Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Engl J Med. DOI: 10.1056/NEJMoa1611310

Supplementary Appendix

Supplement to: MR Mirza, BJ Monk, J Herrstedt, et al. Niraparib Maintenance Therapy in Platinum-Sensitive Recurrent Ovarian Cancer.

Contents

Collaborators 2
Methods 5
Patients 5
Study Oversight 5
Biomarker Test 7
Study Assessments 9
Adverse Event Monitoring 10
Study Endpoint Definitions 11
Missing and Partial Data 12
Statistical Analysis 12
Protocol-mandated Dose Modifications 13
Patient-reported Outcomes 16
Supplemental Tables and Figures 18
Supplemental Figure S1. 18
Supplemental Figure S2 19
Supplemental Figure S3 20
Supplemental Figure S4 21
Supplemental Table S1. 22
Supplemental Table S2 24
Supplemental Table S3 25
Supplemental Table S4. 26
Supplemental Table S5 27
Supplemental Table S6 28
References 29

COLLABORATORS

In addition to the authors, the following investigators participated in the ENGOT-OV16/NOVA trial:

NSGO: Denmark, Norway, Sweden

Bente Lund (*Arhus Universitetshospital-Aalborg Sygehus*); Susanne Malander (*Lund University Hospital*); Kathrine Woie (*Haukeland University Hospital*); Kristina Hellman (*Karolinska Universitetssjukhus–Solna*); Trine Juhler Nøttrup (*Herlev Hospital*); Hanne Havsteen (*Herlev Hospital*).

AGO: Germany

Jalid Sehouli (*Charite - Campus Virchow-Klinikum*); Philipp Harter (*Kliniken Essen-Mitte*); Ulrich Canzler (*Medizinische Fakultät Carl Gustav Carus*); Hans-Joachim Lück (*Facharzt fuer Frauenheilkunde Gynaekologisch-Onkologische*); Linn Wölber (*Universitätsklinikum Hamburg-Eppendorf*); Frederik Marmé (*University Hospital Heidelberg*); Werner Meier (*Evangelisches Krankenhaus Düsseldorf*); Martin Heubner (*Universitätsklinikum Essen*); Felix Hilpert (*Universitätsklinikum Schleswig-Holstein - Campus Kiel*); Günter Emons (*Universitätsmedizin Göttingen*); Alexander Burges (*University of Munich*).

GEICO: Spain

Isabel Maria Bover Barcelo (*H. Son Llàtzer*); Marta Gil Martín *(Institut Catalá d´Oncología (I.C.O.)*); Isabel Palacio Vázquez (*H.U.C. de Asturias*); Antonio Casado Herráez (*Hospital Universitario San Carlos*); José Maria del Campo (*H.U.Vall d'Hebrón*).

GINECO: France

Anne Lesoin (*Centre Oscar Lambret*); Dominique Berton-Rigaud (*ICO*); Thierry N'Guyen (*Hospitalier Jean Minjoz*); Anne-Claire Hardy-Bessard (*Clinique Armoricaine de Radiologie - St. Brieuc*).

NCRI: United Kingdom

Susana Banerjee (*The Royal Marsden NHS Foundation Trust*); Rosemary Lord (*The Clatterbridge Cancer Centre NHS Foundation Trust*); Justin Waters (*Maidstone and Tunbridge Wells NHS Trus*t); Ana Montes (*Guy's and St Thomas' NHS Foundation*); Stephen Chan (*Nottingham University Hospitals NHS Trust - City Hospital*); Sarah J. Williams *(Birmingham City*

Hospital); Claire Barlow (*Yeovil District Hospital, NHS Foundation Trust*); Anna Mullard (*Gwynedd Hospital*).

MITO MaNGO: Italy

Nicoletta Colombo (*IEO - Istituto Europeo di Oncologia*); Giovanni Scambia (*PU A.Gemelli, Università Cattolica del Sacro Cuore*); Germana Tognon (*AO Spedali Civili di Brescia, PO Spedali Civili*); Paolo Scollo (*Ospedale Cannizzaro*).

BGOG: Belgium

Frédéric Kridelka (*CHU de Liège - Domaine Universitaire du Sart Tilman*); Chantal Leroy (*CHR Citadelle*); Philip Debruyne (*AZ Groeninge - Campus Loofstraat*); Manon Huizing (*UZ Antwerpen*).

ISGO: Israel

Ora Rosengarten (*Shaare Zedek Medical Center*); Talia Levy (*The Edith Wolfson Medical Center*); Ronnie Shapira Frommer (*The Chaim Sheba Medical Center*); Ami Fishman (*Meir Medical Center*); David Edelman (*Hadassah Medical Organisation*); Tamar Safra (*Tel Aviv Sourasky Medical Center*); Amnon Amit (*Rambam Health Care Campus*).

CEEGOG: Poland

Joanna Pikiel (*COPERNICUS Podmiot Leczn. Sp z o.o.,Wojew. Centrum Onkologii*); Jacek Suzin (*Wojewodzki Specjalistyczny Szpital im. M. Pirogowa*); Beata Mackowiak-Matejczyk (*Bialostockie Centrum Onkologii im. M. Sklodowskiej–Curie*).

AGO: Austria

Alexander Reinthaller (*Medical University of Vienna*); Edgar Petru (*LKH-Univ. Klinikum Graz*).

Hungary

Tibor Csoszi (*Jasz-Nagykun-Szolnok Megyei Hetenyi Geza Korhaz – Rendeloint*).

Canada

Paul Bessette (*Centre Hospitalier Universitaire de Quebec*); Diane Provencher (*Chum Hospital Notre-Dome*); Susie Lau (*Jewish General Hospital*); Susan Ellard (*British Columbia Cancer Agency*); Prafull Ghatage (*Tom Baker Cancer Center*).

United States

Kathleen Moore (*University of Oklahoma/Sarah Cannon Research Institute*); Robert Wenham (*H. Lee Moffit Cancer Center & Research Institute*); Mario Pineda (*Northwestern University*); Masoud Azodi (*Yale University School of Medicine*); Gina Mantia-Smaldone (*Fox Chase Cancer Center*); Noelle Cloven (*Texas Oncology*); Cheryl Bailey (*Minnesota Oncology*); Christine Lee (*Texas Oncology-The Woodlands*); Angeles Secord (*Duke University Medical Center*); Manish Patel (*Florida Cancer Specialists Clinical Laboratories*); Michael Method (*IU Melvin and Bren Simon Cancer Center*); Michael Callahan (*St. Vincent Hospital*); John Veena (*Northwell Health/Monter Cancer Center*); John Chan (*Sutter Health*); Corrine Zarwan (*Lahey Clinic*); Paul DiSilvestro (*Women and Infants Hospital*); Michael Teneriello (*Texas Oncology-Central Austin Cancer Center*); Divya Gupta (*Weill Cornell Medical Center*); Melissa Geller (*University of Minnesota Medical Center – Fairview*); Howard Burris (*The Sarah Cannon Research Institute*); Brian Slomovitz (*University of Miami*); Andrea Wahner Hendrickson (*Mayo Clinic Cancer Center*); Colleen McCormick (*Northwest Cancer Specialists*); Parviz Hanjani (*Abington Memorial Hospital*); Stephanie Blank (*New York University School of Medicine*); Paul Haluska (*Mayo Clinic Cancer Center – Rochester*); Daniela Matei (*IU Melvin and Bren Simon Cancer Center*); Stephen Vasilev (*Southern California Permanente Medical Group*); Jeffrey Neidhart (*San Juan Regional Cancer Center*); Matthew Boente (*Minnesota Oncology*); Nana Tchabo (*Atlantic Health*); David Miller (*UT Southwestern Medical Center*).

