European Journal of Cancer 189 (2023) 112908

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Original Research

Progression-free survival and safety at 3.5 years of follow-up: results from the randomised phase 3 PRIMA/ENGOT-OV26/GOG-3012 trial of niraparib maintenance treatment in patients with newly diagnosed ovarian cancer

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https://doi.org/10.1016/j.ejca.2023.04.024

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Received 10 March 2023; Received in revised form 18 April 2023; Accepted 19 April 2023
Available online 3 May 2023

KEYWORDS
Advanced ovarian cancer;
Niraparib;
PARP inhibitor;
Maintenance therapy

Abstract ***Purpose:*** To report updated long-term efficacy and safety from the double-blind, placebo-controlled, phase 3 PRIMA/ENGOT-OV26/GOG-3012 study (NCT02655016).
Methods: Patients with newly diagnosed advanced ovarian cancer with complete or partial response (CR or PR) to first-line platinum-based chemotherapy received niraparib or placebo once daily (2:1 ratio). Stratification factors were best response to first-line chemotherapy regimen (CR/PR), receipt of neoadjuvant chemotherapy (yes/no), and homologous recombination deficiency (HRD) status (deficient [HRd]/proficient [HRp] or not determined). Updated (*ad hoc*) progression-free survival (PFS) data (as of November 17, 2021) by investigator assessment (INV) are reported.
Results: In 733 randomised patients (niraparib, 487; placebo, 246), median PFS follow-up was 3.5 years. Median INV-PFS was 24.5 versus 11.2 months (hazard ratio, 0.52; 95% confidence interval [CI], 0.40–0.68) in the HRd population and 13.8 versus 8.2 months (hazard ratio, 0.66; 95% CI, 0.56–0.79) in the overall population for niraparib and placebo, respectively. In the HRp population, median INV-PFS was 8.4 versus 5.4 months (hazard ratio, 0.65; 95% CI, 0.49–0.87), respectively. Results were concordant with the primary analysis. Niraparib-treated patients were more likely to be free of progression or death at 4 years than placebo-treated patients (HRd, 38% versus 17%; overall, 24% versus 14%). The most common grade ≥ 3 treatment-emergent adverse events in niraparib patients were thrombocytopenia (39.7%), anaemia (31.6%), and neutropenia (21.3%). Myelodysplastic syndromes/acute myeloid leukaemia incidence rate (1.2%) was the same for niraparib- and placebo-treated patients. Overall survival remained immature.
Conclusions: Niraparib maintained clinically significant improvements in PFS with 3.5 years of follow-up in patients with newly diagnosed advanced ovarian cancer at high risk of progression irrespective of HRD status. No new safety signals were identified.

1. Introduction

Most patients with ovarian cancer (OC) have advanced disease at diagnosis, which places them at a high risk for disease recurrence and death [1,2]. In patients with distant disease at diagnosis, the estimated 5-year survival rate is approximately 30% [2]. For patients with newly diagnosed advanced OC, the treatment landscape has expanded to include maintenance therapy with poly (ADP-ribose) polymerase (PARP) inhibitors and anti-angiogenic treatments given alone or in combination [3,4].

The phase 3 PRIMA/ENGOT-OV26/GOG-3012 (PRIMA) trial demonstrated the efficacy of the PARP inhibitor niraparib for first-line maintenance therapy in patients with newly diagnosed advanced OC who responded to first-line platinum-based chemotherapy. In the PRIMA primary analysis, the median duration of follow-up was 13.8 months. Niraparib maintenance treatment significantly extended progression-free survival (PFS) assessed by blinded independent central review (BICR) compared with placebo in patients with homologous recombination–deficient (HRd) tumours (21.9 versus 10.4 months; hazard ratio, 0.43; 95% confidence interval [CI], 0.31–0.59; $P < 0.001$) and in the overall population (13.8 versus 8.2 months; hazard ratio, 0.62; 95% CI, 0.50–0.76; $P < 0.001$) [5]. Consistent with the known safety profile of niraparib, the

most common grade ≥ 3 treatment-emergent adverse events (TEAEs) were haematologic in nature [5].

Based on the primary analysis results from PRIMA, niraparib was approved for the maintenance treatment of patients with newly diagnosed advanced OC who responded to first-line platinum-based chemotherapy regardless of biomarker status [6,7]. However, data on the long-term benefits and safety of niraparib for first-line maintenance treatment are lacking, and overall survival (OS) remains immature. To address this knowledge gap, we report here the final PFS data and long-term safety findings from an updated *ad hoc* analysis performed using data from the November 17, 2021, clinical cutoff date. The updated analysis also allowed for the longer observation of patients who received an individualised starting dose, which was introduced through a protocol amendment ≈ 16 months after study initiation.

