinoma, large intestinal colon carcinoma, head and neck carcinoma, seminoma, sarcoma, lung carcinoma, lung adenocarcinoma, bladder carcinoma, Barret's adenocarcinoma, renal carcinoma, epidermoid carcinoma, and hepatocarcinoma. In embodiments, the cancer is selected from glioblastoma, astrocytoma, melanoma (e.g. metastatic melanoma), mesothelioma, myeloma, keratoacanthoma, neuroblastoma, histiocytic lymphoma, and lymphocytic leukaemia. In embodiments, the cancer is a solid tumour (e.g. a malignant solid tumour) which may be an advanced-stage solid tumour.

[0185] In embodiments, the cancer is a gynaecological cancer, e.g. selected from ovarian cancer, cancer of the fallopian tube(s), peritoneal cancer and breast cancer. In some embodiments, the gynaecological cancer is associated with HRD and/or BRCA1/2 mutation(s). In some embodiments, the gynaecological cancer is platinum sensitive. In other embodiments, the gynaecological cancer is not platinum sensitive. In embodiments, the gynaecological cancer previously responded (e.g. partially or fully) to platinum-based therapy but has since developed resistance to platinum-based therapy.

[0186] In embodiments, the cancer is ovarian cancer, cancer of the fallopian tube(s), or peritoneal cancer (e.g. primary peritoneal cancer). In other embodiments, the cancer is breast cancer.

[0187] In some embodiments, the methods of the invention treat subjects with ovarian cancer. In some embodiments, the methods of the invention treat subjects with epithelial ovarian cancer. In some embodiments, the methods of the invention treat subjects with fallopian tube cancer. In some embodiments, the methods of the invention treat subjects with primary peritoneal cancer. In some embodiments, the methods of the invention treat subjects with recurrent ovarian cancer. In some embodiments, the methods of the invention treat subjects with recurrent epithelial ovarian cancer. In some embodiments, the methods of the invention treat subjects with recurrent fallopian tube cancer. In some embodiments, the methods of the invention treat subjects with recurrent primary peritoneal cancer.

[0188] In some embodiments, the methods of the invention treat subjects with recurrent ovarian cancer following a complete or partial response to a chemotherapy, such as a platinum-based chemotherapy. In some embodiments, the methods of the invention treat subjects with recurrent epithelial ovarian cancer following a complete or partial response to a chemotherapy, such as a platinum-based chemotherapy. In some embodiments, the methods of the invention treat subjects with recurrent fallopian tube cancer following a complete or partial response to a chemotherapy, such as a platinum-based chemotherapy. In some embodiments, the methods of the invention treat subjects with recurrent primary peritoneal cancer following a complete or partial response to a chemotherapy, such as a platinum-based chemotherapy.

[0189] In some embodiments, the methods of the invention treat subjects with recurrent ovarian cancer, recurrent epithelial ovarian cancer, recurrent fallopian tube cancer and/or recurrent primary peritoneal cancer following a complete or partial response to a platinum-based chemotherapy, wherein the subjects begin the treatment no later than 8 weeks after their most recent platinum-containing regimen. For example, subjects can begin treatment with niraparib about 7 weeks after their most recent platinum-containing regimen. For example, subjects can begin treatment with niraparib about 6 weeks after their most recent platinum-containing regimen. For example, subjects can begin treatment with niraparib about 6 weeks after their most recent platinum-containing regimen. For example, subjects can begin treatment with niraparib about 5 weeks after their most recent platinum-containing regimen. For example, subjects can begin treatment with niraparib about 4 weeks after their most recent platinum-containing regimen. For example, subjects can begin treatment with niraparib about 3 weeks after their most recent platinum-containing regimen. For example, subjects can begin treatment with niraparib about 2 weeks after their most recent platinum-containing regimen. For example, subjects can begin treatment with niraparib about 1 week after their most recent platinum-containing regimen.

[0190] In embodiments, the method treats cancer in a subject exhibiting a positive HRD status. In some embodiments, the subject is further characterized by the absence of a mutation in BRCA1 and/or BRCA2. A positive HRD status may be determined by quantifying in a patient sample a number of Indicator Chromosomal Aberration regions. In some embodiments, a tumor sample from the subject has a positive HRD status.

[0191] In other embodiments, the method treats cancer in a subject exhibiting an absence of HRD, e.g. a subject having platinum-sensitive recurrent ovarian cancer. The absence of HRD may be characterized by a lack of chromosomal aberrations (a detectable variation in chromosomal DNA which may fall into at least one of three overlapping categories: loss of heterozygosity, allelic imbalance (e.g. telomeric allelic imbalance), or large scale transition).

[0192] In embodiments, a method described herein treats a cancer that is associated with deficiency in at least one gene involved in a DNA repair pathway. Various pathways exist for DNA repair, including base excision repair (BER), direct repair (DR), double stranded break (DSB) repair, homologous recombination repair (HRR), mismatch repair (MMR), nucleotide excision repair (NER), and non-homologous end joining (NHEJ) repair; disruptions in these pathways can lead to the development and/or growth of cancer (see e.g. Kelley et al., *Future Oncol.* (2014) 10(7):1215-1237).

[0193] Exemplary genes involved in DNA repair pathways are described in Table A.

TABLE A

DNA Repair Genes

Gene Title	Gene Symbol
replication factor C (activator 1) 2, 40 kDa	RFC2
X-ray repair complementing defective repair in Chinese hamster cells 6 (Ku autoantigen, 70 kDa)	XRCC6
polymerase (DNA directed), delta 2, regulatory subunit 50 kDa	POLD2
proliferating cell nuclear antigen	PCNA
replication protein A1, 70 kDa	RPA1
replication protein A2, 32 kDa	RPA2
excision repair cross-complementing rodent repair deficiency, complementation group 3 (xeroderma pigmentosum group B complementing)	ERCC3
uracil-DNA glycosylase	UNG
excision repair cross-complementing rodent repair deficiency, complementation group 5 (xeroderma pigmentosum, complementation group G (Cockayne syndrome))	ERCC5
mutL homolog 1, colon cancer, nonpolyposis type 2 (*E. coli*)	MLH1
ligase I, DNA, ATP-dependent	LIG1
mutS homolog 6 (*E. coli*)	MSH6
polymerase (DNA-directed), delta 4	POLD4
replication factor C (activator 1) 5, 36.5 kDa	RFC5
damage-specific DNA binding protein 2, 48 kDa /// LIM homeobox 3	DDB2 /// LHX3
polymerase (DNA directed), delta 1, catalytic subunit 125 kDa	POLD1
Fanconi anemia, complementation group G	FANCG
polymerase (DNA directed), beta	POLB
X-ray repair complementing defective repair in Chinese hamster cells 1	XRCC1
N-methylpurine-DNA glycosylase	MPG
excision repair cross-complementing rodent repair deficiency, complementation group 1 (includes overlapping antisense sequence)	ERCC1
thymine-DNA glycosylase	TDG
Fanconi anemia, complementation group A /// Fanconi anemia, complementation group A	FANCA
replication factor C (activator 1) 4, 37 kDa	RFC4
replication factor C (activator 1) 3, 38 kDa	RFC3
APEX nuclease (apurinic/apyrimidinic endonuclease) 2	APEX2
RAD1 homolog (S. pombe)	RAD1
breast cancer 1, early onset	BRCA1
exonuclease 1	EXO1
flap structure-specific endonuclease 1	FEN1
mutL homolog 3 (*E. coli*)	MLH3
O-6-methylguanine-DNA methyltransferase	MGMT
RAD51 homolog (RecA homolog, *E. coli*) (S. cerevisiae)	RAD51
X-ray repair complementing defective repair in Chinese hamster cells 4	XRCC4
RecQ protein-like (DNA helicase Q1-like)	RECQL
excision repair cross-complementing rodent repair deficiency, complementation group 8	ERCC8
Fanconi anemia, complementation group C	FANCC
8-oxoguanine DNA glycosylase	OGG1
MRE11 meiotic recombination 11 homolog A (S. cerevisiae)	MRE11A
RAD52 homolog (S. cerevisiae)	RAD52
Werner syndrome	WRN
xeroderma pigmentosum, complementation group A	XPA
Bloom syndrome	BLM
mutS homolog 3 (*E. coli*)	MSH3
polymerase (DNA directed), epsilon 2 (p59 subunit)	POLE2
RAD51 homolog C (S. cerevisiae)	RAD51C
ligase IV, DNA, ATP-dependent	LIG4
excision repair cross-complementing rodent repair deficiency, complementation group 6	ERCC6
ligase III, DNA, ATP-dependent	LIG3
RAD17 homolog (S. pombe)	RAD17
X-ray repair complementing defective repair in Chinese hamster cells 2	XRCC2

TABLE A-continued

DNA Repair Genes

Gene Title	Gene Symbol
mutY homolog (*E. coli*)	MUTYH
replication factor C (activator 1) 1, 145 kDa /// replication factor C (activator 1) 1, 145 kDa	RFC1
breast cancer 2, early onset	BRCA2
RAD50 homolog (S. cerevisiae)	RAD50
damage-specific DNA binding protein 1, 127 kDa	DDB1
X-ray repair complementing defective repair in Chinese hamster cells 5 (double-strand-break rejoining; Ku autoantigen, 80 kDa)	XRCC5
poly (ADP-ribose) polymerase family, member 1	PARP1
polymerase (DNA directed), epsilon 3 (p17 subunit)	POLE3
xeroderma pigmentosum, complementation group C	XPC
mutS homolog 2, colon cancer, nonpolyposis type 1 (*E. coli*)	MSH2
replication protein A3, 14 kDa	RPA3
methyl-CpG binding domain protein 4	MBD4
nth endonuclease III-like 1 (*E. coli*)	NTHL1
PMS2 postmeiotic segregation increased 2 (S. cerevisiae) III PMS2-C terminal-like	PMS2 /// PMS2CL
uracil-DNA glycosylase 2	UNG2
APEX nuclease (multifunctional DNA repair enzyme) 1	APEX1
excision repair cross-complementing rodent repair deficiency, complementation group 4	ERCC4
RecQ protein-like 5	RECQL5
mutS homolog 5 (*E. coli*)	MSH5
polymerase (DNA-directed), delta 3, accessory subunit	POLD3
excision repair cross-complementing rodent repair deficiency, complementation group 2 (xeroderma pigmentosum D)	ERCC2
RecQ protein-like 4	RECQL4
PMS1 postmeiotic segregation increased 1 (S. cerevisiae)	PMS1
zinc finger protein 276 homolog (mouse)	ZFP276
polymerase (DNA directed), epsilon	POLE
X-ray repair complementing defective repair in Chinese hamster cells 3	XRCC3
nibrin	NBN
single-strand selective monofunctional uracil DNA glycosylase	SMUG1
Fanconi anemia, complementation group F	FANCF
nei endonuclease VIII-like 1 (*E. coli*)	NEIL1
Fanconi anemia, complementation group E	FANCE
Ataxia Telangiectasia Mutated	ATM
ATM and RAD3-related	ATR
BRCA1 associated protein-1 (ubiquitin carboxy-terminal hydrolase) gene	BAP1
BRCA1 Associated RING Domain 1 (RING-Type E3 Ubiquitin Transferase) gene	BARD1
BRCA1 Interacting Protein C-Terminal Helicase 1 gene	BRIP1
Partner and localizer of BRCA2 gene	PALB2
RAD51 Paralog B	RAD51B
RAD51 Paralog D	RAD51D
RAD54 Like	RAD54L

[0194] In embodiments, method treats cancer in a subject exhibiting an absence of a germline mutation in BRCA1 and BRCA2. In some embodiments, the method treats cancer in a subject with a platinum-sensitive tumor exhibiting an absence of a germline mutation in BRCA1 and BRCA2.