METHODS

PATIENTS

Source documentation of platinum-sensitive disease following the penultimate platinum-based chemotherapy was required and could have included physician or clinic notes. For the last platinum-containing therapy, patients were required to have received a minimum of four cycles of treatment and, following treatment, have an investigator-defined complete or partial response to their last platinum regimen with no observable residual disease of <2 cm and cancer antigen 125 (CA-125) values either within the normal range, or a CA-125 decrease of more than 90% that was stable for at least 7 days. Other inclusion criteria were Eastern Cooperative Oncology Group performance status 0 or 1; adequate hematologic, renal, and liver function; availability of formalin-fixed, paraffin-embedded archival tumor from the primary or recurrent cancer; and no prior use of a PARP inhibitor.

Study patients, Investigators, study personnel at sites, and the Tesaro study team and its representatives were blinded to the identity of the assigned treatment from the time of randomization until final database lock. Patients who were ongoing in the study at the time of database lock remained blinded to their treatment assignments, as did the site investigators and study personnel.

STUDY OVERSIGHT

The study was performed according to the ENGOT model C.[1] The following paragraph lists the requirements for trials between academic groups and industry sponsors:

1. One protocol developed and agreed on by the lead study group and the industry partner and reviewed and approved by the trial steering committee.
2. The statistical analysis plan is agreed upon by the lead study group and the industry partner.
3. One database agreed on by the lead study group and the industry partner.
4. One case report form, preferentially a website-based electronic case report form, agreed by the lead study group and the industry partner.
5. Sponsor: the academic group or industry. The legal sponsor has the final responsibility according to the European Union directive.

6. Monitoring: Central monitoring may be allowed over on-site monitoring, depending on the own group policies of quality control and quality audits, if allowed by the protocol. The financial budget available for such quality controls and legal requirements of the territories covered by each group need to be taken into account.
7. Database property: III. Option C: Database at the CRO; the CRO is contracted by the company. The choice of a CRO is made in mutual agreement between the academic groups and the industry sponsor.
    a. Quality assurance and certified DB software with 100% tracing of any access or changes made.
    b. Audits by the study group or study groupY assigned auditors.
    c. Installation of SOPs for the respective protocol and information system for any violation to the study group.
    d. Transfer of complete database for further scientific evaluations to the study group after final analysis of predefined end points.
8. Statistical analysis and publication:
    a. A study group is responsible for the independent analysis of the complete DB for primary and secondary end points.
        i. The database may be used later for further meta-analyses or subgroup analyses of the study group or within an intergroup consortium.
        ii. The publication is the sole responsibility of the study group.
        iii. The company may comment within a predefined period but cannot prohibit any publication.
    b. Intergroup trials:
        i. Each participating group should receive a data set of patients recruited by the respective study group after final analysis.
        ii. Separate analyses by one participating group on their included patients should not include primary or secondary end points, and the intergroup study leading committee (steering committee) and the principal investigator should be informed on each project.
        iii. Further subgroup analysis of the whole population should be prospectively discussed among the groups and agreed.
    c. The company may perform all the analyses necessary for regulatory or economic purposes.
    d. The official study report must be agreed on by the leading study group.
    e. The company is neither allowed to scientific publishing nor to transfer the DB to any third party for scientific publishing, unless after mutual agreement.
    f. In the publication, it should be mentioned that the trial was performed according to the principles of the current document and to which DB property model (paragraph 7.c option A, B, or C).
9. Non-European Countries: Institutions from non-European countries can participate, and two models are possible:
    a. A non-European academic study group participates in the intergroup consortium.
10. The IDMC: The IDMC is appointed by the academic group in mutual agreement with the industry partner.
    a. Similarly, the industry partner may object against a member suggested by the study group, if they could give rational reasons.

11. Standard operating procedures have to be agreed on by the study group and the company, preferentially based on the SOP of the academic study group modified according to the needs of the protocol, but SOPs of the industry may be acceptable.

BIOMARKER TEST

During the conduct of the ENGOT-OV16/NOVA study, a molecular classifier was independently developed and validated by Myriad Genetics to determine if individual tumors were positive for homologous recombination deficiency (HRD-positive) or not (HRD-negative). The myChoice® HRD test was identified as the biomarker classifier to define a patient population enriched for niraparib sensitivity as described below. In order to determine HRD status, Protocol Amendment 4 required tumor tissue samples from patients in both cohorts to be submitted to Myriad Genetics for evaluation using the myChoice® HRD test; prior to that time tumor tissue samples were not mandatory. All testing was completed prior to database lock. Biopsies were not collected at time of progression, therefore homologous recombination deficiency status at time of progression was not explored in this study. Myriad Genetics has performed an analysis that identified *BRCA1/2* mutations and calculated the HRD score of primary resections and paired biopsies taken at time of recurrence in a set of 60 ovarian cancers.[2] All (100%) of the tumor *BRCA1/2* mutations (germline plus somatic mutations) identified in the primary tissue sample were also identified in the sample taken at time of recurrence. Homologous recombination deficiency status as determined by the HRD score was 100% concordant between the primary and recurrent tumors. One possible reversion mutation was identified in one of the recurrent tumors. These data indicate that changes in HRD status between primary tumor and relapse are rare.

The myChoice® HRD test is an integrated genome-based assay for homologous recombination deficiency that quantitates genomic instability of the tumor and, in parallel, detects and classifies variants in *BRCA1* and *BRCA2*. It is a next-generation sequencing test that uses DNA extracted from formalin-fixed paraffin-embedded tumor tissue. Extracted DNA is

used to create libraries that are hybridized to a custom Agilent SureSelect capture array carrying probes for 54,091 single nucleotide polymorphisms distributed across the human genome, and 685 probes for *BRCA1* and *BRCA2* exons, exon boundaries, and promoter regions. Three algorithms are used to assess genomic instability: loss of heterozygosity profiles,[3] telomeric allelic imbalance,[4] and large-scale state transitions.[5] HRD status is based on the sum of these measurements. Each of the three markers is highly correlated with defects in *BRCA1/2*, along with other DNA repair pathway genes in breast and ovarian cancer tumors; recent analysis demonstrated that the use of all three markers, as assessed in the myChoice® HRD test, provides for a tumor classification of HRD-positive or HRD-negative.[6]

The myChoice® HRD test was used to define the population of patients within the non-g*BRCA*mut cohort whose tumors were deficient in homologous recombination. Subgroups of the HRD-positive group within the non-*BRCA*mut cohort were further defined based on the presence of a somatic *BRCA* mutation (HRD-positive/s*BRCA*mut) or the lack of a mutation (HRD-positive/*BRCA*wt). A negative myChoice® HRD test result was indicative of competent homologous recombination; those patients were included in the non-g*BRCA*mut HRD-negative group. There were 54 patients whose HRD status could not be determined due to inconclusive results or inadequate or missing specimen; these patients were included in the intention-to-treat analysis of the overall non-g*BRCA*mut cohort. The definitions of terminology used in the test results are listed below, and the numbers of patients assigned to the various groups and subgroups are shown in Fig. S1, Supplementary Appendix.