2. Materials and methods

2.1. Trial design

The study design and primary analyses results for the PRIMA/ENGOT-OV26/GOG-3012 (NCT02655016) have been published previously [5]. Briefly, PRIMA was a phase 3, randomised, double-blind placebo-controlled trial in which niraparib maintenance treatment was evaluated in adult patients with newly diagnosed, advanced (International Federation of Gynecology and Obstetrics stage III/IV), high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube cancer (collectively referred to as OC) who responded to first-line platinum-based chemotherapy. Within 12 weeks of completion of first-line treatment, patients were randomised 2:1 to receive niraparib or placebo orally once daily (QD) until progressive disease or intolerable toxicity; patients who were benefitting from treatment were eligible to continue receiving treatment beyond the planned 3-year treatment duration. Patients were stratified by clinical response after first-line platinum-based chemotherapy (complete or partial response), receipt of neoadjuvant chemotherapy (yes or no), and tumour homologous recombination deficiency (HRD) status (deficient versus proficient or not determined) per the myChoice® HRD test (Myriad Genetics, Inc, Salt Lake City, UT). Tumours that had a deleterious *BRCA* mutation (*BRCA*m), a genomic instability score ≥ 42, or both were considered HRd; tumours that were *BRCA* wild-type and had a genomic instability score < 42 were considered HR-proficient (HRp). Per the initial protocol, all patients received a fixed-starting dose (FSD) of 300 mg QD. The protocol amendment on November 27, 2017, incorporated an individualised starting dose (ISD) based on baseline body weight and platelet count, with patients with a baseline body weight < 77 kg or baseline platelet count < 150,000/μl assigned to a starting dose of 200 mg QD and patients with a baseline body weight ≥ 77 kg or baseline platelet count ≥ 150,000/μl assigned to 300 mg QD. Crossover between treatment arms was not permitted. Patients who discontinued from the study could receive subsequent treatments at the investigator's discretion. The study was performed in accordance with the tenets of the Declaration of Helsinki, Good Clinical Practices, and all local laws under the auspices of an independent data and safety monitoring committee; all patients gave informed written consent [5].

2.2. Outcomes

The primary end-point was PFS assessed by BICR analysed by hierarchical testing, first in patients with HRd tumours and then in the overall population (see González-Martín et al. for additional details) [5]. PFS per investigator assessment, safety outcomes, and patient-reported outcomes were secondary end-points. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. In this *ad hoc* analysis, investigator-assessed PFS was evaluated in the HRd and overall populations, and long-term safety findings are reported for the overall population. Additional *ad hoc* analyses for PFS by prespecified subgroups and for safety by starting dose are also reported.

2.3. Statistical analyses

PFS was defined as the time from randomisation after completion of platinum-based chemotherapy to the earliest date of objective disease progression on imaging (Response Evaluation Criteria in Solid Tumors, version 1.1) or by clinical criteria of progression, or death from any cause. Clinical disease progression occurred if patients had cancer antigen 125 progression according to Gynecologic Cancer Intergroup-criteria and had either identification of new lesions or growth of existing lesions determined through diagnostic imaging or definitive clinical signs and symptoms of disease progression. PFS was analysed with a stratified log-rank test using stratification factors from randomisation and summarised using Kaplan-Meier methodology. Hazard ratios with 95% CIs were estimated using a stratified Cox proportional hazards model, with stratification factors used in randomisation. Analyses were performed using data

from the November 17, 2021, clinical cutoff date. The statistical methodology for the updated analysis was prespecified per the PRIMA statistical analysis plan; the inclusion of an updated PFS analysis from the updated data cut was not prespecified. The prespecified final analysis for PRIMA will occur when OS data reach maturity; additional PFS analyses are not planned at the time of the OS analysis.

3. Results

3.1. Patients and duration of follow-up

A total of 733 patients with primary advanced OC who were at high risk for disease progression were enroled in PRIMA (Table S1). The primary analysis clinical cutoff date was May 17, 2019, with a median duration of follow-up of 13.8 months (≈ 1.2 years) [5]. For the November 17, 2021, clinical cutoff date, the median duration of follow-up was ≈ 3.5 years (niraparib, 41.6 months; placebo, 41.9 months). In the overall population, 103 patients (21.3%) in the niraparib arm and 39 patients (16.0%) in the placebo arm had a study treatment duration longer than 3 years. At the time of this analysis, 79 patients (16.3%) were receiving niraparib, and 27 patients (11.1%) were receiving placebo (Fig. 1). In total, 45 patients (9.2%) and 82 patients (33.3%) in the niraparib and placebo arms, respectively, went on to receive subsequent PARP inhibitor therapy during the follow-up period after progression.

3.2. Investigator-assessed PFS

The median investigator-assessed PFS in the HRd population was 24.5 months in the niraparib arm versus 11.2 months in the placebo arm (hazard ratio, 0.52; 95% CI, 0.40–0.68; $P < 0.001$; Fig. 2A). In the overall population, the median PFS was 13.8 months in the niraparib arm versus 8.2 months in the placebo arm (hazard ratio, 0.66; 95% CI, 0.56–0.79; $P < 0.001$; Fig. 2B). These results were consistent with the primary analysis investigator-assessed and BICR-assessed PFS results (Table S2).