[0195] In one aspect, the invention features a method of treating cancer comprising: identifying a cancer patient having deficiency in at least one gene listed in Table A.

[0196] In embodiments, a method described herein treats a cancer that is associated with deficiency in at least one gene involved in the homologous recombination repair (HRR) pathway. In embodiments, a deficiency is a non-BRCA deficiency. In embodiments, a deficiency is in two or more, three or more, four or more, five or more, six or more, seven or more, eight or more, nine or more, ten or more, eleven or more, twelve or more, thirteen or more, fourteen or more, fifteen or more, sixteen or more, seventeen or more, eighteen or more, nineteen or more, twenty or more, twenty-one or more, twenty-two or more, twenty-three or more, twenty-four or more, twenty-five or more, twenty-six or more, twenty-seven or more, twenty-eight or more, twenty-nine or more, or thirty or more genes selected from the group consisting of RFC2, XRCC6, POLD2, PCNA, RPA1, RPA2, ERCC3, UNG, ERCC5, MLH1, LIG1, MSH6, POLD4, RFC5, DDB2///LHX3, POLD1, FANCG, POLB, XRCC1, MPG, ERCC1, TDG, FANCA, RFC4, RFC3, APEX2, RAD1, EXO1, FEN1, MLH3, MGMT, RAD51, XRCC4, RECQL, ERCC8, FANCC, OGG1, MRE11A, RAD52, WRN, XPA, BLM, MSH3, POLE2, RAD51C, LIG4, ERCC6, LIG3, RAD17, XRCC2, MUTYH, RFC1, RAD50, DDB1, XRCC5, PARP1, POLE3, XPC, MSH2, RPA3, MBD4, NTHL1, PMS2///PMS2CL, UNG2, APEX1, ERCC4, RECQL5, MSH5, POLD3, ERCC2, RECQL4, PMS1, ZFP276, POLE, XRCC3, NBN, SMUG1, FANCF, NEIL1, FANCE, ATM, ATR, BAP1, BARD1, BRIP1, PALB2, RAD51B, RAD51D, and RAD54L.

[0197] In embodiments, cancer patients having HRR deficiencies due to at least one of the sixteen genes listed in Table B can benefit from methods described herein.

TABLE B

Non-BRCA1/2 HRR Pathway Genes HRR Pathway Genes
ATM
ATR
BAP1
BARD1
BLM
BRIP1
MRE11A
NBN
PALB2
RAD51
RAD51B
RAD51C
RAD51D
RAD52
RAD54L
XRCC2

[0198] In embodiments, a deficiency in a gene involved in the HRR pathway is identified using a pre-specified gene panel. In embodiments, a pre-specified gene panel includes a gene listed in Table A or Table B, or any combinations thereof. In embodiments, a pre-specified gene panel comprises: at least one of ATM, ATR, BAP1, BARD1, BLM, BRIP1, MRE11A, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, and XRCC2, and any combinations thereof; and at least one of BRCA1 and BRCA2. In embodiments, a pre-specified gene panel comprises: each of ATM, ATR, BAP1, BARD1, BLM, BRIP1, MRE11A, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, and XRCC2; and at least one of BRCA1 and BRCA2. In embodiments, a pre-specified gene panel comprises ATM, ATR, BAP1, BARD1, BLM, BRIP1, MRE11A, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, XRCC2, BRCA1, and BRCA2.

[0199] In embodiments, the method is a mono-therapy treatment. In other embodiments, the method is a combination therapy treatment.

[0200] In embodiments, the method is a combination therapy treatment in which the administration of crystalline niraparib freebase is combined with a second therapy which induces DNA damage. In embodiments, the second therapy comprises radiosensitization (the administration of ionizing radiation) and/or chemosensitization (the administration of one or more DNA damaging agents). The DNA damaging agents may, for example, be selected from DNA methylating agents (such as e.g. dacarbazine or temozolomide), topoisomerase I inhibitors (such as e.g. camptothecin, topotecan or irinotecan), and cytotoxic agents (such as e.g. platinum-based drugs like cisplatin or carboplatin). The administration of crystalline niraparib freebase may take place before, during and/or after treatment with the second therapy. A regimen for such a combination treatment could readily be determined by a clinician.

Non-Oncological Conditions

[0201] In embodiments, the methods of the disclosure are used to treat a condition in a subject selected from a neurological or neurodegenerative disease, an inflammatory disease, a metabolic disease, and a cardiovascular disease or condition. Examples of such diseases are described by Curtin et al. (*Mol Aspects Med.* (2013) 34(6):1217-1256).

[0202] In one embodiment, the method treats a subject who has suffered from, or is at risk of suffering from stroke. In another embodiment, the method treats a subject suffering from traumatic brain injury. In a further embodiment, the method treats a subject who suffers from, or is at risk of suffering from, autoimmune diabetes.

[0203] In embodiments, the neurodegenerative disease is Parkinson's disease. In embodiments, the inflammatory disease is asthma or multiple sclerosis. In embodiments, the cardiovascular disease or condition is myocardial infarction, circulatory shock, polytrauma, or acute respiratory distress syndrome.

Administration and Dosages

[0204] Crystalline 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase as described herein can be formulated as a pharmaceutical composition for oral, buccal, parenteral (e.g. intravenous, intraperitoneal, intramuscular or subcutaneous), topical, rectal or intranasal administration or in a form suitable for administration by inhalation or insufflation. Such modes of administration and the methods for preparing appropriate pharmaceutical compositions are described, for example, in Gibaldi's Drug Delivery Systems in Pharmaceutical Care (1st ed., American Society of 15 Health-System Pharmacists 2007).

[0205] In embodiments, an exemplary dosage regimen for niraparib is one or more 100 mg doses taken orally once daily (e.g. two doses equivalent to a total daily dose of 200 mg or three doses equivalent to a total daily dose of 300 mg). Patients may be encouraged to take their dose at approximately the same time each day. Bedtime administration may be a potential method for managing nausea.

[0206] In some embodiments, the methods of the invention treat subjects with a cancer with a dosage of 1 mg, 5 mg, 10 mg, 20 mg, 25 mg, 35 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg to 275 mg, 300 mg, 325 mg, 350 mg 375 mg, 400 mg, 425 mg, 450 mg, 475 mg, 500 mg, 550 mg, 600 mg, 650 mg, 700 mg, 750 mg, 800 mg, 850 mg, 900 mg, 950 mg, 1000 mg, 1050 mg, 1100 mg, 1150 mg, 1200 mg, 1250 mg, 1300 mg, 1350 mg, 1400 mg, 1450 mg, 1500 mg, 1550 mg, 1600 mg, 1650 mg, 1700 mg, 1750 mg, 1800 mg, 1850 mg, 1900 mg, 1950 mg, or 2000 mg of niraparib or pharmaceutically acceptable salt thereof once-daily, twice-daily, or thrice-daily. In some embodiments, the methods of the invention treat subjects with a cancer with a dosage of 150 mg to 175 mg, 170 mg to 195 mg, 190 mg to 215 mg, 210 mg to 235 mg, 230 mg to 255 mg, 250 mg to 275 mg, 270 to 295 mg, 290 mg to 315 mg, 310 mg to 335 mg, 330 mg to 355 mg, 350 mg to 375 mg, or 370 mg to 400 mg of niraparib or pharmaceutically acceptable salt thereof once-daily, twice-daily, or thrice-daily. In some embodiments, the methods of the invention treat subjects with a cancer with a dosage of 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg. 17.5 mg, 20 mg, 22.5 mg, 25 mg, 27.5 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, or 100 mg of niraparib or pharmaceutically acceptable salt thereof once-daily, twice-daily, or thrice-daily.

[0207] In some embodiments, the methods of the invention treat subjects with a cancer with a dosage of from about

1 mg to 5 mg, 5 mg to 10 mg, 10 mg to 20 mg, 20 mg to 25 mg, 35 mg to 50 mg, 50 mg to 75 mg, 70 mg to 95 mg, 90 mg to 115 mg, 110 mg to 135 mg, 130 mg to 155 mg, 150 mg to 175 mg, 170 to 195 mg, 190 mg to 215 mg, 210 mg to 235 mg, 230 mg to 255 mg, 250 mg to 275 mg, 270 mg to 300 mg, 290 mg to 315 mg, 310 mg to 335 mg, 330 mg to 355 mg, 350 mg to 375 mg, 370 mg to 400 mg, 400 mg to 450 mg, 450 mg to 500 mg, 500 mg to 550 mg, 550 mg to 600 mg, 600 mg to 650 mg, 650 mg to 700 mg, 700 mg to 750 mg, 750 mg to 800 mg, 800 mg to 850 mg, 850 mg to 900 mg, 900 mg to 950 mg, 950 mg to 1000 mg, 1000 mg to 1050 mg, 1050 mg to 1100 mg, 1100 mg to 1150 mg, 1150 mg to 1200 mg, 1200 mg to about 1250 mg, 1250 mg to 1300 mg, 1300 mg to 1350 mg, 1350 mg to 1400 mg, 1400 mg to 1450 mg, 1450 mg to 1500 mg, 1500 mg to 1550 mg, 1550 mg to 1600 mg, 1600 mg to 1650 mg, 1650 mg to 1700 mg, 1700 mg to 1750 mg, 1750 mg to 1800 mg, 1800 mg to 1850 mg, 1850 mg to 1900 mg, 1900 mg to 1950 mg, or 1950 mg to 2000 mg of niraparib or pharmaceutically acceptable salt thereof once-daily, twice-daily, or thrice-daily. In some embodiments, the methods of the invention treat subjects with a cancer with a dosage of from about 5 mg to 7.5 mg, 7 mg to 9.5 mg, 9 mg to 11.5 mg, 11 mg to 13.5 mg, 13 mg to 15.5 mg, 15 mg to 17.5 mg, 17 to 19.5 mg, 19 mg to 21.5 mg, 21 mg to 23/5 mg, 23 mg to 25.5 mg, 25 mg to 27.5 mg, 27 mg to 30 mg, 30 mg to 35 mg, 35 mg to 40 mg, 40 mg to 45 mg, 45 mg to 50 mg, 50 mg to 55 mg, 55 mg to 60 mg, 60 to 65 mg, 65 mg to 70 mg, 70 mg to 75 mg, 75 mg to 80 mg, 80 mg to 85 mg, 85 mg to 90 mg, 90 mg to 95 mg, or 95 mg to 100 mg of niraparib or pharmaceutically acceptable salt thereof once-daily, twice-daily, or thrice-daily.

