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(54) **METHODS OF TREATING OVARIAN CANCER**(71) Applicant: **TESARO, INC.**, Waltham, MA (US)(72) Inventors: **Mary Lynne Hedley**, Waltham, MA (US); **Robert Martell**, Waltham, MA (US)(73) Assignee: **Tesaro, Inc.**, Wilmington, DE (US)

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See application file for complete search history.(56) **References Cited**

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(57) **ABSTRACT**

The present invention provides methods of administering a PARP inhibitor to a cancer patient.

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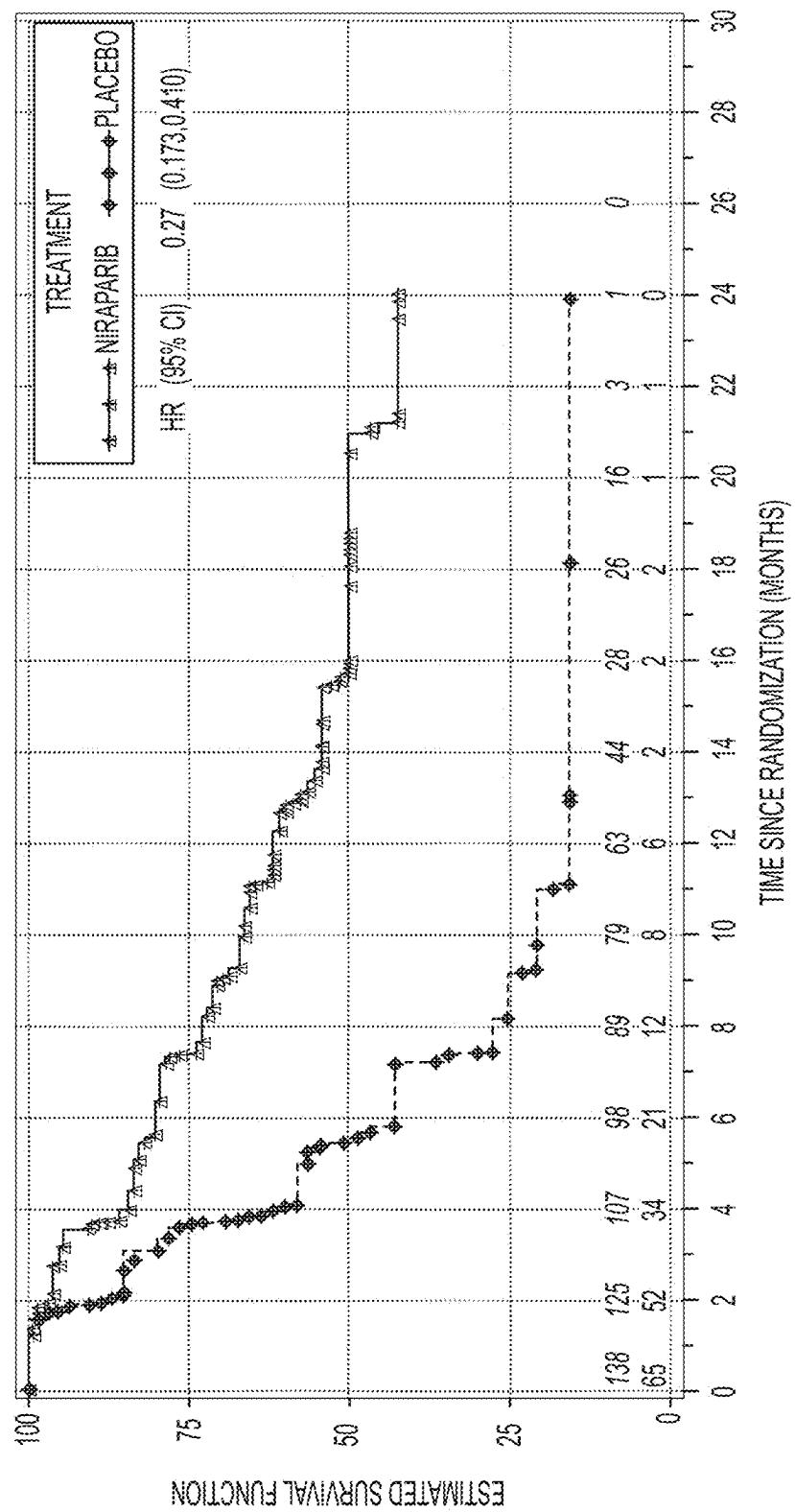