Niraparib treatment also increased investigator-assessed PFS compared with placebo across biomarker subgroups (Fig. 3). The greatest treatment benefit was seen in patients with *BRCA*m HRd tumours, with a median PFS of 31.5 months in the niraparib arm versus 11.5 months in the placebo arm (hazard ratio, 0.45; 95% CI, 0.32–0.64). In patients with *BRCA* wild-type HRd tumours, the median PFS was 19.4 months in the niraparib arm versus 10.4 months in the placebo arm

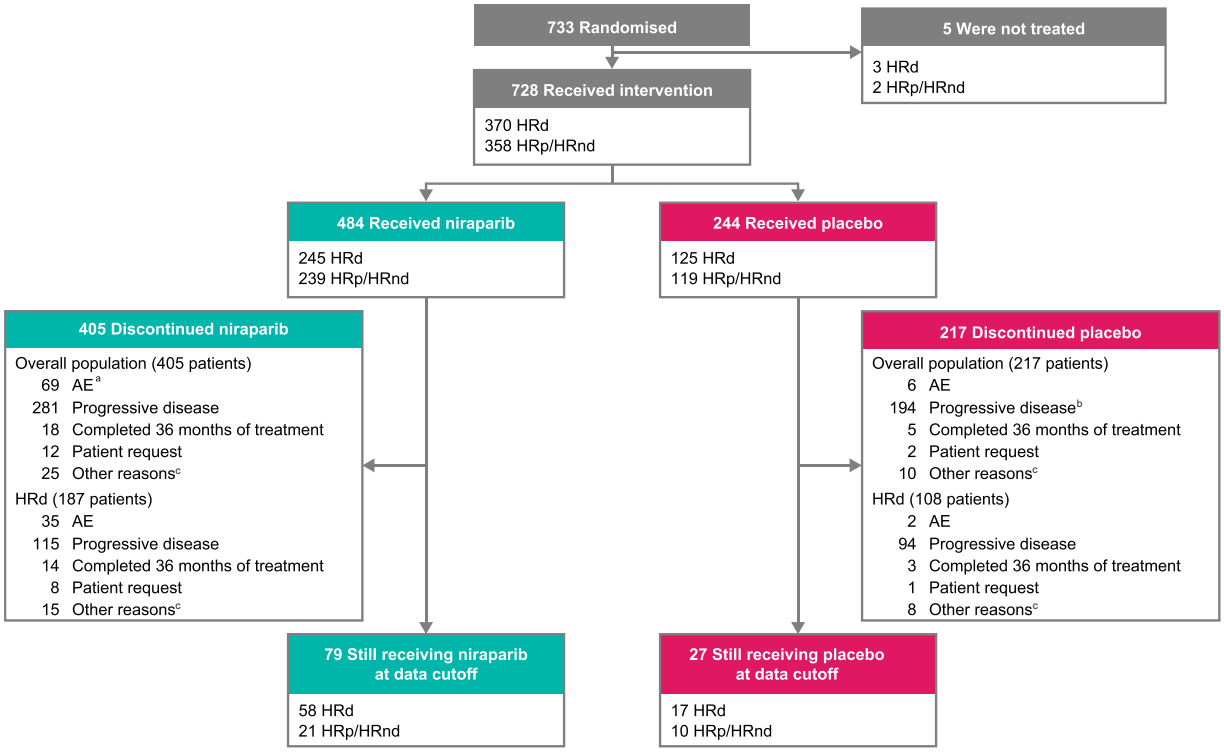

Fig. 1. Patient disposition for homologous recombination-deficient (HRd) and overall populations. [a]Includes 2 patients who experienced a temporary dose interruption because of an adverse event and who subsequently discontinued treatment. [b]Includes 1 patient who also experienced an adverse event (ascites) at the time of discontinuation. [c]Includes patients who discontinued because of investigator decision or non-adherence. AE, adverse event; HRnd, homologous recombination status not determined; HRp, homologous recombination-proficient.

