Pharmaceutical Composition Comprising a Parp Inhibitor and an Androgen Biosynthesis Inhibitor for Treatment of Metastatic Castration-Sensitive Prostate Cancer

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Technical Field

The present invention relates to a pharmaceutical composition comprising a poly(ADP-ribose) polymerase (PARP) inhibitor and an androgen biosynthesis inhibitor for treating metastatic castration-sensitive prostate cancer (mCSPC) in patients harboring homologous recombination repair (HRR) gene alterations. The invention further relates to methods of administering such compositions and diagnostic methods for identifying suitable patient populations.

Background of the Invention

Prostate cancer represents a heterogeneous disease wherein therapeutic benefit varies substantially among patient populations. Metastatic castration-sensitive prostate cancer constitutes a clinical state wherein malignant prostatic cells remain responsive to androgen deprivation therapy. Despite advances in treatment modalities, including the addition of androgen receptor pathway inhibitors to androgen deprivation therapy, a significant proportion of patients experience disease progression and mortality. Deleterious alterations in genes involved in homologous recombination repair occur in approximately 25% of patients with advanced prostate cancer and associate with aggressive disease characteristics and poor prognosis. Among these genetic alterations, BRCA2 represents the most frequently mutated gene, followed by BRCA1 and other HRR pathway genes including BRIP1, PALB2, RAD51B, RAD54L, CDK12, CHEK2, and FANCA.

The biological phenomenon of synthetic lethality has demonstrated that cancers harboring BRCA1 or BRCA2 loss exhibit sensitivity to PARP inhibition. While PARP inhibitor monotherapy has shown efficacy in metastatic castration-resistant prostate cancer (mCRPC), particularly in patients with BRCA alterations, resistance commonly develops through mechanisms including secondary BRCA2 alterations that restore HRR function. Clinical evidence suggests potential synergy between PARP inhibition and androgen receptor signaling inhibition. Current therapeutic approaches typically reserve PARP inhibitor therapy for the castration-resistant disease state, thereby potentially limiting the duration and magnitude of clinical benefit. In other malignancies, such as ovarian cancer, earlier deployment of PARP inhibition at initial diagnosis of advanced disease has demonstrated superior outcomes compared to delayed administration. However, no approved therapeutic regimen currently exists for combining PARP inhibition with androgen receptor pathway inhibition in the metastatic castration-sensitive setting for prostate cancer patients with HRR gene alterations.

Abiraterone acetate represents a potent androgen biosynthesis inhibitor that blocks cytochrome P450 17A1 (CYP17A1), thereby preventing testosterone synthesis. When combined with prednisone to mitigate mineralocorticoid excess, abiraterone acetate plus prednisone (AAP) demonstrates established efficacy in both mCSPC and mCRPC. Niraparib constitutes a highly selective and potent PARP1 and PARP2 inhibitor that has received regulatory approval for various indications in ovarian cancer and, in combination with AAP, for BRCA-mutated mCRPC. The pharmacokinetic profile of niraparib shows minimal drug-drug interaction with abiraterone, unlike certain other agents in this therapeutic class. Despite the established efficacy of both agents individually, no prior art has established the safety, tolerability, or clinical benefit of combining niraparib with AAP in patients with mCSPC harboring HRR gene alterations. Furthermore, no existing therapeutic paradigm addresses the initiation of PARP inhibition within six months of commencing androgen deprivation therapy for metastatic disease in this molecularly defined patient population.

Summary of the Invention

The present invention provides a pharmaceutical composition comprising a PARP inhibitor and an androgen biosynthesis inhibitor for treating metastatic castration-sensitive prostate cancer in patients with homologous recombination repair gene alterations. The composition addresses the unmet medical need of improving radiographic progression-free survival, delaying symptomatic progression, and potentially extending overall survival in this patient population through early combined inhibition of both DNA repair mechanisms and androgen signaling pathways.

In a first aspect, the invention provides a pharmaceutical composition comprising niraparib or a pharmaceutically acceptable salt thereof in combination with abiraterone acetate and prednisone for use in treating metastatic castration-sensitive prostate cancer in a patient having at least one deleterious alteration in a gene selected from BRCA1, BRCA2, BRIP1, PALB2, RAD51B, RAD54L, CDK12, CHEK2, and FANCA. The niraparib is administered at a dose of 200 mg once daily, the abiraterone acetate is administered at a dose of 1000 mg once daily, and the prednisone is administered at a dose of 5 mg once daily. The composition is formulated as a dual-action tablet comprising both niraparib and abiraterone acetate for concurrent oral administration with a separate prednisone formulation. The treatment is initiated within six months of commencing androgen deprivation therapy for metastatic disease and is continued until disease progression or unacceptable toxicity occurs.

In a second aspect, the invention provides a method of treating metastatic castration-sensitive prostate cancer in a patient comprising the steps of identifying a patient with metastatic castration-sensitive prostate cancer who has at least one deleterious alteration in a homologous recombination repair gene, wherein the patient has commenced androgen deprivation therapy within the preceding six months, and administering to said patient a pharmaceutical composition comprising niraparib at 200 mg once daily, abiraterone acetate at 1000 mg once daily, and prednisone at 5 mg once daily in continuous 28-day cycles. The method results in a statistically significant improvement in radiographic progression-free survival compared to administration of abiraterone acetate and prednisone alone. The method achieves a hazard ratio for radiographic progression or death of approximately 0.63 in an intention-to-treat population and approximately 0.52 in patients with BRCA1 or BRCA2 alterations. The method further provides improvement in time to symptomatic progression with a hazard ratio of approximately 0.50 in the intention-to-treat population and approximately 0.44 in patients with BRCA1 or BRCA2 alterations.

In a third aspect, the invention provides a diagnostic method for identifying patients suitable for treatment with the pharmaceutical composition comprising the steps of obtaining a biological sample from a patient with metastatic castration-sensitive prostate cancer, wherein the biological sample comprises tumor tissue, plasma, or germline DNA, and analyzing the biological sample using next-generation sequencing to detect the presence of at least one deleterious alteration in a gene selected from BRCA1, BRCA2, BRIP1, PALB2, RAD51B, RAD54L, CDK12, CHEK2, and FANCA. The diagnostic method utilizes validated assays for detecting somatic or germline mutations, including tissue-based comprehensive genomic profiling, plasma-based circulating tumor DNA analysis, or germline multi-cancer panel testing. Upon confirmation of at least one qualifying HRR gene alteration, the patient is identified as suitable for treatment with the combination of niraparib, abiraterone acetate, and prednisone, provided that androgen deprivation therapy has been initiated within the preceding six months and the patient meets additional eligibility criteria including documented metastatic disease by conventional imaging.

In a fourth aspect, the invention provides a pharmaceutical kit comprising a first container holding a plurality of dual-action tablets, wherein each dual-action tablet comprises 200 mg niraparib and 1000 mg abiraterone acetate, a second container holding a plurality of prednisone tablets, wherein each prednisone tablet comprises 5 mg prednisone, and instructions for use directing once-daily oral administration of one dual-action tablet and one prednisone tablet in continuous 28-day cycles for treating metastatic castration-sensitive prostate cancer in patients with homologous recombination repair gene alterations. The kit further comprises package labeling indicating the specific genetic alterations for which the treatment is indicated, namely deleterious alterations in BRCA1, BRCA2, BRIP1, PALB2, RAD51B, RAD54L, CDK12, CHEK2, or FANCA. The instructions specify that treatment should commence within six months of initiating androgen deprivation therapy for metastatic disease and should continue until radiographic disease progression or unacceptable toxicity occurs.

In a fifth aspect, the invention provides the pharmaceutical composition according to the first aspect for use in a patient subgroup having alterations specifically in BRCA1 or BRCA2 genes, wherein the composition demonstrates superior efficacy compared to the broader HRR-altered population. In this patient subgroup, the median radiographic progression-free survival is not reached in patients receiving the combination therapy compared to 26.0 months in patients receiving abiraterone acetate and prednisone alone, with a hazard ratio of 0.52. The composition achieves this superior efficacy while maintaining an acceptable safety profile through implementation of dose modifications and supportive care measures.

In a sixth aspect, the invention provides a method of dose modification for the pharmaceutical composition comprising reducing the niraparib dose from 200 mg once daily to a lower dose selected from 100 mg once daily or treatment interruption in response to grade 3 or higher adverse events, while maintaining the abiraterone acetate dose at 1000 mg once daily and the prednisone dose at 5 mg once daily unless specific adverse events necessitate modification of these agents. The method of dose modification particularly addresses management of anemia, wherein patients experiencing grade 3 or higher anemia receive dose interruption of niraparib until recovery to grade 2 or lower, followed by dose reduction upon resumption of treatment. The method further provides for supportive care measures including blood transfusions for symptomatic anemia, antihypertensive medications for management of treatment-emergent hypertension, and antiemetic therapy for management of nausea.

In a seventh aspect, the invention provides the pharmaceutical composition according to the first aspect wherein the patient has high-volume metastatic disease, defined as the presence of visceral metastases or four or more bone lesions with at least one beyond the vertebral bodies and pelvis. The composition demonstrates consistent treatment effect across patients with high-volume disease, who represent approximately 78% of the target patient population. The hazard ratio for radiographic progression-free survival in patients with high-volume disease is approximately 0.65, indicating maintained efficacy in this high-risk subgroup.

In an eighth aspect, the invention provides the pharmaceutical composition according to the first aspect wherein the patient has previously received up to six cycles of docetaxel chemotherapy for metastatic castration-sensitive prostate cancer, provided that docetaxel therapy was completed within three months prior to initiating the combination therapy. The composition demonstrates efficacy independent of prior docetaxel exposure, with hazard ratios for radiographic progression-free survival of approximately 0.75 in patients with prior docetaxel use and approximately 0.62 in patients without prior docetaxel use. This aspect enables sequential administration of multiple effective therapies in the metastatic castration-sensitive setting while maintaining the benefit of combined PARP and androgen biosynthesis inhibition.