Figure 1

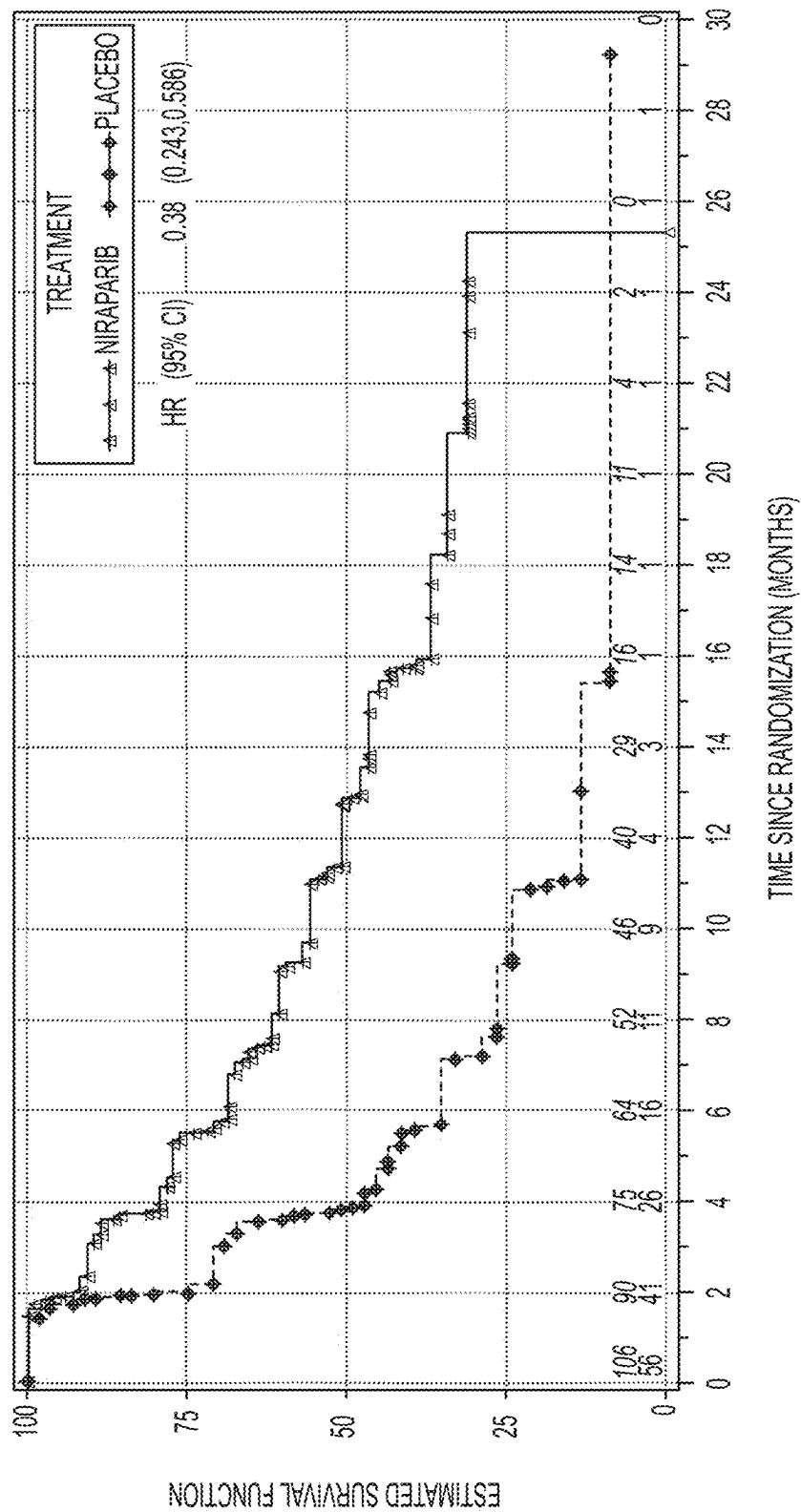


Figure 2

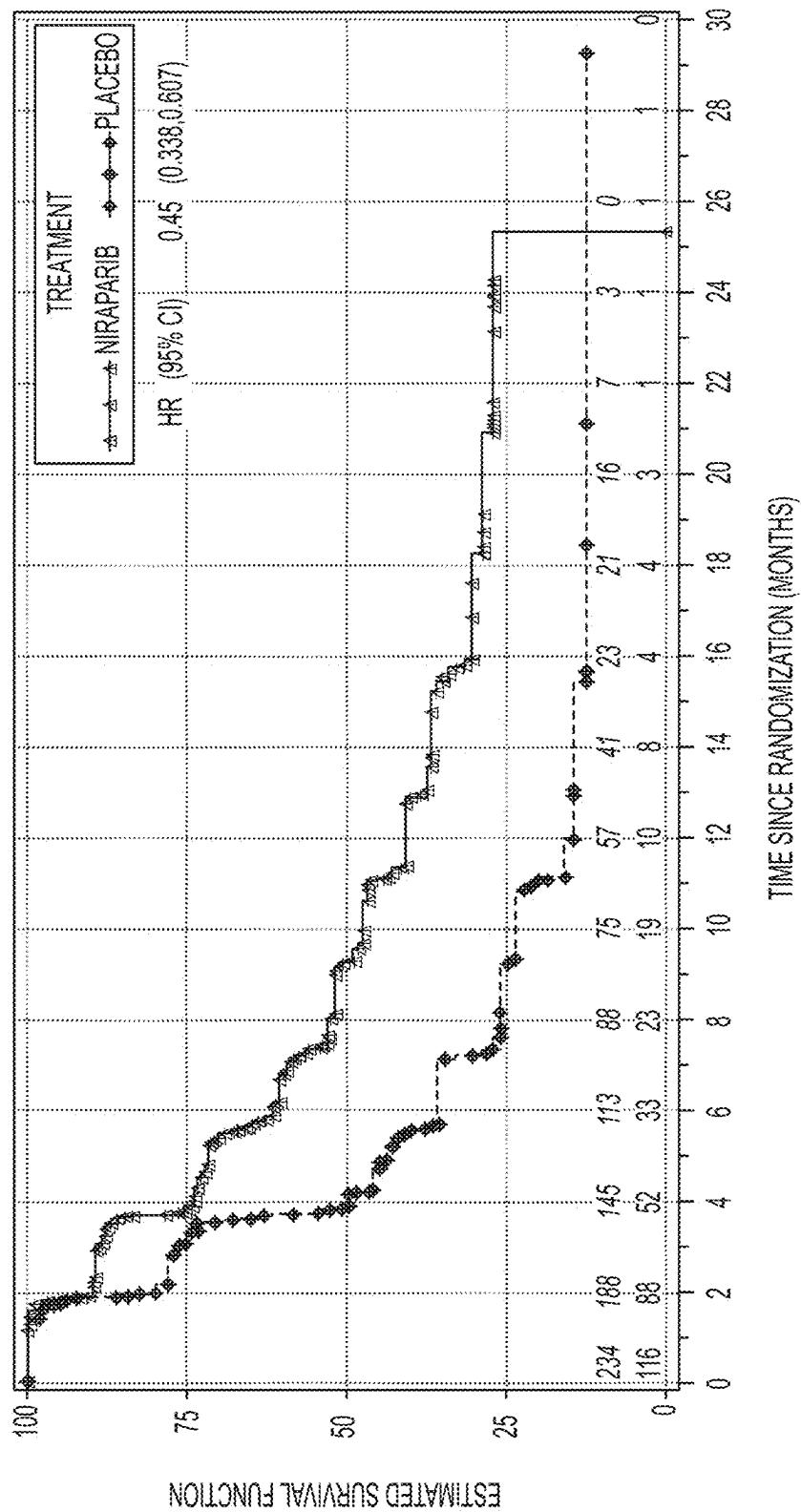


Figure 3

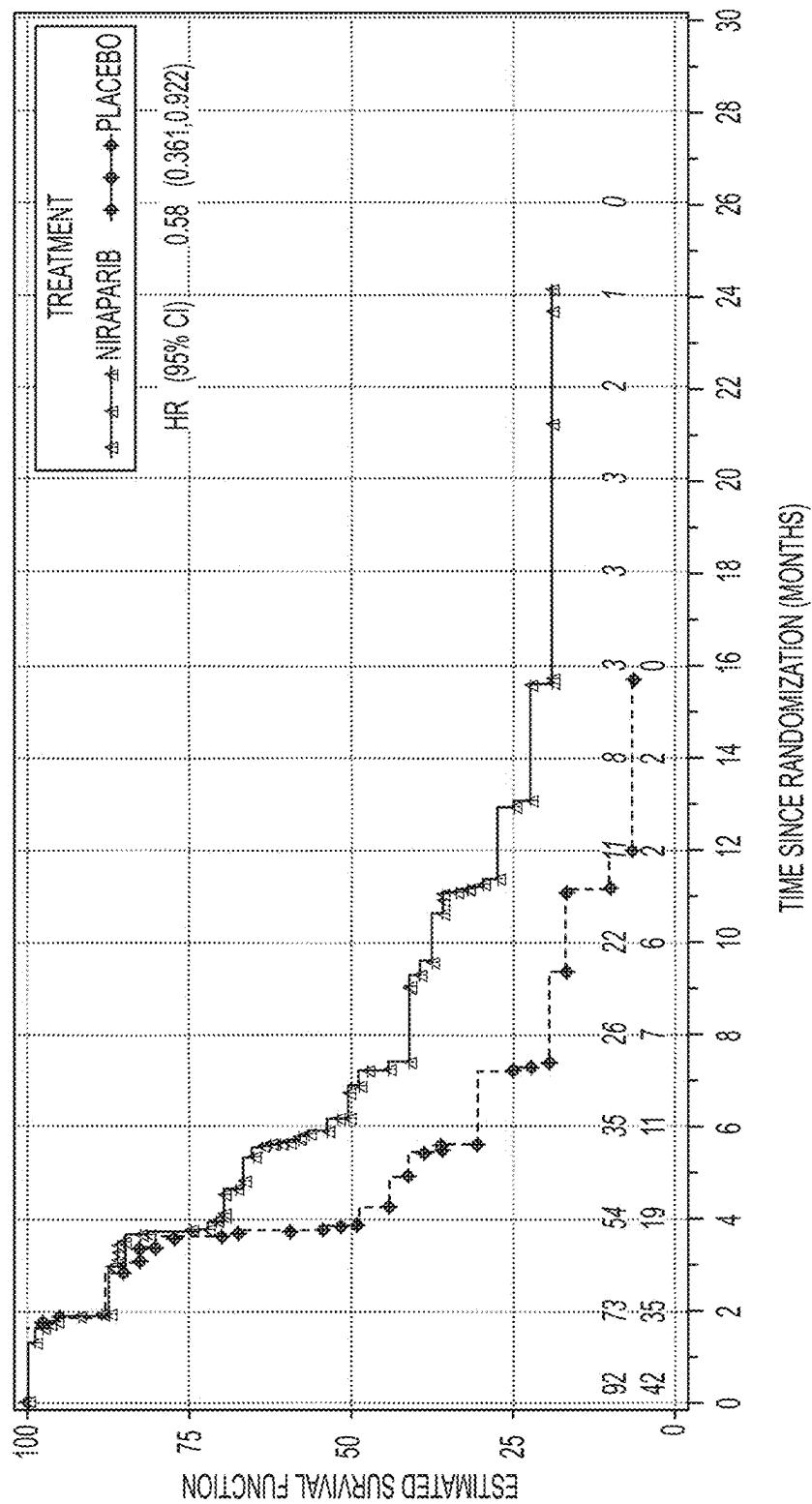


Figure 4

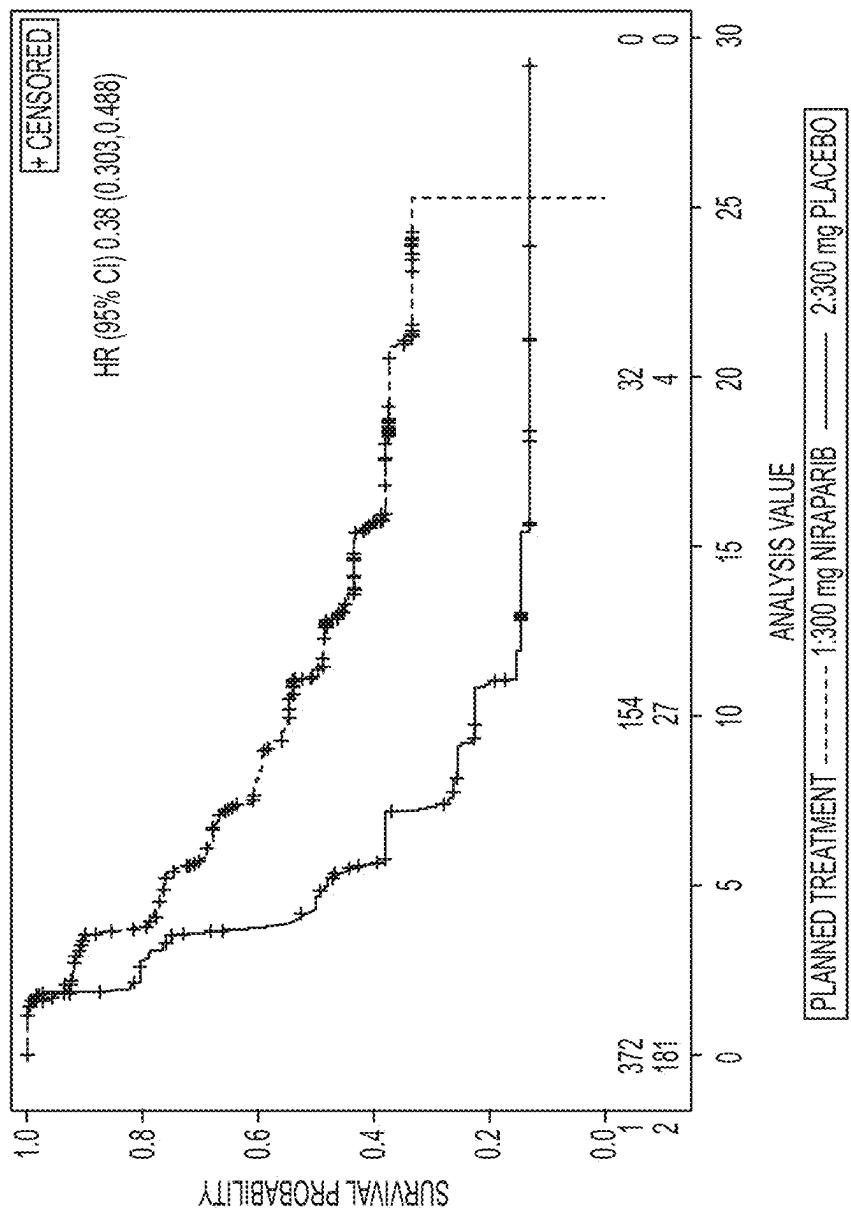


Figure 5

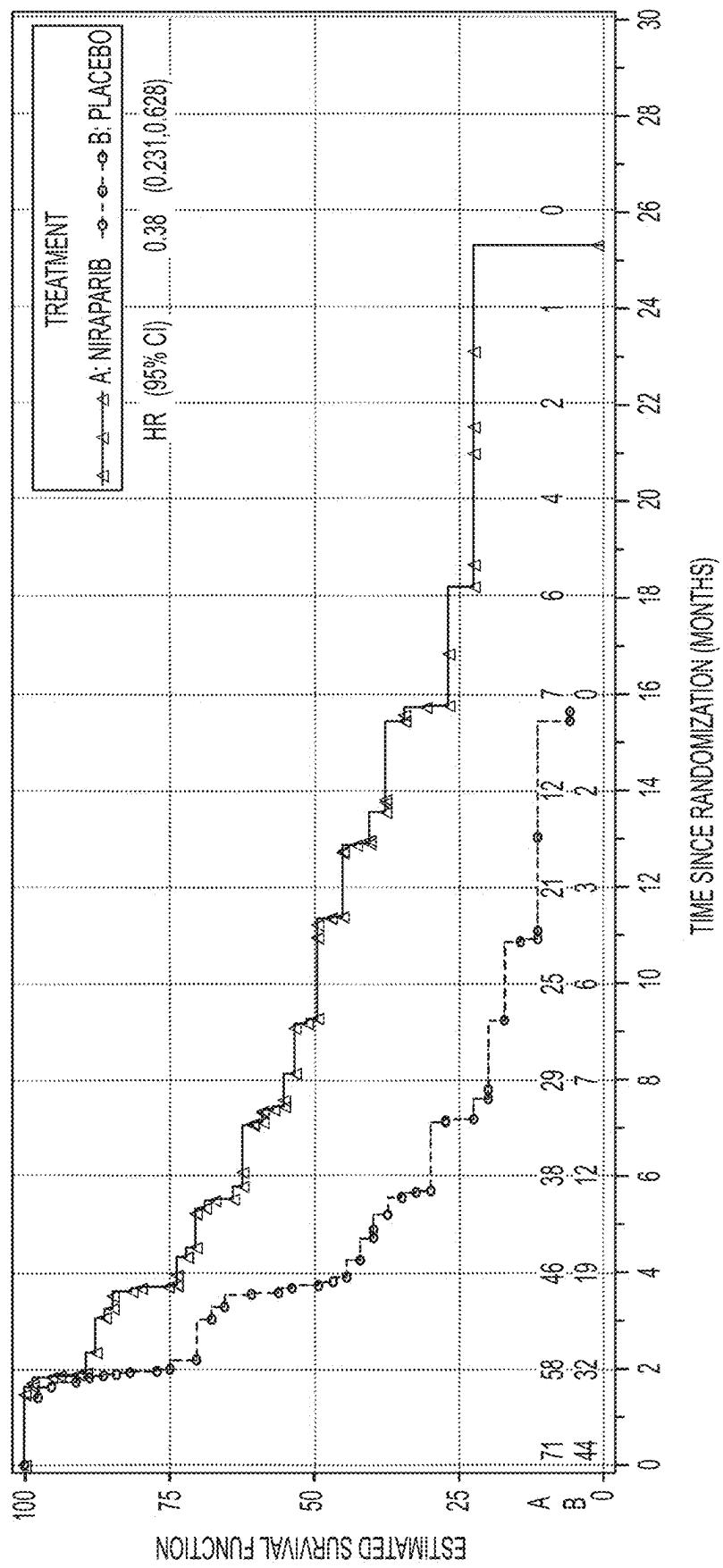


Figure 6

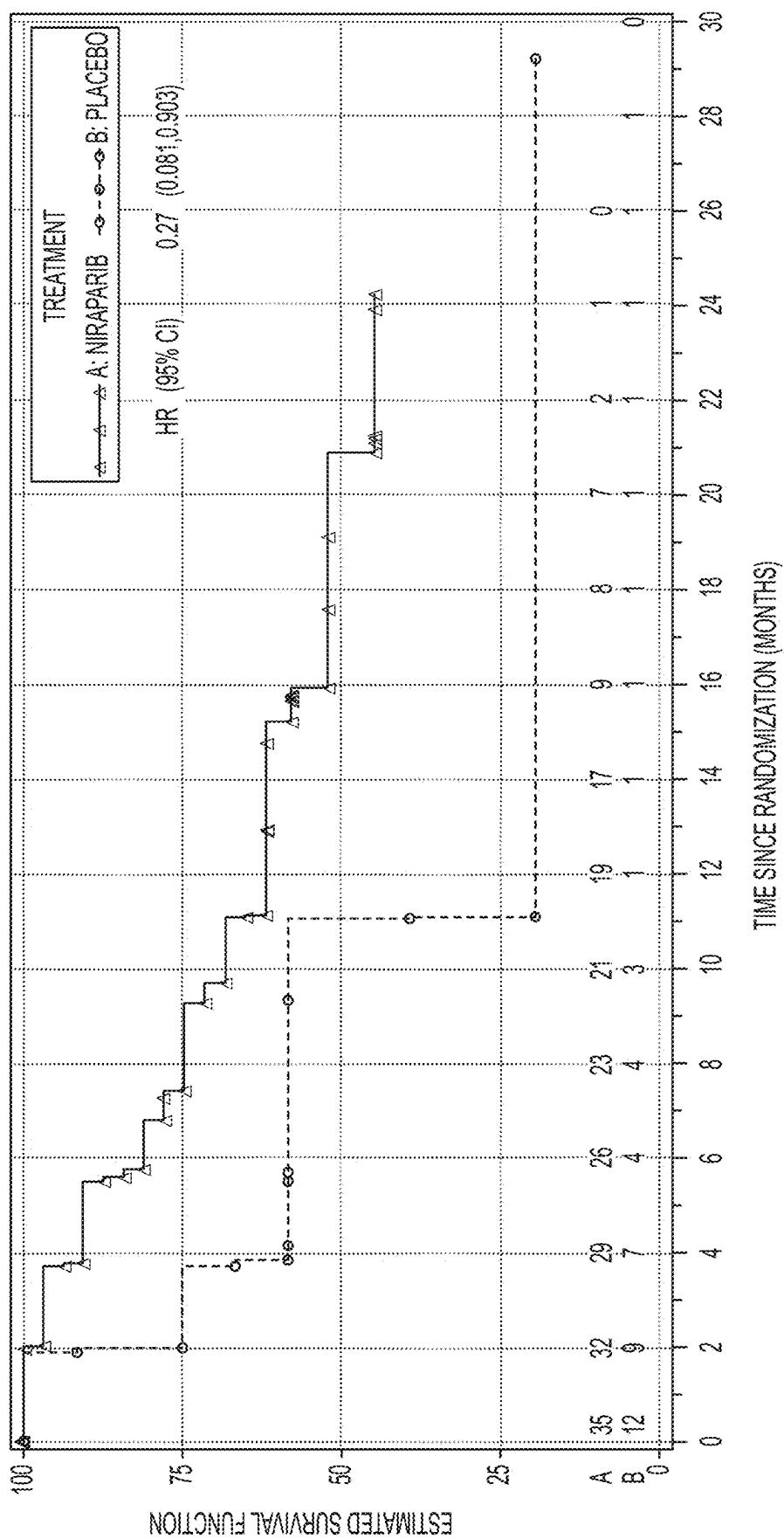


Figure 7

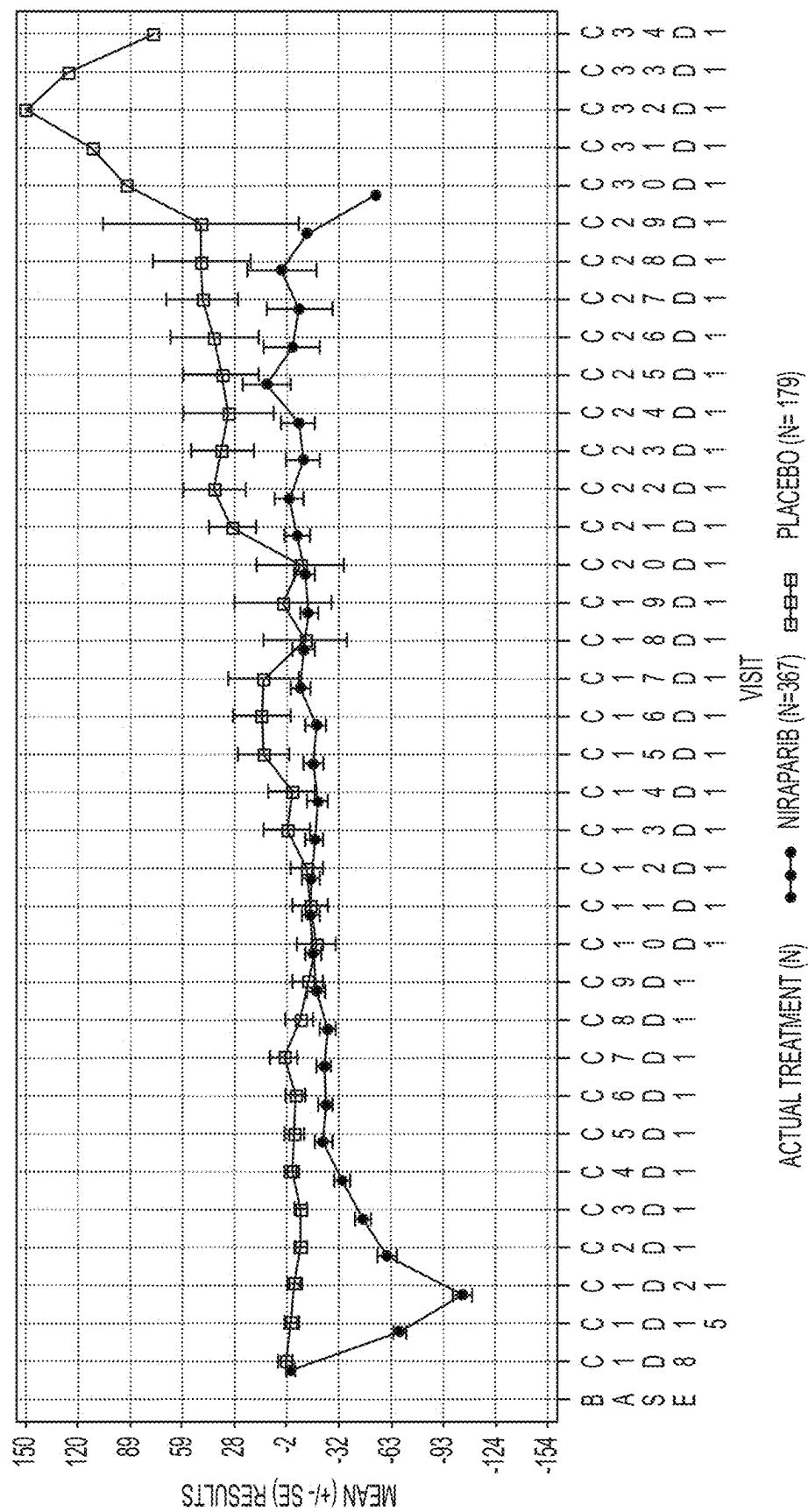


Figure 8

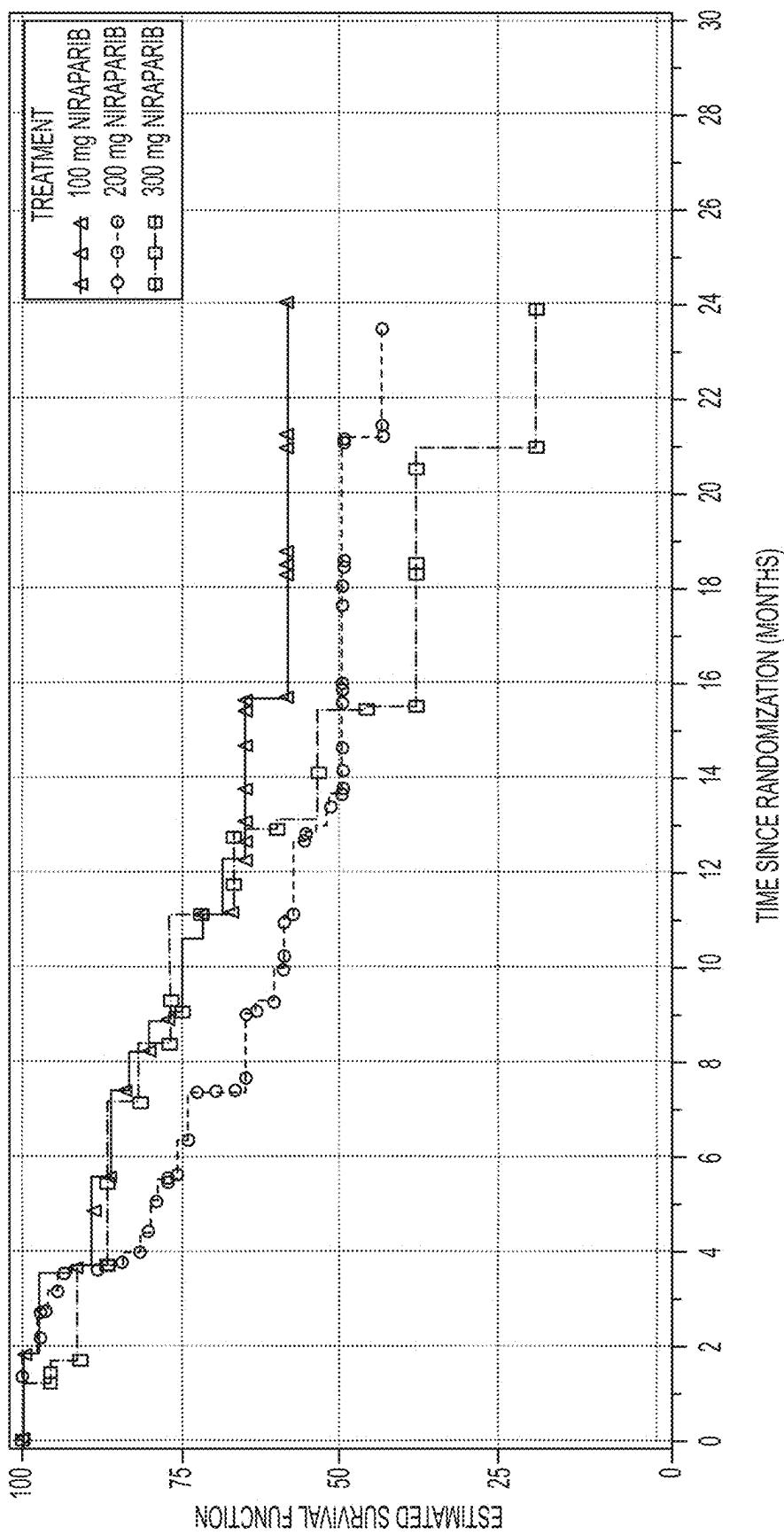


Figure 9

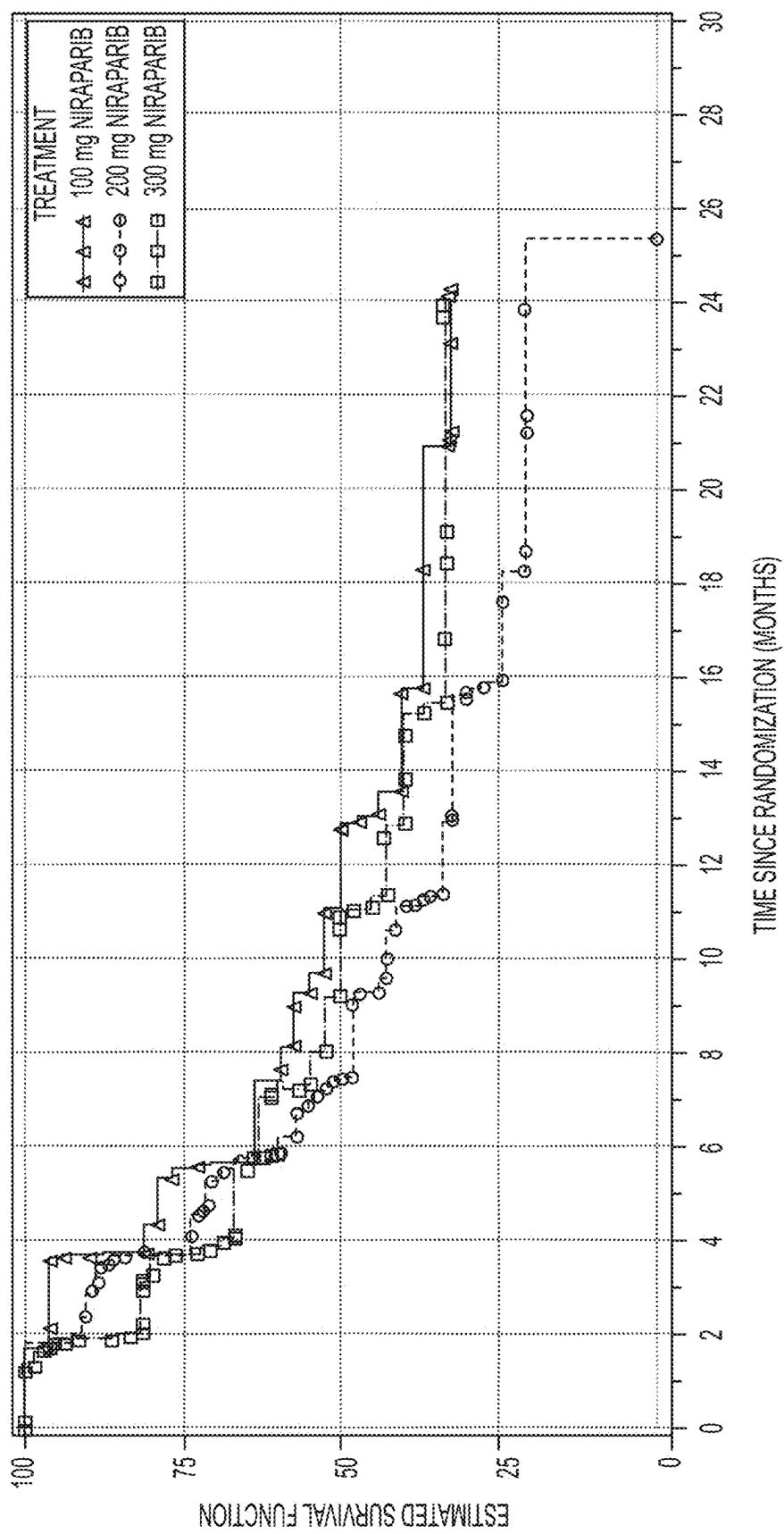
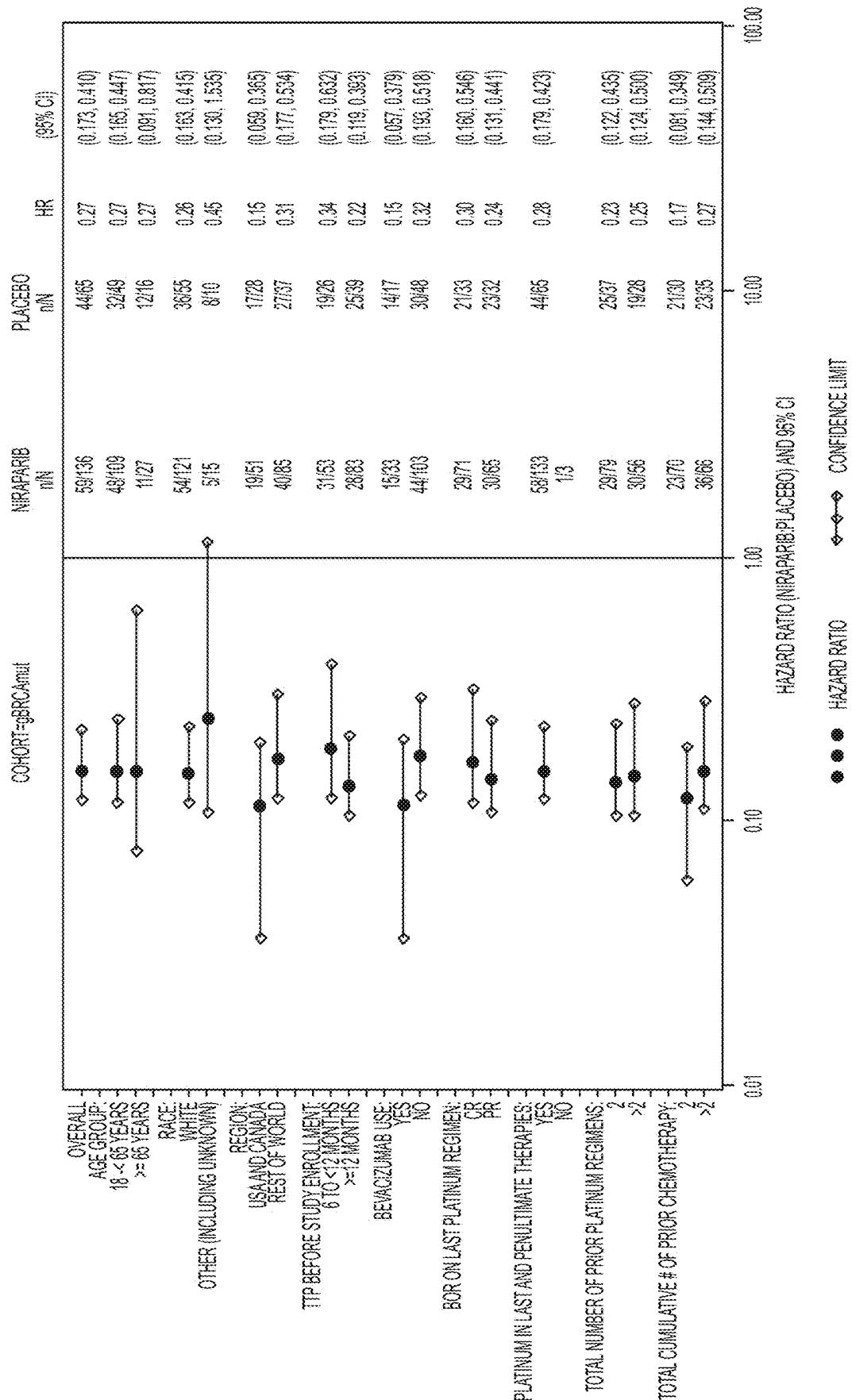
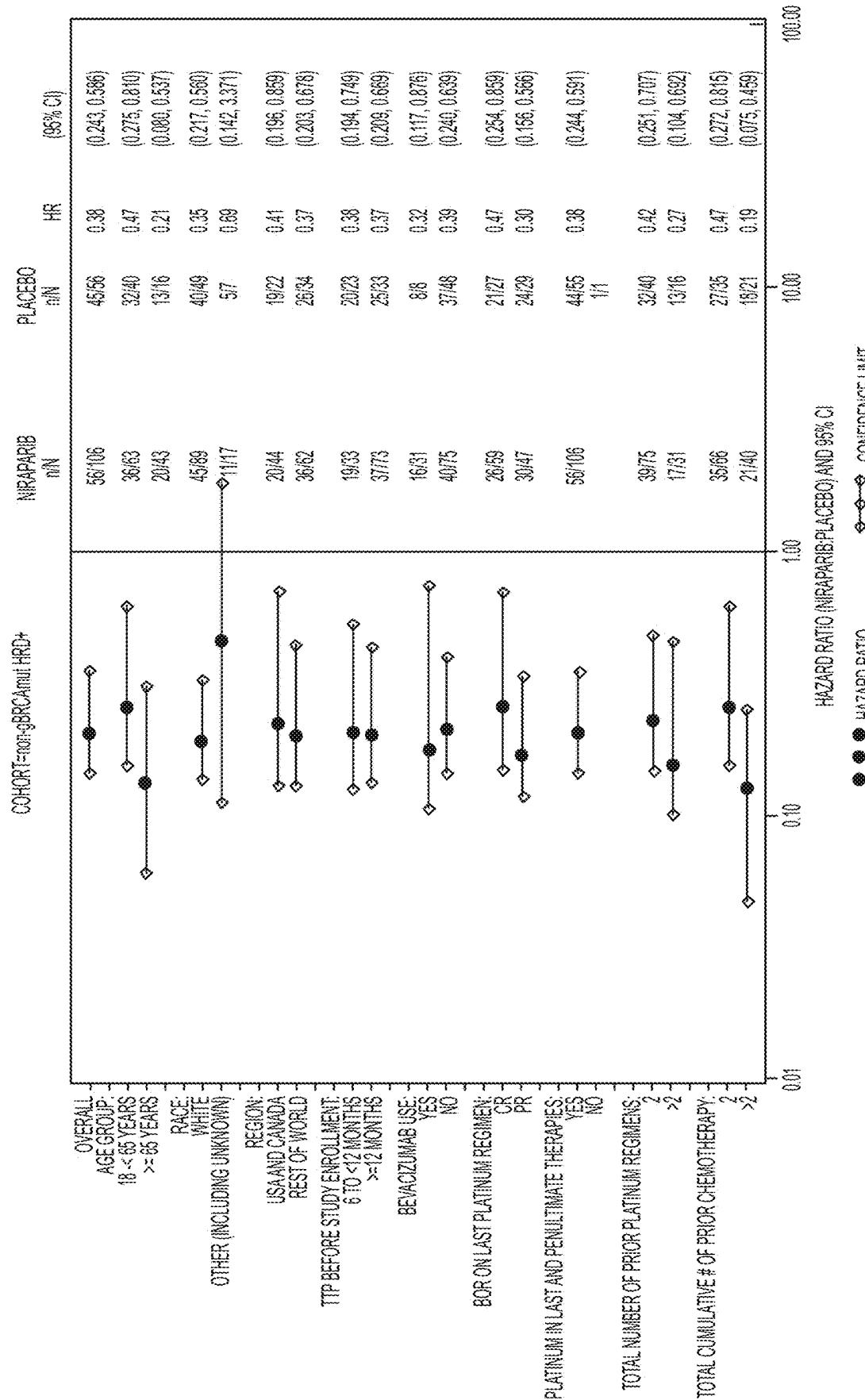


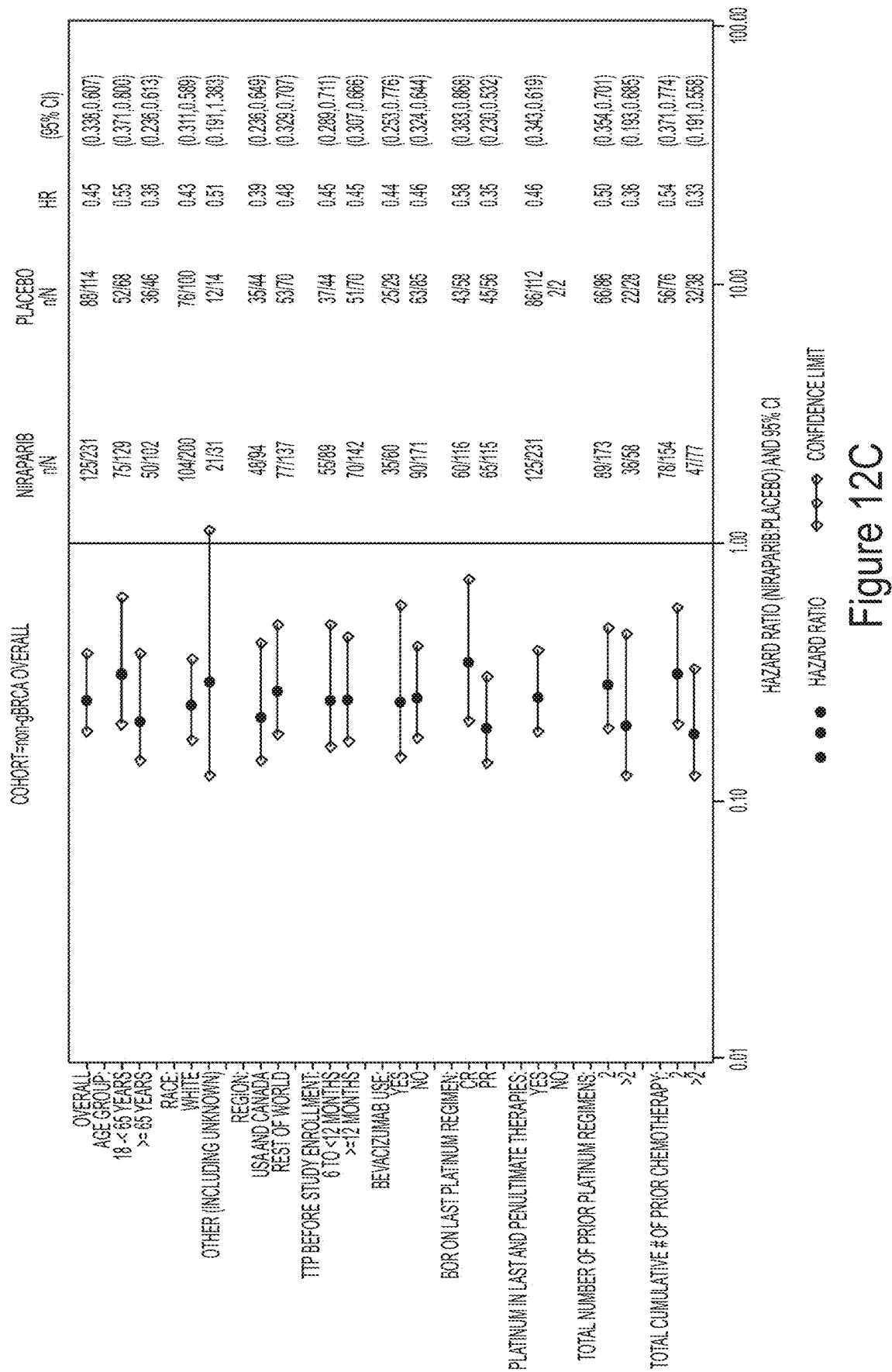
Figure 10

	gBRCAmut		non-gBRCAmut		non-gBRCAmut HRD positive		OVERALL	
END POINT	NIRAPARIB (N=138)	PLACEBO (N=65)	NIRAPARIB (N=106)	PLACEBO (N=56)	NIRAPARIB (N=234)	PLACEBO (N=116)	PLACEBO (N=116)	PLACEBO (N=116)
CHEMOTHERAPY-FREE INTERVAL								
MEDIAN (95% CI) — MO	22.8 (17.9, NR)	9.4 (7.9, 10.6)	18.2 (14.2, 24.3)	7.7 (6.3, 10.6)	12.7 (11.0, 14.7)	8.6 (6.9, 10.0)		
P VALUE	<0.0001		<0.0001		<0.0001		<0.0001	
HAZARD RATIO (95% CI)	0.26 (0.169, 0.414)		0.31 (0.190, 0.493)		0.50 (0.370, 0.6666)			
TIME TO FIRST SUBSEQUENT THERAPY								
MEDIAN (95% CI) — MO	21.0 (17.5, NR)	8.4 (6.6, 10.6)	15.9 (12.4, NR)	6.0 (4.7, 9.8)	11.8 (9.9, 13.1)	7.2 (5.7, 8.5)		
P VALUE	<0.0001		<0.0001		<0.0001		<0.0001	
HAZARD RATIO (95% CI)	0.31 (0.205, 0.481)		0.36 (0.232, 0.565)		0.54 (0.411, 0.719)			
PROGRESSION-FREE SURVIVAL 2								
MEDIAN (95% CI) — MO	25.8 (20.3, NR)	16.0 (10.8, 21.9)	22.3 (18.6, NR)	17.6 (11.8, NR)	18.4 (16.0, 21.1)	15.1 (12.2, 20.3)		
P-VALUE	0.0005		0.0472		0.0078			
HAZARD RATIO (95% CI)	0.41 (0.242, 0.687)		0.58 (0.340, 0.999)		0.64 (0.465, 0.892)			