> **Germline *BRCA* mutation (g*BRCA*mut)** – A germline *BRCA* mutation is an inherited deleterious mutation in either a *BRCA1* or *BRCA2* tumor suppressor gene. Harmful mutations in either of these genes may produce a hereditary breast-ovarian cancer syndrome in affected persons. Cells with deleterious or suspected deleterious germline *BRCA1* or *BRCA2* mutations have a defect in the repair of DNA breaks by the error-free mechanism of homologous recombination. This defect results in the repair of such lesions by error-prone mutagenic pathways, such as single-strand annealing and nonhomologous end joining, leading to genomic instability. Women with harmful

germline mutations in either *BRCA*1 or g*BRCA*2 have a risk of breast cancer that is approximately 5 times the normal risk, and a risk of ovarian cancer that is about 10 to 30 times normal.

Somatic *BRCA* mutation (sBRCAmut) – A somatic *BRCA* mutation is a deleterious or suspected deleterious alteration in the *BRCA*1 or *BRCA*2 genes that is acquired after conception (not hereditary). Somatic mutations can occur in any cell of the body except the germ cells (sperm and egg) and therefore are not passed on to children. A somatic *BRCA* mutation may also confer increased risk of cancer in affected cells. These mutations are not present in the germline.

***BRCA* wild type (*BRCA*wt)** – A tumor which does not possess either a deleterious or suspected deleterious germline or a somatic *BRCA* mutation.

Homologous recombination deficiency (HRD) – Dysregulation in the homologous recombination DNA repair pathway (due to genetic mutations or alterations) leading to cellular genomic instability and an inability to efficiently repair damaged DNA. HRD-positive cells are more susceptible to the effects of DNA damaging agents such as platinum agents or PARP inhibitors.

HRD-positive – HRD positive status in this study was determined by the myChoice® HRD test. Any tumor that scored ≥42 or had a deleterious or suspected deleterious *BRCA1/2* mutation was considered HRD positive via this test. Within the non-g*BRCA*mut cohort, tumors with somatic BRCA mutations were identified by this test. These tumors have a defective homologous recombination repair pathway.

HRD-negative – HRD negative status in this study was determined by the myChoice® HRD test. Any tumor that scored <42 and did not possess a deleterious or suspected deleterious *BRCA1/2* mutation was considered HRD negative via this test. These tumors have a functional homologous recombination repair pathway.

STUDY ASSESSMENTS

CA-125 testing was conducted at screening and day 1 of each cycle; CA-125 progression was assessed per Gynecologic Cancer Intergroup (GCIG) criteria.[7] Physical examinations, vital sign measurements, and clinical laboratory tests were conducted on days 1 and 15 of the first cycle and day 1 of each subsequent cycle; additional complete blood counts were performed on days 8 and 21 of the first cycle. Tumor samples for HRD testing were collected; testing was

completed prior to database lock. Assessment of next subsequent anticancer therapies was assessed every 90 days (± 7 days) following the study treatment discontinuation visit. The following were collected using source documentation: next anticancer therapy (name and/or class); date of start of subsequent therapies; dose limiting toxicities; best response (complete response, partial response, stable disease, partial disease); and date of progression. Survival status was assessed every 90 days (± 7 days) following the study treatment discontinuation visit. New malignancy information was also collected as part of this assessment. Adverse events were monitored throughout the treatment period, described in detail below, and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. The following terms include pooled adverse events: Thrombocytopenia includes reports of thrombocytopenia and decreased platelet count; fatigue includes reports of fatigue, asthenia, malaise, and lethargy; anemia includes reports of anemia and decreased hemoglobin counts; neutropenia includes reports of neutropenia, decreased neutrophil count, and febrile neutropenia.

Patient-reported outcomes were assessed using the disease-specific Functional Assessment of Cancer Therapy–Ovarian Symptom Index questionnaire[8] and the European Quality of Life Scale, the EQ-5D-5L (EuroQol 5-Dimensions) questionnaire[9], both collected every 8 weeks through cycle 14 and then every 12 weeks thereafter until progression of disease, and once 8 weeks after progression of disease. (See below for additional details).

ADVERSE EVENT MONITORING

Adverse events and serious adverse events were collected from the time of signing the main informed consent form through treatment discontinuation. New serious adverse events (including deaths) were collected for 30 days after treatment discontinuation.

Adverse events could be volunteered spontaneously by the patient, or discovered by the study staff during physical examinations or by asking an open, non-leading question such as:

“How have you been feeling since you were last asked?” All adverse events and any required remedial action were recorded. The nature of adverse event, date (and time, if known) of adverse event onset, date (and time, if known) of adverse event outcome to date, severity, and action taken of the adverse event were documented along with the Investigator’s assessment of the seriousness of the adverse event and causal relationship to study drug and/or study procedure.

All adverse events were recorded individually in the patient's own words (verbatim) unless, in the opinion of the Investigator, the adverse events constituted components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome was named rather than each individual symptom. All adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), and severity assessed using Common Terminology Criteria for Adverse Events (CTCAE) v.4.02.

STUDY ENDPOINT DEFINITIONS

- Chemotherapy-free interval: the time from the last platinum dose until initiation of the next anticancer therapy
- Time to first subsequent therapy and time to second subsequent therapy: the time from treatment randomization in the current study to the start date of the first or second subsequent anticancer therapies, respectively
- Progression-free survival 2: the time from treatment randomization to assessment of progression on the next anticancer therapy following study treatment, or death by any cause. This encompasses time to second subsequent treatment if date for the second progression is not known.

MISSING AND PARTIAL DATA

Missing and partial dates were queried. Imputed dates were characterized as another numeric variable. Imputed date values were performed according to the most conservative approach. If any date was imputed and requested on a listing, the original non-imputed date was provided on the same listing as reference. In general, imputed dates were only used for analysis purposes. Missing dates were imputed based on the following algorithm: If the day of the month was missing for any date used in a calculation, the first day of the month was used to replace the missing day unless the calculation resulted in a negative time duration (eg, date of resolution cannot be prior to day of onset). If the day of the month and the month was missing for any date used in a calculation, January 1 was used to replace the missing date.

STATISTICAL ANALYSIS

The ENGOT-OV16/NOVA trial was sized to evaluate the progression-free survival end point and to ensure adequate data to monitor safety and overall survival. The sample size for the g*BRCA*mut cohort was determined based on the assumption that niraparib would result in an improvement in median progression-free survival from 4.8 to 9.6 months (corresponding to a hazard ratio of 0.50 for niraparib relative to placebo). For a true hazard ratio of 0.50, 98 progression-free survival events would provide >90% power assuming 2:1 randomization (1-sided alpha=0.025). To obtain a sufficient number of progression-free survival events, planned enrollment was approximately 180 patients in the g*BRCA*mut cohort and 310 patients in the non-g*BRCA*mut cohort (to obtain a sufficient number of events in the HRD-positive group, because approximately 40% of patients in the non-g*BRCA*mut cohort were assumed to be HRD-positive at the time the study was designed).