In a ninth aspect, the invention provides a method of monitoring treatment response comprising performing radiographic assessments at baseline, within seven days of day one of cycle three, within seven days of day one of cycle five, and then every four cycles thereafter until radiographic progression is documented. The radiographic assessments comprise computed tomography or magnetic resonance imaging of chest, abdomen, and pelvis, and technetium-99m bone scan. Radiographic progression is defined according to Response Evaluation Criteria in Solid Tumors version 1.1 for soft tissue lesions and Prostate Cancer Working Group 3 criteria for bone lesions, wherein bone disease progression requires confirmation by a second scan at least six weeks after the initial scan demonstrating progression. The method enables objective assessment of the primary endpoint of radiographic progression-free survival and supports clinical decision-making regarding treatment continuation or modification.

In a tenth aspect, the invention provides the pharmaceutical composition according to the first aspect wherein the composition achieves improvement in time to subsequent therapy, with a hazard ratio of approximately 0.54 compared to abiraterone acetate and prednisone alone. This endpoint reflects the duration of benefit from the combination therapy and the time until additional anticancer treatment is required. The improvement in time to subsequent therapy provides clinical value by delaying the need for additional systemic therapies, which may have distinct toxicity profiles and diminishing efficacy in later lines of treatment. The composition thereby extends the period during which patients receive benefit from first-line hormonal therapy combinations before requiring alternative treatment approaches.

In an eleventh aspect, the invention provides the pharmaceutical composition according to the first aspect wherein the composition achieves improvement in second progression-free survival, defined as time from randomization to progression after first subsequent therapy, with a hazard ratio of approximately 0.66 and median second progression-free survival not reached in patients receiving the combination therapy compared to 44.0 months in patients receiving abiraterone acetate and prednisone alone. This endpoint demonstrates that the benefit of early combined PARP and androgen biosynthesis inhibition extends beyond first progression and impacts outcomes following subsequent lines of therapy. The improvement in second progression-free survival suggests that early PARP inhibition in the castration-sensitive setting may favorably alter the natural history of the disease in a manner that persists through subsequent treatment lines.

In a twelfth aspect, the invention provides a method of managing treatment-emergent adverse events comprising monitoring complete blood counts at baseline and regularly during treatment to detect hematologic toxicities, monitoring blood pressure at each visit to detect and manage hypertension, and implementing dose modifications according to predefined algorithms based on adverse event severity. The method specifically addresses the most common grade 3 or higher adverse events observed with the combination therapy, namely anemia occurring in approximately 29% of patients and hypertension occurring in approximately 27% of patients. For anemia management, the method comprises dose interruption of niraparib for grade 3 or higher anemia, provision of red blood cell transfusions as clinically indicated, and dose reduction upon treatment resumption. For hypertension management, the method comprises initiation or intensification of antihypertensive medications according to standard clinical practice guidelines while continuing combination therapy at the prescribed doses unless blood pressure remains uncontrolled despite optimal medical management.

In a thirteenth aspect, the invention provides the pharmaceutical composition according to the first aspect wherein the composition maintains health-related quality of life as assessed by Functional Assessment of Cancer Therapy-Prostate (FACT-P) total scores. Following an initial decline in FACT-P scores during cycles two through four, which reflects the toxicity burden of treatment initiation, scores return to baseline levels by cycle five and remain comparable to the abiraterone acetate and prednisone alone group through extended follow-up. This quality of life profile demonstrates that despite higher rates of grade 3 or higher adverse events with the combination therapy, the impact on patient-reported outcomes is transient and acceptable, supporting the clinical utility of the regimen when balanced against the substantial improvements in radiographic progression-free survival and time to symptomatic progression.

In a fourteenth aspect, the invention provides the pharmaceutical composition according to the first aspect wherein the patient has alterations in HRR genes other than BRCA1 or BRCA2, specifically in genes selected from BRIP1, PALB2, RAD51B, RAD54L, CDK12, CHEK2, and FANCA. While the magnitude of treatment effect in patients with non-BRCA HRR alterations demonstrates a hazard ratio of approximately 0.81, which is numerically less favorable than that observed in the BRCA subgroup, the confidence intervals and clinical characteristics support potential benefit in this molecularly defined subset. The composition thereby provides a therapeutic option for patients with HRR alterations beyond BRCA1 and BRCA2, addressing the heterogeneous biology of DNA repair deficiency in prostate cancer.

In a fifteenth aspect, the invention provides the pharmaceutical composition according to the first aspect wherein androgen deprivation therapy comprises administration of a gonadotropin-releasing hormone agonist or antagonist to achieve castrate levels of testosterone, defined as testosterone less than 50 nanograms per deciliter or less than 1.7 nanomoles per liter. The androgen deprivation therapy is initiated at least 14 days prior to commencing the combination therapy and continues throughout the duration of combination treatment. The requirement for concurrent androgen deprivation therapy ensures maintenance of castrate testosterone levels, which is essential for the mechanism of action of abiraterone acetate in blocking residual androgen synthesis and for achieving the synergistic effects of combined androgen and DNA repair pathway inhibition.

In a sixteenth aspect, the invention provides a method of treating metastatic castration-sensitive prostate cancer comprising administering the pharmaceutical composition according to the first aspect continuously until radiographic disease progression, unacceptable toxicity, or patient withdrawal of consent. The continuous administration approach differs from maintenance therapy paradigms employed in other disease settings and is justified by the mechanism of action requiring ongoing inhibition of both PARP and androgen biosynthesis to maintain tumor control. The method achieves median treatment duration of approximately 25.3 months in the combination therapy group with treatment compliance of approximately 97%, demonstrating the feasibility and tolerability of extended continuous administration of this combination regimen.

In a seventeenth aspect, the invention provides the pharmaceutical composition according to the first aspect wherein the dual-action tablet formulation enables concurrent administration of niraparib and abiraterone acetate with simplified dosing compared to separate formulations. The dual-action tablet comprises pharmaceutical excipients suitable for oral administration and achieves bioavailability equivalent to administration of separate niraparib and abiraterone acetate tablets. The formulation maintains stability under standard storage conditions and provides consistent pharmacokinetic profiles across the intended patient population. The single tablet formulation improves medication adherence by reducing pill burden and simplifying the treatment regimen, which is particularly valuable given the continuous long-term nature of the therapy.

In an eighteenth aspect, the invention provides the pharmaceutical composition according to the first aspect for use in patients who have received up to 45 days of prior abiraterone acetate plus prednisone therapy before confirmation of HRR gene alteration status. This aspect recognizes the practical reality that genetic testing results may not be available immediately at the time of metastatic diagnosis and that initiation of androgen receptor pathway inhibition may occur before genetic characterization is complete. The composition demonstrates efficacy in patients with limited prior abiraterone exposure, enabling integration of genetic testing into clinical practice workflows without delaying initiation of standard-of-care androgen receptor pathway inhibition.

In a nineteenth aspect, the invention provides a method of stratifying patients for treatment comprising categorizing patients according to HRR gene alteration type, specifically as BRCA2 alteration versus CDK12 alteration versus other HRR gene alterations, prior docetaxel use, and metastatic disease volume. The stratification method enables personalized risk assessment and treatment planning based on molecular and clinical characteristics that influence prognosis and treatment response. Patients with BRCA1 or BRCA2 alterations represent the subgroup deriving greatest benefit from the combination therapy and should be prioritized for this treatment approach. Patients with other HRR alterations, particularly those in the immediate effector genes BRIP1, PALB2, RAD51B, and RAD54L, also demonstrate clinical benefit, whereas the benefit in patients with CDK12, CHEK2, or FANCA alterations requires further characterization through extended follow-up and potentially alternative trial designs.

In a twentieth aspect, the invention provides the pharmaceutical composition according to the first aspect wherein treatment results in improvement in time to prostate-specific antigen (PSA) progression, with a hazard ratio of approximately 0.50 compared to abiraterone acetate and prednisone alone. PSA progression is defined according to Prostate Cancer Working Group 3 criteria as an increase of 25% or greater and at least 2 nanograms per milliliter above the nadir, confirmed by a second value obtained at least three weeks later. While PSA progression does not constitute a regulatory endpoint for approval, the substantial improvement in time to PSA progression provides supportive evidence of biological activity and clinical benefit. The PSA response rate, defined as decrease of at least 50% from baseline, is similar between treatment groups at approximately 72-74%, but the duration of PSA response is significantly longer in patients receiving the combination therapy.

Detailed Description of the Invention

The present invention provides a pharmaceutical composition comprising niraparib, a poly(ADP-ribose) polymerase inhibitor, in combination with abiraterone acetate, an androgen biosynthesis inhibitor, and prednisone for the treatment of metastatic castration-sensitive prostate cancer in patients harboring deleterious alterations in genes involved in homologous recombination repair. The invention is predicated upon the discovery that early intervention with combined PARP and androgen pathway inhibition within six months of initiating androgen deprivation therapy for metastatic disease provides superior disease control compared to androgen pathway inhibition alone, as evidenced by statistically significant and clinically meaningful improvements in radiographic

progression-free survival, time to symptomatic progression, and multiple secondary efficacy endpoints.

The molecular foundation of the invention rests upon the biological phenomenon of synthetic lethality, wherein cells harboring deficiency in one DNA repair pathway become critically dependent upon alternative repair mechanisms for survival. Homologous recombination repair represents the high-fidelity pathway for repairing DNA double-strand breaks and involves a complex orchestration of proteins encoded by genes including BRCA1, BRCA2, BRIP1, PALB2, RAD51B, RAD54L, and others. When cells harbor deleterious alterations in these genes, they lose the capacity for error-free repair of double-strand breaks and become reliant upon alternative pathways including non-homologous end joining and single-strand break repair mechanisms involving PARP enzymes. Inhibition of PARP in cells already deficient in homologous recombination repair creates a state of irreparable DNA damage accumulation, leading to cell death through mechanisms including mitotic catastrophe, replication fork collapse, and apoptotic signaling.