Figure 11

**Figure 12A**

**Figure 12B**

**Figure 12C**

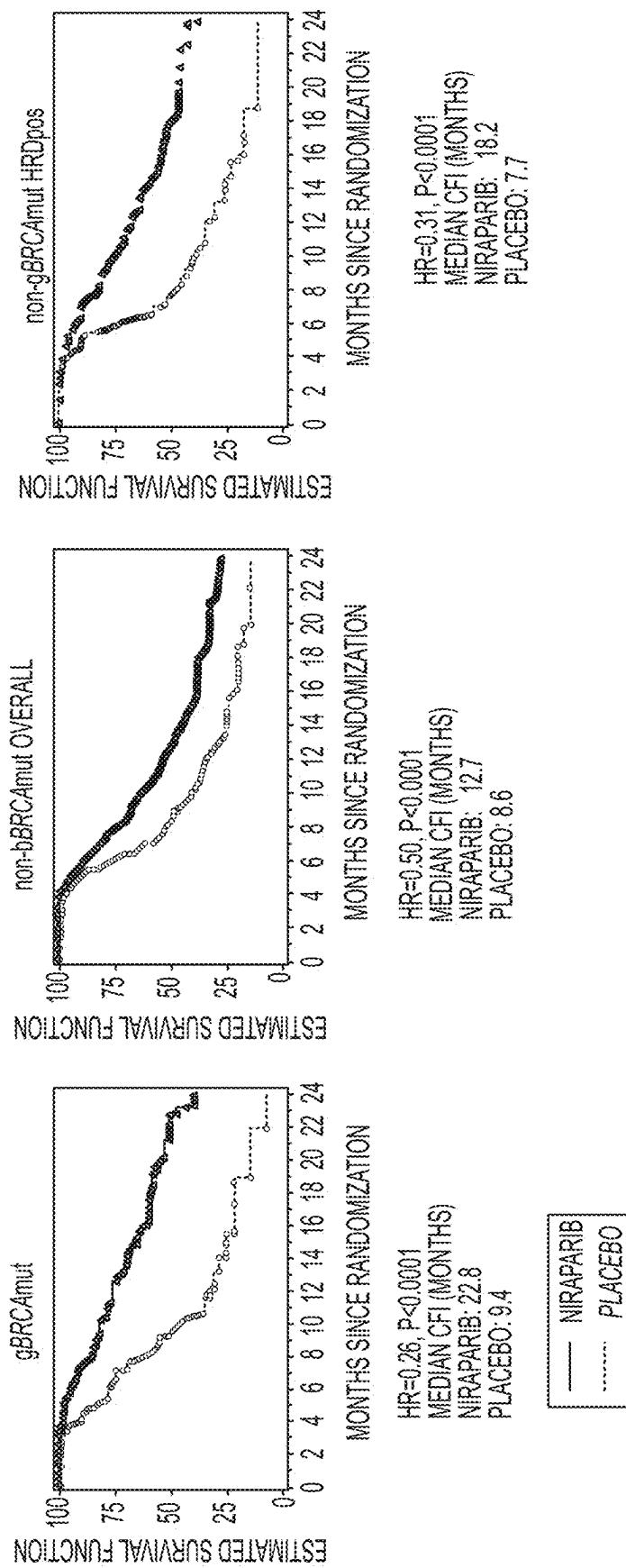


Figure 13

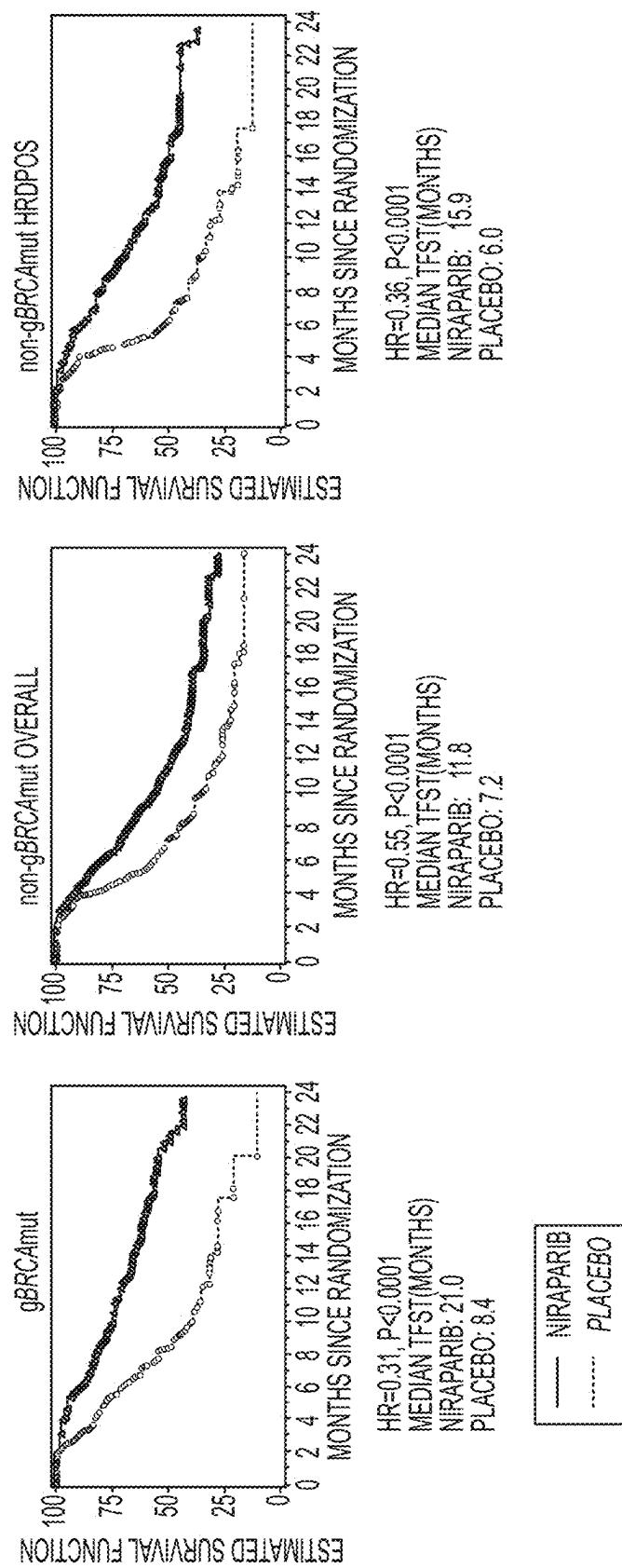


Figure 14

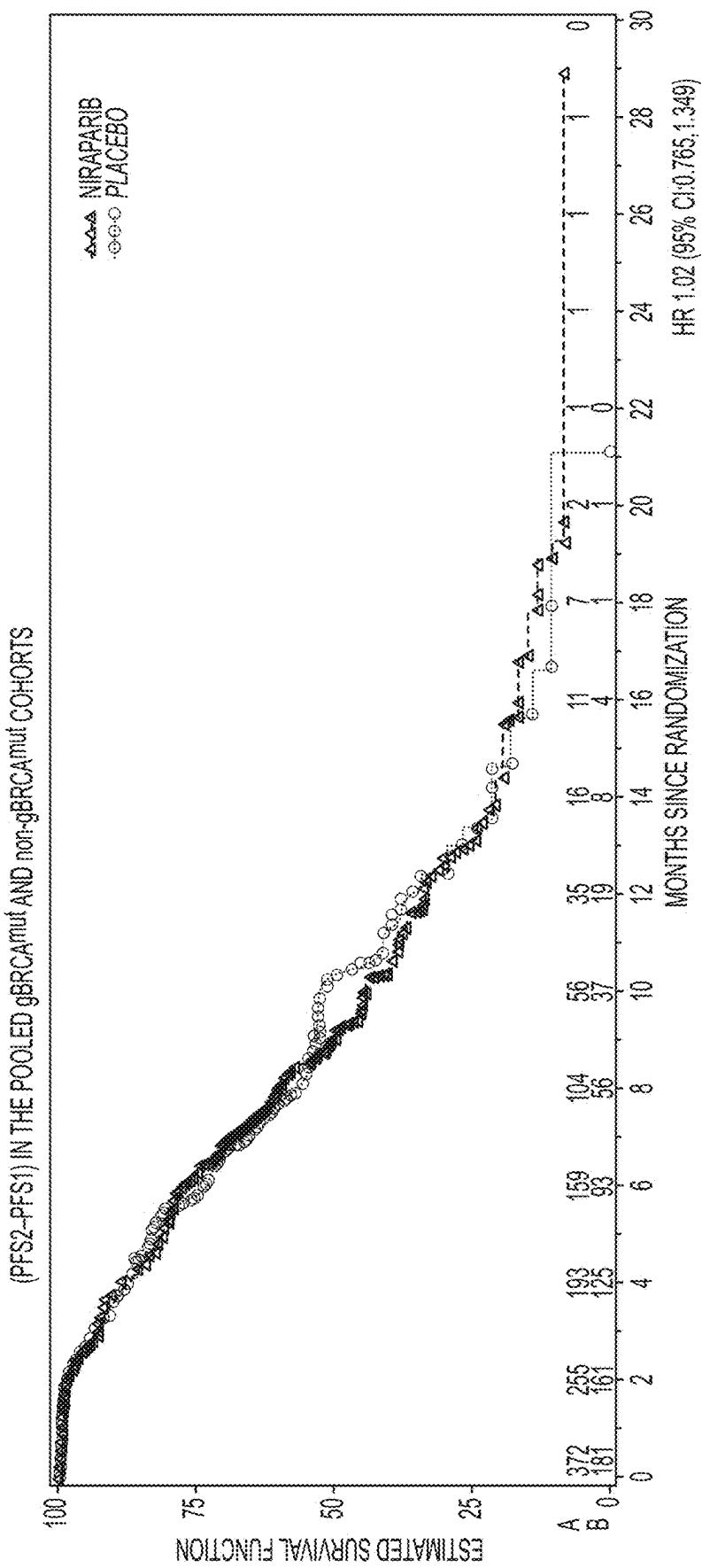


Figure 15

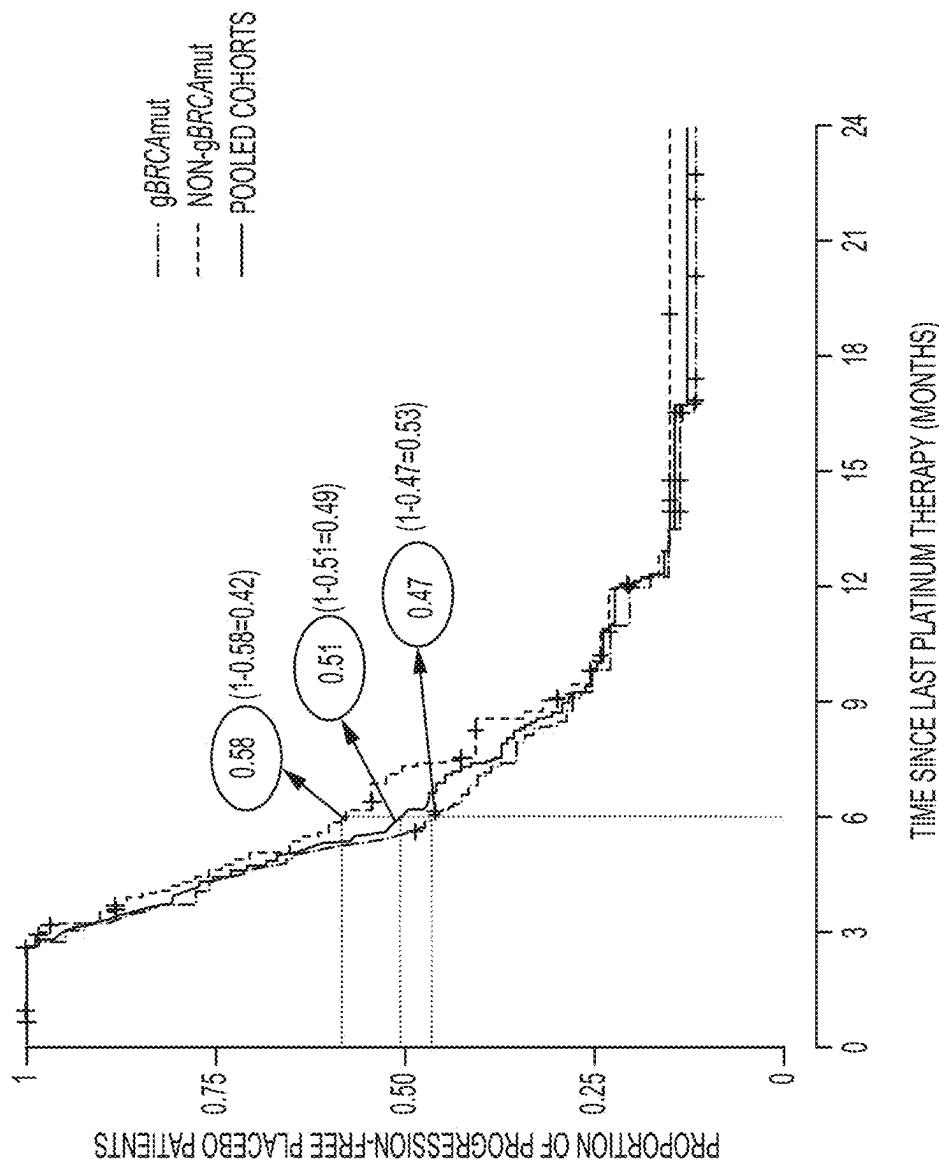


Figure 16

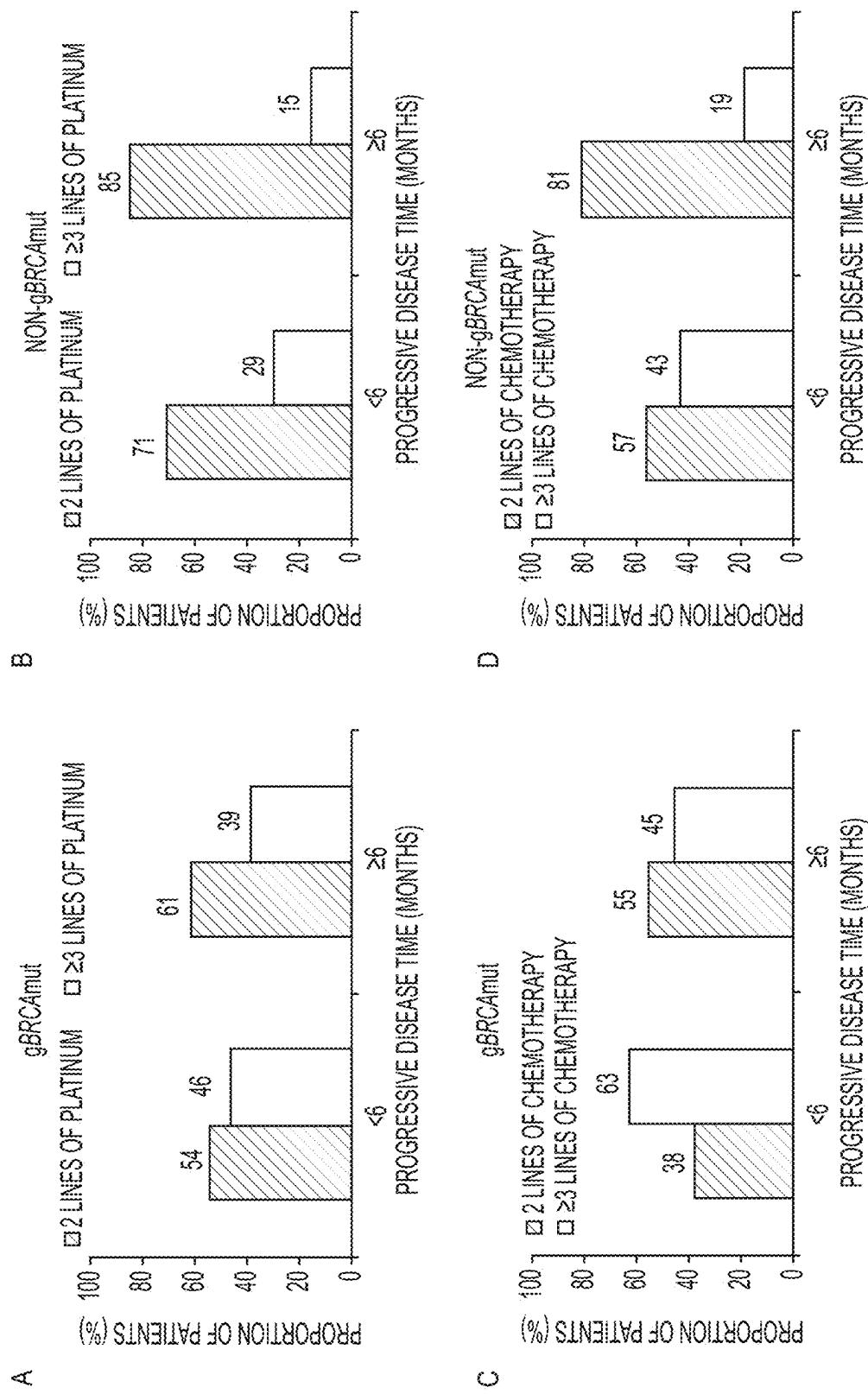


Figure 17

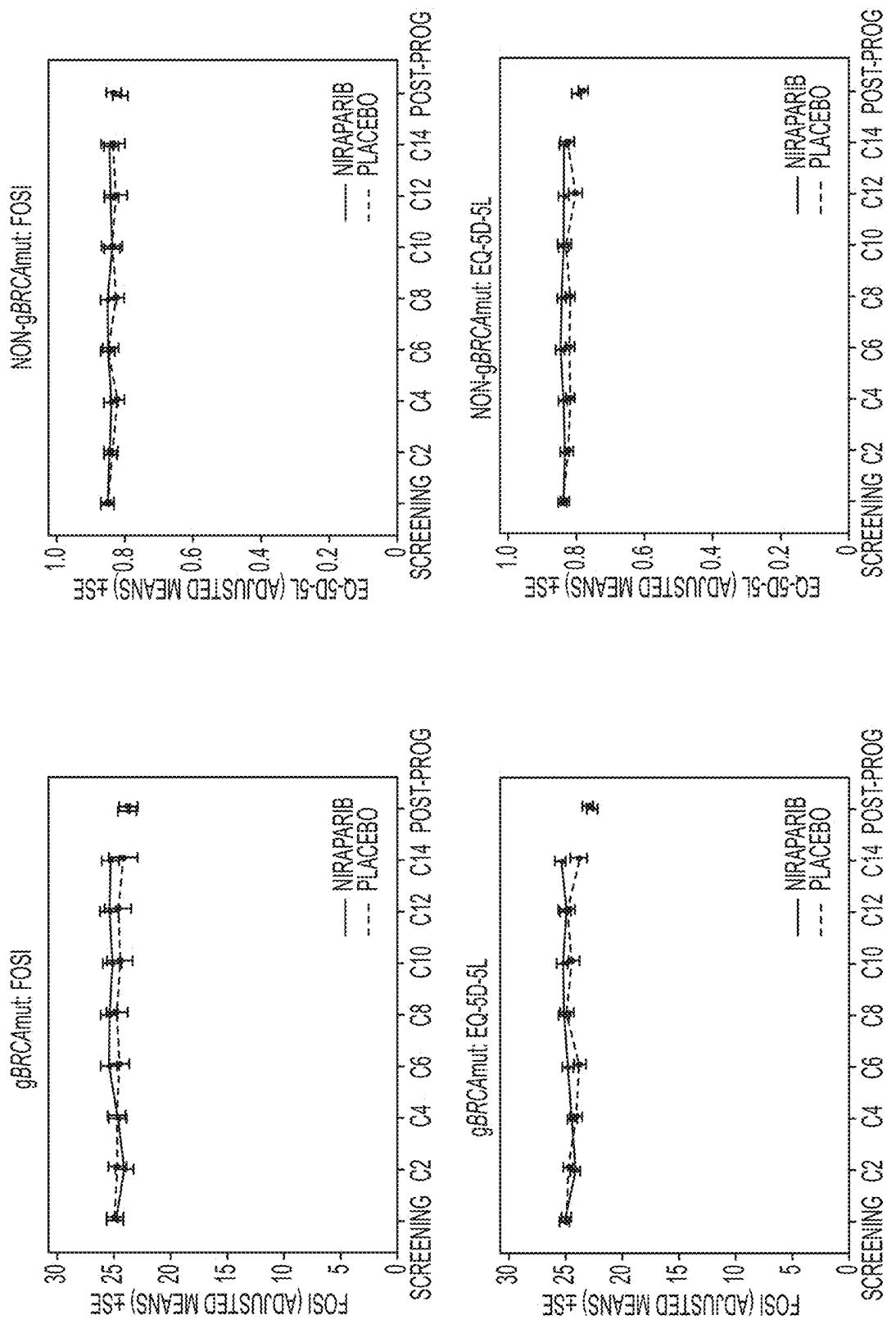


Figure 18

METHODS OF TREATING OVARIAN CANCER

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application is a continuation of International Application No. PCT/US17/40039 filed Jun. 29, 2017; which claims priority to U.S. Provisional Application No. 62/470,141 filed Mar. 10, 2017, U.S. Provisional Application No. 62/402,427 filed Sep. 30, 2016, and U.S. Provisional Application No. 62/356,461 filed Jun. 29, 2016, the disclosures of which are hereby incorporated by reference.

BACKGROUND

Cancer is a serious public health problem, with 562,340 people in the United States of America dying of cancer in 2009 alone. American Cancer Society, Cancer Facts & Figures 2009 (available at American Cancer Society website). One of the primary challenges in cancer treatment is discovering relevant, clinically useful characteristics of a patient's own cancer and then, based on these characteristics, administering a treatment plan best suited to the patient's cancer.

Ovarian cancer is the 5th overall cause for cancer death in women and represents 5% of all cancer deaths in women. In 2014 it is estimated that there will be 21,980 new cases of ovarian cancer and an estimated 14,270 women will die of this disease. The expected incidence of epithelial ovarian cancer in women in the United States in 2012 is approximately 22,280 (15,500 deaths) and in Europe in 2012 was estimated at 65,538 patient cases (42,704 deaths). Epithelial carcinoma makes up 85% to 90% of ovarian cancers. While historically considered to start on the surface of the ovary, new evidence suggests at least some ovarian cancer begins in special cells in a part of the fallopian tube. The fallopian tubes, small ducts that link a woman's ovaries to her uterus, are a part of a woman's reproductive system. In a normal female reproductive system, there are two fallopian tubes, one located on each side of the uterus. Cancer cells that begin in the fallopian tube may go to the surface of the ovary early on. The term 'ovarian cancer' is often used to describe epithelial cancers that begin in the ovary, the fallopian tube, and the lining of the abdominal cavity, called the peritoneum. At diagnosis, most women present with advanced disease, which accounts for the high mortality rate.

Standard therapy for advanced ovarian cancer typically consists of surgical debulking and a chemotherapy regimen. Initial chemotherapy consists of either taxane or platinum chemotherapy, or a combination thereof. While approximately 75% of patients respond to front line therapy, 70% of those patients who initially respond eventually relapse within 1 to 3 years. After relapse, patients respond moderately or poorly to subsequent chemotherapy. Additionally, intolerance to platinum agents is a clinical concern, as the risk of cumulative toxicities increases over the course of continued treatments. There is a significant unmet need due to the high recurrence rate, despite an initially high response rate. Attempts to improve the standard two-drug chemotherapy (carboplatin and paclitaxel) by adding a third cytotoxic drug (topotecan, gemcitabine, or doxil) have failed (du Bois et al., 2006 and Pfisterer et al., 2006). The great challenge for the near future will be the selection of patients with advanced ovarian cancer who will most benefit from specific targeted agents in the frontline treatment or maintenance setting. Maintenance therapy after the achievement

of a response from initial chemotherapy may represent an approach to provide clinical benefit by delaying disease progression side effects, delaying the need for toxic chemotherapy and prolonging overall survival.

Poly(ADP-ribose) polymerases (PARPs) are a family of enzymes involved in various activities in response to DNA damage. PARP-1 is a key DNA repair enzyme that mediates single strand break (SSB) repair through the base excision repair (BER) pathway. PARP inhibitors have been demonstrated to selectively kill tumor cells that harbor BRCA1 and BRCA2 mutations. In addition, pre-clinical and preliminary clinical data suggest that PARP inhibitors are selectively cytotoxic for tumors with homologous recombination repair deficiency caused by dysfunction of genes other than BRCA1 or BRCA2.

SUMMARY

The present invention is based in part on the discovery that PARP inhibitors can be used to treat cancers characterized by wild type or mutant BRCA1 and/or BRCA2 ("BRCA genes"), e.g. in the absence or presence of a mutation in the BRCA genes. Accordingly, aspects of the invention relate to methods for treating cancer patients involving administration of an anti-PARP therapy to a patient independent of BRCA status or independent of the DNA repair status of the patient or cancer. In other aspects, the invention relates to methods for treating cancer patients involving administration of an anti-PARP therapy to a patient, wherein the therapy is commenced prior to determining the BRCA status or HRD status of the patient or the cancer. In other aspects, the invention relates to methods for treating cancer patients involving administration of an anti-PARP therapy to a patient, wherein the therapy is commenced in the absence of determining the BRCA status or DNA repair status of the patient or cancer. In other aspects, the invention relates to methods for treating cancer patients involving administration of an anti-PARP therapy to a patient characterized by an absence of a mutation in BRCA1 and/or BRCA2. In other aspects, the invention relates to methods for treating cancer patients involving administration of an anti-PARP therapy to a patient characterized by an absence of a mutation in a gene involved in DNA repair. In other aspects, the invention relates to methods for treating cancer patients involving administration of an anti-PARP therapy to a patient characterized by an absence of a mutation in a gene involved in homologous recombination. In aspects, the invention relates to methods for treating cancer patients involving administration of an anti-PARP therapy to a patient having a cancer characterized by an absence of a mutation in BRCA1 or BRCA2. In aspects, the invention relates to methods for treating cancer patients involving administration of an anti-PARP therapy to a patient having a cancer characterized by an absence of a mutation in a gene involved in homologous recombination.

In embodiments, the anti-PARP therapy is administered at a dose equivalent to about 100 mg, about 200 mg, or about 300 mg of niraparib or a salt or derivative thereof. In certain embodiments, the anti-PARP therapy is administered at a dose equivalent to about 100 mg of niraparib or a salt or derivative thereof. In certain embodiments, the anti-PARP therapy is administered at a dose equivalent to about 200 mg of niraparib or a salt or derivative thereof. In certain embodiments, the anti-PARP therapy is administered at a dose equivalent to about 300 mg of niraparib or a salt or derivative thereof.

In some embodiments, the anti-PARP therapy is administered in a regimen determined to achieve i) prolonged progression free survival as compared to control, ii) a reduced hazard ratio for disease progression or death as compared to control, iii) prolonged overall survival as compared to control, or iv) an overall response rate of at least 30%.

In embodiments, the anti-PARP therapy comprises administration of an agent that inhibits PARP-1 and/or PARP-2. In some embodiments, the agent is a small molecule, a nucleic acid, a polypeptide (e.g., an antibody), a carbohydrate, a lipid, a metal, or a toxin. In related embodiments, the agent is ABT-767, AZD 2461, BGB-290, BGP 15, CEP 9722, E7016, E7449, fluzoparib, INO1001, JPI 289, MP 124, niraparib, olaparib, ONO2231, rucaparib, SC 101914, talazoparib, veliparib, WW 46, or salts or derivatives thereof. In some related embodiments, the agent is niraparib, olaparib, rucaparib, talazoparib, veliparib, or salts or derivatives thereof. In certain embodiments, the agent is niraparib or a salt or derivative thereof. In certain embodiments, the agent is olaparib or a salt or derivative thereof. In certain embodiments, the agent is rucaparib or a salt or derivative thereof. In certain embodiments, the agent is talazoparib or a salt or derivative thereof. In certain embodiments, the agent is veliparib or a salt or derivative thereof.

In some embodiments, the methods prolong progression free survival as compared to control. In some embodiments, the methods reduce the hazard ratio for disease progression or death as compared to control. In some embodiments, the methods prolong overall survival as compared to control. In some embodiments, the methods achieve an overall response rate of at least 30%. In some embodiments, the methods achieve improved progression free survival as compared to control. In some embodiments, the methods achieve improved chemotherapy free interval as compared to control. In some embodiments, the methods achieve improved time to first subsequent therapy as compared to control. In some embodiments, the methods achieve improved time to second subsequent therapy as compared to control. In some embodiments, the methods have been determined to not have a detrimental effect on Quality of Life as determined by FOSI and/or EQ-5D-5L. In some embodiments, the methods have been determined to not impact the effectiveness of a subsequent treatment with a chemotherapeutic agent (e.g., a platinum agent, including but not limited to, cisplatin, carboplatin, oxaliplatin, nedaplatin, triplatin tetranitrate, phenanthriplatin, picoplatin, or satraplatin).

In some embodiments, such cancers are selected from gynecologic cancers (i.e., cancers of the female reproductive system). In some embodiments, cancers of the female reproductive system include, but are not limited to, ovarian cancer, cancer of the fallopian tube(s), peritoneal cancer and breast cancer. In some embodiments, a gynecologic cancer is associated with homologous recombination repair deficiency/homologous repair deficiency ("HRD") and/or BRCA1/2 mutation(s). In some embodiments, a gynecologic cancer is platinum-sensitive. In some embodiments, a gynecologic cancer has responded to a platinum-based therapy. In some embodiments, a gynecologic cancer has developed resistance to a platinum-based therapy. In some embodiments, a gynecologic cancer has at one time shown a partial or complete response to platinum-based therapy. In some embodiments, a gynecologic cancer is now resistant to platinum-based therapy.

In certain embodiments, the cancer is ovarian cancer, cancer of the fallopian tube(s), or peritoneal cancer. In certain embodiments, the cancer is breast cancer.

In some embodiments, the cancer is a recurrent cancer.

⁵ In some embodiments, anti-PARP therapy is useful in treating cancer patients exhibiting a positive HRD status. In some embodiments, anti-PARP therapy is useful in treating cancer patients exhibiting a positive HRD status, wherein the patients are further characterized by the absence of a mutation in BRCA1 and/or BRCA2. In some embodiments, anti-PARP therapy is useful in treating cancer patients exhibiting a positive HRD status, wherein the patients are further characterized by the absence of a germline mutation in BRCA1 and/or BRCA2. In some embodiments, a positive HRD status is determined by quantifying in a patient sample a number of Indicator Chromosomal Aberration ("CA") regions. In some embodiments, a tumor sample from a patient has a positive HRD status.

¹⁰ In some embodiments, anti-PARP therapy is useful in treating cancer patients exhibiting an absence of a germline mutation in BRCA1 and BRCA2. In some embodiments, anti-PARP therapy is useful in treating cancer patients with platinum sensitive tumors that also exhibit an absence of a germline mutation in BRCA1 and BRCA2.

¹⁵ In some embodiments, anti-PARP therapy is useful in treating cancer patients exhibiting an absence of HRD. In some embodiments, anti-PARP therapy is useful in treating platinum sensitive, recurrent ovarian cancer patients, wherein the patient does not have HRD or wherein the patient is characterized by an absence of HRD. In some embodiments, the absence of HRD is further characterized by lacking "chromosomal aberrations" or "CA". CA refers to a detectable variation in a sample's chromosomal DNA. ²⁰

²⁵ In some embodiments, CA may fall into at least one of three overlapping categories: loss of heterozygosity (LOH), allelic imbalance (e.g., telomeric allelic imbalance (TAI)), or large scale transition (LST).

³⁰ Accordingly, in some embodiments, the present invention provides a method of administering anti-PARP therapy to a patient having recurrent and/or platinum sensitive cancer selected from ovarian cancer, fallopian tube cancer, or primary peritoneal cancer comprising administering anti-PARP therapy to the patient according to a regimen determined to achieve prolonged progression free survival as compared to control.

³⁵ Among other things, the present invention demonstrates remarkable clinical efficacy of niraparib, for example when administered to certain patient populations (e.g., populations suffering from or susceptible to certain tumors; populations characterized by presence or level of a particular marker, such as for example HRD status and/or BRCA1/2 mutation, etc.; populations that may or may not have received or be receiving other therapy, etc.) and/or according to certain regimens. In some embodiments, the present invention provides a method of administering anti-PARP therapy to a patient having a recurrent and/or platinum sensitive cancer selected from ovarian cancer, fallopian tube cancer, or primary peritoneal cancer comprising administering anti-PARP therapy to the patient according to a regimen determined to achieve a reduced hazard ratio for disease progression or death as compared to control.

⁴⁰ In some embodiments, the present invention provides a method of administering anti-PARP therapy to a patient having a recurrent and/or platinum sensitive cancer selected from ovarian cancer, fallopian tube cancer, or primary peritoneal cancer comprising administering anti-PARP

therapy to the patient according to a regimen determined to achieve prolonged overall survival as compared to control.

In some embodiments, the present invention provides a method of administering anti-PARP therapy to a patient having a recurrent and/or platinum sensitive cancer selected from ovarian cancer, fallopian tube cancer, or primary peritoneal cancer comprising administering anti-PARP therapy to the patient according to a regimen determined to achieve an overall response rate of at least 30%. In some embodiments an overall response rate is assessed according to RECIST v1.1 guidelines.

In some embodiments, the method of administering anti-PARP therapy is according to a regimen determined to achieve prolonged progression free survival 2 as compared to control.

In some embodiments, the method of administering anti-PARP therapy is according to a regimen determined to achieve extended chemotherapy free interval as compared to control.

In some embodiments, the method of administering anti-PARP therapy is according to a regimen determined to achieve extended time to first subsequent therapy as compared to control.

In some embodiments, the method of administering anti-PARP therapy is according to a regimen determined to achieve extended time to second subsequent therapy as compared to control.

In some embodiments, the recurrent and/or platinum sensitive cancer is ovarian cancer. In some embodiments, the ovarian cancer is platinum sensitive ovarian cancer at the commencement of anti-PARP therapy administration. In some embodiments, the ovarian cancer is recurrent, platinum sensitive ovarian cancer at the commencement of anti-PARP therapy administration. In some embodiments, the ovarian cancer responded to the most recent platinum-based chemotherapy regimen prior to commencement of anti-PARP therapy administration. In some embodiments, response to the most recent platinum-based chemotherapy regimen is a complete response. In some embodiments, response to the most recent platinum-based chemotherapy regimen is a partial response. In some embodiments, the ovarian cancer responded to the penultimate platinum-based chemotherapy regimen prior to commencement of anti-PARP therapy administration.

In some embodiments, the recurrent and/or platinum sensitive cancer is fallopian tube cancer. In some embodiments, the fallopian tube cancer is platinum sensitive at the commencement of anti-PARP therapy administration. In some embodiments, the recurrent, fallopian tube cancer is platinum sensitive at the commencement of anti-PARP therapy administration. In some embodiments, the fallopian tube cancer responded to the most recent platinum-based chemotherapy regimen prior to commencement of anti-PARP therapy administration. In some embodiments, response to the most recent platinum-based chemotherapy regimen is a complete response. In some embodiments, response to the most recent platinum-based chemotherapy regimen is a partial response. In some embodiments, the fallopian tube cancer responded to the penultimate platinum-based chemotherapy regimen prior to commencement of anti-PARP therapy administration.

In some embodiments, the recurrent and/or platinum sensitive cancer is primary peritoneal cancer. In some embodiments, the primary peritoneal cancer is platinum sensitive at the commencement of anti-PARP therapy administration. In some embodiments, the recurrent, primary peritoneal cancer is platinum sensitive at the com-

mencement of anti-PARP therapy administration. In some embodiments, the primary peritoneal responded to the most recent platinum-based chemotherapy regimen prior to commencement of anti-PARP therapy administration. In some embodiments, response to the most recent platinum-based chemotherapy regimen is a complete response. In some embodiments, response to the most recent platinum-based chemotherapy regimen is a partial response. In some embodiments, the primary peritoneal cancer responded to the penultimate platinum-based chemotherapy regimen prior to commencement of anti-PARP therapy administration.

In some embodiments, the patient has at least one mutation selected from (i) a germline mutation in BRCA1 and/or BRCA2, or (ii) a sporadic mutation in BRCA1 and/or BRCA2.

In some embodiments, the patient has a germline mutation in BRCA1 and/or BRCA2.

In some embodiments, the regimen is determined to achieve a hazard ratio for disease progression of less than about 0.5. In some embodiments, the hazard ratio for disease progression is less than about 0.4. In some embodiments, the hazard ratio for disease progression is less than about 0.3.

In some embodiments, the regimen is determined to achieve prolonged progression free survival of at least 9 months. In some embodiments, the prolonged progression free survival is at least 12 months. In some embodiments, the prolonged progression free survival is at least 15 months. In some embodiments, the prolonged progression free survival is at least 21 months.

In some embodiments, the patient has a sporadic mutation in BRCA1 or BRCA2.

In some embodiments, the patient is characterized by an absence of a germline mutation in BRCA1 or BRCA2. In some embodiments, the patient is characterized by an absence of HRD. In some embodiments, the patient is characterized by an absence of a germline mutation in BRCA1 or BRCA2 and by an absence of HRD.