For each primary efficacy population, progression-free survival was analyzed with a stratified log-rank test using randomization stratification factors, and summarized using the Kaplan-Meier methodology. Hazard ratios with 95% confidence intervals were estimated using a

stratified Cox proportional hazards model, with the stratification factors used in randomization. For each group, the Cox proportional hazards model was fitted and a table showing the hazard ratios and 95% confidence intervals within each subgroup category was provided. A statistical test for the presence of a treatment-by-subgroup interaction was performed by including the interaction term in the primary analysis model using Cox regression. If the treatment-by-subgroup interaction was found to be statistically significant at the 10% level (P<0.10), this may have been taken as evidence of heterogeneity of the treatment effect across the subgroup categories. Secondary time-to-event end points were analyzed in the same manner as progression-free survival. Primary efficacy populations were explored for progression-free survival based on age, race, geographic region, time to progression after the penultimate platinum therapy before study enrollment, use of bevacizumab in conjunction with the penultimate or last platinum regimen, best response during the last platinum regimen, number of prior platinum regimens, and number of prior chemotherapy regimens.

Exploratory analyses were performed on subgroups in the non-g*BRCA*mut cohort to help understand the study results and to inform the design of future studies. These included tumors with somatic *BRCA* mutations (HRD-positive/s*BRCA*mut), those with wild-type *BRCA* genes (HRD-positive/*BRCA*wt), and those that were HRD-negative. Results for tumors with an undetermined HRD status were analyzed separately. Formal hypothesis testing was not performed for the exploratory analyses.

PROTOCOL-MANDATED DOSE MODIFICATIONS

Dose interruption and/or reduction could have been implemented at any time for any grade toxicity considered intolerable by the patient. Treatment was interrupted for any non-hematologic National Cancer Institute (NCI)-CTCAE (v.4.02) Grade 3 or 4 adverse event which the Investigator considered to be related to administration of niraparib or matching placebo. If toxicity was appropriately resolved to baseline or Grade 1 or less within 28 days, the patient

could have restarted treatment with niraparib or matching placebo, but with a dose level reduction according to Table 1 if prophylaxis was not considered feasible. If the event recurred at similar or worse grade, treatment was interrupted again and, upon resolution, a further dose reduction must have been made. No more than 2 dose reductions were permitted.

If the toxicity requiring dose interruption had not resolved completely or to NCI-CTCAE Grade 1 during the maximum 4 week (28 day) dose interruption period, and/or the patient had already undergone a maximum of 2 dose reductions (to a minimum dose of 100 mg QD), the patient permanently discontinued treatment with niraparib or matching placebo. The dose interruption/modification criteria for hematologic parameters were based on blood counts and are outlined in Table 2.

Table 1: Dose Reductions for Non-Hematologic Toxicities

Event[1]	**Dose**[2]
Initial dose	300 mg QD
1st dose reduction for NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE where prophylaxis is not considered feasible	200 mg QD
2nd dose reduction for NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE where prophylaxis is not considered feasible	100 mg QD
Continued NCI-CTCAE Grade 3 or 4 treatment-related SAE/AE ≥ 28 days	Discontinue study medication

Abbreviations: AE=adverse event; NCI-CTCAE=National Cancer Institute - Common Terminology Criteria for Adverse Events; QD=once daily; SAE=serious adverse event.
1. Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the patient; 2. Dose not to be decreased below 100 mg QD.

Table 2. Dose Modification/Reduction for Hematologic Toxicities

Finding	Modification
Platelet count 75,000-99,999/μL (grade 1)	Study drugs must be interrupted until platelet counts are ≥100,000/μL, with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at same dose or reduced dose based on clinical judgment.
Second occurrence of platelet count 75,000-99,999/μL (grade 1)	Study drugs must be interrupted until platelet counts are ≥100,000/μL, with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.
Platelet count <75,000/μL (grade 2 or higher)	Study drugs must be interrupted until platelet counts are ≥100,000/μL, with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.
Neutrophil <1,000/μL (grade 3 or higher)	Study drugs must be interrupted until neutrophil counts ≥1,500/μL, with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.
Hemoglobin <8 g/dL (grade 3 or higher)	Study drugs must be interrupted until hemoglobin is ≥9 g/dL, with weekly blood counts for CBC monitored until recovery. Study drug may then be resumed at a reduced dose.

Abbreviations: CBC=complete blood cell count.

If dose interruption or modification was required at any point on study because of hematologic toxicity, to ensure safety of the new dose, weekly blood draws for complete blood cell count (CBC) were required for an additional 4 weeks after the adverse event had been resolved to the specified levels, after which monitoring every 4 weeks could resume. Weekly blood draws for CBC could be collected either at study site or local laboratories. If the hematologic toxicity had not recovered to the specified levels within 4 weeks (28 days) of the dose interruption period, and/or the patient had already undergone a maximum of 2 dose reductions (to a minimum dose of 100 mg QD), the patient permanently discontinued treatment with niraparib or matching placebo.

Any patient who required transfusion of platelets or red blood cells (1 or more units) or hematopoietic growth factor support had a dose reduction upon recovery if study treatment was resumed. The patient must have been referred to a hematologist for further evaluation (1) if transfusions were required on more than 1 occasion or (2) if the treatment-related hematologic toxicities had not recovered to CTCAE Grade 1 or less after 4 weeks. If a diagnosis of

MDS/AML was confirmed by a hematologist, the patient permanently discontinued study treatment. For major surgery while on treatment, up to 28 days of drug interruption was allowed. Once the dose of study treatment has been reduced, any re-escalation must have been discussed with the medical monitor. All dose interruptions and reductions (including any missed doses), and the reasons for the reductions/interruptions, were recorded in the electronic case report form (eCRF).

PATIENT-REPORTED OUTCOMES

The Functional Assessment of Cancer Therapy–Ovarian Symptom Index (FOSI) is a validated eight−item measure of symptom response to treatment for ovarian cancer based on a subset of questions from the FACT-O questionnaire. For each question, patients responded to their symptom experience over the previous 7 days using a five-point Likert scale of “not at all” (0) to “very much” (4). The FOSI score range is 0 (severely symptomatic) to 32 (asymptomatic).