Niraparib, chemically designated as 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole-7-carboxamide, functions as a potent and selective inhibitor of both PARP1 and PARP2 enzymes. The compound possesses a molecular weight of 320.39 daltons and is formulated as the tosylate salt to optimize pharmaceutical properties. The mechanism of action encompasses two distinct activities that contribute to cytotoxicity in homologous recombination repair-deficient cells. First, niraparib catalytically inhibits the enzymatic activity of PARP enzymes, preventing the synthesis of poly(ADP-ribose) chains that normally recruit DNA repair proteins to sites of single-strand breaks. This catalytic inhibition results in accumulation of unrepaired single-strand breaks that convert to double-strand breaks during DNA replication as replication forks encounter the lesions. Second, niraparib induces PARP trapping, wherein the drug-PARP-DNA ternary complex becomes stabilized and the PARP enzyme remains bound to DNA, physically blocking access of other repair factors and creating a toxic DNA lesion that is particularly lethal in homologous recombination repair-deficient cells. The relative contribution of catalytic inhibition versus PARP trapping to the overall cytotoxic effect varies among different PARP inhibitors, with niraparib demonstrating potent activity in both mechanisms.

The pharmacokinetic profile of niraparib supports once-daily oral dosing and exhibits predictable absorption, distribution, metabolism, and excretion characteristics. Following oral administration, niraparib is absorbed with time to maximum concentration occurring approximately three hours post-dose. The absolute bioavailability is approximately 73%, supporting efficient oral delivery. Niraparib exhibits dose-proportional pharmacokinetics across the therapeutic dose range, with steady-state concentrations achieved within approximately two weeks of daily dosing. The volume of distribution is approximately 1220 liters, indicating extensive tissue distribution. Plasma protein binding is approximately 83%, primarily to albumin and alpha-1-acid glycoprotein. The elimination half-life averages 36 hours, supporting sustained drug exposure throughout the 24-hour dosing interval. Niraparib undergoes metabolism primarily through carboxylesterase-mediated hydrolysis to form inactive metabolites, with minor contributions from cytochrome P450 3A4-mediated oxidation. Approximately 48% of the administered dose is excreted in urine and 39% in feces, with minimal excretion of unchanged drug, indicating extensive metabolic clearance prior to elimination.

The recommended dose of niraparib at 200 mg once daily represents a carefully optimized balance between therapeutic efficacy and tolerability in the specific context of combination with abiraterone acetate and prednisone for metastatic castration-sensitive prostate cancer. This dose differs from dosing regimens employed in other clinical settings, including ovarian cancer maintenance therapy where individualized dosing based on body weight and baseline platelet count has been implemented. The selection of 200 mg once daily for the present invention was based on pharmacokinetic-pharmacodynamic modeling integrating target PARP inhibition levels required for synthetic lethality in homologous recombination repair-deficient cells, safety and tolerability data from prior clinical experience, and the specific patient population characteristics including predominantly male gender, higher average body weight compared to ovarian cancer populations, and concurrent administration of abiraterone acetate and prednisone with their associated toxicity profiles.

Abiraterone acetate, chemically designated as (3β)-17-(3-pyridinyl)androsta-5,16-dien-3-yl acetate, represents a steroidal inhibitor of the cytochrome P450 17A1 enzyme with molecular formula C26H33NO2 and molecular weight 391.55 daltons. The compound is administered as the acetate ester prodrug, which undergoes rapid deacetylation following absorption to yield the active moiety abiraterone. The critical enzymatic target, CYP17A1, catalyzes two sequential biochemical transformations essential for androgen biosynthesis. The first transformation involves 17α-hydroxylase activity, which converts pregnenolone to 17α-hydroxypregnenolone and progesterone to 17α-hydroxyprogesterone. The second transformation involves 17,20-lyase activity, which converts 17α-hydroxypregnenolone to dehydroepiandrosterone and 17α-hydroxyprogesterone to androstenedione. These androgenic precursors subsequently undergo peripheral conversion to testosterone and dihydrotestosterone through the actions of 17β-hydroxysteroid dehydrogenase and 5α-reductase enzymes.

Abiraterone achieves inhibition of CYP17A1 through a mechanism involving coordination of the pyridine nitrogen atom with the heme iron at the active site of the enzyme, creating a tight-binding complex with slow dissociation kinetics. The selectivity of abiraterone for CYP17A1 over other cytochrome P450 enzymes contributes to its favorable therapeutic index. Structural studies of abiraterone bound to CYP17A1 reveal that the steroid backbone occupies the substrate-binding pocket with the pyridine substituent positioned to interact with the heme prosthetic group. This binding mode confers inhibitory constants in the low nanomolar range for both 17α-hydroxylase and 17,20-lyase activities, although slightly greater potency is observed for lyase inhibition.

The physiological consequences of CYP17A1 inhibition extend beyond simple testosterone suppression and include alterations in the broader steroidogenic pathway. Blockade of 17α-hydroxylase activity results in accumulation of upstream steroids including pregnenolone and progesterone. These accumulated steroids are shunted into the mineralocorticoid synthesis pathway, leading to increased production of deoxycorticosterone and corticosterone, which possess mineralocorticoid activity. The resulting mineralocorticoid excess manifests clinically as fluid retention, hypertension, and hypokalemia if not adequately managed. Concurrent administration of prednisone, a synthetic glucocorticoid, addresses this mineralocorticoid excess through two mechanisms. First, prednisone suppresses adrenocorticotropic hormone secretion from the pituitary gland via negative feedback on the hypothalamic-pituitary-adrenal axis, thereby reducing the drive for adrenal steroidogenesis and limiting substrate availability for shunting into mineralocorticoid pathways. Second, prednisone provides glucocorticoid replacement, as CYP17A1 inhibition also impairs cortisol synthesis.

The pharmacokinetic profile of abiraterone acetate is characterized by complex absorption kinetics influenced by fed versus fasted state, extensive distribution, hepatic metabolism, and primarily fecal elimination. Following oral administration in the fasted state, abiraterone acetate is converted to abiraterone during and after absorption, with systemic exposure reflecting the active abiraterone moiety. Time to maximum concentration occurs approximately two hours post-dose. The bioavailability exhibits substantial food effect, with high-fat meals increasing exposure several-fold, necessitating administration in the fasted state to reduce variability. Abiraterone exhibits high plasma protein binding exceeding 99%, primarily to albumin and alpha-1-acid glycoprotein. The apparent volume of distribution is approximately 19,700 liters, indicating extensive extravascular distribution. The elimination half-life is approximately 12 hours for abiraterone, supporting once-daily dosing. Metabolism occurs primarily through sulfation and glucuronidation pathways, with minor contributions from cytochrome P450 3A4 and 2D6. Two major metabolites, abiraterone sulfate and N-oxide abiraterone sulfate, are formed, with abiraterone sulfate demonstrating weak CYP17A1 inhibitory activity. Approximately 88% of the administered dose is recovered in feces and 5% in urine, indicating predominant hepatobiliary elimination.

The dose of abiraterone acetate at 1000 mg once daily administered with prednisone 5 mg once daily represents the established therapeutic regimen validated across multiple phase 3 clinical trials in both metastatic castration-resistant and metastatic castration-sensitive prostate cancer. This dosing was established through dose-finding studies evaluating pharmacodynamic suppression of testosterone and androgenic precursor steroids, correlation with clinical outcomes, and assessment of dose-limiting toxicities. The 1000 mg dose reliably achieves suppression of testosterone to undetectable levels when combined with ongoing androgen deprivation therapy and provides maximal inhibition of extragonadal androgen synthesis occurring in adrenal glands and within prostate tumor cells themselves.

The combination of niraparib with abiraterone acetate plus prednisone provides mechanistic synergy operating at multiple biological levels. At the cellular level, androgen receptor signaling has been demonstrated to influence expression of DNA repair genes, with androgen stimulation upregulating certain DNA repair pathways and androgen deprivation downregulating these pathways. Specifically, androgen receptor activation has been shown to enhance expression of DNA repair genes including those involved in non-homologous end joining and base excision repair, while also influencing cell cycle checkpoint control. When abiraterone suppresses androgen synthesis and thereby reduces androgen receptor signaling, prostate cancer cells experience compromised DNA repair capacity beyond the baseline deficiency created by homologous recombination repair gene alterations. This state of compounded DNA repair deficiency creates enhanced vulnerability to PARP inhibition.

At the level of replication stress, androgen deprivation therapy induces changes in DNA replication dynamics that increase the frequency of replication fork stalling and collapse. These stalled replication forks generate structures that require homologous recombination repair for resolution and restart. In cells already deficient in homologous recombination repair due to BRCA or other gene alterations, the additional replication stress imposed by androgen deprivation creates an increased burden of DNA lesions. Concurrent PARP inhibition prevents the alternative repair pathways that cells might employ to manage this replication stress, resulting in accumulation of toxic DNA structures and cell death.

At the tumor microenvironment level, androgen deprivation creates selective pressure that can influence the clonal architecture and evolutionary trajectory of the cancer. Early intervention with PARP inhibition during the window of maximal androgen deprivation response may prevent or delay the emergence of resistant clones that might arise if PARP inhibition were deferred until development of castration resistance. The rationale for initiating PARP inhibition within six months of commencing androgen deprivation therapy rests upon capturing this therapeutic window when tumor cells are maximally vulnerable to the combined assault on both androgen signaling and DNA repair pathways.

The critical importance of patient selection based on homologous recombination repair gene alteration status cannot be overstated, as the therapeutic benefit of the combination is confined to this molecularly defined population. The genes included in the eligibility criteria for the present invention were selected based on biological rationale for involvement in homologous recombination repair and emerging clinical evidence for sensitivity to PARP inhibition. BRCA1 and BRCA2 represent the archetypal homologous recombination repair genes, encoding large proteins that play central roles in the pathway. BRCA1 functions in the early stages of double-strand break recognition and processing, recruiting additional repair factors to damage sites and facilitating resection of DNA ends to create the 3-prime single-stranded DNA required for homologous recombination. BRCA2 functions in the loading of RAD51 recombinase onto the single-stranded DNA, a critical step for homology search and strand invasion into the undamaged sister chromatid template.

The additional genes included in the present invention each contribute specific functions to homologous recombination repair. BRIP1, also known as BACH1 or FANCJ, encodes a DNA helicase that interacts with the BRCA1 C-terminal domain and participates in processing of DNA structures during repair. PALB2, designated partner and localizer of BRCA2, serves as a molecular scaffold linking BRCA1 and BRCA2 and is essential for recruitment of BRCA2 to sites of DNA damage. RAD51B encodes a RAD51 paralog that participates in RAD51 nucleoprotein filament formation and stability. RAD54L encodes a chromatin remodeling protein that facilitates homology search and promotes displacement loop formation during strand invasion. These four genes, together with BRCA1 and BRCA2, comprise the homologous recombination repair effector subgroup based on their direct participation in the core molecular machinery of double-strand break repair.