In some embodiments, the patient is characterized by an absence of a sporadic mutation in BRCA1 or BRCA2. In some embodiments, the patient is characterized by an absence of HRD. In some embodiments, the patient is characterized by an absence of a sporadic mutation in BRCA1 or BRCA2 and by an absence of HRD. In some embodiments, the absence of HRD is further characterized by lacking "chromosomal aberrations" or "CA". CA refers to a detectable variation in a sample's chromosomal DNA. In some embodiments, CA may fall into at least one of three overlapping categories: loss of heterozygosity (LOH), allelic imbalance (e.g., telomeric allelic imbalance (TAI)), or large scale transition (LST).

In some embodiments, the patient is characterized by an absence of a mutation in BRCA1 or BRCA2 (e.g., lacking both germline BRCA1/2 and sporadic BRCA1/2 mutations).

In some embodiments, the patient has a tumor with a positive homologous recombination deficiency status.

In some embodiments, the present invention provides a method of administering anti-PARP therapy to a patient characterized by an absence of a germline BRCA1/2 mutation, wherein the patient has a tumor with a positive homologous recombination deficiency status.

In some embodiments, the present invention provides a method of administering anti-PARP therapy to a patient having a sporadic mutation in BRCA1 or BRCA2, wherein the patient has a tumor with a positive homologous recombination deficiency status.

In some embodiments, the present invention provides a method of administering anti-PARP therapy to a patient

characterized by an absence of a mutation in BRCA1/2 (i.e., a BRCA^{wt} patient), wherein the patient has a tumor with a positive homologous recombination deficiency status.

In some embodiments, the patient has a tumor with a negative homologous recombination deficiency status. In some embodiments, the patient has a tumor further characterized by being negative for germline mutations in BRCA1 or BRCA2.

In some embodiments, the present invention provides a method of administering anti-PARP therapy to a patient characterized by a germline mutation in BRCA1 or BRCA2 (gBRCA^{mut}) according to a regimen determined to achieve a hazard ratio for disease progression of less than about 0.4. In some such embodiments, the hazard ratio for disease progression is less than about 0.3.

In some embodiments, the present invention provides a method of administering anti-PARP therapy to a patient characterized by a germline mutation in BRCA1 or BRCA2 (gBRCA^{mut}) according to a regimen determined to achieve prolonged progression free survival of at least 9 months. In some such embodiments, the prolonged progression free survival is at least 12 months or at least 21 months.

In some embodiments, the present invention provides a method of administering anti-PARP therapy to a patient characterized by an absence of a germline BRCA1/2 mutation, wherein the patient has a tumor with a positive homologous recombination deficiency status, according to a regimen determined to achieve a hazard ratio for disease progression of less than about 0.5. In some such embodiments, the hazard ratio for disease progression is less than about 0.4.

In some embodiments, the present invention provides a method of administering anti-PARP therapy to a patient characterized by an absence of a germline BRCA1/2 mutation, wherein the patient has a tumor with a positive homologous recombination deficiency status, according to a regimen determined to achieve prolonged progression free survival of at least 12 months.

In some embodiments, the present invention provides a method of administering anti-PARP therapy to a patient characterized by an absence of a germline BRCA1/2 mutation according to a regimen determined to achieve a hazard ratio for disease progression of less than about 0.5.

In some embodiments, the present invention provides a method of administering anti-PARP therapy to a patient characterized by an absence of a germline BRCA1/2 mutation according to a regimen determined to achieve prolonged progression free survival of at least 9 months or at least 12 months.

In some embodiments, the present invention provides a method of administering anti-PARP therapy to a patient having a sporadic mutation in BRCA1 or BRCA2, wherein the patient has a tumor with a positive homologous recombination deficiency status, according to a regimen determined to achieve a hazard ratio for disease progression of less than about 0.4. In some embodiments, the hazard ratio for disease progression is less than about 0.3.

In some embodiments, the present invention provides a method of administering anti-PARP therapy to a patient having a sporadic mutation in BRCA1 or BRCA2, wherein the patient has a tumor with a positive homologous recombination deficiency status, according to a regimen determined to achieve prolonged progression free survival of at least 20 months.

In some embodiments, the present invention provides a method of administering anti-PARP therapy to a patient characterized by an absence of a BRCA1/2 mutation (i.e., a

BRCA^{wt} patient), wherein the patient has a tumor with a positive homologous recombination deficiency status, according to a regimen determined to achieve a hazard ratio for disease progression of less than about 0.5. In some embodiments, the hazard ratio for disease progression is less than about 0.4.

In some embodiments, the present invention provides a method of administering anti-PARP therapy to a patient characterized by an absence of a BRCA1/2 mutation (i.e., a BRCA^{wt} patient), wherein the patient has a tumor with a positive homologous recombination deficiency status, according to a regimen determined to achieve prolonged progression free survival of at least 9 months or at least 12 months.

In some embodiments, the present invention provides a method of administering anti-PARP therapy to a patient characterized by an absence of a germline BRCA1/2 mutation, wherein the patient has a tumor with a negative homologous recombination deficiency status.

In some embodiments, the patient has high grade serous ovarian cancer or high grade predominantly serous histology ovarian cancer.

In some embodiments, the methods involve continued treatment until disease progression or unacceptable toxicity.

In some embodiments, the methods involve reducing the dose of the anti-PARP therapy in response to treatment toxicity. In some related embodiments, the methods involve reducing the dose of the anti-PARP therapy from about a dose equivalent to about 300 mg to a dose equivalent to about 200 mg.

In some embodiments, the regimen comprises a plurality of oral doses.

In some embodiments, the regimen comprises once daily (QD) dosing.

In some embodiments, the regimen comprises at least one 28 day cycle of anti-PARP therapy dosing.

In some embodiments, the oral dose is administered in one or more unit dosage forms.

In some embodiments, the one or more unit dosage forms are capsules.

In some embodiments, the oral dose is an amount of anti-PARP therapy equivalent to a range of about 5 to about 400 mg of niraparib. In some embodiments, the amount of anti-PARP therapy is equivalent to about 5, about 10, about 25, about 50, about 100, about 150, about 200, about 250, about 300, about 350, or about 400 mg of niraparib. In some embodiments, the amount of anti-PARP therapy is equivalent to about 300 mg of niraparib. In some embodiments, the amount of anti-PARP therapy is equivalent to about 200 mg of niraparib.

In some embodiments, each unit dosage form is equivalent to about 100 mg, about 200 mg, or about 300 mg of niraparib.

In some embodiments, each QD dose is equivalent to about 100 mg, about 200 mg, or about 300 mg of niraparib. In some embodiments, each QD dose is administered as three unit dosage forms equivalent to about 100 mg of niraparib.

In some embodiments, progression free survival is characterized by a complete response of one or more target tumors.

In some embodiments, progression free survival is characterized by a partial response of one or more target tumors.

In some embodiments, the patient is in a fasted state.

In some embodiments, the patient is in a fed state.

In some embodiments, the prolonged progression free survival is at least 9 months. In some embodiments, the

prolonged progression free survival is at least 12 months. In some embodiments, the prolonged progression free survival is at least 18 months. In some embodiments, the prolonged progression free survival is at least 21 months. In some embodiments, the prolonged progression free survival is at least 24 months. In some embodiments, the prolonged progression free survival is at least 27 months. In some embodiments, the prolonged progression free survival is at least 30 months. In some embodiments, the prolonged progression free survival is at least 33 months. In some embodiments, the prolonged progression free survival is at least 36 months.

In some embodiments, the hazard ratio for disease progression is about 0.3. In some embodiments, the hazard ratio for disease progression is about 0.45. In some embodiments, the hazard ratio for disease progression is about 0.5. In some embodiments, the hazard ratio for disease progression is less than about 0.5. In some embodiments, the hazard ratio for disease progression is less than about 0.45. In some embodiments, the hazard ratio for disease progression is less than about 0.4. In some embodiments, the hazard ratio for disease progression is less than about 0.35. In some embodiments, the hazard ratio for disease progression is less than about 0.3.

In some embodiments, anti-PARP therapy is administered as a maintenance therapy.

In some embodiments, the anti-PARP therapy maintenance therapy has no significant impact on the efficacy of the next line of therapy (e.g., a subsequent treatment). In some embodiments, the next line of therapy is includes administration of a chemotherapeutic agent. In some embodiments, the chemotherapeutic agent is a platinum agent. In some such embodiments, the platinum agent is selected from cisplatin, carboplatin, oxaliplatin, nedaplatin, triplatin tetranitrate, phenanthriplatin, picoplatin, or satraplatin.

BRIEF DESCRIPTION OF THE DRAWING

FIG. 1 relates to progression-free survival of a gBRCAmut cohort: the figure depicts a graphical representation of the progression free survival of patients harboring a genomic BRCA mutation ($gBRCA^{mut}$) when treated with niraparib or with placebo. The y-axis shows the estimated survival function value and the x-axis shows the time (in months) since randomization. The hazard ratio for disease progression is shown on the graph as HR (95% CI) 0.27 (0.173, 0.410).

FIG. 2 relates to progression-free survival of a non-gBRCA-HRD positive cohort: the figure depicts a graphical representation of the progression free survival of patients who lack a genomic BRCA mutation (non-gBRCA) but have a HRD-positive tumor (positive HRD status) when treated with niraparib or with placebo. The y-axis shows the estimated survival function value and the x-axis shows the time (in months) since randomization. The hazard ratio for disease progression is shown on the graph as HR (95% CI) 0.38 (0.243, 0.586).

FIG. 3 relates to progression-free survival of non-gBRCA overall: the figure depicts a graphical representation of the progression free survival of patients that lack a genomic BRCA mutation (non-gBRCA) when treated with niraparib or with placebo. This population includes patients with or without HRD. The y-axis shows the estimated survival function value and the x-axis shows the time (in months) since randomization. The hazard ratio for disease progression is shown on the graph as HR (95% CI) 0.45 (0.338, 0.607).

FIG. 4 relates to the progression-free survival of a non-gBRCA-HRD negative cohort: the figure depicts a graphical representation of the progression free survival of patients who lack a genomic BRCA mutation (non-gBRCA) and have a HRD-negative tumor (negative HRD status) when treated with niraparib or with placebo. The y-axis shows the estimated survival function value and the x-axis shows the time (in months) since randomization. The hazard ratio for disease progression is shown on the graph as HR (95% CI) 0.58 (0.361, 0.922).

FIG. 5 relates to progression-free survival of a combined study population (2 cohorts combined: gBRCAmut and non-gBRCA mut): the figure depicts a graphical representation of the progression-free survival of the combined study population made up of the gBRCAmut and non-gBRCAmut populations when treated with niraparib or with placebo. The y-axis shows the estimated survival function value and the x-axis shows the time (in months) since randomization.

FIG. 6 depicts a graphical representation of the progression-free survival in the HRDpos/BRCAwt subgroup of the non-gBRCAmut cohort when treated with niraparib or with placebo. The y-axis shows the estimated survival function value and the x-axis shows the time (in months) since randomization.

FIG. 7 depicts a graphical representation (Kaplan-Meier plot) of the progression-free survival in the HRDpos/somatic BRCAmut subgroup of the non-gBRCAmut cohort when treated with niraparib or with placebo. The y-axis shows the estimated survival function value and the x-axis shows the time (in months) since randomization.

FIG. 8 depicts a graphical representation of the mean change from baseline ($\pm SE$) for platelets over time: all patients cohort.

FIG. 9 depicts a graphical representation (Kaplan-Meier plot) of the progression-free survival in the gBRCAmut cohort based on IRC assessment by niraparib dose administered for the longest duration (niraparib patients in the safety population).

FIG. 10 depicts a graphical representation (Kaplan-Meier plot) of the progression-free survival in the non-gBRCAmut cohort based on IRC assessment by niraparib dose administered for the longest duration (niraparib patients in the safety population).

FIG. 11 sets forth a table of secondary endpoints in the primary efficacy populations.

FIG. 12 depicts a graphical representation of analysis of progression-free survival in the (FIG. 12A) gBRCAmut Cohort, (FIG. 12B) non-gBRCAmut, HRDpos Subgroup, and (FIG. 12C) overall non-gBRCAmut Cohort.

FIG. 13 depicts a graphical representation of analysis of chemotherapy-free survival interval in the (left panel) gBRCAmut Cohort, (center) overall non-gBRCAmut Cohort, and (right panel) non-gBRCAmut, HRDpos Subgroup.

FIG. 14 depicts a graphical representation of analysis of time to first subsequent treatment in the (left panel) gBRCAmut Cohort, (center) overall non-gBRCAmut Cohort, and (right panel) non-gBRCAmut, HRDpos Subgroup.

FIG. 15 depicts a graphical representation of analysis of efficacy of next-line treatment in the pooled $gBRCA^{mut}$ and non- $gBRCA^{mut}$ cohorts.

FIG. 16 depicts a graphical representation of the estimated probability of progressive disease at 6 months after the last dose of platinum-based therapy.

FIG. 17 depicts a graphical representation of the effect of the number of lines of chemotherapy on the proportion of patients time to disease progression, shown for platinum-based chemotherapy gBRCAmut (A), platinum-based che-

11

motherapy non-gBRCAmut (B), total chemotherapy gBRCA mut (C) and total chemotherapy non-gBRCAmut (D) cohorts.

FIG. 18 depicts a graphical representation of patient reported outcomes using the Functional Assessment of Cancer Therapy-Ovarian Symptom Index (FOSI) and the EQ-5D-5L: patient-reported outcomes were similar for niraparib and placebo.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

Definitions

As used herein, the term “administration” typically refers to the administration of a composition to a subject or system. Those of ordinary skill in the art will be aware of a variety of routes that may, in appropriate circumstances, be utilized for administration to a subject, for example a human subject. For example, in some embodiments, administration may be ocular, oral, parenteral, topical, etc. In some particular embodiments, administration may be bronchial (e.g., by bronchial instillation), buccal, dermal (which may be or comprise, for example, one or more of topical to the dermis, intradermal, interdermal, transdermal, etc.), enteral, intra-arterial, intradermal, intragastric, intramedullary, intramuscular, intranasal, intraperitoneal, intrathecal, intravenous, intraventricular, within a specific organ (e.g. intrahepatic), mucosal, nasal, oral, rectal, subcutaneous, sublingual, topical, tracheal (e.g., by intratracheal instillation), vaginal, vitreal, etc. In some embodiments, administration may involve dosing that is intermittent (e.g., a plurality of doses separated in time) and/or periodic (e.g., individual doses separated by a common period of time) dosing. In some embodiments, administration may involve continuous dosing (e.g., perfusion) for at least a selected period of time.

As used herein, the terms “dosage form” or “unit dosage form” refer to a physically discrete unit of an active agent (e.g., a therapeutic or diagnostic agent) for administration to a subject. Typically, each such unit contains a predetermined quantity of active agent. In some embodiments, such quantity is a unit dosage amount (or a whole fraction thereof) appropriate for administration in accordance with a regimen that has been determined to correlate with a desired or beneficial outcome when administered to a relevant population (i.e., with a therapeutic regimen). Those of ordinary skill in the art appreciate that the total amount of a therapeutic composition or agent administered to a particular subject is determined by one or more attending physicians and may involve administration of multiple dosage forms.

As used herein, the term “regimen” refers to a set of unit doses (typically more than one) that are administered individually to a subject, typically separated by one or more periods of time. In some embodiments, a given therapeutic agent is administered according to a regimen, which may involve one or more doses. In some embodiments, a regimen comprises a plurality of doses each of which is separated in time from other doses. In some embodiments, individual doses are separated from one another by a time period of the same length; in some embodiments, a regimen comprises a plurality of doses, wherein the doses are separated by time periods of different length. In some embodiments, a regimen comprises doses of the same amount. In some embodiments, a regimen comprises doses of different amounts. In some embodiments, a regimen comprises at least one dose, wherein the dose comprises one unit dose of the therapeutic agent. In some embodiments, a regimen comprises at least

12

one dose, wherein the dose comprises two or more unit doses of the therapeutic agent. For example, a dose of 250 mg can be administered as a single 250 mg unit dose or as two 125 mg unit doses. In some embodiments, a regimen is correlated with or result in a desired or beneficial outcome when administered across a relevant population (i.e., is a therapeutic regimen).

As used herein, the term “patient”, “subject”, or “test subject” refers to any organism to which provided compound or compounds described herein are administered in accordance with the present invention e.g., for experimental, diagnostic, prophylactic, and/or therapeutic purposes. Typical subjects include animals (e.g., mammals such as mice, rats, rabbits, non-human primates, and humans; insects; worms; etc.). In a preferred embodiment, a subject is a human. In some embodiments, a subject may be suffering from, and/or susceptible to a disease, disorder, and/or condition (e.g., cancer such as ovarian cancer, cancer of the fallopian tube(s), peritoneal cancer and breast cancer). In some embodiments, a patient is a human possessing one or more female reproductive organs. In some embodiments, a patient is a human female (i.e., a woman) that has been diagnosed with a gynecological cancer (e.g., cancer such as ovarian cancer, cancer of the fallopian tube(s), peritoneal cancer and breast cancer). As used herein, a “patient population” or “population of subjects” refers to a plurality of patients or subjects.

As used herein, a “therapeutically effective amount” refers to an amount of a therapeutic agent that produces the desired effect for which it is administered. In some embodiments, the term refers to an amount that is sufficient, when administered to a population suffering from or susceptible to a disease, disorder, and/or condition in accordance with a regimen, to treat the disease, disorder, and/or condition. In some embodiments, a therapeutically effective amount is one that reduces the incidence and/or severity of, and/or delays onset of, one or more symptoms of the disease, disorder, and/or condition. Those of ordinary skill in the art will appreciate that the term “therapeutically effective amount” does not in fact require successful treatment be achieved in a particular individual. Rather, a therapeutically effective amount may be that amount that provides a particular desired pharmacological response in a significant number of subjects when administered to patients in need of such treatment. In some embodiments, reference to a therapeutically effective amount may be a reference to an amount as measured in one or more specific tissues (e.g., a tissue affected by the disease, disorder or condition) or fluids (e.g., blood, saliva, serum, sweat, tears, urine, etc.). Those of ordinary skill in the art will appreciate that, in some embodiments, a therapeutically effective amount of a particular agent or therapy may be formulated and/or administered in a single dose. In some embodiments, a therapeutically effective agent may be formulated and/or administered in a plurality of doses, for example, as part of a regimen.

As used herein, a “chemotherapeutic agent” refers to a chemical agent that inhibits the proliferation, growth, lifespan and/or metastatic activity of cancer cells. In some embodiments, a chemotherapeutic agent is a platinum agent. In some such embodiments, the platinum agent is selected from cisplatin, carboplatin, oxaliplatin, nedaplatin, triplatin tetranitrate, phenanthriplatin, picoplatin, or satraplatin.

As used herein, “CA-125” means cancer antigen 125. A CA-125 test is used to measure the amount of the protein CA-125 in the blood of a patient. A CA-125 test may be used to monitor certain cancers during and after treatment, including use to evaluate prolongation of progression free survival.

In some cases, a CA-125 test may be used to look for early signs of ovarian cancer in women with a very high risk of the disease.

As used herein, “homologous recombination” refers to a process wherein nucleotide sequences between distinct strands of DNA are exchanged. Homologous recombination is involved in a number of different biological processes, for example, homologous recombination occurs as part of the DNA repair process (e.g., doubled-strand break repair pathway and synthesis-dependent strand annealing pathway) and during process of meiosis/gametogenesis of eukaryotic organisms. As used herein, “homologous recombination deficiency,” “homologous recombination repair deficiency”, “homologous repair deficiency” or “HRD” refers to a reduction or impairment of the homologous recombination process. Without wishing to be bound by theory, it believed that since homologous recombination is involved in DNA repair, a homologous recombination deficient sample would be unable or have a reduced ability to repair DNA damage such as double-strand breaks. As such, a sample that is HRD would accumulate genomic errors or chromosomal aberrations can be used as a biomarker for HRD. As used herein, “chromosomal aberration” or “CA” refers to a detectable variation in a sample’s chromosomal DNA. In some embodiments, CA may fall into at least one of three overlapping categories: loss of heterozygosity (LOH), allelic imbalance (e.g., telomeric allelic imbalance (TAI)), or large scale transition (LST). In some embodiments, “HRD status” is determined by the detection of CA in a sample (e.g., a tumor sample) obtained from a patient. In some embodiments, a positive HRD status refers to when a sample obtained from a patient meets a threshold number or level of CAs at a specified number of chromosomal indicator regions. In some embodiments, HRD status is determined using a commercially available diagnostic to detect chromosomal aberrations in a sample (e.g. a tumor sample) and/or to assess if a sample is unable to repair double-strand DNA breaks. Commercially available diagnostics to assess HRD status include the myChoice HRD™ diagnostic kit.

As used herein, loss of heterozygosity (LOH) refers to the change from heterozygosity to homozygosity a polymorphic loci of interest. Polymorphic loci within the human genome (e.g., single nucleotide polymorphisms (SNPs)) are generally heterozygous within an individual’s germline since that individual typically receives one copy from the biological father and one copy from the biological mother. Somatically, however, this heterozygosity can change (via mutation) to homozygosity, referred to herein as LOH. LOH may result from several mechanisms. For example, in some cases, a locus of one chromosome can be deleted in a somatic cell. The locus that remains present on the other chromosome (the other non-sex chromosome for males) is an LOH locus as there is only one copy (instead of two copies) of that locus present within the genome of the affected cells. This type of LOH event results in a copy number reduction. In other cases, a locus of one chromosome (e.g., one non-sex chromosome for males) in a somatic cell can be replaced with a copy of that locus from the other chromosome, thereby eliminating any heterozygosity that may have been present within the replaced locus. In such cases, the locus that remains present on each chromosome is an LOH locus and can be referred to as a copy neutral LOH locus. LOH and its use in determining HRD is described in detail in International Application no. PCT/US2011/040953 (published as WO/2011/160063), the entire contents of which are incorporated herein by reference.

A broader class of chromosomal aberration, which encompasses LOH, is allelic imbalance. Allelic imbalance occurs when the relative copy number (i.e., copy proportion) at a particular locus in somatic cells differs from the germline. For example, if the germline has one copy of allele A and one copy of allele B at a particular locus and a somatic cell has two copies of A and one copy of B, there is allelic imbalance at the locus because the copy proportion of the somatic cell (2:1) differs from the germline (1:1). LOH is an example of allelic imbalance since the somatic cell has a copy proportion (1:0 or 2:0) that differs from the germline (1:1). But allelic imbalance encompasses more types of chromosomal aberration, e.g., 2:1 germline going to 1:1 somatic; 1:0 germline going to 1:1 somatic; 1:1 germline going to 2:1 somatic, etc. Analysis of regions of allelic imbalance encompassing the telomeres of chromosomes is particularly useful in the invention. Thus, a “telomeric allelic imbalance region” or “TAI Region” is defined as a region with allelic imbalance that (a) extends to one of the subtelo

meres and (b) does not cross the centromere. TAI and its use in determining HRD is described in detail in International Application no. PCT/US2011/048427 (published as WO/2012/027224), the entire contents of which are incorporated herein by reference.

A class of chromosomal aberrations that is broader still, which encompasses LOH and TAI, is referred to herein as large scale transition (“LST”). LST refers to any somatic copy number transition (i.e., breakpoint) along the length of a chromosome where it is between two regions of at least some minimum length (e.g., at least 3, 4, 5, 6, 7, 8 9, 10, 11 12, 13, 14, 15, 16, 17, 18, 19 or 20 or more megabases) after filtering out regions shorter than some maximum length (e.g., 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.5, 2, 2.5, 3, 3.5, 4 or more megabases). For example, if after filtering out regions shorter than 3 megabases the somatic cell has a copy number of 1:1 for, e.g., at least 10 megabases and then a breakpoint transition to a region of, e.g., at least 10 megabases with copy number 2:2, this is an LST. An alternative way of defining the same phenomenon is as an LST Region, which is genomic region with stable copy number across at least some minimum length (e.g., at least 3, 4, 5, 6, 7, 8, 9, 10, 11 12, 13, 14, 15, 16, 17, 18, 19 or 20 megabases) bounded by breakpoints (i.e., transitions) where the copy number changes for another region also at least this minimum length. For example, if after filtering out regions shorter than 3 megabases the somatic cell has a region of at least 10 megabases with copy number of 1:1 bounded on one side by a breakpoint transition to a region of, e.g., at least 10 megabases with copy number 2:2, and bounded on the other side by a breakpoint transition to a region of, e.g., at least 10 megabases with copy number 1:2, then this is two LSTs. Notice that this is broader than allelic imbalance because such a copy number change would not be considered allelic imbalance (because the copy proportions 1:1 and 2:2 are the same, i.e., there has been no change in copy proportion). LST and its use in determining HRD is described in detail in Popova et al., Ploidy and large-scale genomic instability consistently identify basal-like breast carcinomas with BRCA1/2 inactivation, CANCER RES. (2012) 72:5454-5462.

As used herein, “BRCA mutation” or “mutation of BRCA” refers to a change or difference in the sequence of at least one copy of either or both of the BRCA1 or BRCA2 genes relative to an appropriate reference sequence (e.g., a wild type reference and/or a sequence that is present in non-cancerous cells in the subject). A mutation in the BRCA1/2 gene may result in a BRCA1/2 deficiency, which

may include, for example a loss or reduction in the expression or function of the BRCA gene and/or encoded protein. Such mutations may also be referred to as “deleterious mutations” or may be suspected to be deleterious mutations. A BRCA mutation can be a “germline BRCA mutation,” which indicates it was inherited from one or both parents. Germline mutations affect every cell in an organism and are passed on to offspring. A BRCA mutation can also be acquired during one’s lifetime, i.e. spontaneously arising in any cell in the body (“soma”) at any time during the patient’s life, (i.e., non-inherited), which is referred to herein as a “sporadic BRCA mutation” or a “somatic BRCA mutation” interchangeably. Genetic tests are available, and known by those of skill in the art. For example, the BRACAnalysis CDx® kit is an in vitro diagnostic for detection and classification of BRCA1/2 variants. Using isolated genomic DNA, the BRACAnalysis CDx identifies mutations in the protein coding regions and intron/exon boundaries of the BRCA1 and BRCA2 genes. Single nucleotide variants and small insertions and deletions (indels) may be identified by polymerase chain reaction (PCR) and nucleotide sequencing. Large deletions and duplications in BRCA1 and BRCA2 may be detected using multiplex PCR. Indication of a “BRCA status” refers to, in at least some cases, whether a mutation is present in at least one copy of either BRCA1 or BRCA2. In some embodiments, indication of a BRCA status may refer to the mRNA expression level, methylation level or other epigenetic modification of either or both of BRCA1 and BRCA2. In some embodiments, a patient with a “positive BRCA status” refers to a patient from whom a sample has been determined to contain a mutation in BRCA1 and/or BRCA2. In some embodiments, a positive BRCA status refers to the presence of either a germline BRCA mutation (gBRCA^{mut}) or a somatic BRCA mutation (sBRCA^{mut}). In some embodiments, a patient with a “positive BRCA status” refers to a patient from whom a sample has been determined to have a reduced expression of BRCA1 and/or BRCA2. In some embodiments, BRCA status is determined for germline BRCA mutations (e.g., gBRCA^{mut}) and is performed on a blood sample of a subject. In some embodiments, BRCA status is determined for somatic BRCA mutations (sBRCA^{mut}) or total BRCA mutations (tBRCA^{mut}, which includes both somatic and BRCA germline mutations).

As used herein, the term “genes involved in DNA repair” means any gene involved in repair of DNA in the cell. Table 8 lists a representative set of genes involved in DNA repair. These include genes involved in homologous recombination (“HR”), which is genetic recombination in which nucleotide sequences are exchanged between two similar or identical molecules of DNA. HR is most widely used by cells to accurately repair harmful breaks that occur on both strands of DNA, known as double-strand breaks. For example, BRCA1, BRCA2, ATM, BARD1, BRIP1, CHEK2, DMC1, EME1(MMS4L), EME2, GEN1, GIYD2(SLX1B), MRE11A, MUS81, NBN, PALB2, RAD50, RAD51, RAD51B, RD51C, RAD51D, RAD52, RAD54B, RAD54L, RBBP8, SHFM1 (DSS1), XRCC2, XRCC3 are genes known to be involved in HR. One of skill in the art will be able to determine whether a gene is involved in DNA repair or homologous recombination. DNA repair status refers to the presence or absence of mutations in one or more of a gene involved in DNA repair. In certain embodiments, the invention involves use of a PARP inhibitor to treat a cancer patient regardless of DNA repair status.

As used herein, the term “PARP inhibitor” means an agent that inhibits the activity or decreases the function of any one of the poly(ADP-ribose) polymerase (PARP) family of pro-

teins. This may include inhibitors of any one of more of the over 15 different enzymes in the PARP family, which engage in a variety of cellular functions, including cell cycle regulation, transcription, and repair of DNA damage.

5 As used herein, the term “progression free survival” means the time period for which a subject having a disease (e.g. cancer) survives, without a significant worsening of the disease state. Progression free survival may be assessed as a period of time in which there is no progression of tumor 10 growth and/or wherein the disease status of a patient is not determined to be a progressive disease. In some embodiments, progression free survival of a subject having cancer is assessed by evaluating tumor (lesion) size, tumor (lesion) number, and/or metastasis.

15 As used herein, “progression free survival 2” (PFS2) is defined as time period from treatment randomization to the earlier date of assessment progression on the next anticancer therapy following study treatment or death by any cause. In some embodiments, determination of progression may be 20 assessed by clinical and/or radiographic assessment.

