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.

[0004] 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

[0005] The present disclosure 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, examples of the disclosure 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 examples, the disclosure 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 examples, the disclosure 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 examples, the disclosure 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 examples, the disclosure 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 examples, the disclosure 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 examples, the disclosure 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 examples, the disclosure 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.

[0005a] In one aspect, there is provided use of niraparib in the manufacture of an oral medicament for treating cancer in a patient, wherein the patient is charaterized by previous treatment with a platinum-based therapy and an absence of homologous recombination deficiency (HRD).

[0006] In examples, 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 examples, the anti-PARP therapy is administered at a dose equivalent to about 100 mg of niraparib or a salt or derivative thereof. In certain examples, the anti-PARP therapy is administered at a dose equivalent to about 200 mg of niraparib or a salt or derivative thereof. In certain examples, the anti-PARP therapy is administered at a dose equivalent to about 300 mg of niraparib or a salt or derivative thereof.

[0007] In some examples, 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%.

[0008] In examples, the anti-PARP therapy comprises administration of an agent that inhibits PARP-1 and/or PARP-2. In some examples, 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 examples, 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 examples, the agent is niraparib, olaparib, rucaparib, talazoparib, veliparib, or salts or derivatives thereof. In certain examples, the agent is niraparib or a salt or derivative thereof. In certain examples, the agent is

olaparib or a salt or derivative thereof. In certain examples, the agent is rucaparib or a salt or derivative thereof. In certain examples, the agent is talazoparib or a salt or derivative thereof. In certain examples, the agent is veliparib or a salt or derivative thereof.

[0009] In some examples, the methods prolong progression free survival as compared to control. In some examples, the methods reduce the hazard ratio for disease progression or death as compared to control. In some examples, the methods prolong overall survival as compared to control. In some examples, the methods achieve an overall response rate of at least 30%. In some examples, the methods achieve improved progression free survival 2 as compared to control. In some examples, the methods achieve improved chemotherapy free interval as compared to control. In some examples, the methods achieve improved time to first subsequent therapy as compared to control. In some examples, the methods achieve improved time to second subsequent therapy as compared to control. In some examples, 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 examples, 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.

[0010] In some examples, such cancers are selected from gynecologic cancers (i.e., cancers of the female reproductive system). In some examples, 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 examples, a gynecologic cancer is associated with homologous recombination repair deficiency/homologous repair deficiency ("HRD") and/or BRCA1/2 mutation(s). In some examples, a gynecologic cancer is platinum-sensitive. In some examples, a gynecologic cancer has responded to a platinum-based therapy. In some examples, a gynecologic cancer has developed resistance to a platinum-based therapy. In some examples, a gynecologic cancer has at one time shown a partial or complete response to platinum-based therapy. In some examples, a gynecologic cancer is now resistant to platinum-based therapy.

[0011] In certain examples, the cancer is ovarian cancer, cancer of the fallopian tube(s), or peritoneal cancer. In certain examples, the cancer is breast cancer.

[0012] In some examples, the cancer is a recurrent cancer.

[0013] In some examples, anti-PARP therapy is useful in treating cancer patients exhibiting a positive HRD status. In some examples, 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 examples, 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 examples, a positive HRD status is determined by quantifying in a patient sample a number of Indicator Chromosomal Aberration ("CA") regions. In some examples, a tumor sample from a patient has a positive HRD status.

[0014] In some examples, anti-PARP therapy is useful in treating cancer patients exhibiting an absence of a germline mutation in BRCA1 and BRCA2. In some examples, 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.

[0015] In some examples, anti-PARP therapy is useful in treating cancer patients exhibiting an absence of HRD. In some examples, 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 examples, 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 examples, 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).

[0016] Accordingly, in some examples, the present disclosure 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.

[0017] Among other things, the present disclosure 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 examples, the present disclosure 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.

[0018] In some examples, the present disclosure 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.

[0019] In some examples, the present disclosure 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 examples an overall response rate is assessed according to RECIST v1.1 guidelines.

[0020] In some examples, the method of administering anti-PARP therapy is according to a regimen determined to achieve prolonged progression free survival 2 as compared to control.

[0021] In some examples, the method of administering anti-PARP therapy is according to a regimen determined to achieve extended chemotherapy free interval as compared to control.

[0022] In some examples, 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.

[0023] In some examples, 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.