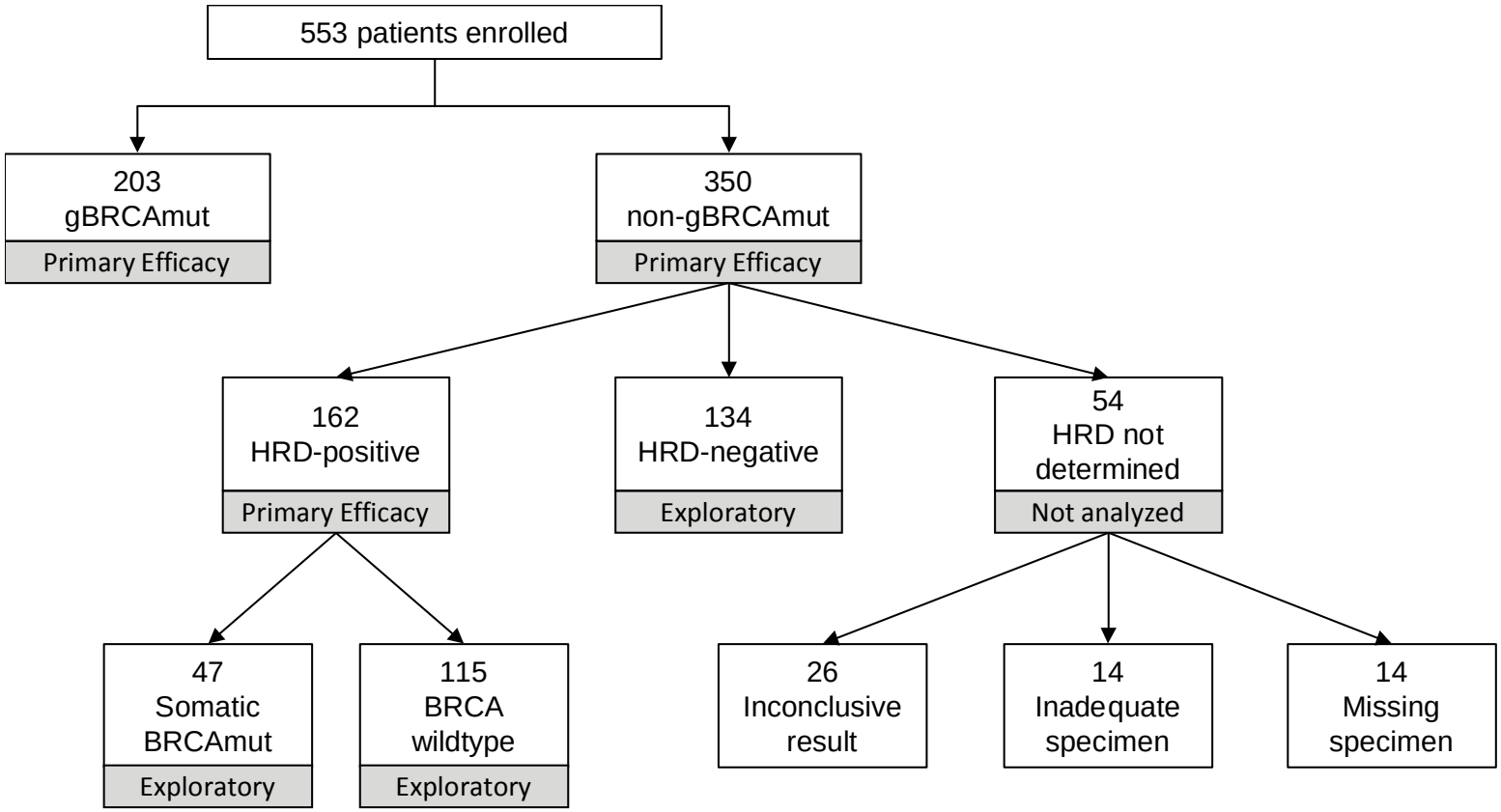
The European Quality of Life scale, 5-Dimensions (EQ-5D-5L) measures the patient’s perceived health state in the following five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each domain has five possible levels: no problems (level 1), slight problems (level 2), moderate problems (level 3), severe problems (level 4), and (level 5) extreme problems. Each domain is assigned a level, which are combined to create a five-digit number describing the patient’s health state (e.g., 11111, 12345). For each patient, an index value is determined from the health states using the US value set. The index value 1 indicates full health; the closer to 1 the better the health of the patient.

The FOSI and EQ-5D-5L were collected in a coordinated fashion with RECIST tumor imaging while patients were on study treatment, and following discontinuation of treatment, regardless of progression status (at the nearest study visit to the imaging exam, after every 2 cycles through cycle 14, and then after every 3 cycles). If the patient discontinued study treatment, assessment of PROs was performed at that time and then 8 weeks (± 2 weeks) later,

regardless of subsequent treatment. The PROs could be completed remotely. It is estimated that PRO evaluations took less than 20 minutes at each time point. Since these were questionnaires, their completion did not interfere with, or preclude, future treatment or clinical studies. After treatment discontinuation, study information on PROs, response, tolerability with subsequent anticancer treatment, and survival continued to be collected.

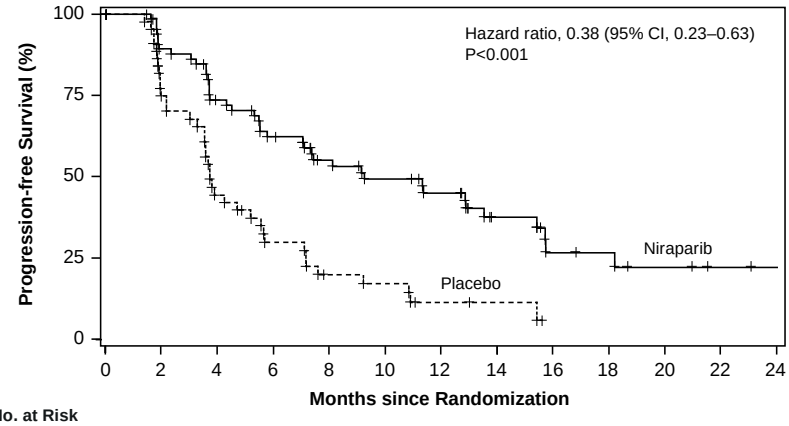
SUPPLEMENTAL TABLES AND FIGURES

SUPPLEMENTAL FIGURE S1. Patient Numbers for Each Biomarker Population. g*BRCA*mut denotes germline *BRCA* mutation, HRD, homologous recombination deficiency.



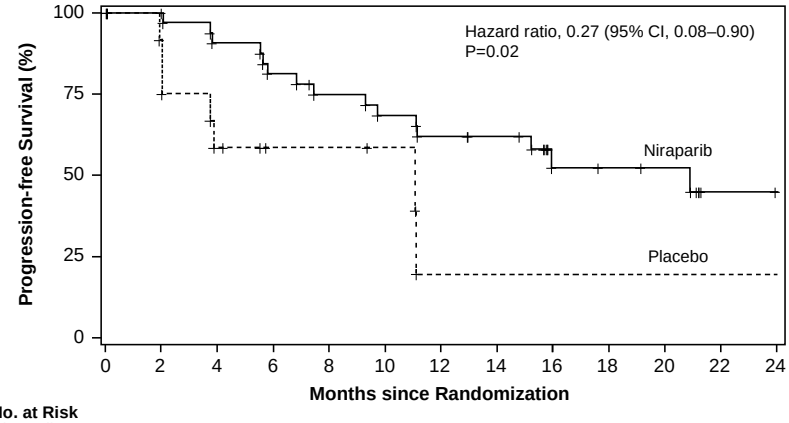
SUPPLEMENTAL FIGURE S2. Kaplan-Meier Estimates of Progression-free Survival within the Sub-populations of the Non-g*BRCA*mut Cohort: (A) HRD-positive/*BRCA*wt Sub-group, (B) HRD-positive/s*BRCA*mut Sub-group, and (C) non-g*BRCA*mut HRD-negative Group. Two-sided P values are from the stratified log-rank test. CI denotes confidence interval.