The term “progression” of tumor growth or a “progressive disease” (PD) as used herein in reference to cancer status indicates an increase in the sum of the diameters of the target lesions (tumors). In some embodiments, progression of 25 tumor growth refers to at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In some embodiments, in addition to a relative increase of 20%, the sum of diameters of target lesions must also demonstrate an absolute increase of at least 30 5 mm. An appearance of one or more new lesions may also be factored into the determination of progression of tumor growth. Progression for the purposes of determining progression free survival may also be determined if at least one 35 of the following criteria is met: 1) tumor assessment by CT/MRI unequivocally shows progressive disease according to RECIST 1.1 criteria; or 2) additional diagnostic tests (e.g. histology/cytology, ultrasound techniques, endoscopy, positron emission tomography) identify new lesions or 40 determine existing lesions qualify for unequivocal progressive disease AND CA-125-progression according to Gynecologic Cancer Intergroup (GCIG)-criteria (see Rustin et al., Int J Gynecol Cancer 2011; 21: 419-423 which is incorporated herein in its entirety); 3) definitive clinical signs and 45 symptoms of PD unrelated to non-malignant or iatrogenic causes ([i] intractable cancer-related pain; [ii] malignant bowel obstruction/worsening dysfunction; or [iii] unequivocal symptomatic worsening of ascites or pleural effusion) AND CA-125-progression according to GCIG-criteria.

50 As used herein, the term “partial response” or “PR” refers to a decrease in tumor progression in a subject as indicated by a decrease in the sum of the diameters of the target lesions, taking as reference the baseline sum diameters. In some embodiments, PR refers to at least a 30% decrease in 55 the sum of diameters of target lesions, taking as reference the baseline sum diameters. Exemplary methods for evaluating partial response are identified by RECIST guidelines. See E. A. Eisenhauer, et al., “New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1),” Eur. J. of Cancer, 45: 228-247 (2009).

60 As used herein, “stabilization” of tumor growth or a “stable disease” (SD) refers to neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. In some embodiments, stabilization refers to a less than 30%, 25%, 20%, 15%, 10% or 5% change (increase or decrease) 65 in the sum of the diameters of the target lesions, taking as reference the baseline sum diameters. Exemplary methods

for evaluating stabilization of tumor growth or a stable disease are identified by RECIST guidelines. See E. A. Eisenhauer, et al., "New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1.)," *Eur. J. of Cancer*, 45: 228-247 (2009).

As used herein, the term "complete response" or "CR" is used to mean the disappearance of all or substantially all target lesions. In some embodiments, CR refers to an 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% decrease in the sum of the diameters of the target lesions (i.e. loss of lesions), taking as reference the baseline sum diameters. In some embodiments, CR indicates that less than 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1% or less of the total lesion diameter remains after treatment. Exemplary methods for evaluating complete response are identified by RECIST guidelines. See E. A. Eisenhauer, et al., "New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1.)," *Eur. J. of Cancer*, 45: 228-247 (2009).

As used herein, a "hazard ratio" (or "HR" when used in the context of niraparib treatment effect calculations, e.g. HR 0.38) is the expression of the hazard or chance of events occurring in the treatment arm as a ratio of the events occurring in the control arm. Hazard ratios may be determined by the Cox model, a regression method for survival data, which provides an estimate of the hazard ratio and its confidence interval. The hazard ratio is an estimate of the ratio of the hazard rate in the treated versus the control group. The hazard rate is the probability that if the event in question has not already occurred, it will occur in the next time interval, divided by the length of that interval. An assumption of proportional hazards regression is that the hazard ratio is constant over time.

In some embodiments, the present invention involves comparisons of results achieved for two or more agents, entities, situations, sets of conditions, populations etc. As will be understood by those of skill in the art, such agents, entities, situations, sets of conditions, populations, etc. can be considered "comparable" to one another when they are not identical but are sufficiently similar to permit comparison there between so that conclusions may reasonably be drawn based on differences or similarities observed. In some embodiments, comparable sets of conditions, circumstances, individuals, or populations are characterized by a plurality of substantially identical features and one or a small number of varied features. Those of ordinary skill in the art will understand, in context, what degree of identity is required in any given circumstance for two or more such agents, entities, situations, sets of conditions, to be considered comparable. For example, those of ordinary skill in the art will appreciate that sets of circumstances, individuals, or populations are comparable to one another when characterized by a sufficient number and type of substantially identical features to warrant a reasonable conclusion that differences in results obtained or phenomena observed under or with different sets of circumstances, individuals, or populations are caused by or indicative of the variation in those features that are varied.

Comparisons as described herein are often made to an appropriate "reference". As used herein, the term "reference" refers to a standard or control relative to which a comparison is performed. For example, in some embodiments, an agent, animal, individual, population, sample, sequence, or value of interest is compared with a reference or control agent, animal, individual, population, sample, sequence, or value. In some embodiments, a reference or control is tested and/or determined substantially simultane-

ously with the testing or determination of interest. In some embodiments, a reference or control is a historical reference or control, optionally embodied in a tangible medium. Typically, as would be understood by those skilled in the art, a reference or control is determined or characterized under comparable conditions or circumstances to those under assessment. Those skilled in the art will appreciate when sufficient similarities are present to justify reliance on and/or comparison to a particular possible reference or control.

As used herein, the term "treatment" (also "treat" or "treating") refers to any administration of a therapy that partially or completely alleviates, ameliorates, relives, inhibits, delays onset of, reduces severity of, and/or reduces incidence of one or more symptoms, features, and/or causes of a particular disease, disorder, and/or condition. In some embodiments, such treatment may be of a subject who does not exhibit signs of the relevant disease, disorder and/or condition and/or of a subject who exhibits only early signs of the disease, disorder, and/or condition. Alternatively or additionally, such treatment may be of a subject who exhibits one or more established signs of the relevant disease, disorder and/or condition. In some embodiments, treatment may be of a subject who has been diagnosed as suffering from the relevant disease, disorder, and/or condition. In some embodiments, treatment may be of a subject known to have one or more susceptibility factors that are statistically correlated with increased risk of development of the relevant disease, disorder, and/or condition.

As used here, the term "fasted state" refers to a state of a subject wherein food has not been consumed by the subject for a certain period of time. In some embodiments, a fasted state indicates that there is substantially no residual food in the stomach of the subject. In some embodiments, a fasted state refers to the state of the subject during the time from about 2 or more hours after food consumption up until about 30 minutes before the next food consumption. In some embodiments, the fasted state of a subject includes the time from about 2 hours after food consumption, 3 hours after food consumption, 3.5 hours after food consumption, 4 hours after food consumption, 6 hours after food consumption, 8 hours after food consumption, or 12 hours after food consumption up until about 30 minutes before the next food consumption, or any time points between, end points inclusive.

As used here, the term "fed state" refers to a state of a subject wherein there is food in the stomach of the subject at the time of administration of a therapeutic agent (e.g., niraparib). In some embodiments, a fed state refers to the state of the subject during the time from the start of food consumption to about 2 hours after food consumption, such as during food consumption, immediately after food consumption, about 30 minutes after food consumption, about 1 hour after food consumption, about 1.5 hours after food consumption, or about 2 hours after food consumption, or any time between any of the two numbers, end points inclusive. As used herein, food consumption refers to consuming a substantial amount of food, such as at least one third of a normal meal of a subject, either by volume or by total number of calories consumed.

As used herein, the term "polymorph" refers to a crystal structure of a compound. As used herein, the term "solvate" refers to a crystal form with either a stoichiometric or non-stoichiometric amount of solvent incorporated into the crystal structure. Similarly, the term "hydrate" refers to a crystal form with either a stoichiometric or non-stoichiometric amount of water incorporated into the crystal structure.

As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al., describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like.

Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}\text{alkyl})_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

As used herein, the term "pharmaceutical composition" refers to a composition in which an active agent is formulated together with one or more pharmaceutically acceptable carriers. In some embodiments, the active agent is present in unit dose amount appropriate for administration in a therapeutic regimen that shows a statistically significant probability of achieving a predetermined therapeutic effect when administered to a relevant population. In some embodiments, a pharmaceutical composition may be specially formulated for administration in solid or liquid form, including those adapted for oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, e.g., those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue. A pharmaceutical composition can also refer to a medicament.

As used herein, the term "niraparib" means any of the free base compound ((3S)-3-[4-(aminocarbonyl)-2H-indazol-2-yl]phenyl)piperidine), a salt form, including pharmaceutically acceptable salts, of (3S)-3-[4-(aminocarbonyl)-2H-indazol-2-yl]phenyl)piperidine (e.g., (3S)-3-[4-(aminocarbonyl)-2H-indazol-2-yl]phenyl)piperidine tosylate), or a solvated or hydrated form thereof (e.g., (3S)-3-[4-(aminocarbonyl)-2H-indazol-2-yl]phenyl)piperidine tosylate monohydrate). In some embodiments, such forms may be individually referred to as "niraparib free

base", "niraparib tosylate" and "niraparib tosylate monohydrate", respectively. Unless otherwise specified, the term "niraparib" includes all forms of the compound (3S)-3-[4-(7-(aminocarbonyl)-2H-indazol-2-yl)phenyl]piperidine.

As used herein, the term "maintenance therapy" or "maintenance treatment" is a treatment that is given to prevent relapse of a disease. For example, a maintenance therapy may prevent or minimize growth of a cancer after it has been substantially reduced or eliminated following an initial therapy (cancer treatment). Maintenance therapy may be a continuous treatment where multiple doses are administered at spaced intervals such as every day, every other day, every week, every 2 weeks, every 3 weeks, every 4 weeks, or every 6 weeks. In some embodiments a maintenance therapy may continue for a predetermined length of time. In some embodiments, a maintenance therapy may continue until unacceptable toxicity occurs and/or disease progression occurs. In the course of maintenance treatment, treatment may be interrupted upon the occurrence of toxicity as indicated by an adverse event. If toxicity is appropriately resolved to baseline or grade 1 or less within 28 days, the patient may restart treatment with niraparib, which may include a dose level reduction, if prophylaxis is not considered feasible.

As used herein, overall survival ("OS") is defined as time from commencement of treatment to death from any cause. With respect to use as a clinical trial endpoint, it is defined as the time from randomization until death from any cause, and is measured in the intent to treat population.

As used herein, "objective response rate ("ORR") is defined as the proportion of patients with tumor size reduction of a predefined amount and for a minimum period of time. Response duration is usually measured from the time of initial response until documented tumor progression. Generally, the ORR can be defined as the sum of partial responses plus complete responses.

As used herein, "time to first subsequent therapy" (TFST) is defined as the date of randomization in the current study to the start date of the first subsequent treatment regimen (e.g., anticancer therapy).

As used herein, "time to second subsequent therapy" (TSST) is defined as the date of randomization in the current study to the start date of the second subsequent treatment regimen (e.g., anticancer therapy).

As used herein, "chemotherapy-free interval" (CFI) is defined as the time from last dose of the last anticancer therapy (e.g., platinum-based chemotherapy) until the initiation of the next Ovarian Cancer

Ovarian cancer begins when healthy cells in an ovary change and grow uncontrollably, forming a mass called a tumor. A tumor can be cancerous or benign. A cancerous tumor is malignant, meaning it can grow and spread to other parts of the body. A benign tumor means the tumor can grow but will not spread. Removing the ovary or the part of the ovary where the tumor is located can treat a noncancerous ovarian tumor. An ovarian cyst, which forms on the surface of the ovary, is different than a noncancerous tumor and usually goes away without treatment. A simple ovarian cyst is not cancerous. They often occur during the normal menstrual cycle. Types of ovarian cancer include: epithelial carcinoma, germ cell tumors, or stromal tumors.

Epithelial carcinoma makes up 85% to 90% of ovarian cancers. While historically considered to start on the surface of the ovary, new evidence suggests at least some ovarian cancer begins in special cells in a part of the fallopian tube. The fallopian tubes are small ducts that link a woman's

ovaries to her uterus that are a part of a woman's reproductive system. Every woman has two fallopian tubes, one located on each side of the uterus. Cancer cells that begin in the fallopian tube may go to the surface of the ovary early on. The term 'ovarian cancer' is often used to describe epithelial cancers that begin in the ovary, in the fallopian tube, and from the lining of the abdominal cavity, called the peritoneum. Germ cell tumor. This uncommon type of ovarian cancer develops in the egg-producing cells of the ovaries. This type of tumor is more common in females ages 10 to 29. Stromal tumor. This rare form of ovarian cancer develops in the connective tissue cells that hold the ovaries together, which sometimes is the tissue that makes female hormones called estrogen. Over 90% of these tumors are adult or childhood granulosa cell tumors. Granulosa cell tumors may secrete estrogen resulting in unusual vaginal bleeding at the time of diagnosis.

The expected incidence of epithelial ovarian cancer in women in the United States in 2012 is approximately 22,280 (15,500 deaths) and in Europe in 2012 was estimated at 65,538 patient cases (42,704 deaths). At diagnosis, most women present with advanced disease, which accounts for the high mortality rate. Initial chemotherapy consists of either taxane or platinum chemotherapy or a combination of both. While approximately 75% of patients respond to front line therapy 70% of those eventually relapse within 1 to 3 years. There is a significant unmet need due to the high recurrence rate, despite an initially high response rate. Attempts to improve the standard two-drug chemotherapy (carboplatin and paclitaxel) by adding a third cytotoxic drug (topotecan, gemcitabine, or doxil) have failed (du Bois et al, 2006 and Pfisterer et al, 2006). The great challenge for the near future will be the selection of patients with advanced ovarian cancer who will most benefit from specific targeted agents in the frontline maintenance setting. Maintenance therapy after the achievement of a response from initial chemotherapy may represent an approach to provide clinical benefit by delaying disease progression side effects, delaying the need for toxic chemotherapy and prolonging overall survival. However there is currently no widely accepted standard of care in the ovarian cancer maintenance setting.

The lack of successful treatment strategies led the Cancer Genome Atlas (TCGA) researchers to comprehensively measure genomic and epigenomic abnormalities on clinically annotated HGS-OvCa samples to identify molecular factors that influence pathophysiology affect outcome and constitute therapeutic targets (TCGA, 2011). Ovarian tumors are characterized by deficiencies in DNA repair such as BRCA mutations. BRCA 1 and 2 were initially identified as tumor suppressor genes that were associated with increased incidence of certain malignancies when defective, including ovarian cancer. BRCA deficiency was noted in 34% of ovarian cancers, owing to a combination of germline and sporadic mutations and promoter hypermethylation. BRCA plays a key role in DNA repair, including homologous recombination. This study estimated over half of high grade serous ovarian cancer suffered from defects in DNA repair. Tumor cells with BRCA deficiency/Homologous Recombination Deficiency (HRD) may provide an opportunity for therapeutic intervention with agents that inhibit DNA repair pathways and exploit synthetic lethality mechanisms of cancer treatment. Recent studies have suggested that HR deficiency in epithelial ovarian cancer (EOC) is not solely due to germline BRCA1 and BRCA2 mutations (Hennessy, 2010; TCGA, 2011; Byler Dann, 2012). The

Cancer Genome Atlas Research Network reported a defect in at least one HR pathway gene in approximately half of the ~500 EOC in the data set.

Role of Poly(ADP-Ribose) Polymerases (PARPs)

Poly(ADP-ribose) polymerases (PARPs) are a family of enzymes that cleave NAD⁺, releasing nicotinamide, and successively add ADP-ribose units to form ADP-ribose polymers. Accordingly, activation of PARP enzymes can lead to depletion of cellular NAD⁺ levels (e.g., PARPs as NAD⁺ consumers) and mediates cellular signaling through ADP-ribosylation of downstream targets. PARP-1 is a zinc-finger DNA-binding enzyme that is activated by binding to DNA double or single strand breaks. It was known that anti-alkylating agents could deplete the NAD⁺ content of tumor cells, and the discovery of PARPs explained these phenomena. (Parp Inhibitors and Cancer Therapy. Curtin N. in Poly ADP Ribosylation. ed. Alexander Burke, Lands Bioscience and Springer Bioscience, 2006: 218-233). Anti-alkylating agents induce DNA strand breaks, which activates PARP-1, which is part of the DNA repair pathway. Poly ADP-ribosylation of nuclear proteins by PARP-1 converts DNA damage into intracellular signals that can either activate DNA repair (e.g. by the base excision repair (BER) pathway); or trigger cell death in the presence of DNA damage that is too extensive and cannot be efficiently repaired.

The role of PARP enzymes in DNA damage response (e.g. repair of DNA in response to genotoxic stress) has led to the compelling suggestion that PARP inhibitors may be useful anti-cancer agents. Numerous studies are directed to investigating of the activity of PARP inhibitors, alone or in combination with other agents, as cancer therapeutics. PARP inhibitors may be particularly effective in treating cancers resulting from germ line or sporadic deficiency in the homologous recombination DNA repair pathway, such as BRCA-1, BRCA-2, and/or ATM deficient cancers. Additionally, simultaneous administration of genotoxic chemotherapy with PARP inhibition may enhance the killing effect of such chemotherapy by suppressing BER.

Pre-clinical ex vivo and in vivo experiments suggest that PARP inhibitors are selectively cytotoxic for tumors with homozygous inactivation of either the BRCA-1 or BRCA-2 genes, which are known to be important in the homologous recombination (HR) DNA repair pathway. The biological basis for the use of PARP-1 inhibitors as single agents in cancers with defects in HR is the requirement of PARP-1 and PARP-2 for base excision repair (BER) of the damaged DNA. Upon formation of single-strand DNA breaks, PARP-1 and PARP-2 bind at sites of lesions, become activated, and catalyze the addition of long polymers of ADP-ribose (PAR chains) on several proteins associated with chromatin, including histones, PARP itself, and various DNA repair proteins. This results in chromatin relaxation and fast recruitment of DNA repair factors that access and repair DNA breaks. Normal cells repair up to 10,000 DNA defects daily and single strand breaks are the most common form of DNA damage. Cells with defects in the BER pathway enter S phase with unrepaired single strand breaks. Pre-existing single strand breaks are converted to double strand breaks as the replication machinery passes through the break. Double strand breaks present during S phase are preferentially repaired by the error-free HR pathway. Cells unable to use HR (i.e., due to inactivation of genes required for HR, such as BRCA-1 or BRCA-2) accumulate stalled replication forks during S phase and may use error-prone non-homologous end joining (NHEJ) to repair damaged DNA. Both the inability to complete S phase (because of

23

stalled replication forks) and error-prone repair by NHEJ, are thought to contribute to cell death.

Without wishing to be bound by theory, it is hypothesized that treatment with PARP inhibitors represents a novel opportunity to selectively kill a subset of cancer cells with deficiencies in DNA repair pathways. For example, a tumor arising in a patient with a germline BRCA mutation has a defective homologous recombination DNA repair pathway and would be increasingly dependent on BER, a pathway blocked by PARP inhibitors, for maintenance of genomic integrity. Non-BRCA deficiencies in homologous recombination DNA repair genes could also enhance tumor cell sensitivity to PARP inhibitors. This concept of inducing death by use of PARP inhibitors to block one DNA repair pathway in tumors with pre-existing deficiencies in a complementary DNA repair pathways is called synthetic lethality.

Germline mutations of BRCA-1 and BRCA-2 genes are found in a majority of patients with an inherited breast or ovarian cancer. Inactivation of BRCA-1 and BRCA-2 gene by other mechanisms, including somatic BRCA-1/2 mutations and/or gene silencing by promoter hypermethylation, occurs in a significant portion of several sporadic cancers. In particular, for ovarian cancer, somatic BRCA-1 or BRCA-2 mutations are found in 10%-15% of all epithelial ovarian carcinomas (EOCs), and strongly reduced expression of BRCA-1 has been observed in a significant portion of sporadic ovarian cancers. Collectively, up to 40%-60% of ovarian cancers might be responsive to PARP inhibitors as a consequence of defects in the BRCA-HR pathway, indicating a great potential for this approach in the therapy of ovarian cancer.

HR is a complex pathway, and several genes other than BRCA-1 and BRCA-2 are required either to sense or repair DNA double strand breaks via the HR pathway. Not surprisingly, therefore, PARP inhibitors are also selectively cytotoxic for cancer cells with deficiencies in DNA repair-proteins other than BRCA-1 and BRCA-2 including RecA homologs (RAD51 and RAD54), X-ray repair complementing defective repair in Chinese hamster cells (XRCC2 and XRCC3), DSS1, replication protein A1 (RPA1), ataxia telangiectasia mutated (ATM), ATM and Rad3-related (ATR), check point kinases (CHK1, CHK2), Nijmegen breakage syndrome 1 (NBS1), and the components of the Fanconi anemia repair pathway. Some of these genes are known to be mutated or down-regulated in different sporadic tumors, which might therefore be "addicted" to HR- but possibly also non-HR mediated DNA repair and therefore respond to PARP inhibitors. More recently, it has been also demonstrated that tumor cells with deletion of the PTEN-gene are indeed sensitive to PARP inhibitors, possibly as a consequence of HR defects.

The therapeutic potential of PARP inhibitors is further expanded by the observation that PARP-1 inhibitors not only have monotherapy activity in HR-deficient tumors, but are also effective in preclinical models in combination with cisplatin, carboplatin, alkylating and methylating agents, radiation therapy, and topoisomerase I inhibitors. In contrast to the rationale for monotherapy in which PARP inhibition alone is sufficient for cell death in HR-deficient cancers (due to endogenous DNA damage), PARP is required for repair of DNA damage induced by standard cytotoxic chemotherapy. In some cases, the specific role of PARP is not known, but PARP-1 is known to be required to release trapped topoisomerase I/irinotecan complexes from DNA. Temozolomide-induced DNA damage is repaired by the BER pathway, which requires PARP to recruit repair proteins. Combination

24

therapies that enhance or synergize with cytotoxic agents without significantly increasing toxicity would provide substantial benefit to ovarian as well other types of cancer patients.

Treatment with PARP inhibitors (e.g., PARP-1/2 inhibitors) represents a novel opportunity to selectively kill a subset of cancer cell types by exploiting their deficiencies in DNA repair. Human cancers exhibit genomic instability and an increased mutation rate due to underlying defects in DNA repair. These deficiencies render cancer cells more dependent on the remaining DNA repair pathways and targeting these pathways is expected to have a much greater impact on the survival of the tumor cells than on normal cells. While PARP inhibitors represent a promising class of potential cancer therapeutics, the clinical efficacy of these compounds is unclear. Specifically, results regarding the clinical outcomes of different PARP inhibitors (e.g., PARP-1/2 inhibitors) as cancer therapeutics are in some cases unclear and potentially even conflicting. For example, an analysis of results of clinical trials testing the PARP inhibitor olaparib have shown conflicting long term outcomes for overall survival in patients with ovarian cancer. For example, an analysis of three clinical trials found that while on average olaparib, when added to a conventional treatment, slowed the progression of platinum-sensitive epithelial ovarian cancer in women with germline BRCA mutations compared with placebo or no-treatment, there was, however, no significant change observed in the overall survival of patients. Further, olaparib trials found that serious adverse events were more common in the olaparib group compared to the control group. See, Wiggins et al., (2015) "Poly(ADP-ribose) polymerase (PARP) inhibitors for the treatment of ovarian cancer." Cochrane Database of Systematic Reviews, Issue 5. Art. No.: CD007929. Another clinical trial with the PARP inhibitor veliparib had a relatively small sample size, and was unable to show any effect of veliparib on the progression of ovarian cancer. Thus, the art has failed to establish clinical efficacy for these PARP inhibitors and there remains a continuing need to identify, characterize, and/or develop PARP inhibitors as effective cancer therapeutics. The present disclosure satisfies this need. Among other things, the present disclosure provides niraparib compositions and methodologies that achieve effective cancer treatment, in particular as therapy for cancers of the female reproductive system (e.g. ovarian cancer). In some embodiments, the present disclosure provides niraparib compositions and/or methods that achieve progression-free survival rates and/or hazard ratios as described herein. In some embodiments, provided compositions and/or methods achieve such effects with an overall treatment emergent adverse event rate (TEAE) that is not more than about three times, or in some embodiments two times, higher than that observed with comparable placebo treatment, provided compositions and/or methods achieve such effects with a serious TEAE rate that is not more than about 5 times, or about 4.5 times, or about 4 times higher than that observed with comparable placebo treatment.

Platinum-sensitive, recurrent ovarian cancer remains an unmet medical need. Both the National Comprehensive Cancer Network (NCCN) and the European Society of Medical Oncology (ESMO) guidelines recommend re-treatment of patients with a platinum-based combination chemotherapy when relapse occurs >6 months after response to an initial platinum-based treatment. Paclitaxel plus carboplatin is the most frequently used regimen for platinum-sensitive patients who have recurred. Most patients who recur and are treated with a second round of platinum-based

chemotherapy do not receive any type of treatment after response to the chemotherapy as there is no approved product for maintenance use after chemotherapy in the US. The standard of care in the US is "watchful waiting."

Unfortunately, the utility of platinum-based chemotherapy diminishes over time; the PFS and platinum-free intervals generally become shorter after each subsequent treatment with tumors ultimately becoming platinum resistant or refractory. Furthermore, patients generally do not receive more than 6 cycles of platinum-based chemotherapy per treatment course due to cumulative toxicities with platinum agents and taxanes. New agents are needed to prolong the response to platinum-based chemotherapy, reduce the risk of recurrence or death, and increase the platinum-free interval.

The poly(ADP-ribose) polymerase (PARP) family of proteins consists of over 15 different enzymes, which engage in a variety of cellular functions, including cell cycle regulation, transcription, and repair of DNA damage. BRCA1, BRCA2 and PALB2 are proteins that are important for the repair of double-strand DNA breaks by the error-free homologous recombinational repair, or HRR, pathway. When the gene for either protein is mutated, the change can lead to errors in DNA repair that can eventually cause cancer, including for example, breast or ovarian cancers.

PARP-1 is the most abundant and best characterized protein in this group and is critical to the repair of single-strand DNA breaks through the base excision repair pathway. If such breaks persist unrepaired until DNA is replicated (which must precede cell division), then the replication itself can cause double strand breaks to form. Effective inhibition of PARP-1 leads to the accumulation of single-strand breaks, which ultimately results in double-strand breaks. Usually such double-strand breaks are repaired by homologous recombination (HR), but in cells with defective HR, PARP inhibition can result in chromosomal instability, cell cycle arrest, and subsequent apoptosis. DNA is damaged thousands of times during each cell cycle, and that damage must be repaired. When subjected to enough damage at one time, the altered gene can cause the death of the cells. Normal cells that don't replicate their DNA as often as cancer cells, and that lack any mutated BRCA1 or BRCA2 still have homologous repair operating, which allows them to survive the inhibition of PARP. PARP inhibitors function by blocking PARP enzyme activity, which prevents the repair of DNA damage and ultimately may cause cell death. They also are believed to function by localizing PARP proteins at sites of DNA damage, which has relevance to their anti-tumor activity. The trapped PARP protein-DNA complexes are highly toxic to cells because they block DNA replication.

PARP proteins are typically released from DNA once the DNA binding and repair process is underway. There is evidence to demonstrate that, when the proteins are bound to PARP inhibitors, they become trapped on DNA. The trapped PARP-DNA complexes are more toxic to cells than the unrepaired single-strand DNA breaks that accumulate in the absence of PARP activity. Therefore, without being limited as to theory, there are at least two mechanisms of PARP inhibitor-inhibition of repair and PARP trapping.

The inability of HR to correct double-stranded breaks has been observed in tumors with mutations in the breast cancer-related genes BRCA1 and BRCA2, which code for proteins essential for normal HR function. The use of small-molecule PARP inhibitors to exploit this genetic vulnerability in DNA damage repair is an example of synthetic lethality, in which the simultaneous inhibition of two pathways leads to cell

death, whereas blocking either pathway alone is not lethal. Encouraging preclinical results for PARP inhibitors in the treatment of BRCA-mutated tumor cells provided strong rationale for the clinical testing of these agents in patient populations most likely to carry these mutations, such as those with breast or ovarian cancer. This therapeutic strategy has now been validated by the recent US Food and Drug Administration (FDA)-accelerated approval for the PARP inhibitors olaparib and rucaparib as monotherapies to treat patients with BRCA-mutated advanced ovarian cancer. Surprisingly, the instant invention demonstrates that PARP inhibition is effective in prolonging progression free survival in human cancer patients regardless of the presence or absence of a mutation in BRCA1 or BRCA2. Niraparib is the first PARP inhibitor to demonstrate this ability, but the result can be achieved with other PARP inhibitors. Niraparib and other such PARP inhibitors are discussed below.

Niraparib, (3S)-3-[4-{7-(aminocarbonyl)-2H-indazol-2-yl}phenyl]piperidine, is an orally available, potent, poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP)-1 and -2 inhibitor. See WO 2008/084261 (published on Jul. 17, 2008) and WO 2009/087381 (published Jul. 16, 2009), the entirety of each of which is hereby incorporated by reference. Niraparib can be prepared according to Scheme 1 of WO 2008/084261.

In some embodiments, niraparib can be prepared as a pharmaceutically acceptable salt. One of skill in the art will appreciate that such salt forms can exist as solvated or hydrated polymorphic forms. In some embodiments, niraparib is prepared in the form of a hydrate.

In certain embodiments, niraparib is prepared in the form of a tosylate salt. In some embodiments, niraparib is prepared in the form of a tosylate monohydrate.

The crystalline tosylate monohydrate salt of niraparib is being developed as a monotherapy agent for tumors with defects in the homologous recombination (HR) deoxyribonucleic acid (DNA) repair pathway and as a sensitizing agent in combination with cytotoxic agents and radiotherapy.