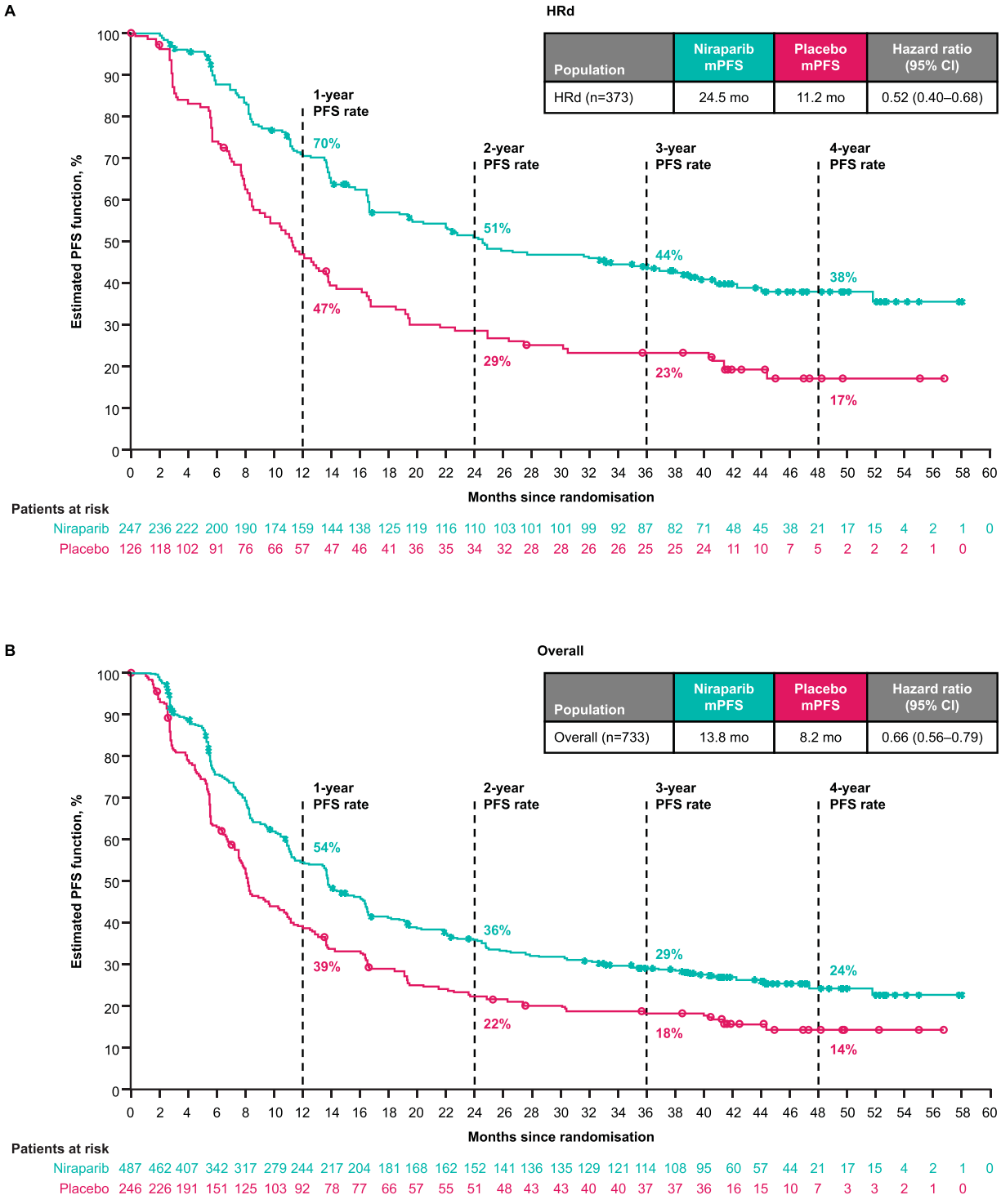

Fig. 2. Kaplan-Meier estimates of investigator-assessed progression-free survival (PFS) by treatment arm in the (A) homologous recombination-deficient (HRd) population and (B) overall population. CI, confidence interval; mPFS, median progression-free survival.