A



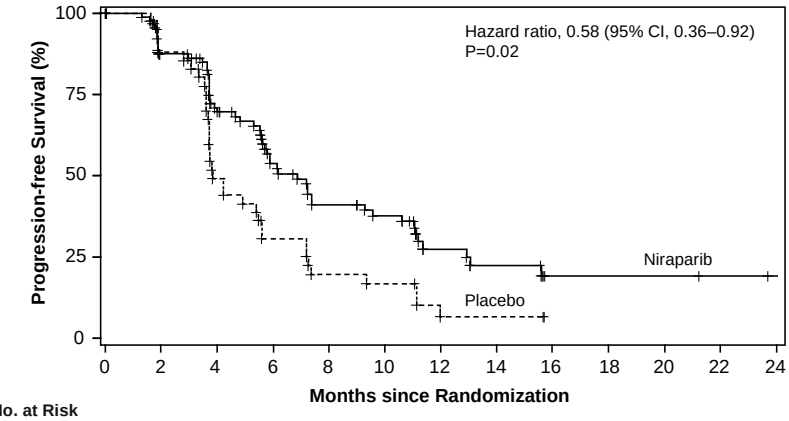
No. at Risk													
Niraparib	71	58	46	38	29	25	21	12	7	6	4	2	1
Placebo	44	32	19	12	7	6	3	2	0				

B



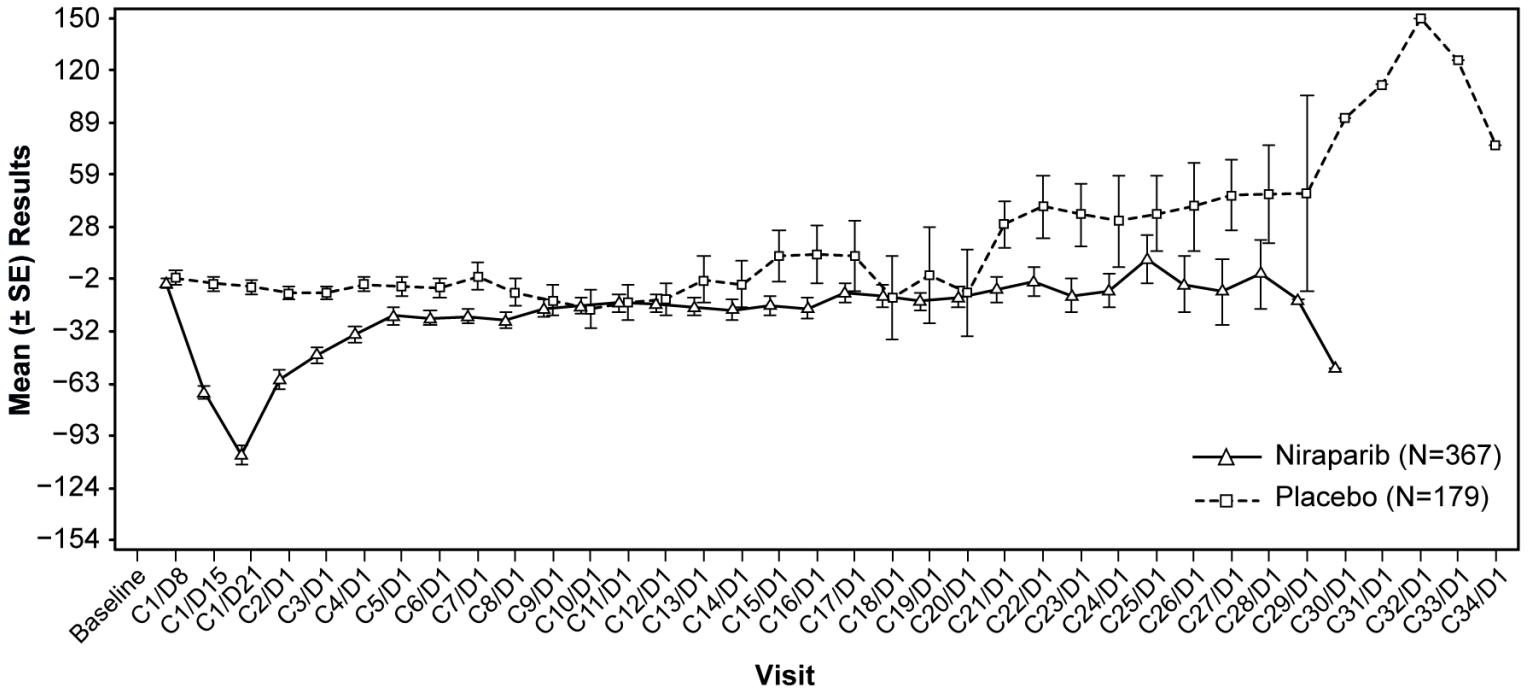
No. at Risk													
Niraparib	35	32	29	26	23	21	19	17	9	8	7	2	1
Placebo	12	9	7	4	4	3	1	1	1	1	1	1	1

C



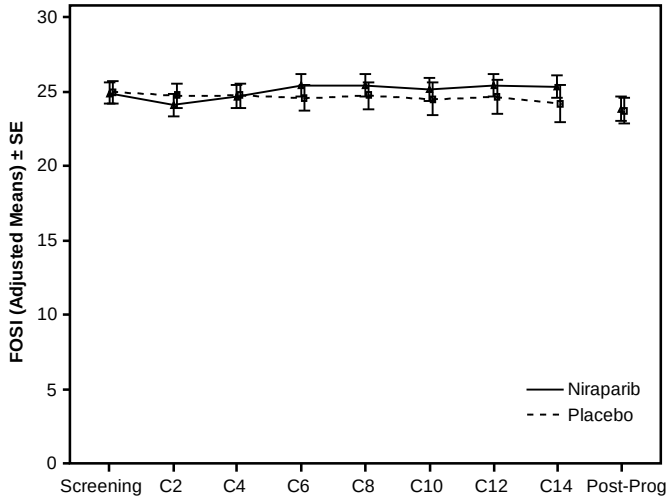
No. at Risk													
Niraparib	92	73	54	35	26	22	11	8	3	3	3	2	1
Placebo	42	35	19	11	7	6	2	2	0				

SUPPLEMENTAL FIGURE S3. Platelet Levels over Time: Data are presented for all patients in the safety population (N=546). SE denotes standard error.



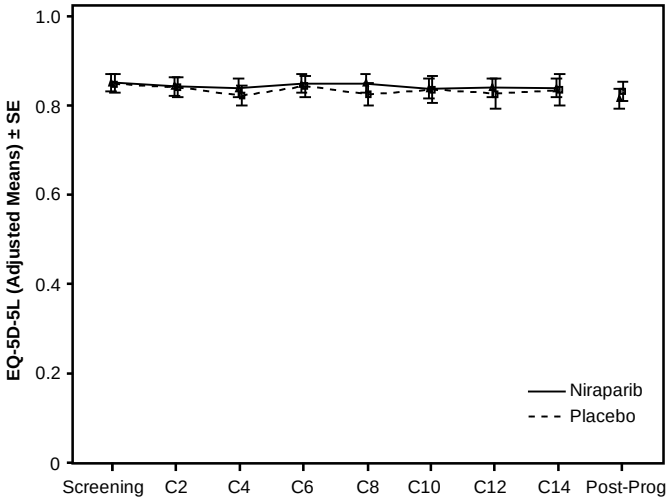
SUPPLEMENTAL FIGURE S4. Patient-reported Outcomes for the Functional Assessment of Cancer Therapy–Ovarian Symptom Index (FOSI) by Study Visit in the (A) g*BRCA*mut Cohort and (B) Non-g*BRCA*mut Cohort, and for the EQ-5D-5L in the (C) g*BRCA*mut Cohort and (D) Non-g*BRCA*mut Cohort. EQ-5D-5L denotes EuroQol 5-Dimensions questionnaire, g*BRCA*mut germline *BRCA* mutation. Values displayed are adjusted means; a higher score indicates fewer symptoms. C denotes cycle, and post-prog denotes post progression.