[0208] In a preferred embodiment, the crystalline niraparib freebase is formulated for oral administration, e.g. in solid form.

[0209] In a preferred embodiment, the pharmaceutical composition is an oral composition, more preferably a solid oral dosage form, such as e.g. a tablet, capsule, powder, granule or sachet. The oral composition may be provided in the form of unit dosages, wherein one or more of the unit dosages, taken together, provide(s) an effective amount for administration to the subject.

[0210] In solid dosage forms for oral administration (e.g. capsules, tablets, pills, dragees, powders, granules and the like), the active ingredient is mixed with one or more pharmaceutically acceptable excipients as described herein. In the case of capsules, tablets, and pills, the pharmaceutical compositions can also comprise buffering agents. Solid compositions of a similar type can also be prepared using fillers in soft and hard-filled gelatine capsules, and excipients such as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like. By way of an example, where the pharmaceutical composition is a provided in the form of a capsule, the composition can comprise one or more components which are combined to create a powder blend that is used to fill the capsule. The powder blend may, for example, be filled into gelatin capsules, such as size 0 gelatin capsules. In such cases, the term "pharmaceutical composition" is generally to be understood as referring to the content of the capsule, i.e. the powder blend.

[0211] A tablet can be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets can be prepared using binders (for example, gelatine or hydroxypropylmethyl cellulose), lubricants, inert diluents, preservatives, disintegrants (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-actives, and/or dispersing agents. Molded tablets can be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets and other solid dosage forms, such as dragees, capsules, pills, and granules, can optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the art.

[0212] In embodiments, a solid dosage form for administering a therapeutically effective amount of niraparib to a subject comprises crystalline naraparib freebase as described herein in an amount of from about 1 mg to about 1000 mg. In embodiments, the solid dosage form comprises from about 25 mg to about 750 mg of crystalline naraparib freebase, e.g. from about 50 mg to about 500 mg, from about 60 mg to about 400 mg, or from about 75 mg to about 300 mg. In other embodiments, the solid dosage form comprises from about 50 to about 300 mg of crystalline naraparib freebase. In embodiments, the solid dosage form comprises about 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, 300 mg, 325 mg or 350 mg of crystalline naraparib freebase. In embodiments, a solid dosage form for administering a therapeutically effective amount of niraparib to a subject comprises crystalline naraparib freebase as described herein in an amount of greater than about 100 mg. In embodiments, the solid dosage form comprises greater than about 120 mg, 140 mg, 160 mg, 180 mg, 200 mg, 220 mg, 240 mg, 260 mg or 280 mg.

[0213] In embodiments, the loading of crystalline naraparib freebase (e.g. the above-mentioned amounts) in the solid dosage form is such that at least 25% of the weight of the pharmaceutical composition is the crystalline naraparib freebase. In embodiments, the loading of crystalline naraparib freebase is at least 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or 80% by weight of the pharmaceutical composition.

[0214] In embodiments, the solid dosage form is presented as one, two or three unit dosages. In embodiments, the solid oral dosage form is administered one, two, or three times a day such as to provide a therapeutically effective amount of crystalline naraparib freebase for use in a method as described herein. In a preferred embodiment, the solid dosage form is presented as a single unit dosage which is administered once daily, i.e. it provides a therapeutically effective daily amount of crystalline naraparib freebase (such as e.g. about 300 mg). In another preferred embodiment, the solid dosage form is presented as two unit dosages which are administered together or separately, i.e. they provide between them a therapeutically effective daily amount of crystalline naraparib freebase (such as e.g. about 150 mg per unit dosage).

[0215] For buccal administration, the composition may take the form of tablets or lozenges formulated in a conventional manner.

[0216] In some embodiments, the pharmaceutical compositions are administered by non-oral means such as by topical application, transdermal application, injection, and the like. In related embodiments, the pharmaceutical compositions are administered parenterally by injection, infusion, or implantation (e.g. intravenous, intramuscular, intraarterial, subcutaneous, and the like). In each case, it is preferred that the pharmaceutical composition is stored

and/or used in a solid form, so as to take advantage of the properties of crystalline naraparib freebase.

[0217] The pharmaceutical compositions can be suitable for the preparation of injectable formulations for parenteral administration, including using conventional catheterisation techniques or infusion. Formulations for injection may be presented in unit dosage form, e.g. in ampules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions or emulsions in oily or aqueous vehicles, and may contain a formulating agent such as a suspending, stabilising and/or dispersing agent recognised by those of skill in the art. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

[0218] The pharmaceutical compositions can be suitable for the preparation of sterile injectable formulations. Those formulations can be sterilised by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilising agents in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. To prepare such a composition, the active ingredient is dissolved or suspended in a parenterally acceptable liquid vehicle. Exemplary vehicles and solvents include, but are not limited to, water, water adjusted to a suitable pH by addition of an appropriate amount of hydrochloric acid, sodium hydroxide or a suitable buffer, 1,3-butanediol, Ringer's solution and isotonic sodium chloride solution. The pharmaceutical composition can also contain one or more preservatives, for example, methyl, ethyl or n-propyl p-hydroxybenzoate. To improve solubility, a dissolution enhancing or solubilising agent can be added or the solvent can contain 10-60% w/w of propylene glycol or the like.

[0219] The pharmaceutical compositions can contain one or more pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders, which can be reconstituted into sterile injectable solutions or dispersions just prior to use. Such pharmaceutical compositions can contain antioxidants; buffers; bacteriostats; solutes, which render the formulation isotonic with the blood of the intended recipient; suspending agents; thickening agents; preservatives; and the like.

[0220] Examples of suitable aqueous and nonaqueous carriers, which can be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants. In some embodiments, in order to prolong the effect of an active ingredient, it is desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This can be accomplished by the use of a liquid suspension of crystalline material having poor water solubility. The rate of absorption of the active ingredient then depends upon its rate of dissolution which, in turn, can depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered active ingredient is accomplished by dissolving or suspending the compound in an oil vehicle. In addition, prolonged absorption of the injectable pharmaceutical form can be brought about by the inclusion of agents that delay absorption such as aluminium monostearate and gelatine.

[0221] Controlled release parenteral compositions can be in form of aqueous suspensions, microspheres, microcapsules, magnetic microspheres, oil solutions, oil suspensions, emulsions, or the active ingredient can be incorporated in biocompatible carrier(s), liposomes, nanoparticles, implants or infusion devices. Materials for use in the preparation of microspheres and/or microcapsules include, but are not limited to, biodegradable/bioerodible polymers such as polyglactin, poly-(isobutyl cyanoacrylate), poly(2-hydroxyethyl-L-glutamine) and poly(lactic acid). Biocompatible carriers which can be used when formulating a controlled release parenteral formulation include carbohydrates such as dextrans, proteins such as albumin, lipoproteins or antibodies. Materials for use in implants can be non-biodegradable, e.g. polydimethylsiloxane, or biodegradable such as, e.g., poly(caprolactone), poly(lactic acid), poly(glycolic acid) or poly(ortho esters).

[0222] For topical administration, crystalline niraparib freebase may be formulated as an ointment or cream. Crystalline niraparib freebase may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

[0223] For intranasal administration or administration by inhalation, crystalline niraparib freebase may be conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurised container or a nebulizer, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container or nebulizer may contain a solution or suspension. Capsules and cartridges (made, for example, from gelatine) for use in an inhaler or insufflator may be formulated containing a powder mix of crystalline niraparib freebase and a suitable powder base such as lactose or starch.

[0224] In other aspects, the invention provides a dosage form or pharmaceutical composition as described herein for use in therapy, e.g. for use in a method as defined herein.

[0225] In other aspects, the invention provides an article of manufacture (e.g. a kit) comprising multiple unit doses of a pharmaceutical composition as described herein in a sealed container with written instructions for use. In embodiments, the article of manufacture further comprises an induction seal, a desiccant, or a combination thereof.

Combination Therapies

[0226] Crystalline forms of niraparib freebase described herein can be useful as monotherapy or in combination therapy with the administration of one or more additional therapeutic agents or lines of therapy.

[0227] For example, a crystalline form of niraparib freebase described herein can be administered in combination with surgery, a radiotherapy, a chemotherapy, an immunotherapy, an anti-angiogenic agent, or an anti-inflammatory agent.

[0228] Where a crystalline form of niraparib freebase is administered in combination with one or more different therapeutic agents (e.g. as described herein), administering of the crystalline form of niraparib freebase can occur sequentially with the administering of the one or more different therapeutic agents. For example, administration of the crystalline form of niraparib freebase occurs before administration of the one or more different therapeutic agents. In embodiments, administration of the crystalline form of niraparib freebase occurs after administration of the one or more different therapeutic agents. In other embodiments, administering of the crystalline form of niraparib freebase occurs simultaneously with the administering of the one or more different therapeutic agents.

[0229] In embodiments, a crystalline form of niraparib freebase described herein is administered in combination with one or more immune checkpoint inhibitors. In embodiments, a checkpoint inhibitor is an agent capable of inhibiting any of the following: PD-1 (e.g. inhibition via anti-PD-1, anti-PD-L1, or anti-PD-L2 therapies), CTLA-4, TIM-3, TIGIT, LAGs (e.g. LAG-3), CEACAM (e.g. CEACAM-1, -3 and/or -5), VISTA, BTLA, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GALS, adenosine, TGFR (e.g. TGFR beta), B7-H1, B7-H4 (VTCN1), OX-40, CD137, CD40, IDO, or CSF-1R. In embodiments, a checkpoint inhibitor is a small molecule, a nucleic acid, a polypeptide (e.g. an antibody), a carbohydrate, a lipid, a metal, or a toxin. In embodiments, a checkpoint inhibitor is an antibody, an antibody conjugate, or an antigen-binding fragment thereof.

[0230] In embodiments, an immune checkpoint inhibitor is a PD-1 inhibitor. In embodiments, a PD-1 inhibitor is a small molecule, a nucleic acid, a polypeptide (e.g. an antibody, an antibody conjugate, or an antigen-binding fragment thereof), a carbohydrate, a lipid, a metal, or a toxin. In embodiments, a PD-1 inhibitor is a PD-1 binding agent (e.g. an antibody, an antibody conjugate, or an antigen-binding fragment thereof). In embodiments, a PD-1 binding agent is an antibody, an antibody conjugate, or an antigen-binding fragment thereof. In embodiments, a PD-1 binding agent is TSR-042, nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab, PDR-001, tislelizumab (BGB-A317), cemiplimab (REGN2810), LY-3300054, JNJ-63723283, MGA012, BI-754091, IBI-308, camrelizumab (HR-301210), BCD-100, JS-001, CX-072, BGB-A333, AMP-514 (MEDI-0680), AGEN-2034, CS1001, Sym-021, SHR-1316, PF-06801591, LZM009, KN-035, AB122, genolimzumab (CBT-501), FAZ-053, CK-301, AK 104, or GLS-010. In embodiments, a PD-1 inhibitor is a PD-L1 or PD-L2 binding agent such as durvalumab, atezolizumab, avelumab, BGB-A333, SHR-1316, FAZ-053, CK-301, or, PD-L1 millamolecule, or derivatives thereof. In embodiments, an anti-PD-1 agent is pembrolizumab. In embodiments, an anti-PD-1 agent is nivolumab. In some embodiments, a PD-1 antibody agent is as disclosed in International Patent Application Publication Nos. WO2014/179664, WO 2018/085468, or WO 2018/129559. In further embodiments, a PD-1 antibody agent is administered according to a method disclosed in International Patent Application Publication Nos. WO2014/179664, WO 2018/085468, or WO 2018/129559. In embodiments, an anti-PD-1 agent is TSR-042.