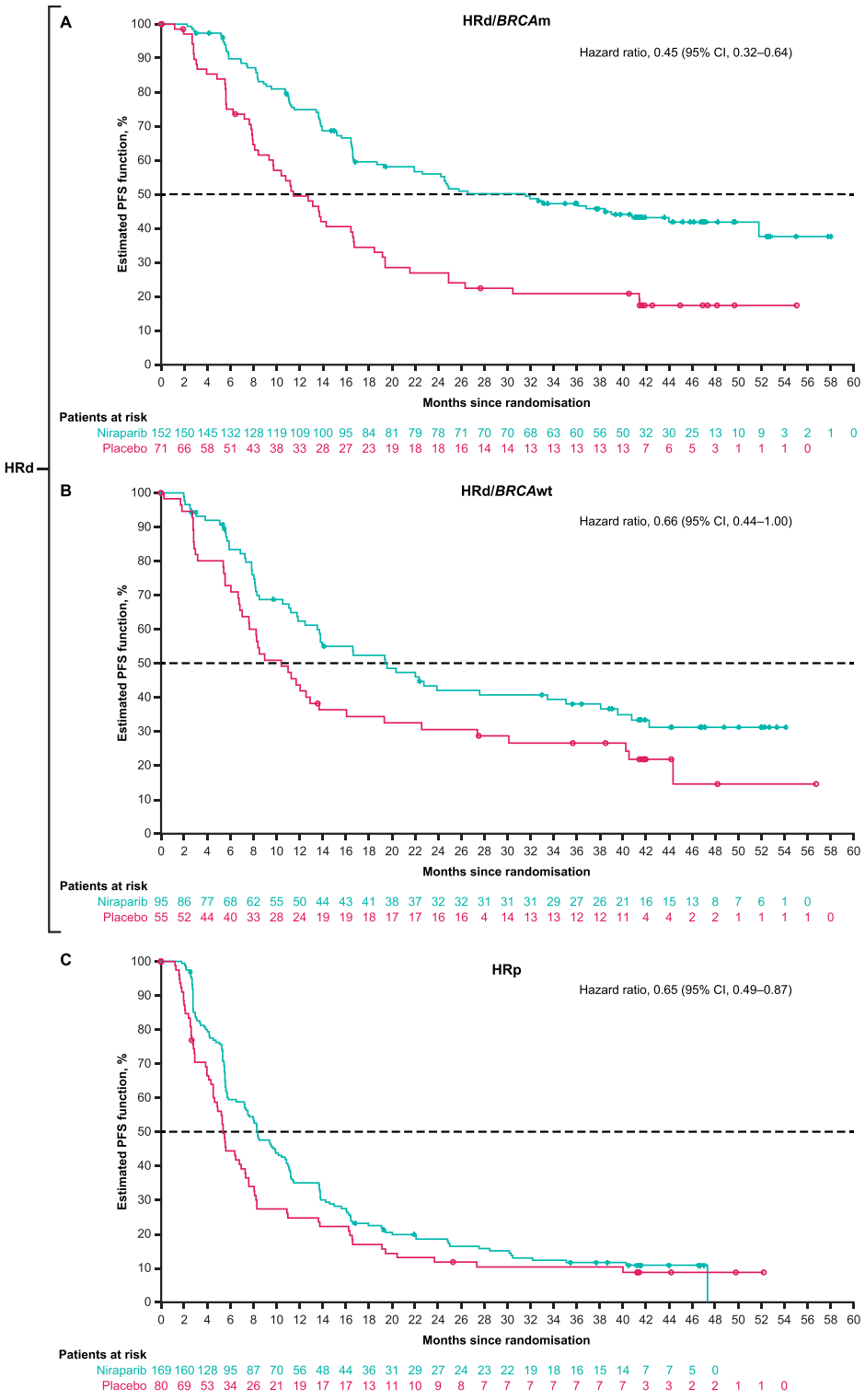

Fig. 3. Kaplan-Meier estimates of investigator-assessed progression-free survival (PFS) by treatment arm for (A) homologous recombination-deficient (HRd)/*BRCA* mutated (*BRCA*m), (B) HRd/*BRCA* wild-type (*BRCA*wt), and (C) homologous recombination-proficient (HRp) populations. CI, confidence interval.

(hazard ratio, 0.66; 95% CI, 0.44–1.00). Patients with tumours that were HRp also benefited from niraparib treatment compared with placebo (median PFS, 8.4 versus 5.4 months; hazard ratio, 0.65; 95% CI, 0.49–0.87).

The treatment benefit of niraparib was also observed across most of the subgroups examined, including patients considered at higher risk of progression because of a partial response to first-line platinum-based chemotherapy (hazard ratio, 0.63; 95% CI, 0.47–0.86),