A. FOSI in the g*BRCA*mut Cohort



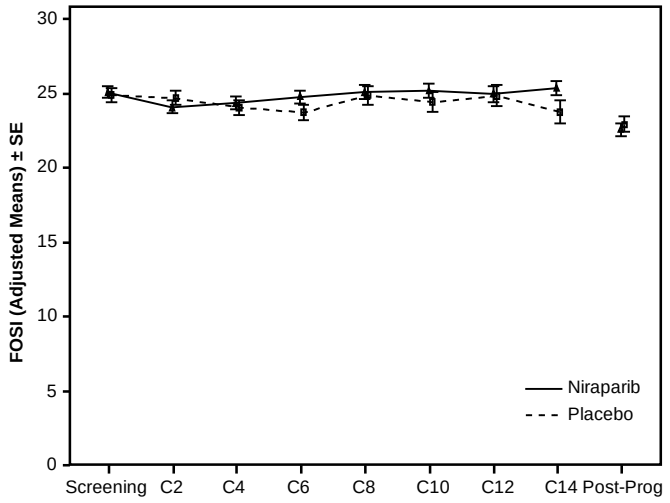
Placebo	24.9	24.6	24.6	24.5	24.6	24.4	24.5	24.1	23.7
Niraparib	24.8	24.0	24.6	25.3	25.3	25.1	25.3	25.2	23.8

C. EQ-5D-5L in the g*BRCA*mut Cohort



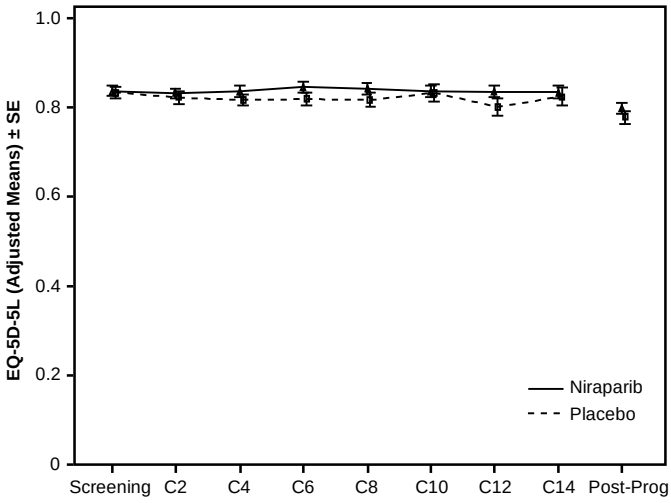
Placebo	0.849	0.841	0.822	0.844	0.825	0.836	0.827	0.834	0.832
Niraparib	0.851	0.843	0.839	0.849	0.849	0.838	0.841	0.840	0.816

B. FOSI in the Non-g*BRCA*mut Cohort



Placebo	24.9	24.6	24.0	23.7	24.8	24.4	24.8	23.7	22.9
Niraparib	25.0	24.0	24.3	24.7	25.1	25.1	24.9	25.3	22.5

D. EQ-5D-5L in the Non-g*BRCA*mut Cohort



Placebo	0.836	0.824	0.819	0.821	0.819	0.835	0.804	0.827	0.780
Niraparib	0.839	0.834	0.839	0.848	0.844	0.838	0.837	0.837	0.800

SUPPLEMENTAL TABLE S1. Complete Listing of Patient Demographics and Baseline Characteristics.

	g*BRCA*mut		non-g*BRCA*mut	
Characteristic	**Niraparib (N=138)**	**Placebo (N=65)**	**Niraparib (N=234)**	**Placebo (N=116)**
Age, median (range) — years	57 (36-83)	58 (38-73)	63 (33-84)	61 (34-82)
Race — no (%)				
White	123 (89.1)	55 (84.6)	201 (85.9)	101 (87.1)
Black/Asian/Other/Unknown	15 (10.9)	10 (15.4)	33 (14.1)	15 (12.9)
Ethnicity — no (%)				
Non-hispanic	121 (87.7)	57 (87.7)	202 (86.3)	99 (85.3)
Hispanic/Other/Unknown	17 (12.3)	8 (12.3)	32 (13.7)	17 (14.7)
Region				
United States, Canada	53 (38.4)	28 (43.1)	96 (41.0)	44 (37.9)
Europe, Israel	85 (61.6)	37 (56.9)	138 (59.0)	72 (62.1)
Eastern Cooperative Oncology Group performance status — no (%)				
0	91 (65.9)	48 (73.8)	160 (68.4)	78 (67.2)
1	47 (34.1)	17 (26.2)	74 (31.6)	38 (32.8)
Primary tumor site — no (%)§				
Ovarian	122 (88.4)	53 (81.5)	192 (82.1)	96 (82.8)
Primary peritoneal	7 (5.1)	6 (9.2)	24 (10.3)	8 (6.9)
Fallopian tube	9 (6.5)	6 (9.2)	18 (7.7)	11 (9.5)
Cancer stage — no (%)*†				
I-II	23 (16.7)	10 (15.4)	22 (9.4)	5 (4.3)
III-IIIB	14 (10.1)	10 (15.4)	24 (10.3)	20 (17.2)
IIIC	81 (58.7)	36 (55.4)	149 (63.7)	66 (56.9)
IV	20 (14.5)	9 (13.8)	38 (16.2)	24 (20.7)
Time to progression after penultimate platinum therapy — no (%)				
6 to <12 months	54 (39.1)	26 (40.0)	90 (38.5)	44 (37.9)
≥12 months	84 (60.9)	39 (60.0)	144 (61.5)	72 (62.1)
Best response to most recent platinum therapy — no (%)				
Complete response	71 (51.4)	33 (50.8)	117 (50.0)	60 (51.7)
Partial response	67 (48.6)	32 (49.2)	117 (50.0)	56 (48.3)
Prior bevacizumab use — no (%)				
Yes	33 (23.9)	17 (26.2)	62 (26.5)	30 (25.9)
No	105 (76.1)	48 (73.8)	172 (73.5)	86 (74.1)

gBRCA mutations — no (%)				
BRCA1 mutation	85 (61.6)	43 (66.2)	NA	NA
BRCA2 mutation	51 (37.0)	18 (27.7)	NA	NA
BRCA1 and/or *BRCA2* rearrangement	9 (6.5)	4 (6.2)	NA	NA
Prior lines of chemotherapy‡ — no (%)				
1	1 (0.7)	0	0	0
2	70 (50.7)	30 (46.2)	155 (66.2)	77 (66.4)
≥3	67 (48.6)	35 (53.8)	79 (33.8)	38 (32.8)
Prior platinum therapies — no (%)				
<2	1 (0.7)	0	0	0
2	79 (57.2)	37 (56.9)	174 (74.4)	87 (75.0)
>2	58 (42.0)	28 (43.1)	60 (25.6)	28 (24.1)
Unknown	0	0	0	1 (0.9)

***** g*BRCA*mut denotes germline *BRCA* mutation. NA denotes not applicable.

§ Data with respect to primary tumor site were not available for one patient in the placebo arm in the non-g*BRCA*mut cohort.

† Staging was performed with the use of the International Federation of Gynecology and Obstetrics system. Data with respect to staging were not available for one patient in the placebo arm in the non-g*BRCA*mut cohort. One patient in the niraparib arm in the non-g*BRCA*mut cohort was stage 0 at time of diagnosis.

‡ Data with respect to prior lines of chemotherapy were not available for one patient in the placebo arm in the non-g*BRCA*mut cohort.