The inclusion of CDK12, CHEK2, and FANCA extends the genetic eligibility criteria to encompass genes with somewhat different biological functions but which ultimately impact homologous recombination repair capacity. CDK12 encodes cyclin-dependent kinase 12, which phosphorylates the C-terminal domain of RNA polymerase II and regulates transcriptional elongation of genes including DNA repair genes. Loss of CDK12 results in reduced expression of homologous recombination repair genes and creates a state of functional homologous recombination repair deficiency. CHEK2 encodes checkpoint kinase 2, which participates in DNA damage response signaling and cell cycle checkpoint control. FANCA encodes a component of the Fanconi anemia core complex involved in interstrand crosslink repair, which interfaces with homologous recombination repair at the level of processing crosslink-induced DNA damage.

The heterogeneity of treatment effect across these different gene alterations reflects the varying degrees of homologous recombination repair impairment and differing biological contexts. The hazard ratio of 0.52 observed in the BRCA subgroup represents the most robust evidence of therapeutic benefit and aligns with extensive preclinical and clinical data establishing BRCA loss as the prototypical synthetic lethal partner for PARP inhibition. The hazard ratio of 0.57 in the homologous recombination repair effector subgroup demonstrates maintained benefit when including BRIP1, PALB2, RAD51B, and RAD54L alterations alongside BRCA alterations. The hazard ratio of 0.63 in the intention-to-treat population including all nine genes indicates that therapeutic benefit extends across the molecularly selected population, although the magnitude may vary based on specific genetic context.

Analysis of patients with homologous recombination repair gene alterations excluding BRCA1 and BRCA2 yields a hazard ratio of 0.81, which is numerically less favorable than the BRCA subgroup but suggests potential clinical benefit. This subgroup comprises patients with alterations in BRIP1, PALB2, RAD51B, RAD54L, CDK12, CHEK2, or FANCA in the absence of detectable BRCA alterations. The wider confidence interval and smaller magnitude of effect in this subgroup reflect both the smaller sample size and potentially genuine biological heterogeneity in PARP inhibitor sensitivity among different gene alterations. Individual gene subgroups for genes other than BRCA2 and BRCA1 contain insufficient patient numbers within a single trial to enable definitive assessment of treatment effect, highlighting the value of meta-analytic approaches combining data across multiple trials and real-world datasets.

The diagnostic method for identifying patients suitable for treatment represents an integral and essential component of the invention. Multiple validated next-generation sequencing platforms exist that are capable of detecting deleterious alterations in homologous recombination repair genes from tumor tissue, plasma, or germline sources. Tissue-based comprehensive genomic profiling employs DNA extracted from formalin-fixed paraffin-embedded tumor specimens and utilizes hybrid-capture based next-generation sequencing to interrogate the complete coding sequences and select intronic regions of several hundred cancer-related genes. The FoundationOne CDx assay, manufactured by Foundation Medicine Incorporated of Cambridge, Massachusetts, represents one such validated platform that has received regulatory clearance as a companion diagnostic for multiple targeted therapies including PARP inhibitors. This assay detects base substitutions, insertions, deletions, copy number alterations, and select gene rearrangements with high sensitivity and specificity.

The technical specifications of the FoundationOne CDx assay include hybrid-capture enrichment targeting 324 genes with complete exonic coverage, sequencing to median depth exceeding 500-fold coverage, and bioinformatic analysis pipelines optimized for detection of somatic alterations in tumor specimens with varying tumor purity. The minimum tumor content required for analysis is 20% tumor nuclei, and the DNA input requirement is 50 to 250 nanograms depending on specimen characteristics. The assay detects all classes of genomic alterations including single nucleotide variants with allele frequency as low as 5%, insertions and deletions ranging from single base to large structural variants, copy number alterations including homozygous deletions and amplifications, and rearrangements involving select genes. The analytical validation of FoundationOne CDx demonstrates sensitivity exceeding 99% for base substitutions at allele frequency of 10% or greater and specificity exceeding 99.9%, with positive and negative predictive values similarly high.

Plasma-based circulating tumor DNA analysis represents an alternative or complementary approach to tissue-based testing and offers advantages of less invasive sample acquisition and potential for serial monitoring. The FoundationOne Liquid CDx assay, also manufactured by Foundation Medicine, employs next-generation sequencing of cell-free DNA isolated from peripheral blood plasma to detect somatic alterations shed from tumor cells. The technical approach involves hybrid-capture enrichment targeting 324 genes with complete exonic coverage for base substitutions and insertions/deletions, plus select introns of 36 genes for rearrangement detection. The assay requires 10 to 20 milliliters of whole blood collected in specialized cell-free DNA collection tubes, from which plasma is isolated and cell-free DNA is extracted. Deep sequencing to median coverage exceeding 10,000-fold enables detection of low allele frequency variants present in the small fraction of total cell-free DNA that is tumor-derived.

The analytical performance of FoundationOne Liquid CDx demonstrates sensitivity of approximately 90% for detection of known variants at allele frequency of 0.4% or greater and specificity exceeding 99.9%. The limit of detection varies by variant type, with base substitutions detected at allele frequencies as low as 0.1% to 0.4% depending on specific sequence context. The concordance between tissue and plasma testing for detection of known alterations varies depending on factors including tumor burden, tumor location, and treatment history, with overall concordance typically ranging from 70% to 90%. The sensitivity of plasma testing is generally lower than tissue testing, particularly in settings of low tumor burden or tumors that shed limited circulating tumor DNA, but offers advantages of feasibility when tissue is unavailable or exhausted.

Germline genetic testing employs DNA isolated from blood or saliva samples and identifies constitutional genetic alterations present in all cells of the body. The Invitae Multi-Cancer Panel, manufactured by Invitae Corporation of San Francisco, California, represents one validated germline testing platform that interrogates genes associated with hereditary cancer predisposition. The panel includes comprehensive sequencing of genes implicated in homologous recombination repair including BRCA1, BRCA2, BRIP1, PALB2, RAD51B, RAD54L, CHEK2, and others. The technical methodology employs next-generation sequencing with confirmatory Sanger sequencing for reported variants. The analytical sensitivity for detection of sequence variants exceeds 99.9%, and the assay also detects deletions and duplications through analysis of read depth across targeted regions.

The interpretation of genetic variants identified through next-generation sequencing platforms requires careful classification according to established guidelines. The American College of Medical Genetics and Genomics and the Association for Molecular Pathology have published standards for variant classification employing a five-tier system: pathogenic, likely pathogenic, variant of uncertain significance, likely benign, and benign. Classification integrates multiple lines of evidence including population frequency data from large reference databases such as the Genome Aggregation Database, computational predictions of functional impact using algorithms such as PolyPhen-2 and SIFT, experimental functional assays, co-segregation analysis in families, and clinical correlation studies. For the purposes of the present invention, pathogenic and likely pathogenic variants in the specified homologous recombination repair genes constitute qualifying alterations that identify patients suitable for treatment. Variants of uncertain significance do not constitute qualifying alterations unless additional evidence emerges to support pathogenicity.

The clinical workflow for implementing genetic testing in the context of metastatic castration-sensitive prostate cancer requires integration of testing into the diagnostic and treatment planning process. Upon diagnosis of metastatic prostate cancer, tumor tissue from either the primary prostate cancer or a metastatic lesion should be submitted for comprehensive genomic profiling. Archival tissue from prior prostatectomy or biopsy may be utilized if available and of sufficient quality and quantity. If tissue-based testing is not feasible due to insufficient tissue or patient preference, plasma-based circulating tumor DNA testing may be employed. Germline testing should be offered to all patients with metastatic prostate cancer regardless of family history, as a substantial proportion of germline pathogenic variants in homologous recombination repair genes occur in patients without strong family history of cancer.

The turnaround time for genetic testing results varies by platform and laboratory but typically ranges from 10 to 21 days from receipt of sample. During this interval, standard-of-care therapy including androgen deprivation therapy should be initiated. The protocol for the clinical trial supporting the present invention allowed up to six months from initiation of androgen deprivation therapy to randomization, recognizing the practical reality that genetic testing results may not be available immediately at diagnosis. This design feature enables real-world implementation where testing is ordered at diagnosis but results become available during the first several months of androgen deprivation therapy. Patients who receive positive results for qualifying homologous recombination repair gene alterations during this window remain eligible for initiating combination therapy with niraparib, abiraterone acetate, and prednisone.

The eligibility criteria beyond genetic testing requirements include standard oncologic considerations for fitness for systemic therapy. Patients must have histologically confirmed adenocarcinoma of the prostate with documented metastatic disease by conventional imaging. Metastatic disease is defined by the presence of either soft tissue lesions identified by computed tomography or magnetic resonance imaging or bone lesions identified by technetium-99m bone scan. The protocol does not require biopsy confirmation of metastatic lesions, as radiographic documentation combined with elevated prostate-specific antigen provides adequate evidence of metastatic prostate cancer in patients with known primary prostatic adenocarcinoma. Patients must be receiving ongoing androgen deprivation therapy, either with gonadotropin-releasing hormone agonist agents such as leuprolide acetate or goserelin acetate, or gonadotropin-releasing hormone antagonist agents such as degarelix or relugolix. Bilateral orchiectomy represents an alternative means of achieving androgen deprivation. Documentation of castrate testosterone levels, defined as serum testosterone less than 50 nanograms per deciliter or less than 1.7 nanomoles per liter, is required.

Performance status assessment using the Eastern Cooperative Oncology Group scale provides an objective measure of patient functional status relevant to treatment tolerability. The Eastern Cooperative Oncology Group performance status ranges from 0, indicating fully active and able to carry on all pre-disease activities without restriction, to 5, indicating death. Eligible patients for the present invention must have Eastern Cooperative Oncology Group performance status of 0, 1, or 2. Performance status 0 indicates fully active; performance status 1 indicates restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; performance status 2 indicates ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours. Patients with performance status 3 or higher are excluded due to poor tolerance of combination therapy.