Niraparib is a potent and selective PARP-1 and PARP-2 inhibitor with inhibitory concentration at 50% of control (IC_{50})=3.8 and 2.1 nM, respectively, and is at least 100-fold selective over other PARP-family members. Niraparib inhibits PARP activity, stimulated as a result of DNA damage caused by addition of hydrogen peroxide, in various cell lines with an IC_{50} and an inhibitory concentration at 90% of control (IC_{90}) of about 4 and 50 nM, respectively.

Niraparib demonstrates selective anti-proliferative activity for cancer cell lines that have been silenced for BRCA-1 or BRCA-2, or carry BRCA-1 or BRCA-2 mutations compared to their wild type counterparts. The antiproliferative activity of niraparib on BRCA-defective cells is a consequence of a cell cycle arrest in G2/M followed by apoptosis. Niraparib is also selectively cytotoxic for selected Ewing's sarcoma, acute lymphocytic leukemia (ALL), non-small cell lung cancer (NSCLC), and small cell lung cancer (SCLC) cell lines, as well as for tumor cell lines carrying homozygous inactivation of the ATM gene. Niraparib demonstrates weak activity on normal human cells. In vivo studies demonstrated strong antitumor activity with BRCA-1 mutant breast cancer (MDA-MB-436), BRCA-2 mutant pancreatic cancer (CAPAN-1), ATM-mutant mantle cell lymphoma (GRANTA-519), serous ovarian cancer (OVCAR3), colorectal cancer (HT29 and DLD-1), patient derived Ewing's sarcoma, and TNBC xenograft models in mice.

Target engagement has also been demonstrated by measuring PARP activity in tumor homogenates from tumor

xenograft studies. Inhibition of PARP activity has also been measured in peripheral blood mononuclear cells (PBMCs) from mice dosed with niraparib. Niraparib has been shown to induce cell cycle arrest, particularly arrest in the G2/M phase of the cell cycle. Accordingly, in some embodiments, the present invention provides a method of inducing cell cycle arrest of a tumor cell, the method comprising administering niraparib to a patient in need thereof. In some embodiments, the present invention provides a method of inducing arrest of the G2/M phase of the cell cycle of a tumor cell, the method comprising administering niraparib to a patient in need thereof. In some embodiments, the present invention provides a method of inducing arrest in the G2/M phase of the cell cycle of BRCA-1 and/or BRCA-2-deficient cells, the method comprising administering niraparib to a patient in need thereof.

Olaparib acts as an inhibitor of the enzyme poly ADP ribose polymerase (PARP), and is termed a PARP inhibitor. The chemical name is 4-[{3-[(4-(cyclopropylcarbonyl)piperazin-1-yl)carbonyl]-4-fluorophenyl)methyl]phthalazin-1 (2H)-one. Clinical trials of olaparib were initiated in breast, ovarian and colorectal cancer. Preliminary activity was seen in ovarian cancer, with 7 responses in 17 patients with BRCA1 or BRCA2 mutations and 11 responses in the 46 who did not have these mutations. However, an interim analysis of a phase II study that looked at using olaparib to maintain progression free survival or response after success with platinum-based chemotherapy indicated that a reported progression-free survival benefit was unlikely to translate into an overall survival benefit for the intent to treat populations. However, planned analysis of the subset of patients who had BRCA mutations found a clear advantage with olaparib (Ledermann et al., New England Journal of Medicine, 366; 15 (2012); Lancet Oncol. 15 (8): 852-61). Olaparib is approved as monotherapy, at a recommended dose of 400 mg taken twice per day, in germline BRCA mutated (gBRCAmut) advanced ovarian cancer that has received three or more prior lines of chemotherapy. BRCA1/2 mutations may be genetically predisposed to development of some forms of cancer, and may be resistant to other forms of cancer treatment. However, these cancers sometimes have a unique vulnerability, as the cancer cells have increased reliance on PARP to repair their DNA and enable them to continue dividing. This means that drugs which selectively inhibit PARP may be of benefit if the cancers are susceptible to this treatment. Thus, the olaparib clinical data demonstrated that PARP inhibitors would not be beneficial to prolong progression free survival in the treatment of cancer characterized by the absence of mutations in BRCA1 or BRCA2.

Similarly, rucaparib acts as an inhibitor of the enzyme poly ADP ribose polymerase (PARP), and is also termed a PARP inhibitor. The chemical name is 8-fluoro-2-{4-[(methylamino)methyl]phenyl}-1,3,4,5-tetrahydro-6H-azepino[5,4,3-cd]indol-6-one ((1S,4R)-7,7-dimethyl-2-oxabicyclo [2.2.1]hept-1-yl)methanesulfonic acid salt. It is also approved as indicated as monotherapy for the treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies. The efficacy of rucaparib was investigated in 106 patients in two multi-center, single-arm, open-label clinical trials, Study 1 and Study 2, in patients with advanced BRCA-mutant ovarian cancer who had progressed after 2 or more prior chemotherapies. All 106 patients received rucaparib 600 mg orally twice daily as monotherapy until disease progression or unacceptable toxicity. Response assessment by independent

radiology review was 42% (95% CI [32, 52]), with a median DOR of 6.7 months (95% CI [5.5, 11.1]). Investigator-assessed ORR was 66% (52/79; 95% CI [54, 76]) in platinum-sensitive patients, 25% (5/20; 95% CI [9, 49]) in platinum-resistant patients, and 0% (0/7; 95% CI [0, 41]) in platinum-refractory patients. ORR was similar for patients with a BRCA1 gene mutation or BRCA2 gene mutation. Thus, the rucaparib clinical data demonstrated that PARP inhibitors would not be beneficial to prolong progression free survival in the treatment of cancer characterized by the absence of mutations in BRCA1 or BRCA2.

Similarly, talazoparib acts as an inhibitor of the enzyme poly ADP ribose polymerase (PARP), and is also termed a PARP inhibitor. It is currently being evaluated in clinical studies for the treatment of patients with gBRCA mutated breast cancer (i.e., advanced breast cancer in patients whose BRCA genes contain germline mutations). The primary objective of the study is to compare PFS of patients treated with talazoparib as a monotherapy relative to those treated with protocol-specified physicians' choice.

Similarly, veliparib acts as an inhibitor of the enzyme poly ADP ribose polymerase (PARP), and is also termed a PARP inhibitor. The chemical name of veliparib is 2-[(R)-2-methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide.

At diagnosis of ovarian cancer, most women present with advanced disease, which accounts for the high mortality rate. Patients with stage 2, 3 or 4 disease will undergo tumor reductive surgery if the disease is potentially resectable and may undergo subsequent chemotherapy for 4-8 cycles. Initial chemotherapy may consist of either IV chemotherapy or a combination of IV and intraperitoneal (IP) chemotherapy. IV chemotherapy usually consists of a taxane (paclitaxel or docetaxel) and a platinum (cisplatin or carboplatin). Approximately 75% of patients respond to front line therapy and are considered platinum sensitive, standardly defined as a minimum duration of 6 months following treatment with no relapse or disease progression. However, up to 70% of patients eventually relapse within 1 to 3 years. Attempts to improve the standard platinum based two-drug chemotherapy by adding a third cytotoxic drug have failed to affect either progression-free survival or overall survival and resulted in an increase in toxic effects (du Bois et al, 2006 and Pfisterer, 2006 et al). There is a high unmet need due to the high recurrence rate, even after an initially high response rate.

The Cancer Genome Atlas (TCGA) researchers tested clinically annotated HGS-OvCa samples to identify molecular factors that influence pathophysiology, affect outcome and constitute therapeutic targets (TCGA, 2011). Ovarian tumors are characterized by deficiencies in DNA repair such as BRCA mutations. BRCA 1 and 2 have been identified as tumor suppressor genes that were associated with increased incidence of certain malignancies when defective, including ovarian cancer. BRCA plays a key role in DNA repair, including homologous recombination. Tumor cells with BRCA deficiency/Homologous Recombination Deficiency (HRD) are particularly sensitive to DNA damage. Niraparib inhibits PARP activity, stimulated as a result of DNA damage and demonstrates selective anti-proliferative activity for cancer cell lines that have been silenced for BRCA1 or BRCA2, or carry BRCA-1 or BRCA-2 mutations compared to their wild type counterparts. The antiproliferative activity of niraparib on BRCA-defective cells is a consequence of a cell cycle arrest in G2/M followed by apoptosis. PARP inhibitors block alt-NHEJ and BER, forcing tumors with BRCA deficiencies to use the error-prone NHEJ to repair double strand breaks. Non-BRCA deficiencies in

homologous recombination DNA repair genes could also enhance tumor cell sensitivity to PARP inhibitors. PARP inhibitors including niraparib is useful for treating individuals with tumors bearing mutations in DNA repair pathways, including those with germline BRCA mutations (gBRCAmut) who develop ovarian cancer.

In an attempt to address the high recurrence rates, anti-PARP therapy may be administered as a maintenance therapy in patients with recurrent and/or platinum sensitive ovarian cancer, including fallopian and peritoneal cancers, as an approach to prolong the initially high response rates associated with frontline platinum chemotherapy, wherein said administration prolongs progression-free survival and/or prolongs overall survival. Such a prolongation of progression free survival may result in a reduced hazard ratio for disease progression or death. Prolonged progression free survival has the potential to provide clinical benefit in several ways, including delay of disease symptoms, delay in toxicity burden of chemotherapy, and delay in quality of life deterioration. In another embodiment, the patients with platinum sensitive ovarian cancer are further characterized as having a BRCA deficiency and/or HRD (e.g., a positive HRD status). In another embodiment, the patients with recurrent and/or platinum sensitive ovarian cancer are further characterized by the absence of a germline BRCA mutation that is deleterious or suspected to be deleterious. In another embodiment, the patients with recurrent and/or platinum sensitive ovarian cancer are further characterized by the absence of a BRCA mutation either germline or sporadic.

The present invention is based in part on the discovery that PARP inhibitors can be used to treat cancers characterized by wild type or mutant BRCA1 and/or BRCA2 ("BRCA genes"), e.g. in the absence or presence of a mutation in the BRCA genes. Accordingly, aspects of the invention relate to methods for treating cancer patients involving administration of an anti-PARP therapy to a patient independent of BRCA status or independent of the DNA repair status of the patient or cancer. In other aspects, the invention relates to methods for treating cancer patients involving administration of an anti-PARP therapy to a patient, wherein the therapy is commenced prior to determining the BRCA status or HRD status of the patient or the cancer. In other aspects, the invention relates to methods for treating cancer patients involving administration of an anti-PARP therapy to a patient, wherein the therapy is commenced in the absence of determining the BRCA status or DNA repair status of the patient or cancer. In other aspects, the invention relates to methods for treating cancer patients involving administration of an anti-PARP therapy to a patient characterized by an absence of a mutation in BRCA1 and/or BRCA2. In other aspects, the invention relates to methods for treating cancer patients involving administration of an anti-PARP therapy to a patient characterized by an absence of a mutation in a gene involved in DNA repair. In other aspects, the invention relates to methods for treating cancer patients involving administration of an anti-PARP therapy to a patient characterized by an absence of a mutation in a gene involved in homologous recombination. In aspects, the invention relates to methods for treating cancer patients involving administration of an anti-PARP therapy to a patient having a cancer characterized by an absence of a mutation in BRCA1 or BRCA2. In aspects, the invention relates to methods for treating cancer patients involving administration of an anti-PARP therapy to a patient having a cancer characterized by an absence of a mutation in a gene involved in homologous recombination.

In embodiments, the anti-PARP therapy is administered at a dose equivalent to about 100 mg, about 200 mg, or about 300 mg of niraparib or a salt or derivative thereof. In certain embodiments, the anti-PARP therapy is administered at a dose equivalent to about 100 mg of niraparib or a salt or derivative thereof. In certain embodiments, the anti-PARP therapy is administered at a dose equivalent to about 200 mg of niraparib or a salt or derivative thereof. In certain embodiments, the anti-PARP therapy is administered at a dose equivalent to about 300 mg of niraparib or a salt or derivative thereof.

In some embodiments, the anti-PARP therapy is administered in a regimen determined to achieve i) prolonged progression free survival as compared to control, ii) a reduced hazard ratio for disease progression or death as compared to control, iii) prolonged overall survival as compared to control, or iv) an overall response rate of at least 30%.

In embodiments, the anti-PARP therapy comprises administration of an agent that inhibits PARP-1 and/or PARP-2. In some embodiments, the agent is a small molecule, a nucleic acid, a polypeptide (e.g., an antibody), a carbohydrate, a lipid, a metal, or a toxin. In related embodiments, the agent is ABT-767, AZD 2461, BGB-290, BGP 15, CEP 9722, E7016, E7449, fluzoparib, INO1001, JPI 289, MP 124, niraparib, olaparib, ON02231, rucaparib, SC 101914, talazoparib, veliparib, WW 46, or salts or derivatives thereof. In some related embodiments, the agent is niraparib, olaparib, rucaparib, talazoparib, veliparib, or salts or derivatives thereof. In certain embodiments, the agent is niraparib or a salt or derivative thereof. In certain embodiments, the agent is olaparib or a salt or derivative thereof. In certain embodiments, the agent is rucaparib or a salt or derivative thereof. In certain embodiments, the agent is talazoparib or a salt or derivative thereof. In certain embodiments, the agent is veliparib or a salt or derivative thereof.

In some embodiments, the methods prolong progression free survival as compared to control. In some embodiments, the methods reduce the hazard ratio for disease progression or death as compared to control. In some embodiments, the methods prolong overall survival as compared to control. In some embodiments, the methods achieve an overall response rate of at least 30%. In some embodiments, the methods achieve improved progression free survival 2 as compared to control. In some embodiments, the methods achieve improved chemotherapy free interval as compared to control. In some embodiments, the methods achieve improved time to first subsequent therapy as compared to control. In some embodiments, the methods achieve improved time to second subsequent therapy as compared to control. In some embodiments, the methods have been determined to not have a detrimental effect on Quality of Life as determined by FOSI and/or EQ-5D-5L. In some embodiments, the methods have been determined to not impact the effectiveness of a subsequent treatment with a chemotherapeutic agent (e.g., a platinum agent, including but not limited to, cisplatin, carboplatin, oxaliplatin, nedaplatin, triplatin tetranitrate, phenanthriplatin, picoplatin, or satraplatin).

In some embodiments, such cancers are selected from gynecologic cancers (i.e., cancers of the female reproductive system). In some embodiments, cancers of the female reproductive system include, but are not limited to, ovarian cancer, cancer of the fallopian tube(s), peritoneal cancer and breast cancer. In some embodiments, a gynecologic cancer is associated with homologous recombination repair deficiency/homologous repair deficiency ("HRD") and/or

31

BRCA1/2 mutation(s). In some embodiments, a gynecologic cancer is platinum-sensitive. In some embodiments, a gynecologic cancer has responded to a platinum-based therapy. In some embodiments, a gynecologic cancer has developed resistance to a platinum-based therapy. In some embodiments, a gynecologic cancer has at one time shown a partial or complete response to platinum-based therapy. In some embodiments, a gynecologic cancer is now resistant to platinum-based therapy.

In certain embodiments, the cancer is ovarian cancer, cancer of the fallopian tube(s), or peritoneal cancer. In certain embodiments, the cancer is breast cancer.

In some embodiments, the cancer is a recurrent cancer.

In one embodiment, niraparib is administered as a maintenance therapy in patients with recurrent ovarian cancer (including fallopian and peritoneal cancers), wherein said administration of niraparib results in prolongation of progression free survival. In one embodiment, niraparib is administered as a monotherapy for the maintenance treatment of patients with recurrent ovarian, fallopian tube, or primary peritoneal cancer, wherein the patient is in response to platinum-based chemotherapy. In one embodiment, niraparib is administered as a monotherapy for the maintenance treatment of patients with deleterious or suspected deleterious germline or somatic BRCA mutated or homologous recombination deficient recurrent ovarian, fallopian tube, or primary peritoneal cancer, wherein the patient is in response to platinum-based chemotherapy.

Such a prolongation of progression free survival may result in a reduced hazard ratio for disease progression or death. Maintenance therapy is administered during the interval between cessation of initial therapy with the goal of delaying disease progression and the subsequent intensive therapies that may present tolerability issues for patients. In another embodiment, the patients with recurrent ovarian cancer are further characterized as having a BRCA deficiency or HRD. In another embodiment, the patients with recurrent ovarian cancer are further characterized by the absence of a germline BRCA mutation that is deleterious or suspected to be deleterious.

In one embodiment, niraparib is administered as a maintenance therapy in patients with recurrent ovarian cancer (including fallopian and peritoneal cancers) who have a complete response or partial response following multiple platinum-based chemotherapy treatment, wherein said administration of niraparib results in prolongation of progression free survival. Such a prolongation of progression free survival may result in a reduced hazard ratio for disease progression or death. Maintenance therapy is administered during the interval between cessation of chemotherapy with the goal of delaying disease progression and the subsequent intensive therapies that may present tolerability issues for patients. In another embodiment, the patients with recurrent ovarian cancer are further characterized as having a BRCA deficiency or HRD. In another embodiment, the patients with recurrent ovarian cancer are further characterized by the absence of a germline BRCA mutation that is deleterious or suspected to be deleterious.

In another embodiment, a second approach to address the high recurrence rate of ovarian cancers is to select patients with advanced ovarian cancer who will most benefit from specific targeted agents in the frontline therapy or maintenance setting. Accordingly, niraparib is administered as a therapy in patients with advanced ovarian cancer, wherein said administration results in an increase in overall survival and wherein administration is either as a treatment (in the case of continued disease following 1-4 prior lines of

32

therapy) or a maintenance treatment (in the case of a patient with a PR or CR to a prior therapy). In another embodiment, the patients with advanced ovarian cancer are further characterized as having a BRCA deficiency or HRD. In another embodiment, the patients with recurrent ovarian cancer are further characterized by the absence of a germline BRCA mutation that is deleterious or suspected to be deleterious.

In some embodiments, the present invention provides a method of administering niraparib to a patient having recurrent or platinum sensitive ovarian cancer, fallopian tube cancer, or primary peritoneal cancer comprising administering niraparib according to a regimen determined to achieve prolonged progression free survival. In some embodiments, the progression free survival is greater in patients receiving niraparib, for example as compared with patients not receiving niraparib. In some embodiments, progression free survival is greater in patients receiving niraparib than in patients receiving alternative cancer therapy, for example such as therapy with a different PARP inhibitor.

In some embodiments, the prolonged progression free survival is at least 9 months. In some embodiments, the progression free survival is at least 12 months. In some embodiments, the progression free survival is at least 15 months. In some embodiments, the progression free survival is at least 18 months. In some embodiments, the progression free survival is at least 21 months. In some embodiments, the progression free survival is at least 24 months. In some embodiments, the progression free survival is at least 27 months. In some embodiments, the progression free survival is at least 30 months. In some embodiments, the progression free survival is at least 33 months. In some embodiments, the progression free survival is at least 36 months.

In some embodiments, the patient has a germline mutation in BRCA1 and/or BRCA2 (*gBRCA^{mut}*). In some embodiments, the prolonged progression free survival is at least 9 months. In some embodiments, the prolonged progression free survival is at least 12 months. In some embodiments, the prolonged progression free survival is at least 15 months. In some embodiments, the prolonged progression free survival is at least 18 months. In some embodiments, the prolonged progression free survival is at least 21 months. In some embodiments, the prolonged progression free survival is at least 24 months. In some embodiments, the prolonged progression free survival is at least 27 months. In some embodiments, the prolonged progression free survival is at least 30 months. In some embodiments, the prolonged progression free survival is at least 33 months. In some embodiments, the prolonged progression free survival is at least 36 months.

In some embodiments, the patient is characterized by an absence of a germline mutation in BRCA1 and/or BRCA2 (*non-gBRCA^{mut}*). In some embodiments, the patient has a tumor with a positive homologous recombination deficiency status. In some embodiments, the patient has a negative recombination deficiency status. In some embodiments, the prolonged progression free survival is at least 9 months. In some embodiments, the prolonged progression free survival is at least 12 months. In some embodiments, the prolonged progression free survival is at least 15 months. In some embodiments, the prolonged progression free survival is at least 18 months. In some embodiments, the prolonged progression free survival is at least 21 months. In some embodiments, the prolonged progression free survival is at least 24 months. In some embodiments, the prolonged progression free survival is at least 27 months. In some embodiments, the prolonged progression free survival is at least 30 months. In some embodiments, the prolonged

progression free survival is at least 33 months. In some embodiments, the prolonged progression free survival is at least 36 months.

In some embodiments, the patient is characterized by an absence of a mutation in BRCA1 and/or BRCA2 (BRCA^{WT}). In some embodiments, the patient has a tumor with a positive homologous recombination deficiency status. In some embodiments, the patient has a negative homologous recombination deficiency status. In some embodiments, the prolonged progression free survival is at least 9 months. In some embodiments, the prolonged progression free survival is at least 12 months. In some embodiments, the prolonged progression free survival is at least 15 months. In some embodiments, the prolonged progression free survival is at least 18 months. In some embodiments, the prolonged progression free survival is at least 21 months. In some embodiments, the prolonged progression free survival is at least 24 months. In some embodiments, the prolonged progression free survival is at least 27 months. In some embodiments, the prolonged progression free survival is at least 30 months. In some embodiments, the prolonged progression free survival is at least 33 months. In some embodiments, the prolonged progression free survival is at least 36 months.

In some embodiments, the present invention provides a method of administering niraparib to a patient having recurrent or platinum sensitive ovarian cancer, fallopian tube cancer, or primary peritoneal cancer comprising administering niraparib according to a regimen determined to achieve a hazard ratio for disease progression or death. In some embodiments, the hazard ratio is improved in patients receiving niraparib, for example as compared with patients not receiving niraparib. In some embodiments, the hazard ratio is improved in patients receiving niraparib than in patients receiving alternative cancer therapy, for example such as therapy with a different PARP inhibitor.

In some embodiments, the hazard ratio for disease progression is about 0.3. In some embodiments, the hazard ratio for disease progression is about 0.4. In some embodiments, the hazard ratio for disease progression is about 0.45. In some embodiments, the hazard ratio for disease progression is about 0.5. In some embodiments, the hazard ratio for disease progression is less than about 0.5. In some embodiments, the hazard ratio for disease progression is less than about 0.45. In some embodiments, the hazard ratio for disease progression is less than about 0.4. In some embodiments, the hazard ratio for disease progression is less than about 0.35. In some embodiments, the hazard ratio for disease progression is less than about 0.3.

In some embodiments, the patient has a germline mutation in BRCA1 and/or BRCA2 (gBRCA^{mut}). In some embodiments, the hazard ratio for disease progression is about 0.3. In some embodiments, the hazard ratio for disease progression is about 0.4. In some embodiments, the hazard ratio for disease progression is about 0.45. In some embodiments, the hazard ratio for disease progression is about 0.5. In some embodiments, the hazard ratio for disease progression is less than about 0.5. In some embodiments, the hazard ratio for disease progression is less than about 0.45. In some embodiments, the hazard ratio for disease progression is less than about 0.4. In some embodiments, the hazard ratio for disease progression is less than about 0.35. In some embodiments, the hazard ratio for disease progression is less than about 0.3.

In some embodiments, the patient is characterized by an absence of a germline mutation in BRCA1 and/or BRCA2 (non-gBRCA^{mut}). In some embodiments, the patient has a

tumor with a positive homologous recombination deficiency status. In some embodiments, the patient has a negative recombination deficiency status. In some embodiments, the hazard ratio for disease progression is about 0.3. In some embodiments, the hazard ratio for disease progression is about 0.4. In some embodiments, the hazard ratio for disease progression is about 0.45. In some embodiments, the hazard ratio for disease progression is about 0.5. In some embodiments, the hazard ratio for disease progression is less than about 0.5. In some embodiments, the hazard ratio for disease progression is less than about 0.45. In some embodiments, the hazard ratio for disease progression is less than about 0.4. In some embodiments, the hazard ratio for disease progression is less than about 0.35. In some embodiments, the hazard ratio for disease progression is less than about 0.3.

In some embodiments, the present invention provides a method of administering niraparib to a patient having recurrent and/or platinum sensitive ovarian cancer, fallopian tube cancer, or primary peritoneal cancer comprising administering niraparib according to a regimen determined to achieve prolonged overall survival. In some embodiments, the prolonged overall survival is greater in patients receiving niraparib, for example as compared with patients not receiving niraparib. In some embodiments, prolonged overall survival is greater in patients receiving niraparib than in patients receiving alternative cancer therapy, for example such as therapy with a different PARP inhibitor.

In some embodiments, the patient has at least (i) a germline mutation in BRCA1 or BRCA2 or (ii) a sporadic mutation in BRCA1 or BRCA2.

In some embodiments, the patient has high grade serous ovarian cancer or high grade predominantly serous histology ovarian cancer.

In some embodiments, the patient is further characterized by an absence of a germline mutation in BRCA1 or BRCA2.

In some embodiments, the patient is further characterized by an absence of a sporadic mutation in BRCA1 or BRCA2.

In some embodiments, the patient is further characterized by a negative BRCA1/2 status. In some embodiments, a germline mutation in BRCA1 or BRCA2 is not detected in a sample from a patient.

In some embodiments, progression for the purposes of determining progression free survival is determined by 1) tumor assessment by CT/MRI showing unequivocal progressive disease according to RECIST 1.1 criteria; and/or 2) additional diagnostic tests (e.g. histology/cytology, ultrasound techniques, endoscopy, positron emission tomography) identifying new lesions.

In some embodiments, the patient is characterized by having homologous recombination deficiency. In some embodiments, the patient has a positive homologous recombination deficiency status. Homologous recombination deficiency status may be established according to methods known by those in the art. For example, in some embodiments, recombinant deficiency status is established by determining in a patient sample the number of Indicator CA Regions. In some embodiments, the number of Indicator CA Regions comprises at least two types chosen from Indicator LOH Regions, Indicator TAI Regions, or Indicator LST Regions in at least two pairs of human chromosomes of a cancer cell. In some embodiments a CA Region (whether an LOH Region, TAI region, or LST Region) is an Indicator CA Region (whether an Indicator LOH Region, Indicator TAI region, or Indicator LST Region) if it is at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, or 100 megabases or more in length.

In some embodiments, Indicator LOH Regions are LOH Regions that are longer than about 1.5, 5, 12, 13, 14, 15, 16, 17 or more (preferably 14, 15, 16 or more, more preferably 15 or more) megabases but shorter than the entire length of the respective chromosome within which the LOH Region is located. Alternatively or additionally, the total combined length of such Indicator LOH Regions may be determined. In some embodiments, Indicator TAI Regions are TAI Regions with allelic imbalance that (a) extend to one of the subtelomeres, (b) do not cross the centromere and (c) are longer than 1.5, 5, 12, 13, 14, 15, 16, 17 or more (preferably 10, 11, 12 or more, more preferably 11 or more) megabases. Alternatively or additionally, the total combined length of such Indicator TAI Regions may be determined. Because the concept of LST already involves regions of some minimum size (such minimum size being determined based on its ability to differentiate HRD from HDR intact samples), Indicator LST Regions as used herein are the same as LST Regions. Furthermore, an LST Region Score can be either derived from the number of regions showing LST as described above or the number of LST breakpoints. In some embodiments the minimum length of the region of stable copy number bounding the LST breakpoint is at least 3, 4, 5, 6, 7, 8, 9, 10, 11 12, 13, 14, 15, 16, 17, 18, 19 or 20 megabases (preferably 8, 9, 10, 11 or more megabases, more preferably 10 megabases) and the maximum region remaining unfiltered is less than 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.5, 2, 2.5, 3, 3.5, 4 or fewer megabases (preferably 2, 2.5, 3, 3.5, or 4 or fewer megabases, more preferably fewer than 3 megabases). As used herein, a patient is determined to have a positive HRD status when a sample from said patient has a number of Indicator CA Regions or a CA Region Score (as defined herein) that exceeds that of a reference or threshold value.

In some embodiments, the present invention provides a method of administering niraparib, the method comprising steps of:

administering niraparib to a population of subjects having
one or more of the following characteristics:
a BRCA mutation;
a positive homologous recombination deficiency status;
or
exhibited response to prior therapy;
according to a regimen determined to achieve prolonged
progression free survival.

In some embodiments, the population of subjects has a BRCA mutation. In some embodiments, the BRCA mutation is a germline BRCA mutation ($gBRCA^{mut}$). In some embodiments, the BRCA mutation is a somatic (or sporadic) BRCA mutation ($sBRCA^{mut}$). In some embodiments, the population of subjects has a positive homologous recombination deficiency status. In some embodiments, the population of subjects exhibits non-mutated BRCA1/2 " $BRCA^{wt}$ " or " $BRCA^{wt}$ ".

Measuring Tumor Response

Tumor response can be measured by, for example, the RECIST v 1.1 guidelines. The guidelines are provided by E. A. Eisenhauer, et al., "New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1)," *Eur. J. of Cancer*, 45: 228-247 (2009), which is incorporated by reference in its entirety. The guidelines require, first, estimation of the overall tumor burden at baseline, which is used as a comparator for subsequent measurements. Tumors can be measured via use of any imaging system known in the art, for example, by a CT scan, or an X-ray. Measurable disease is defined by the presence of at least one measurable lesion. In studies where the primary endpoint is tumor

progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of P15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis.

For example, an abdominal node which is reported as being 20 mm-30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis P10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression.' In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

General Protocol

As described herein, provided methods comprise administering niraparib to a patient, a subject, or a population of subjects according to a regimen that achieves any one of or combination of: prolonged progression free survival; reduced hazard ratio for disease progression or death; and/or prolonged overall survival or a positive overall response rate. In some embodiments, niraparib is administered simultaneously or sequentially with an additional therapeutic agent, such as, for example, a chemotherapeutic agent (e.g.,

a platinum-based agent). In some embodiments, niraparib is administered before, during, or after administration of a chemotherapeutic agent.