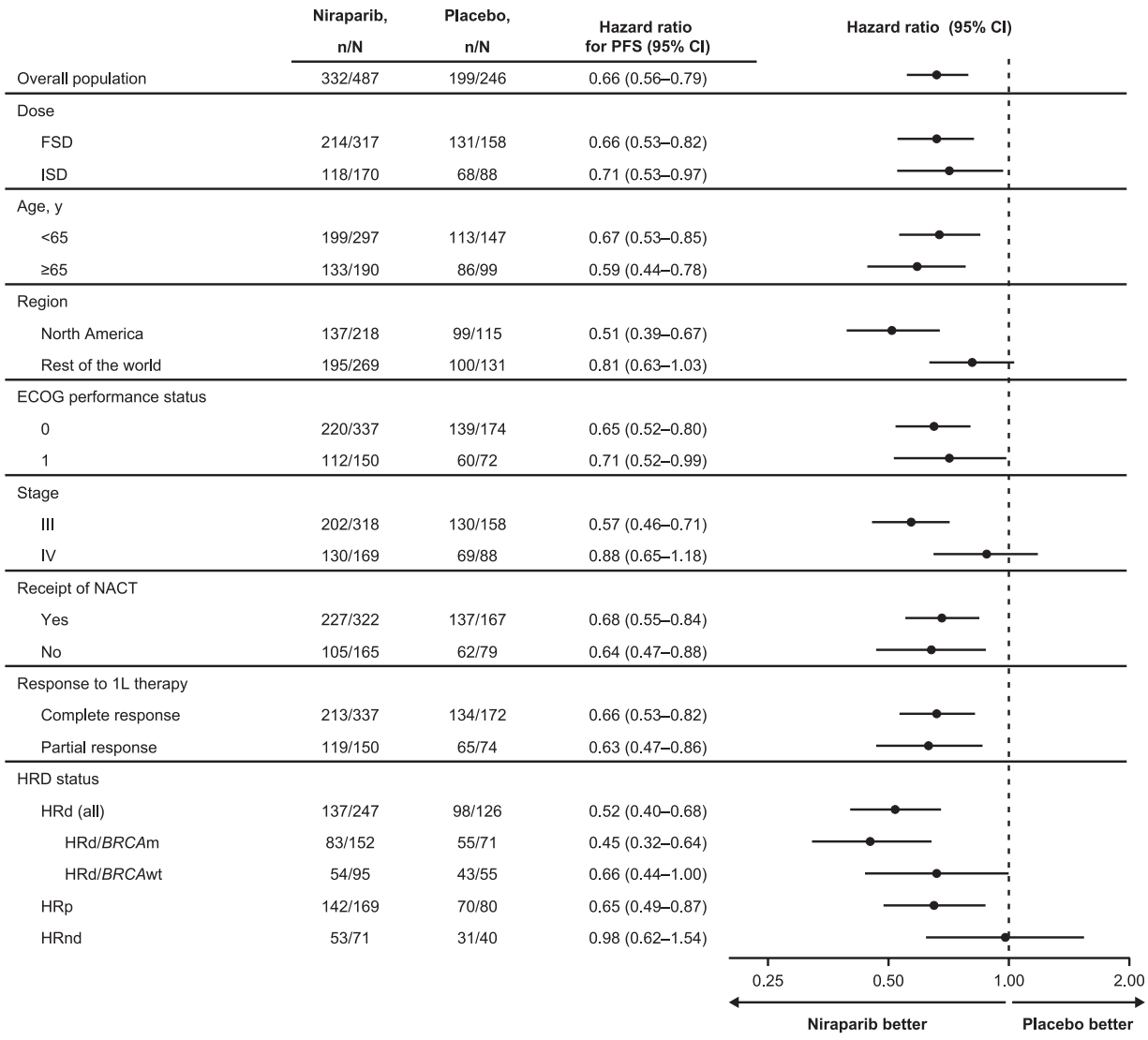

Fig. 4. Forest plot of hazard ratios for investigator-assessed progression-free survival (PFS). 1L, first-line; *BRCA*m, *BRCA* mutated; *BRCA*wt, *BRCA* wild-type; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FSD, fixed starting dose; HR, hazard ratio; ISD, individualised starting dose; HRD, homologous recombination deficiency; HRd, homologous recombination-deficient; HRnd, homologous recombination status not determined; HRp, homologous recombination-proficient; NACT, neoadjuvant chemotherapy.

receipt of neoadjuvant chemotherapy (hazard ratio, 0.68; 95% CI, 0.55–0.84), or having stage IV disease at diagnosis (hazard ratio, 0.88; 95% CI, 0.65–1.18; Fig. 4). Patients who received an ISD also benefited from niraparib treatment (hazard ratio, 0.71; 95% CI, 0.53–0.97).

3.3. OS

OS remained immature at 30.8% for the HRd population and 41.2% for the overall population at the time of this data cutoff. The prespecified final analysis for PRIMA will be performed when OS data reach maturity (60.0%) for the overall population.

3.4. Safety

Niraparib safety findings were consistent with the primary analysis; no new safety signals were observed [5]. Long-term monotherapy was associated with a low rate of discontinuations due to AEs (Table 1); compared with the primary analysis, 11 additional patients discontinued niraparib because of a TEAE (includes 2 patients who initially experienced a treatment interruption but subsequently discontinued study treatment all together). Implementation of the ISD generally improved safety, with reductions in the proportions of niraparib-treated patients who experienced grade ≥ 3 TEAE (62.7% versus 78.4%) and treatment-related

Table 1
Overall safety in the overall population and by niraparib starting dose.

AEs, n (%)	Niraparib			
	Overall	FSD	ISD	Placebo[a]
	(n = 484)	(n = 315)	(n = 169)	(n = 244)
TEAE				
Any grade	479 (99.0)	313 (99.4)	166 (98.2)	229 (93.9)
Grade ≥ 3	353 (72.9)	247 (78.4)	106 (62.7)	56 (23.0)
Grade ≥ 4	146 (30.2)	119 (37.8)	27 (16.0)	7 (2.9)
TRAE				
Any grade	467 (96.5)	307 (97.5)	160 (94.7)	175 (71.7)
Grade ≥ 3	321 (66.3)	230 (73.0)	91 (53.8)	21 (8.6)
Grade ≥ 4	143 (29.5)	117 (37.1)	26 (15.4)	2 (0.8)
Serious AE				
Any	186 (38.4)	130 (41.3)	56 (33.1)	39 (16.0)
Treatment-related	129 (26.7)	89 (28.3)	40 (23.7)	8 (3.3)
TEAE leading to				
Dose interruption	389 (80.4)	266 (84.4)	123 (72.8)	51 (20.9)
Dose reduction	347 (71.7)	241 (76.5)	106 (62.7)	23 (9.4)
Treatment discontinuation	67 (13.8)[b]	41 (13.0)	26 (15.4)	7 (2.9)[c]
Death	5 (1.0)	3 (1.0)	2 (1.2)	2 (0.8)

AE, adverse event; FSD, fixed starting dose; ISD, individualised starting dose; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

[a] Data for the overall placebo population; results were similar in patients who received a fixed or individualised starting dose. [b] Two additional patients who experienced a TEAE leading to a dose interruption subsequently discontinued treatment. [c] Includes 1 patient who experienced the adverse event ascites at the time of disease progression and was recorded as discontinuing treatment because of disease progression.

grade ≥ 3 AEs (53.8% versus 73.0%) in patients who received an ISD versus an FSD.

The proportions of niraparib-treated patients who experienced TEAEs leading to dose interruptions and reductions were also lower with the ISD than the FSD. In the overall population, the most common grade ≥ 3 TEAEs in the niraparib arm were thrombocytopenia (39.7%), anaemia (31.6%), and neutropenia (21.3%; Table 2). Compared with the primary analysis, 4 additional patients experienced grade ≥ 3 thrombocytopenia, 3 additional patients experienced grade ≥ 3 anaemia, and 3 additional patients experienced grade ≥ 3 neutropenia in the niraparib arm. These results are consistent with the primary analysis, which found that most haematologic toxicities in the niraparib arm occurred during the first month of treatment. With the introduction of the ISD, the proportions of patients who experienced grade ≥ 3 events of thrombocytopenia, anaemia, and neutropenia were reduced from 49.2% to 21.9%, from 36.2% to 23.1%, and from 24.8% to 14.8%, respectively (Table 2).