[0024] In some examples, the recurrent and/or platinum sensitive cancer is ovarian cancer. In some examples, the ovarian cancer is platinum sensitive ovarian cancer at the commencement of anti-PARP therapy administration. In some examples, the ovarian cancer is recurrent, platinum sensitive ovarian cancer at the commencement of anti-PARP therapy administration. In some examples, the ovarian cancer responded to the most recent platinum-based chemotherapy regimen prior to commencement of anti-PARP therapy administration. In some examples,

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

[0025] In some examples, the recurrent and/or platinum sensitive cancer is fallopian tube cancer. In some examples, the fallopian tube cancer is platinum sensitive at the commencement of anti-PARP therapy administration. In some examples, the recurrent, fallopian tube cancer is platinum sensitive at the commencement of anti-PARP therapy administration. In some examples, the fallopian tube cancer responded to the most recent platinum-based chemotherapy regimen prior to commencement of anti-PARP therapy administration. In some examples, response to the most recent platinum-based chemotherapy regimen is a complete response. In some examples, response to the most recent platinum-based chemotherapy regimen is a partial response. In some examples, the fallopian tube cancer responded to the penultimate platinum-based chemotherapy regimen prior to commencement of anti-PARP therapy administration.

[0026] In some examples, the recurrent and/or platinum sensitive cancer is primary peritoneal cancer. In some examples, the primary peritoneal cancer is platinum sensitive at the commencement of anti-PARP therapy administration. In some examples, the recurrent, primary peritoneal cancer is platinum sensitive at the commencement of anti-PARP therapy administration. In some examples, the primary peritoneal responded to the most recent platinum-based chemotherapy regimen prior to commencement of anti-PARP therapy administration. In some examples, response to the most recent platinum-based chemotherapy regimen is a complete response. In some examples, response to the most recent platinum-based chemotherapy regimen is a partial response. In some examples, the primary peritoneal cancer responded to the penultimate platinum-based chemotherapy regimen prior to commencement of anti-PARP therapy administration.

[0027] In some examples, 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.

[0028] In some examples, the patient has a germline mutation in BRCA1 and/or BRCA2.

[0029] In some examples, the regimen is determined to achieve a hazard ratio for disease progression of less than about 0.5. In some examples, the hazard ratio for disease progression is

less than about 0.4. In some examples, the hazard ratio for disease progression is less than about 0.3.

[0030] In some examples, the regimen is determined to achieve prolonged progression free survival of at least 9 months. In some examples, the prolonged progression free survival is at least 12 months. In some examples, the prolonged progression free survival is at least 15 months. In some examples, the prolonged progression free survival is at least 21 months.

[0031] In some examples, the patient has a sporadic mutation in BRCA1 or BRCA2.

[0032] In some examples, the patient is characterized by an absence of a germline mutation in BRCA1 or BRCA2. In some examples, the patient is characterized by an absence of HRD. In some examples, the patient is characterized by an absence of a germline mutation in BRCA1 or BRCA2 and by an absence of HRD.

[0033] In some examples, the patient is characterized by an absence of a sporadic mutation in BRCA1 or BRCA2. In some examples, the patient is characterized by an absence of HRD. In some examples, the patient is characterized by an absence of a sporadic mutation in BRCA1 or BRCA2 and by an absence of HRD. In some examples, 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 examples, 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).

[0034] In some examples, 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).

[0035] In some examples, the patient has a tumor with a positive homologous recombination deficiency status.

[0036] In some examples, the present disclosure 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.

[0037] In some examples, the present disclosure 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.

[0038] In some examples, the present disclosure 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.

[0039] In some examples, the patient has a tumor with a negative homologous recombination deficiency status. In some examples, the patient has a tumor further characterized by being negative for germline mutations in BRCA1 or BRCA2.

[0040] In some examples, the present disclosure 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 examples, the hazard ratio for disease progression is less than about 0.3.

[0041] In some examples, the present disclosure 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 examples, the prolonged progression free survival is at least 12 months or at least 21 months.

[0042] In some examples, the present disclosure 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 examples, the hazard ratio for disease progression is less than about 0.4.

[0043] In some examples, the present disclosure 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.

[0044] In some examples, the present disclosure 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.

[0045] In some examples, the present disclosure 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.

[0046] In some examples, the present disclosure 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 examples, the hazard ratio for disease progression is less than about 0.3.

[0047] In some examples, the present disclosure 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.

[0048] In some examples, the present disclosure 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 examples, the hazard ratio for disease progression is less than about 0.4.

[0049] In some examples, the present disclosure 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.

[0050] In some examples, the present disclosure 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.