SUPPLEMENTAL TABLE S2. Secondary Endpoints.*

End point	g*BRCA*mut		non-g*BRCA*mut	
	Niraparib (N=138)	**Placebo (N=65)**	**Niraparib (N=234)**	**Placebo (N=116)**
Chemotherapy-free interval				
Median (95% CI) — mo	22.8 (17.9–NR)	9.4 (7.9–10.6)	12.7 (11.0–14.7)	8.6 (6.9–10.0)
P value	<0.001		<0.001	
Hazard ratio (95% CI)	0.26 (0.17–0.41)		0.50 (0.37–0.67)	
Time to first subsequent treatment				
Median (95% CI) — mo	21.0 (17.5–NR)	8.4 (6.6–10.6)	11.8 (9.7–13.1)	7.2 (5.7–8.5)
P value	<0.001		<0.001	
Hazard ratio (95% CI)	0.31 (0.21–0.48)		0.55 (0.41–0.72)	
Progression-free survival 2				
Median (95% CI) — mo	25.8 (20.3–NR)	19.5 (13.3–NR)	18.6 (16.2–21.7)	15.6 (13.2–20.9)
P value	0.006		0.03	
Hazard ratio (95% CI)	0.48 (0.28–0.82)		0.69 (0.49–0.96)	

* CI denotes confidence interval, g*BRCA*mut germline *BRCA* mutation, and NR not reached.

SUPPLEMENTAL TABLE S3. Summary of Adverse Events.*

Reported — no (%)	Niraparib (N=367)	Placebo (N=179)
Any TEAE	367 (100.0)	171 (95.5)
Any Related TEAE	358 (97.5)	127 (70.9)
Any CTCAE Grade ≥3 TEAE	272 (74.1)	41 (22.9)
Any related CTCAE Grade ≥3 TEAE	237 (64.6)	8 (4.5)
Any Serious TEAE	110 (30.0)	27 (15.1)
Any Related Serious TEAE	62 (16.9)	2 (1.1)
Any TEAE Leading to Treatment Interruption	253 (68.9)	9 (5.0)
Any TEAE Leading to Dose Reduction	244 (66.5)	26 (14.5)
Any TEAE Leading to Treatment Discontinuation	54 (14.7)	4 (2.2)
Any TEAE Leading to Death	0	0

***** CTCAE denotes Common Terminology Criteria for Adverse Events and TEAE treatment-emergent adverse event.

SUPPLEMENTAL TABLE S4. Treatment Discontinuations Due to Myelosuppression Adverse Events of Any Grade.

Event — no (%)	Niraparib (N=367)	Placebo (N=179)
Thrombocytopenia[a]	12 (3.3)	1 (0.6)
Neutropenia[b]	7 (1.9)	0
Leukopenia[c]	7 (1.9)	0
Anemia[d]	5 (1.4)	0
Pancytopenia	3 (0.8)	0

[a]Thrombocytopenia includes reports of thrombocytopenia and decreased platelet count; [b]Neutropenia includes reports of neutropenia, decreased neutrophil count, and febrile neutropenia; [c]Leukopenia includes reports of neutropenia, neutrophil count decrease, white blood cell count decreased, leukopenia, lymphocyte count decreased, lymphopenia, febrile neutropenia, and monocyte count decreased; [d]Anemia includes reports of anemia and decreased hemoglobin counts.

SUPPLEMENTAL TABLE S5. Impact of Dose Modification on Grade 3 or 4 Treatment-Emergent Adverse Events after Cycle 3 through End of Treatment. Presented are the cumulative adverse events that occurred from cycle 3 through the end of treatment.

	Niraparib Dose		
Event — no (%)	**300 mg (N=82)**	**200 mg (N=138)**	**100 mg (N=77)**
Anemia[a]	19 (23.2)	25 (18.1)	6 (7.8)
Thrombocytopenia[b]	1 (1.2)	3 (2.2)	3 (3.9)
Neutropenia[c]	4 (4.9)	4 (2.9)	0
Fatigue[d]	5 (6.1)	4 (2.9)	0

[a]Anemia includes reports of anemia and decreased hemoglobin counts; [b]Thrombocytopenia include reports of thrombocytopenia and decreased platelet count; [c]Neutropenia include reports of neutropenia, decreased neutrophil count, and febrile neutropenia; [d]Fatigue include reports of fatigue, asthenia, malaise, and lethargy.

SUPPLEMENTAL TABLE S6. Functional Assessment of Cancer Therapy-Ovarian Symptom Index (FOSI) Completion Status by Visit.

	g*BRCA*mut		non-g*BRCA*mut	
Number of Completed FOSI — no (%)	**Niraparib**	**Placebo**	**Niraparib**	**Placebo**
Baseline	134/138 (97.1)	62/65 (95.4)	228/234 (97.4)	113/116 (97.4)
Cycle 2	117/132 (88.6)	57/64 (89.1)	186/212 (87.7)	99/113 (87.6)
Cycle 4	113/120 (94.2)	45/54 (83.3)	155/181 (85.6)	79/95 (83.2)
Cycle 6	98/104 (94.2)	36/41 (87.8)	128/144 (88.9)	50/56 (89.3)
Post-progression	51/68 (75.0)	37/46 (80.4)	122/156 (77.6)	78/98 (79.6)

REFERENCES

1. du Bois A, Reuss A, Pujade-Lauraine E, et al. European Network of Gynaecological Oncological Trial Groups' Requirements for Trials Between Academic Groups and Industry Partners--First Update 2015. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society 2015;25:1328-30.
2. Patel JN, Sehouli J, Timms KM, et al. Characteristics of homologous recombination deficiency (HRD) in paired primary and recurrent high-grade serous ovarian cancer (HGSOC). ASCO Annual Meeting; 2015 May 29-June 2; Chicago, IL: Journal of Clinical Oncology.
3. Abkevich V, Timms KM, Hennessy BT, et al. Patterns of genomic loss of heterozygosity predict homologous recombination repair defects in epithelial ovarian cancer. Br J Cancer 2012;107:1776-82.
4. Birkbak NJ, Wang ZC, Kim JY, et al. Telomeric allelic imbalance indicates defective DNA repair and sensitivity to DNA-damaging agents. Cancer Discov 2012;2:366-75.
5. Popova T, Manie E, Rieunier G, et al. Ploidy and large-scale genomic instability consistently identify basal-like breast carcinomas with BRCA1/2 inactivation. Cancer Res 2012;72:5454-62.
6. Telli ML, Timms KM, Reid JE, et al. Homologous Recombination Deficiency (HRD) Score Predicts Response to Platinum-Containing Neoadjuvant Chemotherapy in Patients with Triple Negative Breast Cancer. Clin Cancer Res 2016.
7. Rustin GJ, Vergote I, Eisenhauer E, et al. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG). International journal of gynecological cancer : official journal of the International Gynecological Cancer Society 2011;21:419-23.
8. Beaumont J, Yount S, Lalla D, et al. Validation of the Functional Assessment of Cancer Therapy-Ovarian (FACT-O) Symptom Index (FOSI) in a phase II clinical trial of pertuzumab in patients with advanced ovarian cancer. J Clin Oncol 2007;25:16021.
9. Conner-Spady B, Cumming C, Nabholtz JM, Jacobs P, Stewart D. Responsiveness of the EuroQol in breast cancer patients undergoing high dose chemotherapy. Qual Life Res 2001;10:479-86.