Myelodysplastic syndromes (MDS) or acute myeloid leukaemia (AML) events were reported in the same proportion of patients in the niraparib (6/484, 1.2%) and placebo arms (3/244, 1.2%). In these patients, the duration of study treatment ranged from 3.7 to 29.7 months and from 4.9 to 7.4 months and the time to onset of MDS/AML event from the last study treatment ranged from 0.1 to 42.7 months and from 19.8 to 29.2 months in the niraparib and placebo arms, respectively. *BRCA*m and HRD status data for patients who experienced MDS/AML events are reported in Table S3. Before MDS/AML event occurrence, 3 of 6 niraparib-treated and 3 of 3 placebo-treated patients received subsequent chemotherapy, and all 3 placebo-treated patients received subsequent PARP inhibitor therapy.

4. Discussion

In this updated *ad hoc* analysis of the phase 3 PRIMA trial, maintenance treatment with niraparib resulted in a sustained and durable PFS benefit compared with placebo in the HRd and overall populations per investigator assessment after a median of 3.5 years of follow-up. Hazard ratios over the additional follow-up time were consistent with the primary analysis, regardless of biomarker status. In the HRd and HRp populations, respectively, a clinically meaningful 48% and 35% reduction of the risk of progression or death was observed. Niraparib-treated patients were also notably more likely to be free of progression or death at 4 years than placebo-treated patients in both the HRd (38% versus 17%) and overall (24% versus 14%) populations. Long-term niraparib monotherapy was associated with a low rate of discontinuations due to TEAEs. No new safety signals were reported with additional follow-up, and AE findings were consistent with those of the primary analysis. The additional follow-up also confirmed that the ISD improved the safety profile of niraparib without sacrificing the PFS benefit. Taken together, the data confirm the efficacy and tolerability of niraparib

Table 2
Most common AEs in the overall population and by niraparib starting dose.

Most common TEAE, n (%)[b]	Niraparib			Placebo[a]
	Overall	FSD	ISD	
	(n = 484)	(n = 315)	(n = 169)	(n = 244)
Thrombocytopenia[c]				
Any grade	325 (67.1)	233 (74.0)	92 (54.4)	12 (4.9)
Grade ≥ 3	192 (39.7)	155 (49.2)	37 (21.9)	1 (0.4)
Grade ≥ 4	130 (26.9)	111 (35.2)	19 (11.2)	1 (0.4)
Anaemia[d]				
Any grade	315 (65.1)	227 (72.1)	88 (52.1)	48 (19.7)
Grade ≥ 3	153 (31.6)	114 (36.2)	39 (23.1)	5 (2.0)
Grade ≥ 4	3 (0.6)	2 (0.6)	1 (0.6)	0
Nausea				
Any grade	282 (58.3)	189 (60.0)	93 (55.0)	73 (29.9)
Grade ≥ 3	6 (1.2)	4 (1.3)	2 (1.2)	2 (0.8)
Grade ≥ 4	0	0	0	0
Neutropenia[e]				
Any grade	209 (43.2)	149 (47.3)	60 (35.5)	19 (7.8)
Grade ≥ 3	103 (21.3)	78 (24.8)	25 (14.8)	4 (1.6)
Grade ≥ 4	36 (7.4)	28 (8.9)	8 (4.7)	1 (0.4)
Constipation				
Any grade	202 (41.7)	144 (45.7)	58 (34.3)	52 (21.3)
Grade ≥ 3	2 (0.4)	1 (0.3)	1 (0.6)	0
Grade ≥ 4	0	0	0	0
Fatigue				
Any grade	177 (36.6)	119 (37.8)	58 (34.3)	76 (31.1)
Grade ≥ 3	11 (2.3)	7 (2.2)	4 (2.4)	1 (0.4)
Grade ≥ 4	0	0	0	0
Headache				
Any grade	133 (27.5)	94 (29.8)	39 (23.1)	41 (16.8)
Grade ≥ 3	2 (0.4)	1 (0.3)	1 (0.6)	0
Grade ≥ 4	0	0	0	0
Insomnia				
Any grade	124 (25.6)	86 (27.3)	38 (22.5)	37 (15.2)
Grade ≥ 3	5 (1.0)	5 (1.6)	0	1 (0.4)
Grade ≥ 4	0	0	0	0
Abdominal pain				
Any grade	119 (24.6)	82 (26.0)	37 (21.9)	79 (32.4)
Grade ≥ 3	10 (2.1)	5 (1.6)	5 (3.0)	1 (0.4)
Grade ≥ 4	0	0	0	0
Vomiting				
Any grade	118 (24.4)	82 (26.0)	36 (21.3)	32 (13.1)
Grade ≥ 3	4 (0.8)	4 (1.3)	0	2 (0.8)
Grade ≥ 4	0	0	0	0
Arthralgia				
Any grade	100 (20.7)	66 (21.0)	34 (20.1)	62 (25.4)
Grade ≥ 3	3 (0.6)	3 (1.0)	0	0
Grade ≥ 4	0	0	0	0
Hypertension[f]				
Any grade	99 (20.5)	70 (22.2)	29 (17.2)	22 (9.0)
Grade ≥ 3	35 (7.2)	26 (8.3)	9 (5.3)	5 (2.0)
Grade ≥ 4	0	0	0	0
Diarrhoea				
Any grade	95 (19.6)	69 (21.9)	26 (15.4)	60 (24.6)
Grade ≥ 3	4 (0.8)	1 (0.3)	3 (1.8)	1 (0.4)
Grade ≥ 4	0	0	0	0

AE, adverse event; FSD, fixed starting dose; ISD, individualised starting dose; TEAE, treatment-emergent adverse event.