[0051] In some examples, the patient has high grade serous ovarian cancer or high grade predominantly serous histology ovarian cancer.

[0052] In some examples, the methods involve continued treatment until disease progression or unacceptable toxicity.

[0053] In some examples, the methods involve reducing the dose of the anti-PARP therapy in response to treatment toxicity. In some related examples, 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.

[0054] In some examples, the regimen comprises a plurality of oral doses.

[0055] In some examples, the regimen comprises once daily (QD) dosing.

[0056] In some examples, the regimen comprises at least one 28 day cycle of anti-PARP therapy dosing.

[0057] In some examples, the oral dose is administered in one or more unit dosage forms.

[0058] In some examples, the one or more unit dosage forms are capsules.

[0059] In some examples, 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 examples, 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 examples, the amount of anti-PARP therapy is equivalent to about 300 mg of niraparib. In some examples, the amount of anti-PARP therapy is equivalent to about 200 mg of niraparib.

[0060] In some examples, each unit dosage form is equivalent to about 100 mg, about 200 mg, or about 300 mg of niraparib.

[0061] In some examples, each QD dose is equivalent to about 100 mg, about 200 mg, or about 300 mg of niraparib. In some examples, each QD dose is administered as three unit dosage forms equivalent to about 100 mg of niraparib.

[0062] In some examples, progression free survival is characterized by a complete response of one or more target tumors.

[0063] In some examples, progression free survival is characterized by a partial response of one or more target tumors.

[0064] In some examples, the patient is in a fasted state.

[0065] In some examples, the patient is in a fed state.

[0066] In some examples, the prolonged progression free survival is at least 9 months. In some examples, the prolonged progression free survival is at least 12 months. In some examples, the prolonged progression free survival is at least 18 months. In some examples, the prolonged progression free survival is at least 21 months. In some examples, the prolonged progression

free survival is at least 24 months. In some examples, the prolonged progression free survival is at least 27 months. In some examples, the prolonged progression free survival is at least 30 months. In some examples, the prolonged progression free survival is at least 33 months. In some examples, the prolonged progression free survival is at least 36 months.

[0067] In some examples, the hazard ratio for disease progression is about 0.3. In some examples, the hazard ratio for disease progression is about 0.45. In some examples, the hazard ratio for disease progression is about 0.5. In some examples, the hazard ratio for disease progression is less than about 0.5. In some examples, the hazard ratio for disease progression is less than about 0.45. In some examples, the hazard ratio for disease progression is less than about 0.4. In some examples, the hazard ratio for disease progression is less than about 0.35. In some examples, the hazard ratio for disease progression is less than about 0.3.

[0068] In some examples, anti-PARP therapy is administered as a maintenance therapy.

[0069] In some examples, 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 examples, the next line of therapy is includes administration of a chemotherapeutic agent. In some examples, the chemotherapeutic agent is a platinum agent. In some such examples, the platinum agent is selected from cisplatin, carboplatin, oxaliplatin, nedaplatin, triplatin tetranitrate, phenanthriplatin, picoplatin, or satraplatin.

BRIEF DESCRIPTION OF THE DRAWING

[0070] ***Figure 1*** 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).

[0071] ***Figure 2*** 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

CLAIMS

1. Use of niraparib in the manufacture of an oral medicament for treating cancer in a patient, wherein the patient is characterized by previous treatment with a platinum-based therapy and an absence of homologous recombination deficiency (HRD).

2. The use of claim 1, wherein the patient is characterized by an absence of a germline or somatic mutation in BRCA1 and/or BRCA2.

3. The use of claims 1 or 2, wherein the patient has a tumor with a negative HRD status.

4. The use of any one of claims 1-3, wherein the niraparib is administered to the patient prior to determining that the patient is HRD negative.

5. The use of claim 4, wherein the niraparib is prepared in the form of a tosylate monohydrate.

6. The use of claims 4 or 5, wherein the niraparib is administered as a maintenance therapy following complete or partial response to at least one platinum-based therapy.

7. The use of any one of claims 1-6, wherein the cancer is a gynecological cancer, wherein the gynecological cancer is selected from the group consisting of: ovarian cancer, fallopian tube cancer, peritoneal cancer, and breast cancer.

8. The use of any one of claims 1-7, wherein the cancer is a recurrent cancer.

9. The use of any claims 4 or 5, wherein the ovarian cancer, fallopian tube cancer or peritoneal cancer is sensitive at the commencement of treatment.