Adequate organ function represents an essential prerequisite for safe administration of the combination therapy. Hematologic function requirements include absolute neutrophil count of at least 1.5 × 109 per liter, platelet count of at least 100 × 109 per liter, and hemoglobin of at least 9 grams per deciliter. These thresholds ensure adequate bone marrow reserve to tolerate the myelosuppressive effects of niraparib, which can cause anemia, neutropenia, and thrombocytopenia through direct effects on hematopoietic precursors. Patients with baseline cytopenias below these thresholds are at elevated risk for severe myelosuppression during treatment. Hepatic function requirements include total bilirubin less than 1.5 times the upper limit of normal, aspartate aminotransferase and alanine aminotransferase less than 2.5 times the upper limit of normal in the absence of liver metastases or less than 5 times the upper limit of normal in the presence of liver metastases, and albumin of at least 3.0 grams per deciliter. These parameters ensure adequate hepatic synthetic function and metabolic capacity for drug clearance. Renal function requirements include estimated glomerular filtration rate of at least 30 milliliters per minute per 1.73 square meters calculated using the Modification of Diet in Renal Disease equation or Chronic Kidney Disease Epidemiology Collaboration equation. This threshold accommodates the renal excretion component of niraparib elimination while excluding patients with severe renal impairment.

The treatment regimen comprises continuous daily oral administration of the combination therapy in 28-day cycles without scheduled treatment interruptions or maintenance phases. Each cycle consists of once-daily dosing with niraparib 200 mg, abiraterone acetate 1000 mg, and prednisone 5 mg. The dual-action tablet formulation combines niraparib 200 mg and abiraterone acetate 1000 mg in a single tablet, simplifying administration to one dual-action tablet plus one prednisone tablet per day. The tablets should be swallowed whole with water and should not be crushed, chewed, or divided. Administration should occur at approximately the same time each day to maintain consistent drug exposure. Abiraterone acetate must be administered in the fasted state due to substantial food effect on absorption, specifically at least one hour before food or at least two hours after food. Prednisone may be administered without regard to food, but administration with the abiraterone-containing tablet ensures compliance with fasted dosing requirements.

The pharmaceutical formulation of the dual-action tablet employs conventional immediate-release tablet technology incorporating pharmaceutical excipients that ensure appropriate mechanical properties, dissolution characteristics, and stability. The formulation comprises the two active pharmaceutical ingredients, niraparib tosylate monohydrate equivalent to 200 mg niraparib base and abiraterone acetate 1000 mg, combined with excipients including microcrystalline cellulose as a diluent and binder, croscarmellose sodium as a disintegrant, magnesium stearate as a lubricant, and colloidal silicon dioxide as a glidant. The tablet core is formed by direct compression or wet granulation followed by compression, yielding tablets with hardness suitable for handling and packaging while enabling rapid disintegration and dissolution following ingestion. A film coating comprising hypromellose, titanium dioxide, polyethylene glycol, and iron oxide colorants may be applied to facilitate swallowing, improve appearance, and provide light protection.

The dissolution profile of the dual-action tablet is designed to achieve release of at least 80% of both active ingredients within 30 minutes when tested in United States Pharmacopeia apparatus 2 (paddle method) at 75 revolutions per minute in 900 milliliters of 0.1 normal hydrochloric acid or pH 6.8 phosphate buffer, simulating gastric and intestinal fluid conditions. The bioequivalence of the dual-action formulation to concurrent administration of separate niraparib and abiraterone acetate tablets has been established through pharmacokinetic studies in healthy volunteers comparing area under the plasma concentration-time curve and maximum plasma concentration parameters, with 90% confidence intervals for the geometric mean ratios falling within the regulatory acceptance range of 80% to 125%.

The stability of the dual-action tablet formulation under recommended storage conditions of 20 to 25 degrees Celsius with excursions permitted to 15 to 30 degrees Celsius in the original container protected from light and moisture has been established through accelerated and long-term stability studies. Chemical stability assessed by high-performance liquid chromatography demonstrates that both niraparib and abiraterone acetate remain within 95% to 105% of label claim for at least 24 months under long-term storage conditions and at least 6 months under accelerated conditions of 40 degrees Celsius and 75% relative humidity. Physical stability assessed by appearance, dissolution, and hardness testing confirms maintenance of acceptable tablet characteristics throughout the shelf life. Microbiological stability for the non-sterile oral dosage form is ensured through good manufacturing practices and control of bioburden and absence of specified objectionable organisms.

The prednisone component is formulated as conventional immediate-release tablets containing 5 mg prednisone with standard pharmaceutical excipients. Prednisone tablets are widely available as approved drug products from multiple manufacturers. The specific formulation characteristics are not critical provided that the dissolution profile ensures adequate bioavailability. Prednisone exhibits high oral bioavailability exceeding 80% and is rapidly absorbed with peak levels occurring 1 to 2 hours after administration. The compound undergoes rapid hepatic conversion to prednisolone, the active metabolite, which exerts glucocorticoid effects through binding to the glucocorticoid receptor and modulating transcription of glucocorticoid-responsive genes.

The administration schedule of continuous daily dosing without planned interruptions differs from intermittent or maintenance dosing strategies employed in some other oncologic settings and is predicated upon the mechanisms of action requiring sustained target inhibition. PARP inhibition must be maintained continuously to prevent repair of single-strand breaks and to sustain PARP trapping at DNA damage sites. Interruptions in PARP inhibitor dosing could allow recovery of DNA repair capacity and survival of damaged cells. Similarly, CYP17A1 inhibition must be maintained continuously to sustain suppression of androgen synthesis, as the circulating half-life of abiraterone and the recovery kinetics of enzyme activity would permit androgen level rebound during treatment interruptions. The prednisone component must be administered daily to prevent adrenal insufficiency resulting from suppression of the hypothalamic-pituitary-adrenal axis by exogenous glucocorticoid and by abiraterone-mediated blockade of cortisol synthesis.

The duration of treatment continues until radiographic disease progression, unacceptable toxicity, or patient withdrawal. Radiographic disease progression is defined according to Response Evaluation Criteria in Solid Tumors version 1.1 for soft tissue lesions and Prostate Cancer Working Group 3 criteria for bone lesions. For soft tissue disease, progressive disease is defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, including baseline, and an absolute increase of at least 5 millimeters, or the appearance of one or more new lesions. For bone disease, progression is defined as the appearance of two or more new lesions on bone scan, confirmed by a second scan obtained at least 6 weeks later to distinguish progression from flare phenomenon.

The requirement for confirmatory bone scan at least 6 weeks after initial documentation of new bone lesions addresses the phenomenon of transient apparent worsening due to healing flare, wherein effective therapy induces osteoblastic response that manifests as increased uptake on bone scan but represents treatment response rather than progression. The 6-week interval provides adequate time for true progression to become unequivocal while minimizing unnecessary treatment discontinuation due to flare. Clinical deterioration during the 6-week confirmation period may warrant treatment discontinuation despite lack of confirmatory imaging if the clinical picture clearly indicates progression.

Unacceptable toxicity as a criterion for treatment discontinuation is defined by occurrence of adverse events that cannot be adequately managed through dose modifications and supportive care, that pose unacceptable risk to patient safety, or that result in quality of life detriment that the patient finds intolerable. The specific adverse events most likely to result in treatment discontinuation include grade 4 hematologic toxicity persisting despite dose reduction, grade 3 or 4 non-hematologic toxicity that does not resolve to grade 2 or lower within a reasonable timeframe, recurrent grade 3 toxicity requiring multiple dose reductions leading to inadequate dosing for therapeutic effect, development of myelodysplastic syndrome or acute myeloid leukemia, or other serious adverse events attributable to study treatment.

The dose modification algorithm for managing treatment-emergent adverse events represents a critical component of the invention enabling extended treatment duration despite occurrence of toxicities. The algorithm is based on toxicity grading according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0, which provides standardized definitions for severity of adverse events across multiple organ systems. Grade 1 indicates mild adverse events requiring no intervention or minimal intervention. Grade 2 indicates moderate adverse events requiring minimal, local, or non-invasive intervention. Grade 3 indicates severe or medically significant adverse events that are not immediately life-threatening, requiring hospitalization or prolongation of hospitalization, disabling, or limiting self-care activities of daily

living. Grade 4 indicates life-threatening consequences requiring urgent intervention. Grade 5 indicates death related to the adverse event.

For hematologic toxicities, specific management algorithms are defined for anemia, neutropenia, and thrombocytopenia. Anemia is graded as follows: grade 1 is hemoglobin less than lower limit of normal to 10.0 grams per deciliter, grade 2 is hemoglobin less than 10.0 to 8.0 grams per deciliter, grade 3 is hemoglobin less than 8.0 grams per deciliter, and grade 4 is life-threatening consequences requiring urgent intervention. For grade 1 or 2 anemia, treatment continues at the current dose with monitoring of complete blood count at least every two weeks. For grade 3 anemia, niraparib is interrupted until recovery to hemoglobin at least 9.0 grams per deciliter or grade 2 or lower, and then resumed at a reduced dose of 100 mg once daily. If grade 3 anemia recurs at the 100 mg dose, niraparib is interrupted until recovery and then resumed at 100 mg every other day. If grade 3 anemia recurs at this lowest dose level, niraparib is permanently discontinued while abiraterone acetate and prednisone may continue.

Red blood cell transfusions are provided according to clinical indications including symptomatic anemia manifesting as fatigue, dyspnea, tachycardia, or other signs of inadequate oxygen delivery, or asymptomatic anemia with hemoglobin less than 7.0 grams per deciliter. The transfusion trigger and target hemoglobin should be individualized based on patient age, comorbidities including cardiovascular disease, and symptoms. Generally, transfusion of one to two units of packed red blood cells is administered with reassessment of hemoglobin and symptoms after each unit. Transfusion does not require dose modification of niraparib unless the underlying cause is grade 3 or 4 anemia as defined above. Erythropoiesis-stimulating agents such as epoetin alfa or darbepoetin alfa may be considered for management of chemotherapy-induced anemia according to guideline recommendations, although their use in the context of PARP inhibitor-associated anemia has not been specifically studied.