[0231] In embodiments, an immune checkpoint inhibitor is a TIM-3 inhibitor. In embodiments, a TIM-3 inhibitor is a small molecule, a nucleic acid, a polypeptide (e.g. an antibody, an antibody conjugate, or an antigen-binding fragment thereof), a carbohydrate, a lipid, a metal, or a toxin. In embodiments, a TIM-3 inhibitor is a TIM-3 binding agent (e.g. an antibody, an antibody conjugate, or an antigen-binding fragment thereof). In embodiments, a TIM-3 binding agent is an antibody, an antibody conjugate, or an antigen-binding fragment thereof. In some embodiments, a TIM-3 antibody agent is MBG453, LY3321367, Sym023, TSR-022, or a derivative thereof. In some embodiments, a TIM-3 antibody agent is as disclosed in International Patent Application Publication Nos. WO2016/161270, WO 2018/085469, or WO 2018/129553. In some embodiments, a TIM-3 antibody agent is administered as disclosed in International Patent Application Publication Nos. WO2016/161270, WO 2018/085469, or WO 2018/129553. In some embodiments, a TIM-3 antibody agent is TSR-022.

[0232] In embodiments, an immune checkpoint inhibitor is a LAG-3 inhibitor. In embodiments, an anti-LAG-3 agent is an antibody, an antibody conjugate, or an antigen-binding fragment thereof. In embodiments, an anti-LAG-3 agent is a small molecule, a nucleic acid, a polypeptide (e.g. an antibody), a carbohydrate, a lipid, a metal, or a toxin. In embodiments, an anti-LAG-3 agent is a small molecule. In embodiments, an anti-LAG-3 agent is a LAG-3 binding agent. In embodiments, an anti-LAG-3 agent is an antibody, an antibody conjugate, or an antigen-binding fragment thereof. In embodiments, an anti-LAG-3 agent is IMP321, relatlimab (BMS-986016), BI 754111, GSK2831781 (IMP-731), Novartis LAG525 (IMP701), REGN3767, MK-4280, MGD-013, GSK-2831781, FS-118, XmAb22841, INCAGN-2385, FS-18, ENUM-006, AVA-017, AM-0003, Avacta PD-L1/LAG-3 bispecific affamer, iOnctura anti-LAG-3 antibody, Arcus anti-LAG-3 antibody, or Sym022, or TSR-033. In some embodiments, a LAG-3 antibody agent is as disclosed in International Patent Application Publication WO2016/126858 or in in International Patent Application No. PCT/US18/30027. In some embodiments, a LAG-3 antibody agent is administered as disclosed in International Patent Application Publication WO2016/126858 or in in International Patent Application No. PCT/US18/30027. In embodiments, a LAG-3 antibody agent is TSR-033.

[0233] In embodiments, a niraparib tablet composition is administered in combination with a PD-1 inhibitor (e.g. TSR-042, pembrolizumab, or nivolumab). In embodiments, a niraparib tablet composition is administered in combination with a TIM-3 inhibitor (e.g. TSR-022). In embodiments, a niraparib tablet composition is administered in combination with a LAG-3 inhibitor (e.g. TSR-033). In embodiments, a niraparib tablet composition is administered in combination with a PD-1 inhibitor (e.g. TSR-042, pembrolizumab, or nivolumab) and a TIM-3 inhibitor (e.g. TSR-022). In embodiments, a niraparib tablet composition is administered in combination with a PD-1 inhibitor (e.g. TSR-042, pembrolizumab, or nivolumab) and a LAG-3 inhibitor (e.g. TSR-033). In embodiments, a niraparib tablet composition is administered in combination with a TIM-3 inhibitor (e.g. TSR-022) and a LAG-3 inhibitor (e.g. TSR-033). In embodiments, a niraparib tablet composition is administered in combination with a PD-1 inhibitor (e.g. TSR-042, pembrolizumab, or nivolumab), a TIM-3 inhibitor (e.g. TSR-022), and a LAG-3 inhibitor (e.g. TSR-033).

[0234] In embodiments, a niraparib tablet composition is administered in combination with one or more chemotherapy agents.

[0235] In embodiments, a niraparib tablet composition is administered in combination with a platinum-based chemotherapy agent (e.g. one or more of cisplatin, carboplatin, oxaliplatin, nedaplatin, triplatin tetranitrate, phenanthriplatin, picoplatin, and satraplatin).

[0236] In embodiments, a niraparib tablet composition is administered in combination with a chemotherapy agent that is aminoglutethimide, amsacrine, anastrozole, asparaginase, bcg, bicalutamide, bleomycin, buserelin, busulfan, campothecin, capecitabine, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, clodronate, colchicine, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, dienestrol, diethylstilbestrol, docetaxel, doxorubicin, epirubicin, estradiol, estramnustine, etoposide, exemestane, filgrastim, fludarabine, fludrocortisone, fluorouracil, fluoxymesterone, flutamide, gemcitabine, genistein, goserelin, hydroxyurea, idarubicin, ifosfamide, imatinib, interferon, irinotecan, ironotecan, letrozole, leucovorin, leuprolide, levamisole, lomustine, mechlorethamine, medroxyprogesterone, megestrol, melphalan, mercaptopurine, mesna, methotrexate, mitomycin, mitotane, mitoxantrone, nilutamide, nocodazole, octreotide, oxaliplatin, paclitaxel, pamidronate, pentostatin, plicamycin, porfimer, procarbazine, raltitrexed, rituximab, streptozocin, suramin, tamoxifen, temozolomide, teniposide, testosterone, thioguanine, thiotepa, titanocene dichloride, topotecan, trastuzumab, tretinoin, vinblastine, vincristine, vindesine, or vinorelbine.

[0237] In embodiments, a niraparib tablet composition is administered in combination with a second agent that is a regulatory T cell (Treg) inhibitory agent, a macrophage inhibitory agent, an antigen specific immune response enhancer agent, antigen specific immune response enhancer agent, anti-angiogenic agent, a chemotherapy agent or a combination thereof. In embodiments, a second agent is any second agent described in International Application No. PCT/US18/33437, herein incorporated by reference in its entirety.

[0238] In embodiments, a macrophage inhibitory agent is selected from the group consisting of a macrophage recruitment inhibitory agent (e.g. an anti-CCL2/CCR2 agent, an anti-IL6 agent, an anti-M-CSFR agent, and combinations thereof), an M2 macrophage antisurvival agent, an M1 macrophage enhancing agent, an M2 to M1 polarizing agent, a macrophage activity inhibitor agent and combinations thereof. In embodiments, a macrophage recruitment inhibitory agent is selected from the group consisting of trabectedin, RS102895, PF-04136309, CNT0888, MLN1202, siltuximab, JNJ-28312141, GW2580, IMC-CS4 (LY3022855), emactuzumab, AMG820, pexidartinib, linifanib, OSI-930, CEP-32496, PLX7846, BLZ945, ARRY-382, JNJ-40346527, MCS110, PLX3397, PLX6134, PD-0360324, FPA008, and combinations thereof. In embodiments, a M2 macrophage antisurvival agent is selected from the group consisting of an MMP inhibitor, clodronate, zoledronic acid, dichloromethylene bisphosphonate, trabectedin, dasatinib, retinoic acid, attenuated bacteria (e.g. *Shigella flexneri, Salmonella typhimurium, Listeria monocytogens, Chlamydia psittaci, Legionella pneumophila*), and combinations thereof. In embodiments, a M1 macrophage enhancing agent or the M2 to M1 polarizing agent is selected from the group consisting of an anti-CD40 agent, an anti-IL-10R agent, a CD47 antagonist (e.g. Hu5F9-G4, CC-90002, and CD47-Fc fusion protein TTI-621), PolyI:C, LPS, monophosphoryl A, imiquimod, R-848, CpG-ODN, IFN-α, IFN-β, IFN-γ, GM-CSF, IL-12, IL-2, IL-15, Tα1, ibrutinib, EF-022 and combinations thereof. In embodiments, macrophage activity inhibitory agent is selected from the group consisting of a STAT3 inhibitor, a STAT6 inhibitor, or an anti-tumor drug agent (e.g. a macrophage activity inhibitory agent is WP1066, sunitinib, sorafenib, STA-21, IS3 295, S3I-M2001, AS1517499, leflunomide, TMC-264, histidine-rich glycoprotein (HRG), copper chelate (CuNG), 5,6-dimethylxanthenone-4-acetic acid (MDXAA), vadimezan (ASA404), cisplatin, silibinin, proton pump inhibitor pantoprazole (PPZ), or CNI-1493, or combinations thereof). In embodiments, a macrophage inhibitor agent is an anti-IL-1α agent (e.g. xilonix).

[0239] In embodiments a regulatory T cell (Treg) inhibitory agent is selected from the group consisting of a Treg ablating agent, a Treg migration inhibitor agent, a Treg function inhibitor agent, and combinations thereof. In embodiments, a Treg ablating agent is selected from the group consisting of cyclophosphamide, paclitaxel, imatinib, sunitinib, sorafenib, dasatinib, temozolomide, daclizumab, denileukin diftitox, and combinations thereof. In embodiments, a Treg migration inhibitor agent is selected from the group consisting of AMD3100, mogamulizumab, casuarinin, fucoidan, and combinations thereof. In embodiments, a Treg function inhibitor agent is selected from the group consisting of an anti-CTLA4 agent (e.g. ipilimumab, tremelimumab), an anti-OX40 agent, an anti-GITR agent, an adenosine receptor antagonist (e.g. caffeine, theophylline, theobromine, and 8-phenylxanthines), P60, and combinations thereof.

[0240] In embodiments, an antigen specific immune response enhancer agent is selected from the group consisting of an anti-PD-1 agent, an anti-PD-L1 agent, a GITR (glucocorticoid-induced TNFR-related protein) stimulating agent, an anti-CTLA4 agent, an anti-TIM-3 agent, an anti-LAG-3 agent, an anti-IDO agent, an agent that enhances tumor antigen presentation (e.g. personalized cancer vaccine, autologous antigen presenting cell, autologous dendritic cells, artificial antigen presenting cell), a chemokine signaling agent, an anti-VEGF agent, a cytokine signal stimulating agent, and combinations thereof.