Administration of niraparib simultaneously or sequentially with an additional therapeutic agent (e.g., a chemotherapeutic agent) is referred to as “combination therapy.” In combination therapy, niraparib can be administered prior to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concurrently with, or subsequent to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of the chemotherapeutic agent to a subject in need thereof. In some embodiments niraparib and the chemotherapeutic agent are administered 1 minute apart, 10 minutes apart, 30 minutes apart, less than 1 hour apart, 1 hour to 2 hours apart, 2 hours to 3 hours apart, 3 hours to 4 hours apart, 4 hours to 5 hours apart, 5 hours to 6 hours apart, 6 hours to 7 hours apart, 7 hours to 8 hours apart, 8 hours to 9 hours apart, 9 hours to 10 hours apart, 10 hours to 11 hours apart, 11 hours to 12 hours apart, no more than 24 hours apart, or no more than 48 hours apart.

In some embodiments, niraparib is administered to a patient or population of subjects who has exhibited response to prior therapy. In some embodiments, the patient or population of subjects has exhibited response to prior therapy with a chemotherapeutic agent. In some such embodiments, the chemotherapeutic agent is a platinum agent.

In some embodiments, niraparib is administered as a maintenance therapy following complete or partial response to at least one platinum based therapy. In some embodiments, the at least one platinum-based therapy comprises administering to a patient in need thereof a platinum-based agent selected from cisplatin, carboplatin, oxaliplatin, nedaplatin, triplatin tetranitrate, phenanthriplatin, picoplatin, or satraplatin. In some embodiments, response to the most recent platinum-based chemotherapy regimen is a complete response. In some embodiments, response to the most recent platinum-based chemotherapy regimen is a partial response.

In some embodiments, the regimen comprises at least one oral dose of niraparib. In some embodiments, the regimen comprises a plurality of oral doses. In some embodiments, the regimen comprises once daily (QD) dosing.

In some embodiments, the regimen comprises at least one 28 day cycle. In some embodiments, the regimen comprises a plurality of 28 day cycles. In some embodiments, the regimen comprises one 28 day cycle. In some embodiments, the regimen comprises two 28 day cycles. In some embodiments, the regimen comprises three 28 day cycles. In some embodiments, the regimen comprises continuous 28 day cycles. In some embodiments, the regimen comprises administration of an effective dose of niraparib daily until disease progression or unacceptable toxicity occurs. In some embodiments, the regimen comprises a daily dose of at least 100, 200 or 300 mg niraparib per day dosed until disease progression or unacceptable toxicity occurs.

In some embodiments, the oral dose is an amount of niraparib within a range of about 5 to about 400 mg. In some embodiments, the amount of niraparib is about 5, about 10, about 25, about 50, about 100, about 150, about 200, about 250, about 300, about 350, or about 400 mg. In some embodiments, the amount of niraparib is about 300 mg of

niraparib. In some embodiments, the regimen comprises administration of 300 mg of niraparib once daily.

In some embodiments, the oral dose is administered in one or more unit dosage forms. In some embodiments, the one or more unit dosage forms are capsules. In some embodiments, each unit dosage form comprises about 5, about 10, about 25, about 50, or about 100 mg of niraparib. It is understood that any combination of unit dosage forms can be combined to form a once daily (QD) dose. For example, three 100 mg unit dosage forms can be taken once daily such that 300 mg or niraparib is administered once daily. In some embodiments, niraparib is administered as a single 300 mg unit dosage form. In some embodiments, niraparib is administered 300 mg QD. In some embodiments, niraparib is administered as 3×100 mg QD (i.e., niraparib is administered as three unit dosage forms of 100 mg). In some embodiments, niraparib is administered as 2×150 mg QD (i.e., niraparib is administered as two unit dosage forms of 150 mg)

20 Pharmacokinetics

Pharmacokinetic data can be obtained by known techniques in the art. Due to the inherent variation in pharmacokinetic and pharmacodynamic parameters of drug metabolism in human subjects, appropriate pharmacokinetic and pharmacodynamic profile components describing a particular composition can vary. Typically, pharmacokinetic and pharmacodynamic profiles are based on the determination of the mean parameters of a group of subjects. The group of subjects includes any reasonable number of subjects suitable for determining a representative mean, for example, 5 subjects, 10 subjects, 16 subjects, 20 subjects, 25 subjects, 30 subjects, 35 subjects, or more. The mean is determined by calculating the average of all subject's measurements for each parameter measured.

In some embodiments, the pharmacokinetic parameter(s) can be any parameters suitable for describing the present composition. For example, in some embodiments, the C_{max} is not less than about 500 ng/ml; not less than about 550 ng/ml; not less than about 600 ng/ml; not less than about 700 ng/ml; not less than about 800 ng/ml; not less than about 880 ng/ml, not less than about 900 ng/ml; not less than about 100 ng/ml; not less than about 1250 ng/ml; not less than about 1500 ng/ml, not less than about 1700 ng/ml, or any other C_{max} appropriate for describing a pharmacokinetic profile of niraparib.

In some embodiments wherein the active metabolite is formed in vivo after administration of a drug to a subject, the C_{max} is not less than about 500 pg/ml; not less than about 550 pg/ml; not less than about 600 pg/ml; not less than about 700 pg/ml; not less than about 800 pg/ml; not less than about 880 pg/ml, not less than about 900 pg/ml; not less than about 1000 pg/ml; not less than about 1250 pg/ml; not less than about 1500 pg/ml, not less than about 1700 pg/ml, or any other C_{max} appropriate for describing a pharmacokinetic profile of a compound formed in vivo after administration of niraparib to a subject.

In some embodiments, the T_{max} is, for example, not greater than about 0.5 hours, not greater than about 1.0 hours, not greater than about 1.5 hours, not greater than about 2.0 hours, not greater than about 2.5 hours, or not greater than about 3.0 hours, or any other T_{max} appropriate for describing a pharmacokinetic profile of niraparib.

In general, AUC as described herein is the measure of the area under the curve that corresponds to the concentration of an analyte over a selected time period following administration of a dose of a therapeutic agent. In some embodiments, such time period begins at the dose administration

(i.e., 0 hours after dose administration) and extends for about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 14, about 16, about 18, about 20, about 22, about 24, about 30, about 40, or more hours after the dose administration. In some embodiments, AUC is that achieved from 0 hours to 12 hours following administration of a dose described herein. In some embodiments, AUC is that achieved from 0 hours to 18 hours following administration of a dose described herein. In some embodiments, AUC is that achieved from 0 hours to 24 hours following administration of a dose described herein. In some embodiments, AUC is that achieved from 0 hours to 36 hours following administration of a dose described herein.

The AUC_(0-inf) can be, for example, not less than about 590 ng·hr/mL, not less than about 1500 ng·hr/mL, not less than about 2000 ng·hr/mL, not less than about 3000 ng-times·hr/ml, not less than about 3500 ng·hr/mL, not less than about 4000 ng·hr/mL, not less than about 5000 ng·hr/mL, not less than about 6000 ng·hr/mL, not less than about 7000 ng·hr/mL, not less than about 8000 ng·hr/mL, not less than about 9000 ng·hr/mL, or any other AUC_{co-int}) appropriate for describing a pharmacokinetic profile of a therapeutic agent (e.g., niraparib). In some embodiments wherein an active metabolite is formed in vivo after administration of a therapeutic agent (e.g., niraparib) to a subject; the AUC_(0-inf) can be, for example, not less than about 590 pg·hr/mL, not less than about 1500 pg·hr/mL, not less than about 2000 pg·hr/mL, not less than about 3000 pg·hr/mL, not less than about 3500 pg·hr/mL, not less than about 4000 pg·hr/mL, not less than about 5000 pg·hr/mL, not less than about 6000 pg·hr/mL, not less than about 7000 pg·hr/mL, not less than about 8000 pg·hr/mL, not less than about 9000 pg·hr/mL, or any other AUC_(0-inf) appropriate for describing a pharmacokinetic profile of a compound formed in vivo after administration of niraparib to a subject.

The plasma concentration of niraparib about one hour after administration can be, for example, not less than about 140 ng/ml, not less than about 425 ng/ml, not less than about 550 ng/ml, not less than about 640 ng/ml, not less than about 720 ng/ml, not less than about 750 ng/ml, not less than about 800 ng/ml, not less than about 900 ng/ml, not less than about 1000 ng/ml, not less than about 1200 ng/ml, or any other plasma concentration of niraparib.

In some embodiments, a patient population includes one or more subjects ("a population of subjects") suffering from metastatic disease.

In some embodiments, a patient population includes one or more subjects that are suffering from or susceptible to cancer. In some such embodiments, the cancer is ovarian cancer, cancer of the fallopian tubes, peritoneal cancer or breast cancer. In some embodiments, a patient population includes one or more subjects (e.g., comprises or consists of subjects) suffering from cancer. For example, in some embodiments, a patient population suffering from cancer may have previously been treated with chemotherapy, such as, e.g., treatment with a chemotherapeutic agent such as a platinum-based agent.

In some embodiments, the present disclosure provides methodologies that surprisingly can achieve substantially the same PK profile for niraparib when administered to a patient in a fed state or in a fasted state. Niraparib can be administered to a patient in either a fed or fasted state. Specifically, it has been surprisingly discovered that the bioavailability of niraparib is substantially similar for patients being administered niraparib in either a fed or fasted state. In some embodiments, administration of niraparib to a

patient in a fed or fasted state produces substantially bioequivalent niraparib plasma C_{max} values. In some embodiments, administration to the patient in a fed or fasted state produces bioequivalent niraparib plasma T_{max} values. In some embodiments, administration to the patient in a fed or fasted state produces bioequivalent niraparib plasma AUC values. Accordingly, in some embodiments, niraparib is administered in either a fed or a fasted state. In some embodiments, niraparib is administered in a fasted state. In another embodiment, niraparib is administered in a fed state.

In some embodiments, a unit dose of niraparib can be administered to a patient in a fasted state. In some embodiments, a unit dose of niraparib can be administered to a patient in a fed state. In some embodiments, administration in one of the fed or fasted states is excluded. In some embodiments, the unit dose can be administered for therapeutic purposes in either the fed or the fasted state, with the subject having the option for each individual dose as to whether to take it with or without food. In some embodiments, the unit dose of niraparib can be administered immediately prior to food intake (e.g., within 30 or within 60 minutes before), with food, right after food intake (e.g., within 30, 60 or 120 minutes after food intake). In some embodiments, it can be administered, for example, at least 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, or more after food intake, or any time there between. In some embodiments, the unit dose of niraparib is administered after overnight fasting. In some embodiments, the unit dose of the composition can be administered 30 minutes before food intake, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours or more before food intake, or any time there between.

EXAMPLES

The following examples are provided to illustrate, but not limit the claimed invention.

Example 1. Treatment of Platinum Sensitive Ovarian Cancer

In NOVA, platinum-sensitive recurrent ovarian cancer patients who were in response following platinum-based treatment were prospectively randomized to receive either niraparib or placebo. Two cohorts were treated: the germline BRCA mutant positive cohort (gBRCA^{mut}) and the non-germline BRCA cohort (non-gBRCA^{mut}). Therefore, the gBRCA^{mut} cohort of NOVA was designed to prospectively test the treatment effect of niraparib versus placebo in patients with platinum-sensitive recurrent ovarian cancer who were in response after platinum-based treatment. Patients in this cohort were germline BRCA mutation carriers as assessed by the FDA-approved Integrated BRACAnalysis test. Patients in the non-gBRCA^{mut} were negative in the FDA-approved Integrated BRACAnalysis test.

The double-blind, 2:1 randomized, study evaluated niraparib as maintenance therapy in patients with recurrent and/or platinum sensitive ovarian cancer who had either gBRCA^{mut} or a tumor with high-grade serous histology. The study compared maintenance treatment with niraparib with to placebo and is evaluating the efficacy of niraparib as maintenance therapy in patients who have recurrent ovarian cancer as assessed by the prolongation of progression-free survival (PFS). This objective is independently evaluated in a cohort of patients with germline BRCA mutation (gBRCA^{mut}) and in a cohort of patients who have high grade

serous or high grade predominantly serous histology but without such gBRCA mutations (non-gBRCA^{mut}). Some patients in the non-gBRCA^{mut} cohort have been reported to share distinctive DNA repair defects with gBRCA^{mut} carriers, a phenomenon broadly described as “BRCA-ness.” (See Turner, N., A. Tutt, and A. Ashworth, Hallmarks of ‘BRCA-ness’ in sporadic cancers. *Nat. Rev. Cancer* 4(10), 814-9, (2004)). Recent studies have suggested that homologous recombination deficiency (HRD) in epithelial ovarian cancer (EOC) is not solely due to germline BRCA1 and BRCA2 mutations. (See Hennessy, B. T. et al. Somatic mutations in BRCA1 and BRCA2 could expand the number of patients that benefit from poly (ADP ribose) polymerase inhibitors in ovarian cancer. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology* 28, 3570-3576, (2010); TCGA “Integrated genomic analyses of ovarian carcinoma.” *Nature* 474(7353), 609-615, (2011); and Dann R B, DeLoia J A, Timms K M, Zorn K K, Potter J, Flake D D 2nd, Lanchbury J S, Krivak T C. BRCA 1/2 mutations and expression: Response to platinum chemotherapy in patients with advanced stage epithelial ovarian cancer. *Gynecol Oncol.* 125(3), 677-82, (2012)). Non-BRCA deficiencies in homologous recombination DNA repair genes could also enhance tumor cell sensitivity to PARP inhibitors. Accordingly, HRD is used as a tumor biomarker classifier to be evaluated.

Patients enrolled in this study had received at least two platinum-based regimens, had a response (complete or partial) to their last regimen, and had no measurable disease >2 cm and normal cancer antigen CA125 (or >90% decrease) following their last treatment. Patients were assigned to one of two independent cohorts—one with deleterious gBRCA mutations (gBRCA^{mut}) and the other with high-grade serous histology but without such gBRCA mutations (non-gBRCA^{mut}) according to the following criteria:

Mutation Status	Cohort for Randomization
Positive for a Deleterious Mutation	gBRCA ^{mut} cohort
Genetic Variant, Suspected Deleterious	gBRCA ^{mut} cohort
Genetic Variant, Favor Polymorphism	non-gBRCA ^{mut} cohort
Genetic Variant of Uncertain Significance	non-gBRCA ^{mut} cohort
No Mutation Detected	non-gBRCA ^{mut} cohort

Patients were also assessed for HRD status and were further classified as HRD positive (HRDpos) or HRD negative (HRDneg).

Study treatment was dispensed to patients on Day 1 and every cycle (28 days) thereafter until the patient discontinued study treatment. Study treatment was administered orally once daily continuously. Three capsules of 100 mg strength were taken at each dose administration. Clinic visits occurred in each cycle (every 4 weeks±3 days). Response evaluation criteria in solid tumors (RECIST) tumor assessment via computed tomography (CT) or magnetic resonance imaging (MRI) scan of abdomen/pelvis and clinically indicated areas was required at the end of every 2 cycles (8 weeks with a window of ±7 days from date of visit) through Cycle 14, then at the end of every 3 cycles (12 weeks with a window of ±7 days from date of visit) until progression.

Patients were assessed by the prolongation of progression-free survival (PFS). More specifically, progression was determined if at least one of the following criteria is met: 1) tumor assessment by CT/MRI unequivocally shows progressive disease according to RECIST 1.1 criteria; 2) additional diagnostic tests (e.g. histology/cytology, ultrasound techniques, endoscopy, positron emission tomography) identify

new lesions or determine existing lesions qualify for unequivocal progressive disease and CA-125 progression according to Gynecologic Cancer Intergroup (GCIG)-criteria (see Rustin et al., *Int J Gynecol Cancer* 2011; 21: 419-423); 3) definitive clinical signs and symptoms of PD unrelated to non-malignant or iatrogenic causes ([i] intractable cancer-related pain; [ii] malignant bowel obstruction/worsening dysfunction; or [iii] unequivocal symptomatic worsening of ascites or pleural effusion and CA-125 progression according to GCIG-criteria. Response Evaluation Criteria in Solid Tumors (RECIST) was used for tumor assessment via a computed tomography (CT) or magnetic resonance imaging (MRI) scan of abdomen/pelvis and clinically indicated areas, which was required at the end of every 2 cycles (8 weeks) through cycle 14 (56 weeks), and then at the end of every 3 cycles (12 weeks) until progression.

Patients continued to receive their assigned treatment until disease progression, unacceptable toxicity, death, withdrawal of consent, and/or lost to follow-up. Dose interruption and/or reduction were available at any time for any grade toxicity considered intolerable by the patient.

Results

Niraparib significantly prolonged PFS compared to control among patients who are germline BRCA mutation (gBRCA^{mut}) carriers irrespective of HRD status, among patients who are not germline BRCA mutation (non-gBRCA^{mut}) carriers but who have homologous recombination deficient (HRD) tumors, and overall in patients who are non-gBRCA^{mut}. The overall population in the non-gBRCA^{mut} cohort also included patients with tumors that were HRDneg. Analyses demonstrated that the HRDneg population also benefitted from niraparib treatment. The determination of gBRCA status and HRD status can include determinations made by a standardized laboratory test, such as the Myriad myChoice® HRD test and also including those tests approved by a relevant regulatory authority.

For all populations, median PFS was significantly longer for patients who received niraparib than for patients who received placebo. Both of the primary efficacy populations in the non-gBRCA^{mut} cohort (HRD positive and overall) demonstrated a significant treatment effect of niraparib compared to placebo (HR 0.38 versus HR 0.45, respectively; HR=hazard ratio). All populations exhibited a consistent and durable niraparib treatment effect as evidenced by the Kaplan Meyer curves (see FIGS. 1-4). Importantly, this same consistent durable benefit of niraparib treatment was observed in all exploratory subgroups tested within this cohort. In the non-gBRCA^{mut} cohort, the HRD positive group included patients with somatic tumor BRCA mutations (HRDpos/sBRCA^{mut}) and patients who were wildtype for BRCA (HRDpos/BRCA^{wt}). Importantly, the observed treatment benefit within the HRDpos group was not driven solely by the effect in the HRDpos/sBRCA^{mut} subgroup. The HRDpos/BRCA^{wt} subgroup also experienced a consistent, durable benefit from niraparib treatment relative to the HRDpos overall group; with a hazard ratio of 0.38 (FIG. 6).

Among patients who were germline BRCA mutation carriers (gBRCA^{mut}), the niraparib arm successfully achieved statistical significance over the control arm for the primary endpoint of PFS, with a hazard ratio of 0.27. The median PFS for patients treated with niraparib was 21.0 months, compared to 5.5 months for control ($p<0.0001$). FIG. 1 depicts the PFS curve for gBRCA^{mut} patients treated with niraparib and placebo. These results were markedly better than those from “Study 19” (N Engl J Med. 2012; 366(15):1382-1392), which was similar to NOVA in study design and assessed the activity of the PARP inhibitor

US 12,383,542 B2

43

olaparib versus placebo in a similar patient population. Study 19 reported a median PFS of 11.2 versus 4.3 months in the olaparib versus control arm for patients with BRCA mutations. For patients who were not germline BRCA mutation carriers (non-gBRCA^{mut}) but whose tumors were determined to be HRD positive using the Myriad myChoice® HRD test, the niraparib arm successfully achieved statistical significance over the control arm for the primary endpoint of PFS, with a hazard ratio of 0.38. The median PFS for patients with HRD-positive tumors who were treated with niraparib was 12.9 months, compared to 3.8 months for control ($p<0.0001$). FIG. 2 depicts the PFS curve for non-gBRCA^{mut}/HRD positive patients treated with niraparib and placebo.

Niraparib also showed statistical significance in the overall non-germline BRCA mutant cohort (non-gBRCA^{mut}), which included patients with both HRD-positive and HRD-negative tumors. The niraparib arm successfully achieved statistical significance over the control arm for the primary endpoint of PFS, with a hazard ratio of 0.45. The median PFS for patients treated with niraparib was 9.3 months, compared to 3.9 months for control ($p<0.0001$). FIG. 3 depicts the PFS curve for non-gBRCA^{mut} patients (including both HRD-positive and HRD-negative patients) treated with niraparib and placebo.

44

Niraparib also showed statistical significance in the non-germline BRCA mutant (non-gBRCA^{mut}) patients with HRD-negative tumors. The niraparib arm successfully achieved statistical significance over the control arm for the primary endpoint of PFS, with a hazard ratio of 0.58. The median PFS for patients treated with niraparib was 6.9 months, compared to 3.8 months for control ($p<0.0226$). The PFS for non-germline BRCA mutant (non-gBRCA^{mut}) patients with HRD-negative tumors is shown in FIG. 4.

In an exploratory pooled analysis looking at the combined study population (2 cohorts combined gBRCA^{mut} and non-gBRCA^{mut}), PFS was longer with niraparib than with placebo. The median PFS for all patients treated with niraparib was 11.3 months compared to 4.7 months for placebo treated patients, HR 0.38, 95% CI, 0.303, 0.488, $p<0.0001$) (FIG. 5). In addition, the treatment effect, as observed in the Kaplan Meier (KM) curves from the gBRCA^{mut} and non-gBRCA^{mut} cohort, the subgroups within the non-gBRCA^{mut} cohort and the combined cohort analysis, was substantial, durable, and consistent.

A summary of the Progression Free Survival of the different patient cohorts is provided in Tables 1 through 3, below. “NR” means “not reached.” “95% CI” means a 95% confidence interval. Exploratory analyses of biomarker-related subgroups in the non-gBRCA^{mut} cohort were performed; the subgroups analyzed were HRDpos/somatic BRCA^{mut}, HRDpos/BRCA^{wt}, and HRDneg.

TABLE 1

Progression Free Survival (Primary)					
gBRCA ^{mut} Cohort		HRD-positive, non-gBRCA		Overall non-gBRCA	
Niraparib N = 35	Placebo N = 12	Niraparib N = 71	Placebo N = 44	Niraparib N = 92	Placebo N = 42
PFS (Months):	21.0	5.5	12.9	3.8	9.3
Median (95% CI)	(12.9, NR)	(3.8, 7.2)	(8.1, 15.9)	(3.5, 5.7)	(7.2, 11.2)
p-value	<0.0001		<0.0001		<0.0001
Hazard Ratio, Niraparib: Placebo (95% CI)	0.27 (0.173, 0.410)		0.38 (0.243, 0.586)		0.45 (0.338, 0.607)

TABLE 2

Progression Free Survival, non-gBRCA					
Somatic BRCA ^{mut} , HRD positive		BRCA ^{wt} , HRD positive		HRD negative	
Niraparib N = 35	Placebo N = 12	Niraparib N = 71	Placebo N = 44	Niraparib N = 92	Placebo N = 42
PFS (Months):	20.9	11.0	9.3	3.7	6.9
Median (95% CI)	(9.7, NR)	(2.0, NR)	(5.8, 15.4)	(3.3, 5.6)	(5.6, 9.6)
p-value	0.0248		0.0001		0.0226
Hazard Ratio, Niraparib: Placebo (95% CI)	0.27 (0.081, 0.903)		0.38 (0.231, 0.628)		0.58 (0.361, 0.922)

TABLE 3

Treatment Effect of Niraparib versus Placebo in NOVA Patient Populations						
Treatment	(Months)	Median PFS ⁽¹⁾ (95% CI)	Hazard Ratio ⁽²⁾ (95% CI)	% of Patients without Progression or Death at: ⁽⁴⁾		
				6 Months	12 Months	18 Months
gBRCAmut Cohort						
Niraparib (N = 138)	21.0 (12.9, NE)	0.27 (0.173, 0.410)	80%	62%	50%	
Placebo (N = 65)	5.5 (3.8, 7.2)	p < 0.0001	43%	16%	16%	
HRDpos Group						
Niraparib (N = 106)	12.9 (8.1, 15.9)	0.38 (0.243, 0.586)	69%	51%	37%	
Placebo (N = 56)	3.8 (3.5, 5.7)	p < 0.0001	35%	13%	9%	
HRDneg Group						
Niraparib (N = 92)	6.9 (5.6, 9.6)	0.58 (0.361, 0.922)	54%	27%	19%	
Placebo (N = 42)	3.8 (3.7, 5.6)	p < 0.0226	31%	7%	7%	
Non-gBRCAmut Cohort						
Niraparib (N = 234)	9.3 (7.2, 11.2)	0.45 (0.338, 0.607)	61%	41%	30%	
Placebo (N = 116)	3.9 (3.7, 5.5)	p < 0.0001	36%	14%	12%	

CI = confidence interval;

PFS = progression-free survival;

NR = not reached;

sBRCAmut = somatic BRCA mutation;

BRCAwt = BRCA wild type;

HRD = homologous recombination deficiency

⁽¹⁾Progression-free survival is defined as the time in months from the date of randomization to progression or death.⁽²⁾Niraparib: Placebo, based on the stratified Cox Proportional Hazards Model using randomization stratification factors.⁽³⁾Based on stratified log-rank test using randomization stratification factors.⁽⁴⁾Estimates from product-limit method. Confidence intervals constructed using log-log transformation.

The most common (>10%) treatment-emergent grade 3/4 adverse events among all patients treated with niraparib were thrombocytopenia (28.3%), anemia (24.8%) and neutropenia (11.2%). Adverse events were managed via dose modifications among all patients. The rates of MDS/AML in the niraparib (1.3%) and control (1.2%) arms were similar in the ITT population. There were no deaths among patients during study treatment.

In this study, both of the primary efficacy populations in the non-gBRCA^{mut} cohort (HRDpos and overall) demonstrated a significant treatment effect of niraparib compared to placebo (HR 0.38 versus HR 0.45, respectively; (Table 3). Both populations exhibited a consistent and durable niraparib treatment effect as evidenced by the Kaplan-Meier curves. This same consistent durable benefit of niraparib treatment was observed in all exploratory subgroups tested within this cohort.

In the non-gBRCA^{mut} cohort, the HRDpos group included patients with somatic tumor BRCA mutations (HRDpos/sBRCA^{mut}) and patients who were wildtype for BRCA (HRDpos/BRCA^{wt}). The observed treatment benefit within the HRDpos group was not driven solely by the effect in the HRDpos/sBRCA^{mut} subgroup. The HRDpos/BRCA^{wt} subgroup also experienced a consistent, durable benefit from niraparib treatment relative to the HRDpos overall group; with a hazard ratio of 0.38 (FIG. 6).

Of note, the HR observed in the gBRCA^{mut} cohort (0.27) was identical to the HR observed in the HRDpos/sBRCA^{mut} subgroup demonstrating the consistency of the niraparib treatment effect across cohorts and in two independent patient populations with similar underlying tumor biology (FIG. 7).

All of the point estimates for the hazard ratios were <1, indicating a longer progression-free survival for patients who received niraparib, for the gBRCA^{mut} cohort (FIG.

12A), the HRD positive group of the non-gBRCA^{mut} cohort p (FIG. 12B), and the overall non-gBRCA^{mut} cohort (FIG. 12C).

Subgroup Analyses within the Non gBRCAmut Cohort

As detailed previously, the non-gBRCA^{mut} cohort comprises 3 groups of patients: HRDpos, HRDneg, and those whose tumor HRD status could not be determined (HRDnd). Further, the HRDpos group includes 2 additional subgroups, women with somatic BRCA mutated tumors (sBRCA^{mut}) and those who had HRDpos tumors due to non-BRCA related defects in the HR pathway (HRDpos/BRCA^{wt}).

Within the HRDpos group of the non gBRCA^{mut} cohort, 47 patients had sBRCAmut tumors and 115 had BRCA^{wt} tumors. Results for the PFS analysis on these 2 subgroups of patients are provided in FIG. 7 and FIG. 6.

Among patients with HRDpos/sBRCA^{mut}, median PFS was 20.9 months (95% CI: 9.7, NE) in the niraparib arm versus 11.0 months (95% CI: 2.0, NE) in the placebo arm (11.0 months). The HR was 0.27 (95% CI: 0.081, 0.903) (p=0.0248). (See FIG. 7) The HR of 0.27 in the sBRCA^{mut} subgroup confirms the 0.27 HR observed in the gBRCA^{mut} cohort.

In patients with HRDpos/BRCA^{wt} tumors, median PFS was 9.3 months (95% CI: 5.8, 15.4) in the niraparib arm versus 3.7 months (95% CI: 3.3, 5.6) in the placebo arm. The HR for was 0.38 (95% CI: 0.231, 0.628) (p=0.0001) showing a robust treatment effect for HRD patients even in the absence of sBRCA mutations. (See FIG. 6).

The overall population in the non-gBRCA^{mut} cohort also included patients with tumors that were HRDneg and exploratory analyses demonstrated that this population experienced a benefit from niraparib treatment (HR 0.58). The Kaplan-Meier curves (FIG. 4) show a consistent and durable effect of niraparib versus placebo, albeit of a lower magnitude. Impact and durability of the niraparib effect is important in assessing the benefit of PFS. For example,

probability of remaining progression-free at 12 months was 27% versus 7% in the niraparib versus placebo arms. At 18 months, more than twice as many niraparib versus placebo-treated patients estimated to be progression-free (19% versus 7%; Table 3). The benefit for these 20-25% of recurrent ovarian cancer patients is an important, surprising advance in the treatment of cancer.