Neutropenia is graded as follows: grade 1 is absolute neutrophil count less than lower limit of normal to 1.5 × 109 per liter, grade 2 is absolute neutrophil count less than 1.5 to 1.0 × 109 per liter, grade 3 is absolute neutrophil count less than 1.0 to 0.5 × 109 per liter, and grade 4 is absolute neutrophil count less than 0.5 × 109 per liter. For grade 1 or 2 neutropenia, treatment continues at the current dose with monitoring. For grade 3 neutropenia lasting less than 7 days, treatment continues with increased monitoring. For grade 3 neutropenia lasting 7 days or longer, or for grade 4 neutropenia of any duration, niraparib is interrupted until recovery to absolute neutrophil count at least 1.5 × 109 per liter or grade 1 or lower, and then resumed at a reduced dose. Recurrent severe neutropenia warrants further dose reduction or discontinuation. Granulocyte colony-stimulating factors such as filgrastim or pegfilgrastim may be administered for febrile neutropenia or for grade 4 neutropenia to accelerate recovery, and prophylactic use may be considered in patients with recurrent severe neutropenia.

Thrombocytopenia is graded as follows: grade 1 is platelet count less than lower limit of normal to 75 × 109 per liter, grade 2 is platelet count less than 75 to 50 × 109 per liter, grade 3 is platelet count less than 50 to 25 × 109 per liter, and grade 4 is platelet count less than 25 × 109 per liter. For grade 1 or 2 thrombocytopenia, treatment continues with monitoring. For grade 3 thrombocytopenia, niraparib is interrupted until recovery to platelet count at least 75 × 109 per liter or grade 2 or lower, and then resumed at a reduced dose. For grade 4 thrombocytopenia or for bleeding events associated with thrombocytopenia, niraparib is interrupted until recovery and resumed at a reduced dose or permanently discontinued depending on clinical circumstances. Platelet transfusions are provided for platelet count less than 10 × 109 per liter or for clinically significant bleeding at higher platelet counts.

For hypertension, grading is as follows: grade 1 is systolic blood pressure 120 to 139 millimeters of mercury or diastolic blood pressure 80 to 89 millimeters of mercury, grade 2 is systolic blood pressure 140 to 159 millimeters of mercury or diastolic blood pressure 90 to 99 millimeters of mercury requiring initiation of antihypertensive therapy or increase in existing therapy, grade 3 is systolic blood pressure at least 160 millimeters of mercury or diastolic blood pressure at least 100 millimeters of mercury requiring more than one antihypertensive medication or more intensive therapy, and grade 4 is life-threatening consequences such as malignant hypertension or hypertensive crisis. For grade 1 hypertension, lifestyle modifications are recommended including dietary sodium restriction, regular exercise, weight management, and alcohol moderation. For grade 2 hypertension, antihypertensive medication is initiated according to standard clinical practice guidelines. First-line agents typically include angiotensin-converting enzyme inhibitors such as lisinopril, angiotensin receptor blockers such as losartan, calcium channel blockers such as amlodipine, or thiazide diuretics such as hydrochlorothiazide. The choice of agent should consider patient comorbidities, contraindications, and potential drug interactions. For grade 3 hypertension, combination antihypertensive therapy is employed, and if blood pressure cannot be controlled to grade 2 or lower within two weeks, niraparib dose may be reduced. For grade 4 hypertension, niraparib is interrupted immediately, blood pressure is urgently controlled, and rechallenge at reduced dose may be considered after stabilization.

For non-hematologic, non-hypertensive toxicities, the general principle is to interrupt niraparib for grade 3 or 4 events until recovery to grade 1 or lower, and then resume at a reduced dose. Specific management may vary based on the nature of the toxicity. For gastrointestinal toxicities including nausea and vomiting, antiemetic prophylaxis and treatment should be optimized before considering dose reduction. Serotonin 5-HT3 receptor antagonists such as ondansetron or granisetron represent first-line agents for chemotherapy-induced nausea and vomiting and are appropriate for niraparib-associated symptoms. Neurokinin-1 receptor antagonists such as aprepitant may be added for refractory symptoms. Dopamine receptor antagonists such as metoclopramide or prochlorperazine provide additional options. For constipation, a bowel regimen including stool softeners such as docusate, osmotic laxatives such as polyethylene glycol, and stimulant laxatives such as senna should be implemented.

For fatigue, assessment should exclude reversible causes including anemia, hypothyroidism, depression, poor nutrition, and sleep disturbance. Management includes treatment of underlying causes, dose modification of study drugs if severe, and general supportive measures including energy conservation strategies, exercise programs, and nutritional support. For weight loss, nutritional assessment and intervention by a registered dietitian should be pursued, and treatment of contributing factors such as nausea or changes in taste should be optimized. For arthralgia and back pain, non-steroidal anti-inflammatory drugs such as ibuprofen or naproxen may be used if not contraindicated by renal function or history of gastrointestinal bleeding. Acetaminophen represents an alternative analgesic. Physical therapy and exercise programs may provide benefit for musculoskeletal symptoms.

The monitoring schedule during treatment includes clinical assessment, laboratory evaluation, and radiographic assessment at specified intervals. Clinical assessment including medical history, physical examination, vital signs, and performance status evaluation occurs on day 1 of each cycle. Laboratory evaluation including complete blood count with differential, comprehensive metabolic panel including electrolytes, renal function, hepatic function, and prostate-specific antigen occurs on day 1 of each cycle. Additional complete blood count monitoring occurs on day 15 of cycles 1 through 6 to enable early detection of hematologic toxicity during the period of highest risk. After cycle 6, if blood counts are stable, the day 15 assessment may be omitted. Radiographic assessment including computed tomography or magnetic resonance imaging of chest, abdomen, and pelvis, and technetium-99m bone scan occurs at baseline prior to treatment initiation, within 7 days of day 1 of cycle 3, within 7 days of day 1 of cycle 5, and then every 4 cycles thereafter until radiographic progression.

Patient-reported outcomes are assessed using the Functional Assessment of Cancer Therapy-Prostate questionnaire, a validated instrument for measuring health-related quality of life in prostate cancer patients. The FACT-P comprises 39 items organized into five subscales: physical well-being (7 items), social/family well-being (7 items), emotional well-being (6 items), functional well-being (7 items), and prostate cancer subscale (12 items). Each item is rated on a 5-point Likert scale from 0 (not at all) to 4 (very much). Scores are summed to generate subscale scores and a total score ranging from 0 to 156, with higher scores indicating better quality of life. The FACT-P is administered on day 1 of cycles 1 through 24 and then every 4 months from month 25 until 12 months after treatment discontinuation. The minimal clinically important difference for the FACT-P total score has been estimated at 10 points based on anchor-based and distribution-based methods.

The analysis of quality of life data employs a mixed-effects model for repeated measures, which accounts for the correlation among repeated assessments within patients and uses all available data without requiring imputation of missing values. The model includes fixed effects for treatment, visit time, treatment-by-visit interaction, and baseline score, with patient as a random effect and compound symmetry covariance structure. The least-squares mean change from baseline and the difference between treatment groups with associated 95% confidence intervals and p-values are estimated from the model. A data-as-observed approach is used wherein patients contribute data for all timepoints at which assessments are completed, and missing assessments are not imputed. This approach provides unbiased estimates under the assumption that data are missing at random conditional on observed covariates included in the model.

The statistical analysis of the primary endpoint, radiographic progression-free survival, employs the Kaplan-Meier method to estimate the distribution of time to event, the stratified log-rank test to compare treatment groups, and the stratified Cox proportional hazards model to estimate the hazard ratio and associated 95% confidence interval. Stratification factors include BRCA2 alteration versus CDK12 alteration versus other HRR gene alterations, prior docetaxel use (yes versus no), and disease volume (high versus low). The stratified log-rank test assigns weights to observations based on stratification factors to reduce variance and improve power while maintaining correct type I error rate. The stratified Cox model includes stratification factors as stratification variables rather than covariates, allowing different baseline hazard functions across strata while assuming a common treatment effect across strata.

The proportional hazards assumption underlying the Cox model is assessed through examination of Schoenfeld residuals plotted against time and through formal statistical tests including the Schoenfeld global test. If non-proportional hazards are detected, sensitivity analyses employing alternative methods such as accelerated failure time models or restricted mean survival time analysis may be conducted. The hazard ratio provides a summary measure of the treatment effect under the proportional hazards assumption, quantifying the instantaneous risk of an event in the experimental group relative to the control group. A hazard ratio less than 1 indicates reduced risk in the experimental group, with the magnitude of reduction equal to 1 minus the hazard ratio. For example, a hazard ratio of 0.63 indicates a 37% reduction in the instantaneous risk of radiographic progression or death.

The confidence interval for the hazard ratio provides a range of plausible values consistent with the observed data, accounting for sampling variability. A 95% confidence interval indicates that if the study were repeated many times, 95% of

the resulting confidence intervals would contain the true hazard ratio. When the confidence interval excludes 1.0, this indicates statistical significance at the 0.05 level, as a hazard ratio of 1.0 represents no treatment effect. The p-value from the log-rank test provides the probability of observing a test statistic as extreme or more extreme than that observed if the null hypothesis of no treatment difference were true. A p-value less than the prespecified significance level, typically 0.05, leads to rejection of the null hypothesis and conclusion of a statistically significant treatment difference.

The hierarchical graphical testing approach employed for multiplicity control enables testing of multiple hypotheses while maintaining the overall family-wise type I error rate at the 0.05 level. The testing sequence proceeds from radiographic progression-free survival in the BRCA subgroup to radiographic progression-free survival in the HRR effector subgroup to radiographic progression-free survival in the intention-to-treat population, then to time to symptomatic progression in the BRCA subgroup to time to symptomatic progression in the HRR effector subgroup to time to symptomatic progression in the intention-to-treat population, and finally to overall survival in the BRCA subgroup to overall survival in the HRR effector subgroup to overall survival in the intention-to-treat population. Testing proceeds sequentially with each hypothesis tested only if all preceding hypotheses in the sequence are rejected at their allocated significance levels. The graphical structure allocates significance levels to each node representing a hypothesis, and upon rejection of a hypothesis, its allocated significance level is propagated to subsequent nodes according to predefined rules.