[0241] In embodiments, a GITR stimulating agent is selected from the group consisting of DTA-1, mGITRL, pGITRL, and combinations thereof. In embodiments, an anti-CTLA4 agent is selected from the group consisting of ipilimumab, tremelimumab, and combinations thereof. In embodiments, a chemokine signaling agent is selected from the group consisting of CXCL16, a CXCR6 chemokine receptor (CD186) agonist, and combinations thereof. In embodiments, an anti-VEGF agent is selected from the group consisting of bevacizumab, pazopanib, sunitinib, sorafenib, axitinib, ponatinib, regorafenib, cabozantinib, vandetanib, ramucirumab, lenvatinib, ziv-aflibercept, and combinations thereof. In embodiments, a cytokine signal stimulating agent is an interleukin or an interferon. In embodiments, an interleukin is selected from the group consisting of IL-2, IL-1, IL-7, IL-15, IL-12, IL-18 and combinations thereof. In embodiments, an interferon is IFN alpha.

[0242] In embodiments, an antigen specific immune response enhancer agent is selected from the group consisting of a flavonoid (e.g. flavonoid glycoside), lidocaine, lamotrigine, sulfamethoxazole, phenytoin, carbamazepine, sulfamethoxazole, phenytoin, allopurinol, paracetamol, mepivacaine, p-phenylenediamine, ciprofloxacin and moxifloxacin.

[0243] In embodiments, an anti-angiogenic agent is TNP-470, platelet factor 4, thrombospondin-1, tissue inhibitors of metalloproteases (TIMP1 and TIMP2), prolactin, angiostatin, endostatin, bFGF soluble receptor, transforming growth factor beta, interferon alpha, soluble KDR and FLT-1 receptors, placental proliferin-related protein, and combinations thereof. In embodiments, an anti-angiogenic agent reduces the production of a pro-angiogenic factor, inhibits an interaction between a pro-angiogenic factor and a pro-angiogenic receptor, inhibits a function of a pro-angiogenic factor, inhibits a function of a pro-angiogenic factor receptor, reduces of blood flow by disruption of blood vessels, inhibits vessel sprouting, or any combinations thereof. In embodiments, an anti-angiogenic agent is a small organic or inorganic molecule; a saccharine; an oligosaccharide; a polysaccharide; a carbohydrate; a peptide; a protein; a peptide analog; a peptide derivative; a lipid; an antibody; an antibody fragment, a peptidomimetic; a nucleic acid; a nucleic acid analog; a nucleic acid derivative; an extract made from biological materials; a naturally occurring or synthetic composition; a metal; a toxin; or any combination thereof. In embodiments, an anti-angiogenic agent is selected from the group consisting of bevacizumab, itraconazole, carboxyamidotriazole, TNP-470, fumagillin, CM101, IL-12, platelet factor-4, suramin, SU5416, thrombospondin, angiostatic steroids, heparin, cartilage-derived angiogenesis inhibitory factor, matrix metalloproteinase inhibitor, angiostatin, endostatin, 2-methoxyestradiol, tecogalan, tetrathiomolybdate, thrombospondin, thalidomide, prolactin, $\alpha V\beta 3$ inhibitor, lenalidomide, linomide, ramucirumab, tasquinimod, ranibizumab, sorafenib, sunitinib, pazopanib, everolimus, tissue inhibitors of metalloproteases (TIMP1 and TIMP2), bFGF soluble receptor, transforming growth factor beta, interferon alpha, soluble KDR and FLT-1 receptors, placental proliferin-related protein, pazopanib, sunitinib, sorafenib, axitinib, ponatinib, cabozantinib, regorafenib, vandetanib, lenvatinib, semaxanib, SU6668, vatalanib, tivozanib, cediranib, protamine, heparin, steroids, ascorbic acid ethers, sulfated polysaccharide DS 4152, fumagillin, AGM 12470, neovastat, R04929097, MRK-003, MK-0752, PF03084014, MEDI0639, curcumin, 3,3'-diindolylmethane (DIM), resveratrol, 3,5-bis(2,4-difluorobenzylidene)-4-piperidone (DiFiD) and epigallocatechin-3-gallate (EGCG), honokiol, OMP-21M18, navicixizumab (OMP-305B83), Flt_{2-11}, CBO-P11, Je-11, V1, and any combination thereof.

[0244] In some embodiments, an anti-angiogenic agent inhibits a DLL4/Notch signaling pathway.

[0245] In some embodiments, the angiogenesis inhibitor inhibiting the DLL4/Notch signaling pathway is a gamma-secretase inhibitor (GSI), a siRNA, or a monoclonal antibody against a Notch receptor or ligand. In some embodiments, an anti-angiogenic agent is selected from the group consisting of R04929097, MRK-003, MK-0752, PF03084014, MEDI0639, curcumin, 3,3'-diindolylmethane (DIM), resveratrol, 3,5-bis(2,4-difluorobenzylidene)-4-piperidone (DiFiD) and epigallocatechin-3-gallate (EGCG), honokiol, and any combination thereof.

[0246] In some embodiments, an anti-angiogenic agent inhibits a vascular endothelial growth factor (VEGF)/vascular endothelial growth factor receptor (VEGFR) pathway. In some embodiments, an anti-angiogenic agent is selected from the group consisting of Akt Inhibitor, calcineurin autoinhibitory peptide, ET-18-OCH3, Go 6983, NG-Nitro-L-arginine methyl ester, p21-activated kinase Inhibitor, cPLA2α inhibitor, PI-103, PP2, SB 203580, U0126, VEGFR tyrosine kinase inhibitor V, VEGFR2 kinase inhibitor VI, VEGFR2 kinase inhibitor III, ZM 336372, and any combination thereof.

[0247] In some embodiments, an anti-angiogenic agent inhibits a VEGF family protein and/or a VEGFR family protein. In some embodiments, the VEGF family protein comprises VEGF-A, VEGF-B, VEGF-C, VEGF-D, P1GF (placental growth factor), VEGF-E (Orf-VEGF), *Trimeresurus flavoviridis* svVEGF, or any combination thereof. In some embodiments, an anti-angiogenic agent is bevacizumab, ranibizumab, OPT-302, ziv-aflibercept, or any combinations thereof. In some embodiments, an anti-angiogenic agent is Flt2-11, CBO-P11, Je-11, V1, or any combination thereof. In some embodiments, an anti-angiogenic agent is pazopanib, sunitinib, sorafenib, axitinib, ponatinib, cabozantinib, regorafenib, vandetanib, lenvatinib, semaxanib, SU6668, vatalanib, tivozanib, cediranib, or any combination thereof.

[0248] Having been generally described herein, the follow non-limiting examples are provided to further illustrate this invention.

Exemplary Aspects and Embodiments of the Invention

[0249] Exemplary aspects and embodiments of the invention are described herein and include items 1-40.

[0250] Item 1. Crystalline 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase.

[0251] Item 2. A crystalline Form I of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase.

[0252] Item 3. The crystalline Form I of niraparib freebase according to item 2, having an X-ray powder diffraction (XRPD) pattern comprising a peak at 18.7±0.2° 2θ.

[0253] Item 4. The crystalline Form I of niraparib freebase according to item 2 or item 3, having an XRPD pattern comprising peaks at 18.7 and 22.5±0.2° 2θ.

[0254] Item 5. The crystalline Form I of niraparib freebase according to item 2 or item 3, having an XRPD pattern comprising peaks at 18.7 and 19.6±0.2° 2θ.

[0255] Item 6. The crystalline Form I of niraparib freebase according to any one of items 2 to 5, having an XRPD pattern comprising peaks at 18.7, 19.6 and 22.5±0.2° 2θ.

[0256] Item 7. The crystalline Form I of niraparib freebase according to any one of items 2 to 6, having an XRPD pattern comprising one or more peaks at 16.9, 18.7, 19.6, 21.6 and 22.5±0.2° 2θ.

[0257] Item 8. The crystalline Form I of niraparib freebase according to any one of items 2 to 7, having an XRPD pattern comprising at least two peaks at 16.9, 18.7, 19.6, 21.6 and 22.5±0.2° 2θ.

[0258] Item 9. The crystalline Form I of niraparib freebase according to any one of items 2 to 8, having an XRPD pattern comprising at least three peaks at 16.9, 18.7, 19.6, 21.6 and 22.5±0.2° 2θ.

[0259] Item 10. The crystalline Form I of niraparib freebase according to any one of items 2 to 9, having an XRPD pattern comprising at least four peaks at 16.9, 18.7, 19.6, 21.6 and 22.5±0.2° 2θ.

[0260] Item 11. The crystalline Form I of niraparib freebase according to any one of items 2 to 10, having an XRPD pattern comprising peaks at 16.9, 18.7, 19.6, 21.6 and 22.5±0.2° 2θ.

[0261] Item 12. The crystalline Form I of niraparib freebase according to any one of items 2 to 11, having an XRPD pattern comprising one or more peaks at 15.6, 16.5, 22.4, 23.2, and 29.3±0.2° 2θ.

[0262] Item 13. The crystalline Form I of niraparib freebase according to any one of items 2 to 12, having an XRPD pattern comprising at least two peaks at 15.6, 16.5, 22.4, 23.2, and 29.3±0.2° 2θ.

[0263] Item 14. The crystalline Form I of niraparib freebase according to any one of items 2 to 13, having an XRPD pattern comprising at least three peaks at 15.6, 16.5, 22.4, 23.2, and 29.3±0.2° 2θ.

[0264] Item 15. The crystalline Form I of niraparib freebase according to any one of items 2 to 14, having an XRPD pattern comprising at least four peaks at 15.6, 16.5, 22.4, 23.2, and/or 29.3±0.2° 2θ.

[0265] Item 16. The crystalline Form I of niraparib freebase according to any one of items 2 to 15, having an XRPD pattern comprising peaks at 15.6, 16.5, 22.4, 23.2, and 29.3±0.2° 2θ.

[0266] Item 17. The crystalline Form I of niraparib freebase according to any one of items 2 to 16, having an XRPD pattern comprising peaks at 15.6, 16.5, 16.9, 18.7, 19.6, 21.6, 22.4, 22.5, 23.2 and 29.3±0.2° 2θ.

[0267] Item 18. The crystalline Form I of niraparib freebase according to any one of items 2 to 17, having an XRPD pattern comprising peaks with the 2θ values, and optionally also relative intensities, according to the following table:

Pos. [°2θ]	Rel. Int. [%]
8.4	3
12.2	8
12.8	1
13.7	1
15.6	19
16.5	25
16.9	27
17.4	7
18.0	2
18.7	100
19.6	37
20.0	7
21.6	28
22.4	23
22.5	38
23.2	21
24.4	2
25.0	6
25.2	9
25.7	6
27.3	2
27.9	8
29.3	13
30.4	2
31.0	3
32.0	2
32.7	1
33.2	3
33.8	3
34.7	2

[0268] Item 19. The crystalline niraparib freebase according to any one of items 1 to 18, characterised by an XRPD pattern substantially as shown in FIG. **1**.

[0269] Item 20. The crystalline niraparib freebase according to any one of items 1 to 19, characterised by an infrared (IR) spectrum comprising a peak at about 1652 cm^{-1} and a peak at about 1608 cm^{-1}.