Dose interruption and/or reduction could be implemented at any time for any grade toxicity considered intolerable by the patient. Treatment was required to be interrupted for any non-hematologic AE that was Grade 3 or 4, per NCI CTCAE v.4.02 if the Investigator considered the event to be related to administration of study drug. If toxicity was appropriately resolved to baseline or Grade 1 or less within 28 days, the patient was allowed to restart treatment with study drug, but with a dose level reduction according to Table 4, if prophylaxis was not considered feasible. If the event recurred at a similar or worse grade, the patient's treatment was again to be interrupted; upon event resolution, a further dose reduction was required; no more than 2 dose reductions were permitted for any patient.

TABLE 4

Dose Reductions for Non-Hematologic Toxicities	
Event ⁽¹⁾	Dose ⁽²⁾
Initial dose	300 mg QD
First dose reduction for NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE where prophylaxis is not considered feasible	200 mg QD
Second dose reduction for NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE where prophylaxis is not considered feasible	100 mg QD
Continued NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE ≥ 28 days	Discontinue study drug

Abbreviations:

AE = adverse event;

NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events;

QD = once daily;

SAE = serious adverse event

⁽¹⁾Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the patient.⁽²⁾Dose not to be decreased below 100 mg QD

If the toxicity requiring dose interruption did not resolve completely or to NCI CTCAE Grade 1 or less during the maximum 28-day dose interruption period, and/or the patient had already undergone a maximum of 2 dose reductions (to a minimum dose of 100 mg QD), the patient was required to permanently discontinue treatment with study drug.

There were no on-treatment deaths reported during the study. Most patients in both treatment arms experienced at least 1 TEAE, including all patients who received niraparib and 96% patients who received placebo. The high rate of TEAEs in the placebo arm indicates the lingering effects of prior chemotherapy and the patient's underlying ovarian cancer.

Overall, the incidence of treatment-related TEAEs was 98% in the niraparib arm and 71% in the placebo arm; the high rate of treatment-related TEAEs in patients receiving placebo shows the challenges of attributing events as related to study treatment and confirms the importance of including a placebo arm in the evaluation of safety in this population.

In niraparib versus placebo treated patients, the incidence of TEAEs was as follows: CTCAE Grade ≥3 TEAEs, 74% versus 23%; SAEs, 30% versus 15%; TEAEs leading to treatment interruption, 69% versus 5%; TEAEs leading to dose reduction, 67% versus 15%; and TEAEs leading to

treatment discontinuation, 15% versus 2%. The most frequently reported TEAEs in the niraparib group were consistent with the known safety profile of niraparib and other PARP inhibitors. Most of the common TEAEs were reported at a higher incidence in the niraparib group than in the placebo group, with the exception of disease-related symptoms, including abdominal pain and distension, and other pain-related symptoms, including back pain, arthralgia, and myalgia.

Although Grade 3 or 4 TEAEs were frequent, dose modification was effective in reducing the frequency of these events during the treatment period. The incidence of thrombocytopenia over time exemplifies the effectiveness of the dose modifications. FIG. 8 shows the mean platelet count over time for the overall niraparib treated population. As platelet counts were collected weekly during the first cycle, the first four time points include C1D1, C1D8, C1D15, and C1D21. The subsequent time points were Day 1 of all remaining cycles. The mean platelet count decreased substantially by day 15; however, platelet counts continued to increase after this time point and generally returned to near baseline by Cycle 4.

Importantly, efficacy was not compromised in patients who were adjusted to a lower dose level. In order to assess the possible impact of dose reduction on the efficacy of niraparib, analyses of PFS were conducted based on each patient's last prescribed dose and on the dose that they received for the longest duration. Note that for these analyses, only patients who received at least 1 dose of niraparib were included. Results of the KM analyses by niraparib dose based on longest duration are provided in FIG. 9.

The most common dose of longest duration was 200 mg in both the gBRCA^{mut} (74 of 136, 54%) and non-gBRCA^{mut} (107 of 231, 46%) cohorts; 300 mg was the dose of longest duration in 25 (18%) and 73 (32%) patients in the gBRCA^{mut} and non-gBRCA^{mut} cohorts, respectively, and 100 mg was the dose of longest duration in 37 (27%) and 51 (22%) patients, respectively.

FIG. 9 and FIG. 10 present KM plots for PFS by niraparib dose of longest duration for the gBRCA^{mut} and non gBRCA^{mut} cohorts, respectively; as shown, PFS at all 3 doses was consistent with the overall population indicating that patients who required dose reduction do not have decreased efficacy relative to those who remain at the 300 mg starting dose.

Secondary Efficacy Analyses of Niraparib

Secondary efficacy endpoints include time to first subsequent treatment (TFST), time to second subsequent treatment (TSST), progression-free survival 2 (PFS2), chemotherapy-free interval (CFI), and overall survival (OS). Niraparib had greater efficacy than placebo across a majority of secondary efficacy end points that were evaluated (FIG. 11). Secondary endpoints such as PFS2, OS and CFI were analyzed using a stratified log-rank test. Stratified Cox proportional hazard models were used to estimate the treatment HR and its 95% CI. Maintenance treatment with niraparib significantly improved and chemotherapy-free interval and time to first subsequent treatment for patients in both cohorts; patients who received placebo required initiation with a subsequent treatment sooner than patients who were treated with niraparib, regardless of their biomarker status (FIGS. 11, 13 and 14). Progression-free survival 2 was significantly longer for patients who received niraparib for both cohorts. For patients in the gBRCA^{mut} cohort, the progression-free survival 2 was 25.8 months in the niraparib group compared to 19.5 months in the placebo group (hazard ratio, 0.48; 95% CI, 0.280 to 0.821; P=0.0062). In the

overall non-gBRCA^{mut} cohort, the median PFS 2 was 18.64 months for niraparib compared to 15 months for placebo; hazard ratio, 0.649; 95% CI 0.494, 0.964; P=0.0293). The time to second subsequent therapy was also a secondary endpoint, however at the time of data cutoff too few patients had received a second treatment to perform this analysis (34/138 niraparib and 26/65 placebo in the gBRCA^{mut} cohort, and 90/234 niraparib and 53/116 placebo in the non-gBRCA^{mut} cohort).

A pooled analysis looking at the combined study population (2 cohorts combined gBRCA^{mut} and non-gBRCA^{mut}) for efficacy of next-line treatment. PFS2-PFS1 was similar in niraparib and placebo treated patients. (See FIG. 15).

A summary of the Secondary Efficacy Analysis of the gBRCA^{mut}, non-gBRCA^{mut} and combined patient cohorts is provided in Table 5, below. "HR" indicates Hazard Ratio and "95% CI" means a 95% confidence interval.

TABLE 5

Secondary Efficacy Analysis - PFS2, Time to Subsequent Treatment and Overall Survival in gBRCA ^{mut} , non-gBRCA ^{mut} and combined patient cohorts.	
PFS2 (data are immature, <50% of events)	
gBRCAmut:	HR 0.48 (95% CI: 0.280, 0.821)
Non-gBRCAmut:	HR 0.69 (95% CI: 0.494, 0.964)
Time to second subsequent treatment (data are immature, <40% of events)	
gBRCA mut:	HR 0.48 (95% CI: 0.272, 0.851)
Non-gBRCAmut:	HR 0.74 (95% CI: 0.519, 1.066)
Overall Survival (data are immature, 80% of patients censored) <20% patient deaths in either treatment arm	
Combined cohorts:	HR 0.73 (95% CI: 0.480, 1.125)

Secondary endpoints, including CFI, TFST, TSST, and PFS2 demonstrated a persistent treatment effect in favor of the niraparib treatment arm in both gBRCA^{mut} and non-gBRCA^{mut} cohorts. Furthermore, no detrimental impact of niraparib treatment on OS was observed.

In niraparib versus placebo treated patients, the incidence of TEAEs was as follows: MDS/AML occurred in 1.4% (5 of 367) patients who received niraparib and 1.1% (2 of 179) patients who received placebo. No patient had a grade 3 or 4 bleeding event, although 1 patient had grade 3 petechiae and hematoma concurrent with pancytopenia. No grade 5 events occurred. Hematologic treatment-related TEAEs grade ≥ 3 were manageable through dose individualization. Subgroup Analyses Based on Last Platinum-Based Chemotherapy Response

Platinum resistance status was assessed in patients receiving placebo treatment. Platinum resistance status was defined as a duration of response to platinum <6 months to

the most recent (ultimate) platinum regimen. Estimated probability of patients having disease progression 6 months after the last dose of their most recent platinum therapy was calculated using Kaplan-Meier methodology. 181 patients were randomized to placebo (65 gBRCA^{mut} and 116 non-gBRCA^{mut}). Platinum resistance rate estimates were for the gBRCA^{mut}, non-gBRCA^{mut}, and pooled cohorts were 42%, 53% and 49%, respectively, see FIG. 16. Therefore approximately half of the patients in trial had developed platinum resistance to their last line of chemotherapy. Disease progression after 12 months was also evaluated for each of the cohorts. A summary of the disease progression within 6 months and 12 months is shown in Table 6.

TABLE 6

Estimated Percentage of Placebo Patients with PD <6 or <12 Months After Their Last Dose of Platinum-Based Therapy			
Outcome	gBRCAmut (n = 65)	Non-gBRCAmut (n = 116)	Pooled Cohorts (n = 181)
PD <6 months	42%	53%	49%
PD <12 months	82%	78%	79%

gBRCAmut = germline breast cancer susceptibility gene mutation;

PD = progression of disease.

Patients were stratified based on their response to their most recent platinum treatment (CR or PR). 49% of patients in the gBRCA^{mut} cohort (niraparib: 67/138; placebo: 32/65) and ~49% of patients in the non-gBRCA^{mut} cohort (niraparib: 117/234 [50%]; placebo: 56/116 [48%]) entered the NOVA trial with a PR following their most recent platinum-based chemotherapy. At the time of unblinding, 30(45%) niraparib and 23 (72%) of placebo patients in the gBRCA^{mut} cohort and 65 (56%) niraparib and 45 (80%) of placebo patients in the non-gBRCA^{mut} cohort had PFS events. PFS hazard ratios (95% CI) were 0.24 (0.131-0.441) in gBRCA^{mut} and 0.35 (0.230-0.532) in non-gBRCA^{mut} cohorts for patients who had a PR to their most recent platinum regimen. The response in subjects who had a partial response in their most recent platinum-based chemotherapy treatment compares favorably to the overall NOVA study results described above.

Placebo-treated patients were further stratified based on their response to the last two platinum treatments. The characteristics of these placebo-treated patients are shown in Table 7. In the non-gBRCAmut cohort, a greater proportion of patients with PD <6 months (platinum resistant) had a PR following both the penultimate and the last platinum-based chemotherapy compared to those with PD ≥ 6 months (platinum sensitive) (39.7% vs 14.6% for the penultimate, and 65.5% vs 22.9% for the last).

TABLE 7

Placebo-Treated Patient Characteristics at Baseline				
Parameter	gBRCAmut	Non-gBRCAmut		
Age, median (min, max)	61.0 (42, 73)	58.0 (38, 73)	63.5 (41, 79)	59.0 (38, 82)
Time from completion of last platinum therapy to randomization, median (min, max), days	38.5 (21, 60)	40 (11, 68)	42 (22, 63)	41.5 (20, 64)
Time to PD after penultimate platinum-based dose, n (%)				
6 to <12 months	12 (50.0)	10 (32.3)	29 (50.0)	10 (20.8)
≥ 12 months	12 (50.0)	21 (67.7)	29 (50.0)	38 (79.2)

TABLE 7-continued

Placebo-Treated Patient Characteristics at Baseline				
Parameter	gBRCAmut		Non-gBRCAmut	
Best response to penultimate platinum-based therapy ^a				
CR	19 (79.2)	22 (71.0)	35 (60.3)	40 (83.3)
PR	5 (20.8)	9 (29.0)	23 (39.7)	7 (14.6)
Best response to last platinum-based therapy				
CR	11 (45.8)	19 (61.3)	20 (34.5)	37 (77.1)
PR	13 (54.2)	12 (38.7)	38 (65.5)	11 (22.9)

^aOne patient did not have last platinum-based chemotherapy information available.

CR = complete response;

gBRCAmut = germline breast cancer susceptibility gene mutation;

PD = progression of disease;

PR = partial response

Placebo-treated patients were also stratified based on the number of lines of prior treatment they have received (2 versus 3 or more) and the results are shown in FIG. 17. The patients with PD <6 months after their last chemotherapy had received more prior lines of platinum-based therapy (FIG. 17, panels A and B) and more total lines of chemotherapy (FIG. 17, panels C and D) than those with PD ≥6 months after their most recent platinum-based chemotherapy.

Patient-Reported Outcomes

Patient-reported outcomes were measured using the Functional Assessment of Cancer Therapy—Ovarian Symptom Index (FOSI) and the EQ-5D-5L Health Utility Index (HUI) scores. Patient-reported outcomes (PRO) surveys were collected at: screening visit, every other cycle through cycle 14 and post progression. A mixed-effects growth curve model was constructed to model the relationship between treatment and PRO score for each measure. Responder proportions were assessed using minimally important difference thresholds and change from baseline values. The relationship between health status and patient-reported health outcomes was evaluated through a cross-sectional analysis of adjusted EQ-5D-5L Health Utility Index (HUI) scores. Compliance rates were high and similar between the two treatment arms: niraparib: FOSI completion rate ranged from 75.0% to 97.1% and placebo: FOSI completion rate ranged from 77.6% to 97.4%. PROs were similar for niraparib and placebo throughout the study in both the gBRCA^{mut}, non-gBRCA^{mut} cohorts. See FIG. 18. No significant difference in mean PRO scores was observed between niraparib and placebo arms in either cohort. The analysis of responder proportions also did not demonstrate any significant difference, except in the non-gBRCA^{mut} cohort at cycle 2. Adjusted HUI scores were similar in both arms at baseline, but average adjusted HUI pre-progression scores trended higher in the niraparib arm (0.812 vs. 0.803 in gBRCA^{mut} cohort; 0.845 vs. 0.828 in non-gBRCA^{mut} cohort). Hematologic toxicities had no detrimental effect on patients' overall health utility. These data support that patients with recurrent ovarian cancer treated with niraparib following complete or partial response to platinum-based chemotherapy can maintain their quality of life while on treatment with niraparib (e.g., while receiving niraparib maintenance therapy).

Conclusions

This study represents the first time a PARP inhibitor has demonstrated definitive activity in a patient population who may best be defined by their platinum sensitivity. These data support the expanded use of a PARP inhibitor beyond those cancers with a BRCA mutation, and shows efficacy of

niraparib in both HRD positive and non-gBRCA ovarian cancers, including HRD negative ovarian cancers. A once daily dose of niraparib significantly extended the progression-free survival time of patients in all three primary efficacy populations: the gBRCAmut cohort, the prospectively defined subgroup of patients with HRD positive tumors in the non-gBRCAmut cohort, and the overall non-gBRCAmut cohort. The niraparib treatment effect, as manifest in the Kaplan-Meier curves, was clinically meaningful, consistent, and durable for all three primary efficacy populations. In addition, the secondary endpoints of chemotherapy-free interval, time to first subsequent therapy, and progression-free survival 2 were statistically significant and clinically meaningful for the niraparib treatment arm in both cohorts. Importantly, the patient-reported outcomes showed an outcome for niraparib maintenance therapy that was at least as good as placebo. Collectively, these data are strongly supportive of the use of niraparib in this patient population who might otherwise receive no treatment at all.

Exploratory analyses, and the resultant Kaplan-Meier curves, indicate that treatment with niraparib provides a consistent and durable benefit to patients compared to placebo in all exploratory subgroups, regardless of biomarker status, a finding that is consistent with observations made for the primary efficacy populations. Although there is variation in the response to niraparib among the different biomarker populations, significantly improved progression-free survival was observed for patients who lacked a BRCA mutation and had tumors that were not deficient in homologous recombination (HRD negative).

Secondary endpoints improved with niraparib as demonstrated by significantly prolonged PFS2, CFI, and TFST. Moreover, niraparib had no impact on the efficacy of the next line of therapy, suggesting a prolonged clinical benefit. Niraparib significantly improved outcome in patients with recurrent ovarian cancer following a partial or complete response to platinum-based chemotherapy regimen, regardless of BRCA mutation or HRD status.

The niraparib side effect profile was manageable, and acceptable for long-term dosing following a response to platinum-based chemotherapy. The dose of 300 mg is appropriate for the majority of patients, and acceptable given the life-threatening nature of the disease; this dose can be adapted for individual patients if necessary, greatly reducing the need to discontinue the drug due to side effects. Overall there were no deaths during treatment, and ~85% of patients remained on niraparib for the duration of the study, further indicating that side effects were acceptable and tolerated. Adverse events can be monitored routinely using standard

assessments of hematological laboratory parameters, as is standard for patients receiving anticancer therapies. The incidence of myelodysplastic syndrome and/or acute myeloid leukemia was very low (1%) with similar rates in the niraparib and placebo treatment arms.

Niraparib is a daily oral treatment that prolongs the effect of platinum-based chemotherapy by substantially improving progression-free survival without reducing quality of life, delaying the need for additional platinum-based chemotherapy with its associated cumulative toxicities in patients with recurrent ovarian cancer, regardless of their biomarker status. Niraparib treatment provided significant efficacy in a broad population of patients, now expanding the benefit of PARP inhibitors to non-BRCA ovarian cancer patients who have platinum-sensitive, recurrent ovarian cancer following a response to platinum chemotherapy.

Example 2. Food Effects of Niraparib

A 14-day, open-label, 2-treatment, crossover sub-study evaluated the effect of a high fat meal on niraparib (single dose) exposure.

Patients with ovarian cancer regardless of platinum sensitivity and burden of disease were randomized to either Group A or Group B with 6 patients assigned to each group. In Group A, patients fasted (nothing to eat or drink except water) for at least 10 hours before receiving a single dose of 300 mg niraparib; patients continued to fast for at least 2 hours following the dose. In Group B, patients fasted for at least 10 hours before consuming a high fat meal. Within 5 minutes of finishing the meal, a single dose of 300 mg niraparib was administered orally and patients resumed fasting for at least 4 hours. After a 7-day PK assessment and wash-out period, all patients received their second single dose of niraparib on Day 8 under the opposite (fasting vs high fat meal) circumstance: the previous 6 patients in Group A received their single dose of niraparib after a high fat meal and patients in Group B received their second single dose of niraparib under fasting conditions. After the completion of the 14-day food effect sub-study, patients began daily dosing at 300 mg QD niraparib on Cycle 1/Day 1, approximately 2 weeks after the start of the study.

Having thus described several aspects of this invention, it is to be appreciated that various alterations, modifications, and improvements will readily be apparent to those skilled in the art. Such alterations, modifications, and improvements are intended to be part of this disclosure, and are intended to be within the spirit and scope of the invention. Accordingly, the foregoing description and drawings are by way of example only and the invention is described in detail by the claims that follow.

Example 3. DNA Repair Genes

TABLE 8

is a list of 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

TABLE 8-continued

is a list of DNA Repair genes	
Gene Title	Gene Symbol
replication protein A1, 70 kDa	RPA1
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 (<i>E. coli</i>)	MLH1
ligase I, DNA, ATP-dependent	LIG1
nibrin	NBN
nibrin	NBN
nibrin	NBN
mutS homolog 6 (<i>E. coli</i>)	MSH6
polymerase (DNA-directed), delta 4	POLD4
replication factor C (activator 1) 5, 36.5 kDa	RFC5
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 polymerase (DNA directed), beta	FANCG
X-ray repair complementing defective repair in Chinese hamster cells 1	POLB
X-ray repair complementing defective repair in Chinese hamster cells 1	XRCC1
N-methylpurine-DNA glycosylase	MPG
replication factor C (activator 1) 2, 40 kDa	RFC2
excision repair cross-complementing rodent repair deficiency, complementation group 1 (includes overlapping antisense sequence)	ERCC1
excision repair cross-complementing rodent repair deficiency, complementation group 1 (includes overlapping antisense sequence)	ERCC1
thymine-DNA glycosylase	TDG
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
replication factor C (activator 1) 3, 38 kDa	RFC3
APEX nuclease (apurinic/apyrimidinic endonuclease) 2	APEX2
RAD1 homolog (<i>S. pombe</i>)	RAD1
RAD1 homolog (<i>S. pombe</i>)	RAD1
breast cancer 1, early onset	BRCA1
exonuclease 1	EXO1
flap structure-specific endonuclease 1	FEN1
flap structure-specific endonuclease 1	FEN1
mutL homolog 3 (<i>E. coli</i>)	MLH3
O-6-methylguanine-DNA methyltransferase	MGMT
RAD51 homolog (RecA homolog, <i>E. coli</i>) (<i>S. cerevisiae</i>)	RAD51
RAD51 homolog (RecA homolog, <i>E. coli</i>) (<i>S. cerevisiae</i>)	RAD51
X-ray repair complementing defective repair in Chinese hamster cells 4	XRCC4
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 (<i>S. cerevisiae</i>)	MRE11A
RAD52 homolog (<i>S. cerevisiae</i>)	RAD52
Werner syndrome	WRN
xeroderma pigmentosum, complementation group A	XPA
Bloom syndrome	BLM
8-oxoguanine DNA glycosylase	OGG1

TABLE 8-continued

is a list of DNA Repair genes	
Gene Title	Gene Symbol
mutS homolog 3 (<i>E. coli</i>)	MSH3
polymerase (DNA directed), epsilon 2 (p59 subunit)	POLE2
RAD51 homolog C (<i>S. cerevisiae</i>)	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 (<i>S. pombe</i>)	RAD17
X-ray repair complementing defective repair in Chinese hamster cells 2	XRCC2
mutY homolog (<i>E. coli</i>)	MUTYH
replication factor C (activator 1) 1, 145 kDa // replication factor C (activator 1) 1, 145 kDa	RFC1
replication factor C (activator 1) 1, 145 kDa	RFC1
breast cancer 2, early onset	BRCA2
RAD50 homolog (<i>S. cerevisiae</i>)	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
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
replication factor C (activator 1) 1, 145 kDa	RFC1
RAD50 homolog (<i>S. cerevisiae</i>)	RAD50
xeroderma pigmentosum, complementation group C	XPC
mutS homolog 2, colon cancer, nonpolyposis type 1 (<i>E. coli</i>)	MSH2
replication protein A3, 14 kDa	RPA3
methyl-CpG binding domain protein 4	MBD4
methyl-CpG binding domain protein 4	MBD4
nth endonuclease III-like 1 (<i>E. coli</i>)	NTHL1
PMS2 postmeiotic segregation increased 2 (<i>S. cerevisiae</i>) // PMS2-C terminal-like	PMS2 // PMS2CL
RAD51 homolog C (<i>S. cerevisiae</i>)	RAD51C
uracil-DNA glycosylase 2	UNG2
APEX nuclease (multifunctional DNA repair enzyme) 1	APEX1
excision repair cross-complementing rodent repair deficiency, complementation group 4	ERCC4
RAD1 homolog (<i>S. pombe</i>)	RAD1
RecQ protein-like 5	RECQL5
mutS homolog 5 (<i>E. coli</i>)	MSH5
RecQ protein-like (DNA helicase Q1-like)	RECQL
RAD52 homolog (<i>S. cerevisiae</i>)	RAD52
X-ray repair complementing defective repair in Chinese hamster cells 4	XRCC4
X-ray repair complementing defective repair in Chinese hamster cells 4	XRCC4
RAD17 homolog (<i>S. pombe</i>)	RAD17
mutS homolog 3 (<i>E. coli</i>)	MSH3
MRE11 meiotic recombination 11 homolog A (<i>S. cerevisiae</i>)	MRE11A
mutS homolog 6 (<i>E. coli</i>)	MSH6
mutS homolog 6 (<i>E. coli</i>)	MSH6
RecQ protein-like 5	RECQL5
breast cancer 1, early onset	BRCA1
RAD52 homolog (<i>S. cerevisiae</i>)	RAD52
polymerase (DNA-directed), delta 3, accessory subunit	POLD3
mutS homolog 5 (<i>E. coli</i>)	MSH5
excision repair cross-complementing rodent repair deficiency, complementation group 2 (xeroderma pigmentosum D)	ERCC2
RecQ protein-like 4	RECQL4
PMS1 postmeiotic segregation increased 1 (<i>S. cerevisiae</i>)	PMS1
zinc finger protein 276 homolog (mouse)	ZFP276
methyl-CpG binding domain protein 4	MBD4

TABLE 8-continued

is a list of DNA Repair genes	
Gene Title	Gene Symbol
methyl-CpG binding domain protein 4	MBD4
mutL homolog 3 (<i>E. coli</i>)	MLH3
Fanconi anemia, complementation group A	FANCA
polymerase (DNA directed), epsilon	POLE
X-ray repair complementing defective repair in Chinese hamster cells 3	XRCC3
mutL homolog 3 (<i>E. coli</i>)	MLH3
nibrin	NBN
single-strand selective monofunctional uracil DNA glycosylase	SMUG1
Fanconi anemia, complementation group F	FANCF
nei endonuclease VIII-like 1 (<i>E. coli</i>)	NEIL1
Fanconi anemia, complementation group E	FANCE
mutS homolog 5 (<i>E. coli</i>)	MSH5
RecQ protein-like 5	RECQL5

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EQUIVALENTS

The articles "a" and "an" as used herein in the specification and in the claims, unless clearly indicated to the contrary, should be understood to include the plural referents. Claims or descriptions that include "or" between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention also includes embodiments in which more than one, or the entire group members are present in, employed in, or otherwise relevant to a given product or process. Furthermore, it is to be understood that the invention encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, descriptive terms, etc., from one or more of the listed claims is introduced into another claim dependent on the same base claim (or, as relevant, any other claim) unless otherwise

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indicated or unless it would be evident to one of ordinary skill in the art that a contradiction or inconsistency would arise. Where elements are presented as lists, (e.g., in Markush group or similar format) it is to be understood that each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should be understood that, in general, where the invention, or aspects of the invention, is/are referred to as comprising particular elements, features, etc., certain embodiments of the invention or aspects of the invention consist, or consist essentially of, such elements, features, etc. For purposes of simplicity those embodiments have not in every case been specifically set forth in so many words herein. It should also be understood that any embodiment or aspect of the invention can be explicitly excluded from the claims, regardless of whether the specific exclusion is recited in the specification. The publications, websites and other reference materials referenced herein to describe the background of the invention and to provide additional detail regarding its practice are hereby incorporated by reference.

The invention claimed is:

1. A method of treating a patient diagnosed with ovarian cancer, fallopian tube cancer, or primary peritoneal cancer, comprising

administering daily to said patient an oral dose of niraparib equivalent to 200 mg or 300 mg of niraparib free base,

wherein the patient has undergone at least one cycle of platinum-based chemotherapy; and

wherein the patient carries no germline or somatic mutation in BRCA1 or BRCA2 genes and the cancer has no homologous recombination deficiency.

2. The method of claim 1, wherein the ovarian cancer, fallopian tube cancer, or primary peritoneal cancer is platinum sensitive.

3. The method of claim 1, wherein the patient has undergone at least two cycles of platinum-based chemotherapy.

4. The method of claim 3, wherein the patient has a complete response to the platinum-based chemotherapy.

5. The method of claim 3, wherein the patient has a partial response to the platinum-based chemotherapy.

6. The method of claim 3, wherein the administration of niraparib is commenced within 8 weeks of the end of the last cycle of platinum-based chemotherapy.

7. The method of claim 1, comprising administering the niraparib in continuous 28-day cycles.

8. The method of claim 1, wherein the niraparib is administered daily for a period of 6.9 months, and wherein administration is continued until disease progression occurs.

9. The method of claim 1, comprising administering daily to said patient an oral dose of niraparib tosylate monohydrate.

10. The method of claim 9, comprising administering daily to said patient an oral dose of niraparib tosylate monohydrate equivalent to 200 mg of niraparib free base.

11. The method of claim 9, comprising administering daily to said patient an oral dose of niraparib tosylate monohydrate equivalent to 300 mg of niraparib free base.

12. A method of treating a patient diagnosed with ovarian cancer, fallopian tube cancer, or primary peritoneal cancer, consisting of

administering daily to said patient an oral dose of niraparib equivalent to 200 mg or 300 mg of niraparib free base,

wherein the patient has undergone at least one cycle of

platinum-based chemotherapy; and

wherein the patient carries no germline or somatic mutation in BRCA1 or BRCA2 genes and the cancer has no homologous recombination deficiency.

13. The method of claim 12, wherein the ovarian cancer, fallopian tube cancer, or primary peritoneal cancer is platinum sensitive.

14. The method of claim 12, wherein the patient has undergone at least two cycles of platinum-based chemotherapy.

15. The method of claim 14, wherein the patient has a complete response to the platinum-based chemotherapy.

16. The method of claim 14, wherein the patient has a partial response to the platinum-based chemotherapy.

17. The method of claim 14, wherein the administration of niraparib is commenced within 8 weeks of the end of the last cycle of platinum-based chemotherapy.

18. The method of claim 12, comprising administering the niraparib in continuous 28-day cycles.

19. The method of claim 12, wherein the niraparib is administered daily for a period of 6.9 months, and wherein administration is continued until disease progression occurs.

20. The method of claim 12, comprising administering daily to said patient an oral dose of niraparib tosylate monohydrate.

21. The method of claim 20, comprising administering daily to said patient an oral dose of niraparib tosylate monohydrate equivalent to 200 mg of niraparib free base.

22. The method of claim 20, comprising administering daily to said patient an oral dose of niraparib tosylate monohydrate equivalent to 300 mg of niraparib free base.

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