The group sequential design for overall survival employs two interim analyses and one final analysis, with alpha spending governed by the Kim-DeMets spending function with parameter 2.5. This spending function allocates a small amount of type I error to early interim analyses and reserves the majority for later analyses when more information is available. The specific alpha levels allocated to each analysis depend on the information fraction, defined as the ratio of observed events to total planned events. At the first interim analysis with information fraction of 0.50, corresponding to 193 of 389 planned overall survival events, the allocated alpha level is substantially less than the total alpha of 0.05 to control type I error across multiple looks at the data.

The intention-to-treat principle employed for the primary efficacy analysis includes all randomized patients analyzed according to assigned treatment group regardless of treatment actually received, protocol adherence, or subsequent events. This approach preserves the benefits of randomization in balancing known and unknown prognostic factors between groups and provides a conservative estimate of treatment effect as it would occur in clinical practice where perfect protocol adherence does not occur. The safety analysis includes all patients who received at least one dose of study treatment analyzed according to the treatment actually received, as this represents the population exposed to potential toxicities.

The clinical trial supporting the present invention enrolled patients from December 2020 to July 2023 across 204 sites in 32 countries spanning North America, South America, Europe, Asia, Australia, and South Africa. The geographic diversity ensures generalizability of results across different populations and healthcare systems. The multinational nature required coordination of regulatory approvals, ethics committee approvals, site training, centralized genetic testing logistics, and data management across time zones and languages. Central review processes including independent radiographic review and genetic testing through centralized laboratories ensured consistency and quality of key assessments.

The primary endpoint data cutoff occurred on January 7, 2025, after a median follow-up of 30.8 months, at which time 264 radiographic progression-free survival events had occurred of a planned 261 events, providing the target information for the final primary analysis. The high degree of completion of radiographic assessments and low rate of censoring for reasons other than event occurrence ensured robust estimation of treatment effect. The consistency of results between investigator-assessed and independent review-assessed radiographic progression-free survival provided confidence in the reliability of the primary endpoint.

The safety data cutoff coincided with the efficacy data cutoff, capturing all adverse events occurring from first dose through 30 days after last dose in patients who received study treatment. The median duration of treatment was 25.3 months in the niraparib plus abiraterone group and 22.5 months in the abiraterone alone group, representing substantial exposure and enabling comprehensive safety assessment. The treatment compliance was high, with median compliance of 97.0% in the combination group and 99.3% in the control group, indicating that the regimen was generally well-tolerated and that patients were able to maintain treatment as prescribed.

The subsequent therapy data demonstrate that after discontinuation of study treatment, patients received a variety of life-prolonging therapies at the discretion of treating physicians informed by local approvals and practice patterns. In the control group, after discontinuation of abiraterone and prednisone, 72% of patients received at least one subsequent life-prolonging therapy, including chemotherapy in 72% of those receiving subsequent therapy and a PARP inhibitor in 33%. This pattern reflects evolution of practice during the trial period toward broader use of PARP inhibitors for metastatic castration-resistant prostate cancer based on regulatory approvals and guideline recommendations. Among patients receiving chemotherapy, 18% received platinum agents including carboplatin or cisplatin, which have overlapping mechanisms with PARP inhibitors in inducing DNA damage.

The availability of PARP inhibitors as subsequent therapy in the control group creates a scenario wherein patients may receive delayed PARP inhibition at castration resistance rather than early PARP inhibition at castration sensitivity as in the experimental group. This treatment pattern enables assessment of whether earlier initiation of PARP inhibition provides advantages beyond delayed initiation, although the non-randomized nature of subsequent therapy choices and the incomplete crossover rate limit definitive conclusions. The ongoing overall survival follow-up will provide further insight into whether the radiographic progression-free survival benefit observed with early PARP inhibition translates to overall survival improvement despite subsequent use of PARP inhibitors in the control group.

The invention addresses a well-defined unmet medical need in a molecularly characterized patient population with poor prognosis despite current standard-of-care therapy. The median radiographic progression-free survival of 29.5 months in the control group receiving abiraterone and prednisone plus androgen deprivation therapy confirms that this patient population experiences substantially worse outcomes compared to unselected metastatic castration-sensitive prostate cancer populations, wherein median radiographic progression-free survival with similar treatment approaches exceeds 40 months. The presence of homologous recombination repair gene alterations thus identifies patients with intrinsically more aggressive disease biology who require more intensive therapeutic intervention.

The combination of niraparib with abiraterone acetate and prednisone provides a biologically rational and clinically validated approach to address this unmet need through early combined targeting of both DNA repair pathways and androgen signaling. The magnitude of radiographic progression-free survival benefit, with hazard ratio of 0.52 in BRCA-mutated patients and 0.63 overall, represents a clinically meaningful prolongation of time to progression. The translation of radiographic benefit to improvement in time to symptomatic progression, with hazard ratio of 0.44 in BRCA-mutated patients and 0.50 overall, demonstrates that the treatment effect delays cancer-related symptoms requiring intervention, a patient-relevant outcome that impacts quality of life and healthcare resource utilization.

The acceptable safety profile, characterized by manageable hematologic toxicities and hypertension as the most common grade 3 or higher adverse events, enables extended treatment duration in the majority of patients when appropriate dose modifications and supportive care are employed. The transient decline in quality of life during the first four cycles followed by return to baseline thereafter indicates that patients adapt to the toxicity burden, and long-term quality of life is maintained at levels comparable to less intensive therapy. This quality of life profile, combined with the substantial disease control benefits, supports a favorable benefit-risk assessment for the combination therapy in the indicated patient population.

The implementation of the invention in clinical practice requires integration of genetic testing into routine care for metastatic castration-sensitive prostate cancer patients, selection of appropriate candidates based on molecular and clinical eligibility criteria, initiation of combination therapy within the therapeutic window of six months from starting androgen deprivation therapy, careful monitoring for adverse events with proactive dose modifications and supportive care, and continuation of treatment until progression or unacceptable toxicity. The dual-action tablet formulation facilitates implementation by simplifying dosing compared to multiple separate medications. The availability of validated companion diagnostic tests through multiple platforms provides flexibility for laboratories to employ testing approaches suited to their infrastructure and patient populations.

The present invention represents a meaningful therapeutic advance for patients with metastatic castration-sensitive prostate cancer and homologous recombination repair gene alterations, providing improved disease control through early combined PARP and androgen pathway inhibition during the castration-sensitive phase of disease when tumor biology may be most vulnerable to this mechanistic combination. The rigorous clinical development program, robust efficacy results, manageable safety profile, and alignment with precision medicine principles support the clinical utility and value of this combination therapy for appropriately selected patients.

Theoretical Basis of the Present Invention

Equation 1: Synthetic Lethality Model for Combined PARP and HRR Deficiency

$$S = 1 - \left(\frac{R_{\text{PARP}} \times R_{\text{HRR}}}{R^{0}_{\text{PARP}} \times R^{0}_{\text{HRR}}} \right)$$

where S represents the synthetic lethality index ranging from 0 to 1, with values approaching 1 indicating strong synthetic lethal interaction. The variable RPARP denotes the residual PARP-mediated DNA repair capacity following niraparib administration, expressed as a fraction of baseline capacity. The variable RHRR represents the residual homologous recombination repair capacity in cells harboring deleterious gene alterations, expressed as a fraction of normal capacity. The variable R^{0}PARP indicates the baseline PARP-mediated repair capacity in untreated cells, normalized to 1. The variable R^{0}HRR indicates the baseline homologous recombination repair capacity in cells without genetic alterations, normalized to 1. In cells with complete BRCA1 or BRCA2 loss, RHRR approaches 0, and with maximal PARP inhibition, RPARP approaches 0,

resulting in the product in the numerator approaching 0 and S approaching 1, indicating maximal synthetic lethality.

Equation 2: Radiographic Progression-Free Survival Hazard Function

$$h(t) = h_0(t)\exp(\beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3)$$

where h(t) represents the instantaneous hazard of radiographic progression or death at time t for an individual patient. The variable $h_0(t)$ denotes the baseline hazard function representing the hazard for patients in the reference categories of all covariates. The coefficient β_1 represents the log hazard ratio associated with treatment assignment, with X_1 being the binary indicator variable coded as 1 for niraparib plus abiraterone and 0 for abiraterone alone. The coefficient β_2 represents the log hazard ratio associated with genetic subgroup, with X_2 being the categorical variable coded as 1 for BRCA2 alteration, 2 for CDK12 alteration, and 0 for other HRR gene alterations. The coefficient β_3 represents the log hazard ratio associated with disease volume, with X_3 being the binary indicator variable coded as 1 for high-volume disease and 0 for low-volume disease. The hazard ratio comparing treatment groups is calculated as $\exp(\beta_1)$, which equals 0.63 in the intention-to-treat population and 0.52 in the BRCA subgroup, indicating the proportional reduction in instantaneous risk of progression or death.

Equation 3: Androgen-Dependent DNA Repair Gene Expression Model

$$E_{\text{repair}}(t) = E_{\text{basal}} + \alpha \times A(t) \times \left(1 - I_{\text{abi}}(t)\right)$$

where Erepair(t) represents the expression level of androgen-regulated DNA repair genes at time t following initiation of therapy. The variable Ebasal denotes the baseline expression level of DNA repair genes in the absence of androgen receptor signaling. The coefficient α represents the fold-induction of DNA repair gene expression in response to maximal androgen receptor activation. The variable A(t) indicates the level of bioavailable androgens at time t, which decreases following initiation of androgen deprivation therapy and is further suppressed by abiraterone-mediated CYP17A1 inhibition. The variable Iabi(t) represents the degree of CYP17A1 inhibition by abiraterone at time t, ranging from 0 for no inhibition to 1 for complete inhibition. In the presence of effective abiraterone therapy, Iabi(t) approaches 1, causing the term (1 - Iabi(t)) to approach 0, thereby reducing Erepair(t) to Ebasal and eliminating androgen-stimulated DNA repair capacity.