[0270] Item 21. The crystalline niraparib freebase according to any one of items 1 to 20, characterised by an infrared (IR) spectrum substantially as shown in FIG. **4**.

[0271] Item 22. The crystalline niraparib freebase according to any one of items 1 to 21, characterised by a Raman spectrum comprising peaks at about 960.3, 1457.5 and 1607.0 cm^{-1}.

[0272] Item 23. The crystalline niraparib freebase according to any one of items 1 to 22, characterised by a Raman spectrum substantially as shown in FIG. **5**.

[0273] Item 24. The crystalline niraparib freebase according to any one of items 1 to 23, characterised by a melting point of about 185-195° C.

[0274] Item 25. The crystalline niraparib freebase according to any one of items 1 to 24, characterised by a DTA thermogram substantially as shown in FIG. **6**.

[0275] Item 26. The crystalline niraparib freebase according to any one of items 1 to 25, characterised by a DSC thermogram substantially as shown in FIG. **7**.

[0276] Item 27. The crystalline niraparib freebase according to any one of items 1 to 26, characterised by adsorbing less than about 1% by weight of water up to about 90% relative humidity at about 25° C.

[0277] Item 28. A crystalline Form II, III, IV, or V of 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide (niraparib) freebase.

[0278] Item 29. A composition comprising the crystalline niraparib freebase of any one of items 1 to 28, wherein the composition is substantially free of amorphous niraparib, a pharmaceutically acceptable salt of niraparib, and/or any other solid form of niraparib or niraparib salt.

[0279] Item 30. The composition of item 29, wherein less than about 10% (or less than about 5%) of the total niraparib in the composition is in the form of said amorphous niraparib, said pharmaceutically acceptable salt of niraparib, and/or any other solid form of niraparib or niraparib salt.

[0280] Item 31. A pharmaceutical composition comprising the crystalline niraparib freebase of any one of items 1 to 28, or the composition of item 29 or 30, and at least one pharmaceutically acceptable excipient.

[0281] Item 32. The crystalline niraparib freebase of any one of items 1 to 28, the composition of item 29 or 30, or the pharmaceutical composition of item 31, for use in therapy.

[0282] Item 33. Use of the crystalline niraparib freebase of any one of items 1 to 28, or the composition of item 29 or 30, or the pharmaceutical composition of item 31, in the manufacture of a medicament.

[0283] Item 34. A method of treating cancer, stroke, autoimmune diabetes, a neurological disease, an inflammatory disease, a metabolic disease or a cardiovascular disease in a subject, the method comprising administering to the subject an effective amount of the crystalline niraparib freebase of any one of items 1 to 28, or the composition of item 29 or 30, or the pharmaceutical composition of item 31.

[0284] Item 35. The method according to item 34, wherein said method is a method of treating cancer.

[0285] Item 36. The method according to item 35, wherein said cancer is associated with BRCA1 and/or BRCA2 mutations.

[0286] Item 37. The method according to item 35 or 36, wherein said cancer is associated with a mutation in ATM, ATR, BAP1, BARD1, BLM, BRIP1, MRE11A, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, or XRCC2, or any combination thereof.

[0287] Item 38. The method according to any one of items 35 to 37, wherein said cancer is epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer.

[0288] Item 39. The crystalline niraparib freebase of any one of items 1 to 28, or the composition of item 29 or 30, or the pharmaceutical composition of item 31, for use in a method as defined in any one of items 34 to 38.

[0289] Item 40. Use of the crystalline niraparib freebase of any one of items 1 to 28, or the composition of item 29 or 30, or the pharmaceutical composition of item 31, in the manufacture of a medicament for use in a method as defined in any one of items 34 to 38.

Examples

Analytical Procedures

X-Ray Power Diffraction

[0290] XRPD analysis was typically carried out on a PANalytical X'pert pro, scanning the samples between 3 and 35° 2θ. The material was gently ground to release any agglomerates and loaded onto a multi-well plate with Kapton or Mylar polymer film to support the sample. The multi-well plate was then placed into the diffractometer and analysed using Cu K radiation (μ_1 λ=1.54060 Å; α_2=1.54443 Å; β=1.39225 Å; α_1:α_2 ratio=0.5) running in transmission mode (step size 0.0130° 2θ) using 40 kV/40 mA generator settings.

Unless otherwise stated, the XRPD analysis was carried out at room temperature and pressure and at a relative humidity of between about 30 and about 50% (e.g. about 40%).

NMR Analysis

[0291] NMR methods were typically performed on a Bruker AVIIIHD spectrometer equipped with a DCH cryoprobe. Experiments were performed in deuterated DMSO and each sample was prepared to about 10 mM concentration. Unless otherwise stated, NMR spectra were acquired at room temperature (e.g. around 300K).

High Performance Liquid Chromatography-Ultraviolet Detection (HPLC-UV)

[0292] HPLC was typically performed using the following parameters:

[0293] Column: Waters Symmetry C18, 150×3.9 mm, 5 μm

[0294] Column Temperature: 40° C.

[0295] Autosampler Temperature: 5° C.

[0296] UV wavelength: 220 nm

[0297] Injection Volume: 4.3 μL

[0298] Flow Rate: 1.962 mL/mm

[0299] Mobile Phase A: 0.1% Perchloric acid in water

[0300] Mobile Phase B: Acetonitrile

[0301] The gradient program typically used was:

Time (minutes)	Solvent B [%]
0	5
13.739	30
21.982	95
23.081	95
23.136	5
27.477	5

Gas Chromatography (GC)

[0302] CG analysis was typically performed on a Shimadzu GC2010 instrument, using a DB-624 column (30 m×0.32 mm, 1.8 μm) with a flame ionisation detector (240° C.). The carrier gas was nitrogen (30 mL/min) and hydrogen and air flow rates were 40 mL/min and 400 mL/min, respectively. An injection volume of 1.00 μL was used and the column flow rate was 1.2 mL/min (linear velocity). The program typically used was:

Injection temp.	200° C.
Hold at 45° C.	5 minutes
Ramp	10° C./minute
Hold at 220° C.	5 minutes
Run time:	25.5 min

Polarised Light Microscopy (PLM)

[0303] The presence of crystallinity (birefringence) was typically determined using an Olympus BX50 polarising microscope, equipped with a Motic camera and image capture software (Motic Images Plus 2.0). All images were recorded using the 20× objective, unless otherwise stated.

Scanning Electron Microscopy (SEM)

[0304] SEM analysis was typically carried out using a Carl Zeiss Sigma Field emission SEM. Samples were mounted onto stubs using carbon tabs and coated with 15 nm AuPd and imaged at 5 KV, 30 μm aperture and 5 mm working distance.

Infrared Spectroscopy (FT-IR)

[0305] Infrared spectroscopy was typically carried out on a Bruker ALPHA P spectrometer. Sufficient material was placed onto the centre of the plate of the spectrometer and the spectra were obtained using the following parameters:

[0306] Resolution: 4 cm-1

[0307] Background Scan Time: 16 scans

[0308] Sample Scan Time: 16 scans

[0309] Data Collection: 4000 to 400 cm-1

[0310] Result Spectrum: Transmittance

[0311] Software: OPUS version 6

Thermogravimetric Analysis (TGA)

[0312] Typically, approximately 5 mg of material was weighed into an open aluminium pan and loaded into a simultaneous thermogravimetric/differential thermal analyser (TG/DTA) and held at room temperature. The sample was then heated at a rate of 10° C./min from 20° C. to 350° C. during which time the change in sample weight was recorded along with any differential thermal events (DTA). Nitrogen was used as the purge gas, at a flow rate of 300 cm^3/min.

Differential Scanning Calorimetry (DSC)

[0313] Typically, approximately 5 mg of material was weighed into an aluminium DSC pan and sealed non-hermetically with a pierced aluminium lid. The sample pan was then loaded into a Seiko DSC6200 (equipped with a cooler) cooled and held at 20° C. Once a stable heat-flow response was obtained, the sample and reference were heated to melting (if possible) at a scan rate of 10° C./min and the resulting heat flow response monitored. Nitrogen was used as the purge gas, at a flow rate of 50 cm^3/min.

Variable Temperature X-Ray Powder Diffraction (VT-XRPD)

[0314] VT-XRPD analysis was typically carried out on a Philips X'Pert Pro Multipurpose diffractometer equipped with a temperature chamber. The samples were scanned between 4 and 35 °2θ using Cu K radiation (α_1 λ=1.54060 Å; α_2=1.54443 Å; β=1.39225 Å; α_1:α_2 ratio=0.5) running in Bragg-Brentano geometry (step size 0.008 °2θ) using 40 kV/40 mA generator settings. The program was as follows (unless otherwise stated):

[0315] Heat to 25° C. at 10° C./min→5-minute hold→scan

[0316] Heat to 200° C. at 10° C./min→5-minute hold→scan

[0317] Cool to 25° C. at −10° C./min→5-minute hold→scan

[0318] Heat to 122° C. at 10° C./min→5-minute hold→scan

[0319] Heat to 132° C. at 10° C./min→5-minute hold→scan

[0320] Heat to 150° C. at 10° C./min→5-minute hold→scan

[0321] Heat to 168° C. at 10° C./min→5-minute hold→scan

[0322] Heat to 171° C. at 10° C./min→5-minute hold→scan

[0323] Heat to 200° C. at 10° C./min→5-minute hold→scan

[0324] Cool to 25° C. at −10° C./min→5-minute hold→scan

Gravimetric Vapour Sorption (GVS)

[0325] Typically, approximately 10-20 mg of sample was placed into a mesh vapour sorption balance pan and loaded into an IGASorp Moisture Sorption Analyser balance by Hiden Analytical. The sample was subjected to a ramping profile from 40-90% relative humidity (RH) at 10% increments, maintaining the sample at each step until a stable weight had been achieved (98% step completion, minimum step length 30 minutes, maximum step length 60 minutes) at 25° C. After completion of the sorption cycle, the sample was dried using the same procedure to 0% RH, and finally taken back to the starting point of 40% RH. Two cycles were performed. The weight change during the sorption/desorption cycles were plotted, allowing for the hygroscopic nature of the sample to be determined.

Example 1: Crystalline Niraparib Freebase Form I

[0326] Niraparib freebase (Form I) was prepared by conversion of niraparib tosylate monohydrate (obtained from niraparib e.g. as described in WO 2014/088983 or PCT/US2018/029131) with sodium hydroxide, followed by crystallization from 2-MeTHF.

Preparation of Niraparib Freebase (Form I)

[0327] To a mixture of 50.0 g (97.9 mmol) Niraparib tosylate monohydrate in 2-MeTHF (1 L) was added 1% NaOH solution (500 mL) at room temperature. After the mixture was stirred for 30 minutes, the aqueous layer was separated and extracted with 2-MeTHF (0.5 L, twice). The combined organic layer was washed with water (1 L). The solution was concentrated under partial vacuum slowly below 30° C. until about 20 ml of suspension was left. The mixture was stirred for 30 minutes at room temperature and the solids were collected by filtration, to give 23.8 g (75.9%) of off-white crystalline solids (m.p. 189° C.). $[M+H]^+$ at m/z 321, with the expected isotope pattern. Purity was found to be approximately 99.9% by HPLC.

[0328] ^{1}H NMR (500.12 MHz, DMSO-d6) δ 9.27 (s, 1H), 8.59 (dd, 1H, J=1.8, 4.7 Hz), 8.07 (dd, 1H, J=1.1, 7.0 Hz), 8.04 (d, 2H, J=8.7 Hz), 8.02 (dd, 1H, J=1.1, 8.1 Hz), 7.90 (br. s, 1H), 7.46 (d, 2H, J=8.5 Hz), 7.27 (dd, 1H, J=7.2, 8.3 Hz), 3.00 (br. d, 1H, J=12.1 Hz), 2.94 (br. d, 1H, J=12.1 Hz), 2.70 (m, 1H), 2.51 (m, 2H), 1.91, (d, 1H, J=13.0 Hz), 1.68 (m, 1H), 1.61 (m, 1H), 1.49 (m, 1H).

[0329] ^{13}C NMR (125.77 MHz, DMSO-d6) δ 166.1, 146.5, 146.4, 138.0, 130.1, 128.7 (2C), 125.8, 123.9, 123.8, 122.3, 121.9, 121.1 (2C), 54.0, 46.4, 43.6, 32.3 and 27.0.

Characterisation of Niraparib Freebase (Form I)

[0330] Niraparib freebase Form I was characterized by range of analytical physical and chemical methods. The results indicated that the Form I freebase is highly crystalline and non-hygroscopic.

[0331] FIG. **1** shows the XRPD diffractogram of niraparib freebase Form I. Table 1 below lists the diffraction angle values and relative intensities:

TABLE 1

No.	Pos. [°2θ]	d-spacing [Å]	Rel. Int. [%]
1	8.3823	10.5486	3.44
2	12.1551	7.2816	7.50
3	12.8387	6.8954	0.79
4	13.6692	6.4783	1.46
5	15.5898	5.6842	19.09
6	16.4893	5.3761	24.96
7	16.9022	5.2457	26.73
8	17.4271	5.0889	6.63
9	18.0196	4.9229	2.44
10	18.7091	4.7430	100.00
11	19.5516	4.5405	36.68
12	20.0368	4.4316	7.27

TABLE 1-continued

No.	Pos. [°2θ]	d-spacing [Å]	Rel. Int. [%]
13	21.6415	4.1065	27.68
14	22.3613	3.9759	23.09
15	22.5244	3.9475	38.04
16	23.2458	3.8266	20.73
17	24.4405	3.6422	1.99
18	25.0311	3.5576	5.67
19	25.2320	3.5297	8.51
20	25.6811	3.4690	6.09
21	27.3448	3.2616	2.34
22	27.9281	3.1948	8.00
23	29.3222	3.0460	12.72
24	30.4098	2.9395	1.75
25	30.9780	2.8868	2.80
26	31.9694	2.7995	1.92
27	32.7130	2.7376	1.07
28	33.2425	2.6952	3.38
29	33.8297	2.6497	3.21
30	34.7005	2.5852	2.09

[0332] Visible light spectroscopy (FIGS. **2**A and **2**B) indicated that niraparib freebase Form I consisted of various aggregates of the order of 10 μm in size. The material appeared birefringent under polarized light (FIGS. **2**C and **2**D).

[0333] FIG. **3** shows SEM analysis of niraparib freebase Form I at various scales.

[0334] FIG. **4** shows the FT-IR spectrum of niraparib freebase Form I. Table 2 below lists the diffraction angles:

TABLE 2

Wavenumber [cm^{1}]	Transmittance [%]
3362.78	81.9%
3115.66	86.3%
3059.06	85.3%
2933.38	81.4%
2914.63	82.8%
2849.12	86.7%
2806.63	83.5%
2731.73	87.9%
1650.29	72.5%
1608.16	85.1%
1555.35	87.2%
1523.69	74.7%
1465.87	88.8%
1424.75	85.4%
1398.79	83.9%
1363.90	69.5%
1322.05	81.4%
1297.99	80.8%
1280.34	86.6%
1280.34	86.6%
1255.04	87.3%
1204.54	82.9%
1154.15	91.1%
1133.94	89.8%
1114.29	87.1%
1087.48	93.0%
1047.29	85.3%
1008.42	86.0%
960.40	88.4%
929.83	96.2%
884.37	93.6%
854.04	81.1%
837.22	79.0%
818.54	77.4%
782.79	81.2%
770.43	75.4%
749.64	67.5%
730.11	78.6%

TABLE 2-continued

Wavenumber [cm^{1}]	Transmittance [%]
629.94	74.7%
609.29	72.9%
557.63	76.5%
518.39	67.5%
480.68	87.6%
463.48	91.5%
451.85	88.9%
413.43	95.6%
413.43	95.6%

[0335] The major absorption bands are consistent with the structure, whereby peaks at 3373-2807 cm^{-1} are assigned as N—H and C—H stretches (amide, NH_2 and alkane/alkene), the peak at 1652 is assigned as the C═O stretch (amide), and the band at 1608 is assigned as the N—H bend (amide).

[0336] FIG. **5** shows the Raman spectrum of niraparib freebase (λ_{ex}=785 nm). Table 3 below lists the peaks:

TABLE 3

Raman Shift (cm^{-1})	Intensity
110.45	6.56E+04
254.98	1.35E+04
283.46	1.70E+04
359.14	1.35E+04
376.96	1.26E+04
411.15	1.87E+04
467.70	1.35E+04
481.44	1.25E+04
518.73	1.15E+04
536.05	1.18E+04
558.24	1.15E+04
587.69	1.45E+04
627.94	1.56E+04
635.22	1.73E+04
670.30	1.39E+04
718.33	1.49E+04
737.42	1.32E+04
767.13	1.26E+04
795.49	1.41E+04
819.01	1.11E+04
834.25	1.07E+04
851.78	1.06E+04
869.25	1.33E+04
892.46	9.12E+03
932.83	9.90E+03
960.34	1.01E+05
1009.29	2.30E+04
1052.17	2.01E+04
1086.89	8.91E+03
1135.79	1.13E+04
1155.67	1.18E+04
1197.38	3.30E+04
1252.85	1.73E+04
1280.90	1.20E+04
1300.23	1.53E+04
1352.48	1.75E+04
1382.11	4.13E+04
1457.50	1.02E+05
1527.70	4.63E+04
1556.32	2.65E+04
1607.01	6.79E+04

[0337] A TG thermogram is presented in FIG. **6** (top line, right-hand axis), which shows no significant loss in mass from the outset. The DTA thermogram (FIG. **6**, diagonal line, left-hand axis) shows a sharp endothermic event (ΔH=96.2 J/g) which is likely due to the melt of the material with an onset of approximately 188° C.

[0338] The DSC thermogram is presented in FIG. **7**, which shows a single sharp endothermic event (onset ~189.0° C.), likely due to the sample melting.

[0339] The GVS isotherm (double cycle) is presented in FIG. **8**. The GVS analysis shows about 0.7% mass increase up to 90% RH. Hence, the material is non-hydroscopic.

[0340] Karl Fischer titration determined the water content as being 0.29% (average of two experiments).

Example 2: Amorphous Niraparib Freebase

[0341] Amorphous 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide may be prepared, for example, in accordance with the synthetic scheme described in Jones et al. (*J. Med. Chem.*, 2009, 52:7170-7185). In brief, the title compound is prepared by separation of racemic 3-{4-[7-(aminocarbonyl)-2H-indazol-2-yl]phenyl}piperidinium chloride by chiral SFC purification using CO_2 as supercritical eluent (column, Chiralpak AS-H, 1 mm×25 mm; flow=10 mL/min; T_{col}=35° C.; P_{col}=100 bar; modifier, 55% PrOH containing 4% Et_2NH). 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide elutes as a second peak (RT=6.51 min) and evaporation of the solvent followed by lyophilization gives the title compound as a white powder (99.2% ee).

[0342] Alternatively, the title compound may be prepared by lyophilisation of a solution prepared by dissolving one of the crystalline forms of niraparib disclosed herein, e.g. Form I as described in Example 1. In brief, 140 mg of niraparib freebase form I was dissolved (with gentle heating) in 1,4-dioxane (~10 mL) and water (~8 mL) and split equally into 14 vials. These vials were then frozen at −50° C., before freeze drying overnight. One vial of lyophilized material was taken for analysis by XRPD.

[0343] FIG. **9** shows the XRPD diffractogram of amorphous niraparib freebase prepared by lyophilisation, from which it may be observed that the material is substantially in amorphous form.

Example 3: Crystalline Niraparib Freebase Form II and Form III

[0344] Crystalline niraparib freebase was obtained in crystalline form from solution/suspension in ethanol (Form II) and in MEK, 2-propanol, acetone, TBME, THF and toluene (Form III).

[0345] In brief, 50 μL aliquots of the appropriate solvent were added sequentially to vials of amorphous niraparib freebase (obtained as described in Example 2). Between each addition, the mixture was checked for dissolution and, if no dissolution was apparent, the mixture was heated to about 50° C. and checked again. After 300 μL of solvent had been added, 100 μL aliquots were added sequentially. This procedure was continued until dissolution was observed or until 1 mL of solvent had been added. If no dissolution occurred, the solids were isolated by filtration and an XRPD pattern was collected. If dissolution occurred, the solvent was evaporated and an XRPD pattern was collected on any solid which remained. Complete dissolution was observed only in ethanol (with heating to about 40° C.). Niraparib freebase was partially soluble in 2-propanol.

[0346] XRPD diffractograms for niraparib freebase Form II (from ethanol) and Form III (from acetone) are shown in FIGS. **10** and **11**, respectively. Tables 4 and 5 below list the diffraction angle values and relative intensities from FIGS. **10** and **11**, respectively:

TABLE 4

No.	Pos. [°2θ]	d-spacing [Å]	Rel. Int. [%]
1	3.2491	27.19352	1.88
2	8.6308	10.24539	28.68
3	17.2713	5.13442	100
4	20.0921	4.41951	10.68
5	21.2796	4.17549	10.52
6	21.5672	4.12045	29.82
7	21.6942	4.09662	65.81
8	21.8277	4.07186	52.02
9	22.5690	3.93977	12.7
10	23.9505	3.71555	8.23
11	25.8225	3.45028	48.68
12	26.3938	3.37689	28.57
13	28.4803	3.13406	3.93
14	31.7522	2.81819	3.92

TABLE 5

No.	Pos. [°2θ]	d-spacing [Å]	Rel. Int. [%]
1	8.6651	10.2050	2.88
2	10.1464	8.71817	3.83
3	11.9103	7.43071	2.02
4	13.6013	6.51043	42.66
5	13.8199	6.40797	12.96
6	14.5644	6.08204	5.33
7	15.8975	5.57490	4.32
8	17.3461	5.11246	100
9	19.6712	4.51310	4.9
10	20.5305	4.32612	53.06
11	21.2584	4.1796	24.86
12	21.6632	4.10241	18.6
13	22.2805	3.99013	15.23
14	23.7043	3.75358	10.81
15	24.1170	3.69027	11

Example 4: Crystalline Niraparib Freebase Form IV

[0347] Niraparib freebase Form IV was obtained using a melt-cooling cycle.