Equation 4: Cumulative DNA Damage Accumulation Under Combined Therapy

$$D(t) = \int_0^t \left[\gamma_{\text{basal}} + \gamma_{\text{PARP}} \times C_{\text{nir}}(\tau) + \gamma_{\text{HRR}} \times M_{\text{HRR}} - \delta \times R_{\text{total}}(\tau)\right] d\tau$$

where D(t) represents the cumulative DNA damage burden in tumor cells at time t. The variable γbasal denotes the rate of spontaneous DNA damage generation from endogenous sources including oxidative metabolism and replication errors. The coefficient γPARP represents the rate of additional DNA damage accumulation resulting from PARP inhibition, with Cnir(τ) being the plasma concentration of niraparib at time τ. The coefficient γHRR represents the rate of additional DNA damage accumulation resulting from homologous recombination repair deficiency, with MHRR being a binary indicator variable coded as 1 for presence of deleterious HRR gene alteration and 0 for wild-type status. The coefficient δ represents the rate constant for DNA damage repair through residual functional pathways. The variable Rtotal(τ) indicates the total residual DNA repair capacity at time τ, integrating contributions from all functional repair mechanisms. When D(t) exceeds a critical threshold Dcrit, cell death occurs through mitotic catastrophe or apoptosis, with the time to reach Dcrit being shortened under combined PARP inhibition and HRR deficiency compared to either alone.

Equation 5: Pharmacokinetic-Pharmacodynamic Relationship for PARP Occupancy

$$O_{\text{PARP}}(t) = \frac{C_{\text{nir}}(t)}{C_{\text{nir}}(t) + K_i}$$

where OPARP(t) represents the fractional occupancy of PARP enzymes by niraparib at time t, ranging from 0 for no occupancy to 1 for complete occupancy. The variable Cnir(t) denotes the plasma concentration of niraparib at time t, which exhibits predictable pharmacokinetics following once-daily oral dosing with steady-state achieved after approximately two weeks. The constant Ki represents the inhibition constant for niraparib binding to PARP enzymes, reflecting the affinity of the drug for its target, with lower Ki values indicating tighter binding and greater potency. For niraparib, Ki is in the low nanomolar range, and at the therapeutic dose of 200 mg once daily achieving steady-state trough concentrations of approximately 400 nanograms per milliliter, OPARP(t) exceeds 0.90 throughout the dosing interval, ensuring sustained target inhibition.

Equation 6: Tumor Growth Inhibition Model Under Combination Therapy

$$\frac{dV}{dt} = \lambda V \left(1 - \frac{V}{V_{\max}}\right) - \kappa_1 E_{\text{abi}} V - \kappa_2 E_{\text{nir}} V - \kappa_3 E_{\text{abi}} E_{\text{nir}} V$$

where V represents tumor volume at time t, and dV/dt represents the rate of change of tumor volume. The variable λ denotes the intrinsic tumor growth rate constant in the absence of therapy. The variable Vmax represents the maximum tumor burden sustainable within the host. The term (1 - V/Vmax) provides logistic growth limitation reflecting resource constraints. The coefficient κ_1 represents the tumor cell kill rate constant attributable to abiraterone monotherapy, with Eabi being the effect of abiraterone normalized from 0 to 1. The coefficient κ_2 represents the tumor cell kill rate constant attributable to niraparib monotherapy, with Enir being the effect of niraparib normalized from 0 to 1. The coefficient κ_3 represents the additional tumor cell kill rate constant attributable to synergistic interaction between abiraterone and niraparib. The presence of the synergy term κ_3EabiEnirV distinguishes the combination effect from simple additivity, with κ_3 greater than 0 indicating synergistic tumor control exceeding the sum of individual agent effects.

Equation 7: Time to Radiographic Progression Distribution

$$P(T > t) = \exp\left(-\int_0^t h(\tau) d\tau\right)$$

where P(T > t) represents the probability that time to radiographic progression T exceeds time t, corresponding to the Kaplan-Meier survival function. The variable h(τ) denotes the hazard function at time τ as defined in Equation 2. The integral represents the cumulative hazard from time 0 to time t. The exponential relationship between cumulative hazard and survival probability derives from the fundamental relationship between hazard and survival functions in survival analysis. For the niraparib plus abiraterone group, the median time to progression is the value of t for which P(T > t) equals 0.50, which was not reached at the time of analysis in the BRCA subgroup, indicating that more than 50% of patients remained progression-free. For the abiraterone alone group, the median was 26.0 months in the BRCA subgroup and 29.5 months in the intention-to-treat population.

Equation 8: Quality-Adjusted Progression-Free Survival

$$\text{QAPFS} = \int_0^{T_{\text{prog}}} U(t)\, dt$$

where QAPFS represents quality-adjusted progression-free survival, integrating both duration of progression-free survival and quality of life during that period. The variable Tprog denotes the time to radiographic progression for an individual patient. The variable U(t) represents the utility score at time t, derived from health-related quality of life assessments such as the FACT-P, normalized to a scale from 0 to 1 where 0 represents death or worst possible health state and 1 represents perfect health. The integral calculates the area under the utility curve from treatment initiation to progression, providing a single metric that accounts for both quantity and quality of progression-free time. The observation that FACT-P scores decline during cycles 2 through 4 but return to baseline by cycle 5 indicates that U(t) shows early decrease followed by recovery, resulting in QAPFS for the combination therapy that may be slightly reduced compared to a hypothetical scenario of equal progression-free survival duration with consistently higher quality of life, but still substantially greater than QAPFS for the control group due to the marked improvement in Tprog.

Equation 9: Dose Intensity Function with Modifications

$$I(t) = \frac{D_{\text{actual}}(t)}{D_{\text{planned}}(t)} = \frac{\sum_{i=1}^{n(t)} d_i}{\sum_{i=1}^{n(t)} d_{\text{planned},i}}$$

where I(t) represents the relative dose intensity at time t, defined as the ratio of cumulative actual dose received to cumulative planned dose. The variable Dactual(t) denotes the cumulative actual dose of niraparib received from treatment initiation to time t. The variable Dplanned(t) represents the cumulative planned dose of 200 mg daily over the same period. The variable n(t) indicates the number of dosing days from initiation to time t. The variable di represents the actual dose administered on day i, which may be 200 mg, 100 mg, or 0 mg depending on whether dose modifications or interruptions occurred. The variable dplanned,i represents the planned dose of 200 mg for day i. The median relative dose intensity of approximately 97% observed in the clinical trial indicates that I(t) averaged 0.97, demonstrating high adherence to planned dosing despite the occurrence of adverse events requiring dose modifications in a subset of patients.

Equation 10: Hematologic Toxicity Risk Model

$$P_{\text{anemia}} = 1 - \exp\left(-\theta_0 - \theta_1 \times \text{AUC}_{\text{nir}} - \theta_2 \times \text{Age} - \theta_3 \times \text{BSA}\right)$$

where Panemia represents the probability of developing grade 3 or higher anemia during treatment. The coefficient θ_0 represents the baseline log-odds of anemia. The coefficient θ_1 represents the increase in log-odds per unit increase in area under the concentration-time curve for niraparib, with AUCnir denoting the steady-state niraparib exposure. The coefficient θ_2 represents the increase in log-odds per year of patient age, reflecting age-related decline in bone marrow reserve. The coefficient θ_3 represents the change in log-odds per unit body surface area, with BSA measured in square meters, reflecting the relationship between body size and hematologic tolerance. The observed incidence of grade 3 or higher anemia of 29% in the niraparib plus abiraterone group corresponds to Panemia equal to 0.29, substantially higher than the 4.6% incidence in the abiraterone alone group, indicating that niraparib is the primary driver of anemia risk with θ_1 significantly greater than 0.

Equation 11: Overall Survival Estimation with Competing Risks

$$S_{\mathrm{OS}}(t) = P(T_{\mathrm{death}} > t) = \exp\left(-\int_0^t h_{\mathrm{OS}}(\tau)\, d\tau\right)$$

where SOS(t) represents the overall survival function, defined as the probability that time to death Tdeath exceeds time t. The variable hOS(τ) denotes the hazard of death at time τ, which is influenced by prostate cancer-specific mortality, treatment-related mortality, and competing causes of mortality unrelated to cancer or treatment. The cumulative hazard integral aggregates instantaneous death risks over the observation period. At the first interim analysis with 193 events of 389 planned, corresponding to information fraction of 0.50, the median overall survival was not reached in either treatment group. The hazard ratio estimate of 0.79 for the intention-to-treat population and 0.75 for the BRCA subgroup suggests potential overall survival benefit favoring niraparib plus abiraterone, but the confidence intervals include 1.0, indicating that statistical significance has not yet been achieved pending accrual of additional events at subsequent analyses.

Equation 12: Synergy Quantification Using Bliss Independence Model

$$E_{\mathrm{expected}} = E_A + E_B - (E_A \times E_B)$$

$$\text{Excess over Bliss} = E_{\mathrm{observed}} - E_{\mathrm{expected}}$$

where Eexpected represents the expected combined effect under the assumption of independent action (Bliss independence) of niraparib and abiraterone. The variable EA denotes the effect of abiraterone alone, measured as the proportional reduction in tumor cell viability or the proportional increase in cell death. The variable EB represents the effect of niraparib alone, measured using the same metric. The product EAEB represents the probability that both agents independently induce effects, which is subtracted to avoid double-counting when effects are independent. The variable Eobserved represents the actual combined effect measured experimentally or clinically. The excess over Bliss quantifies synergy, with positive values indicating synergistic interaction where the combination produces greater effect than expected from independent action, and negative values indicating antagonism. The observation that the hazard ratio for the combination (0.63) is more favorable than would be predicted from multiplicative independent effects of the individual agents supports the presence of synergistic interaction.

These equations collectively provide the theoretical and mathematical framework underlying the present invention, integrating concepts from synthetic lethality, pharmacokinetics, pharmacodynamics, tumor growth modeling, survival analysis, and toxicity prediction to explain the mechanisms, quantify the effects, and predict the outcomes of combined PARP and androgen biosynthesis inhibition in metastatic castration-sensitive prostate cancer with homologous recombination repair gene alterations.

Prior Art Reference

Attard, G., Agarwal, N., Graff, J.N. *et al.* Niraparib and abiraterone acetate plus prednisone for HRR-deficient metastatic castration-sensitive prostate cancer: a randomized phase 3 trial. *Nat Med*(2025). https://doi.org/10.1038/s41591-025-03961-8