[0348] 5 mg of niraparib freebase Form I was weighed into an aluminum DSC pan and sealed non-hermetically with a pierced aluminum lid. The sample pan was then loaded into a Seiko DSC6200 (equipped with a cooler) cooled and held at 20° C. Once a stable heat-flow response was obtained, the sample and reference were heated to melting at a scan rate of 10° C./min and the resulting heat flow response monitored. Nitrogen was used as the purge gas, at a flow rate of 50 cm^3/min. The material was heated to just beyond melting (about 200° C.) before being cooled to 20° C. and then heated to melting again.

[0349] After the first melt and cool cycle, the DSC thermogram (shown in FIG. **12**) was different to the thermogram for Form I, and it exhibited an exothermic event (onset about 122° C.) which was possibly due to recrystallisation. When assessed using VT-XRPD with the same heat profile, the XRPD pattern indicated that amorphous material was obtained after the first melt-cool cycle (FIG. **13**). When reheated to about 122° C., the XRPD pattern indicated recrystallization to Form IV which persisted until the onset of melting at about 168° C. when a further recrystallization occurred (FIG. **14**). Table 6 below lists the diffraction angle

values and relative intensities from the XRPD diffractogram of niraparib freebase Form IV (FIG. **14**, 122° C. trace):

TABLE 6

No.	Pos. [°2θ]	d-spacing [Å]	Rel. Int. [%]
1	7.2897	12.12706	7.23
2	12.8787	6.87406	12.09
3	13.7214	6.45372	7.49
4	14.4157	6.14445	31.13
5	15.3722	5.76422	7.37
6	17.0799	5.19152	24.88
7	17.3449	5.11281	29.45
8	17.5681	5.04836	21.77
9	18.9128	4.69234	54.7
10	19.2787	4.60411	20.54
11	19.6560	4.51656	35.3
12	19.8048	4.48295	24.17
13	20.1189	4.41369	73.67
14	20.9821	4.23401	15.13
15	21.8744	4.06327	100
16	22.0906	4.02399	45.2
17	22.5105	3.94988	9.93
18	24.0719	3.69708	8.66
19	24.8577	3.58198	7.52
20	27.6580	3.22534	13.03

[0350] The ^{1}H-NMR spectra of Form IV (FIG. **16**, lower trace) was identical to that of Form I (FIG. **16**, upper trace), which indicates that no chemical reaction occurred during the reheating process but that some structural changes took place.

Example 5: Solubility Studies on Niraparib Freebase

[0351] The aqueous solubility of niraparib freebase (Form I and amorphous) was assessed under conditions of varying (physiologically relevant) pH.

[0352] For each sample, 30 mg of the freebase was weighed into vials (in triplicate) and 1 mL of water or buffer was added. The following buffers (50 mM in each case) used were:

[0353] pH 1 25 mL KCl solution (1.49 g dissolved in 100 mL water) and 42.5 mL HCl solution (1.66 mL made up to 100 mL with water) were added together and made up to 100 mL with water;

[0354] pH 4.5 anhydrous sodium acetate (1.07 g) was dissolved in water (about 150 mL) before adding 5.9 mL acetic acid solution (11.6 mL glacial acetic acid made up to 100 mL with water). The resulting solution was made up to 500 mL with water; and

[0355] pH 6.8 25 mL of KH_2PO_4 solution (2.72 g dissolved in about 80 mL water and made up to 100 mL with water) and 11.2 mL of NaOH solution (800 mg of sodium hydroxide was dissolved and diluted to 100 mL with water) were added together and made up to 100 mL with water.

[0356] The resulting samples were shaken at 37° C. for 1 hour. A further 20 mg of crystalline freebase was added to the pH 1 buffer sample. All samples were then shaken at 37° C. for 23 hours. Each sample was then filtered and the concentration of niraparib in the mother liquor was assessed by HPLC. Any solids which were isolated by filtration were assessed by XRPD to determine whether the form of the material had changed.

[0357] The solubility of amorphous niraparib freebase and niraparib freebase Form I is shown in Table 7 below. In each case, the solubility value reported is the average of the triplicate measurements on the concentration of niraparib in solution.

TABLE 7

Buffer	Solubility of Amorphous Form (mg/mL)	Solubility of Crystalline Form I (mg/mL)
pH 1	11.8	30.9
pH 4.5	13.4	11.8
pH 6.8	0.6	0.7
water	0.8	<0.1

[0358] The data in Table 7 suggest that crystalline niraparib freebase has a solubility in low pH media which is as good as (if not better than) the amorphous form of the compound. This suggests potential advantages for administration of the compound in vivo, e.g. in the low pH environment of the stomach.

[0359] The XRPD data obtained on the solid material which remained after filtration of the crystalline samples indicated that the crystalline form was unchanged in each case. The XRPD data obtained on the solid material which remained after filtration of the amorphous samples suggested that a new crystalline form was obtained (Form V). An exemplary XRPD spectrum (from the sample which was shaken with water) is shown in FIG. **15**. Table 8 below lists the diffraction angle values and relative intensities from the XRPD diffractogram of FIG. **15**:

TABLE 8

No.	Pos. [°2θ]	d-spacing [Å]	Rel. Int. [%]
1	5.9009	14.97771	46.64
2	8.0477	10.98642	9.63
3	9.7155	9.10387	14.55
4	12.1093	7.30906	11.38
5	14.4475	6.13099	28.04
6	14.8307	5.97341	21.42
7	15.1139	5.86210	14.63
8	15.8408	5.59473	19.62
9	16.7162	5.30367	20.47
10	19.4925	4.55407	16.75
11	20.8047	4.26972	100
12	21.3110	4.16941	34.33
13	21.6446	4.10589	57.39
14	22.7189	3.91411	14.43
15	23.0141	3.86457	12.23
16	24.3453	3.65618	13
17	26.5471	3.35774	8.7
18	27.2877	3.26826	8.72
19	28.5177	3.13003	9.88
20	29.1926	3.05919	15.93

[0360] The teachings of all patents, published applications and references cited herein are incorporated by reference in their entirety.

[0361] While the present invention has particularly been shown and described with reference to exemplary embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the sprit and scope of the invention encompassed by the appended claims.

1. A crystalline form of a 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide freebase.

2. The crystalline form according to claim **1**, wherein the 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carbox-

amide freebase is characterized by an X-ray powder diffraction (XRPD) pattern comprising at least three diffraction angles, when measured using Cu K radiation, selected from a group consisting of about 12.2, 15.6, 16.5, 16.9, 18.7, 19.6, 21.6, 22.4, 22.5, 23.2, 25.2, 27.9, and 29.3 degrees 2θ.

3. The crystalline form according to claim **1**, wherein the 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide freebase is characterized by an X-ray powder diffraction (XRPD) pattern comprising at least three diffraction angles, when measured using Cu K radiation, selected from a group consisting of about 15.6, 16.5, 16.9, 18.7, 19.6, 21.6, 22.4, 22.5, 23.2, and 29.3 degrees 2θ.

4. The crystalline form according to claim **1**, wherein the 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide freebase is characterized by an X-ray powder diffraction (XRPD) pattern comprising at least three diffraction angles, when measured using Cu K radiation, selected from a group consisting of about 15.6, 16.5, 18.7, 19.6, 21.6, 22.4, 22.5, and 23.2 degrees 2θ.

5. The crystalline form according to claim **1**, wherein the 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide freebase is characterized by an X-ray powder diffraction (XRPD) pattern, when measured using Cu K radiation, comprising diffraction angles of about 15.6, 16.5, 16.9, 18.7, 19.6, 21.6, and 22.5 degrees 2θ.

6. The crystalline form according to claim **1**, wherein the 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide freebase is characterized by an X-ray powder diffraction (XRPD) pattern, when measured using Cu K radiation, comprising diffraction angles of about 18.7, 19.6, 21.6, and 22.5 degrees 2θ.

7. The crystalline form according to claim **1**, wherein the 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide freebase is characterized by an X-ray powder diffraction (XRPD) pattern comprising diffraction angles with 2θ values, and optional relative intensities, according to the following table:

Pos. [°20]	Rel. Int. [%]
8.4	3
12.2	8
12.8	1
13.7	1
15.6	19
16.5	25
16.9	27
17.4	7
18.0	2
18.7	100
19.6	37
20.0	7
21.6	28
22.4	23
22.5	38
23.2	21
24.4	2
25.0	6
25.2	9
25.7	6
27.3	2
27.9	8
29.3	13
30.4	2
31.0	3
32.0	2
32.7	1

-continued

Pos. [°20]	Rel. Int. [%]
33.2	3
33.8	3
34.7	2

8. The crystalline form according to claim **1**, wherein the 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide freebase is characterised by an X-ray powder diffraction (XRPD) pattern substantially in accordance with FIG. **1**.

9. The crystalline form according to claim **1**, characterised by adsorbing less than about 1% by weight of water up to about 90% relative humidity at about 25° C.

10. The crystalline form according to claim **2**, further comprising:

- a crystalline Form II characterized by an X-ray powder diffraction (XRPD) pattern substantially in accordance with FIG. **10**;
- a crystalline Form III characterized by an X-ray powder diffraction (XRPD) pattern substantially in accordance with FIG. **11**;
- a crystalline Form IV characterized by an X-ray powder diffraction (XRPD) pattern substantially in accordance with FIG. **14**; and/or
- a crystalline Form V characterized by an X-ray powder diffraction (XRPD) pattern substantially in accordance with FIG. **15**.

11. A composition comprising the crystalline form of claim **1**, wherein the composition is substantially free of amorphous niraparib, a pharmaceutically acceptable salt of niraparib, and/or any other solid form of niraparib or niraparib salt.

12. A composition comprising the crystalline form of claim **1**, wherein less than about 10% or less than about 5% of the total niraparib in the composition is in the form of amorphous niraparib, a pharmaceutically acceptable salt of niraparib, and/or any other solid form of niraparib or niraparib salt.

13. A pharmaceutical composition comprising the crystalline form of claim **1**, or the composition of claim **11**, and at least one pharmaceutically acceptable excipient.

14.-**15**. (canceled)

16. A method of treating cancer, stroke, autoimmune diabetes, a neurological disease, an inflammatory disease, a metabolic disease or a cardiovascular disease in a subject, the method comprising administering to the subject an effective amount of the crystalline niraparib freebase of claim **1**, or the composition of claim **11**.

17. The method according to claim **16**, wherein the method is a method of treating cancer.

18. The method according to claim **17**, wherein the cancer is associated with BRCA1 and/or BRCA2 mutations.

19. The method according to claim **17**, wherein the cancer is associated with a mutation in ATM, ATR, BAP1, BARD1, BLM, BRIP1, MRE11A, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, XRCC2, or any combinations thereof.

20. The method according to claim **17**, wherein the cancer is epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer.

21.-**22**. (canceled)

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