[a] Data for the overall placebo population; results were similar in patients who received a fixed or individualised starting dose.

[b] The most common TEAEs reported in ≥ 20% of niraparib-treated patients in the overall population.

[c] Includes thrombocytopenia and platelet count decreased.

[d] Includes anaemia, haemoglobin decreased, red blood cell decreased, haematocrit decreased, and anaemia macrocytic.

[e] Includes neutropenia, neutrophil count decreased, febrile neutropenia, and neutropenic sepsis.

[f] Includes hypertension, blood pressure increased, and blood pressure fluctuation.

maintenance therapy and support the use of niraparib in accordance with treatment recommendations [8].

In patients with newly diagnosed advanced OC who respond to first-line platinum-based chemotherapy, there is strong evidence to support the use of maintenance treatment with PARP inhibitor monotherapy. In addition to the results from the PRIMA and PRIME trials that demonstrated the benefit of niraparib across biomarker subgroups [5,9], results from the SOLO-1 trial demonstrated the PFS benefit of olaparib monotherapy in patients with *BRCA*m disease [10]. More recently, the ATHENA-Mono/GOG-3020/ENGOT-OV45 trial results demonstrated that rucaparib significantly extended PFS compared with placebo in the HRd and overall populations [11]. Although median PFS was longer with rucaparib in the ATHENA-Mono trial than with niraparib in PRIMA, these trials cannot be directly compared because of differences in trial design, patient population, and clinical risk factors for disease progression [5,11,12].

The literature on the long-term benefits and safety of first-line PARP inhibitor maintenance is beginning to take shape, with long-term data from SOLO-1 and PAOLA-1 being released [13,14]. In the 7-year SOLO-1 analysis, OS data remained immature in this *BRCA*m only population. Although not statistically significant, a clinically meaningful benefit with olaparib maintenance treatment was observed compared with placebo (7-year OS rate, 67.0% versus 46.5%) [13]. In PAOLA-1, the OS benefit of olaparib plus bevacizumab maintenance therapy was restricted to the HRd population (hazard ratio, 0.62; 95% CI 0.45–0.85), but the efficacy contribution of bevacizumab to maintenance PARP inhibitor remains unclear [14]. In contrast to SOLO-1 in which patients with *BRCA*m tumours with no evidence of disease at 2 years stopped olaparib [10], PRIMA enroled an all-comer population and patients without disease progression were eligible to receive niraparib for 3 years or more [5]. In this PRIMA analysis, the PFS benefit of niraparib was found to be sustained and durable after a median of 3.5 years of follow-up across biomarker subgroups, and results were consistent with those of the primary analysis. Although direct comparisons of PRIMA and SOLO-1 remain difficult because of differences in patient populations, study design, and duration of follow-up, data from both trials indicate long-term benefit from PARP inhibitor maintenance monotherapy treatment [5,10,13]. Importantly,

the effect of first-line PARP inhibitor maintenance monotherapy on OS in patients with newly diagnosed OC remains an open question because mature OS data from PRIMA, PRIME, SOLO-1, and ATHENA-Mono have yet to be published.

In PRIMA, extended follow-up did not result in the detection of any new safety signals related to niraparib, and most AEs occurred during the primary analysis. Compared with the PRIMA primary analysis, five additional patients in the niraparib arm and three additional patients in the placebo arm reported MDS/AML events, resulting in a total incidence of 1.2% in each arm. PARP inhibitor use and platinum-based chemotherapy are known risk factors for MDS and AML [15,16]. In PRIMA, all nine patients who developed MDS/AML received PARP inhibitor treatment as study treatment or as subsequent therapy; for chemotherapy, all nine patients received first-line platinum-based chemotherapy (inclusion criterion), and six of nine patients received additional chemotherapy during follow-up. In SOLO-1, after a 7-year follow-up similar MDS/AML incidence rates of 1.5% and 0.8% were reported for the olaparib and placebo arms, respectively [13]. In PARP inhibitor clinical trials, MDS/AML incidence rates appear to be lower in the newly diagnosed setting compared with use in the recurrent setting [5,10,13,17–19]. The potential contribution of PARP inhibitors to MDS/AML events cannot be overlooked, but additional work is needed to better understand this association and what roles other treatments and genetic factors play in MDS/AML development. For example, in the AGO-TR-1 study, higher age and prior platinum-based chemotherapy lines were of higher risk to acquire clonal-hematopoiesis-associated gene mutations, with an increased probability of *PPM1D* and *TP53* mutations observed in patients with germline *BRCA*m [20]. An additional analysis also suggested that pre-existing *TP53* clonality may be a risk factor for MDS/AML development in PARP inhibitor-treated patients [21]. In PRIMA, more patients who experienced MDS/AML events had tumours that were HRd than HRp, but no trend was observed for *BRCA*m status.

The *ad hoc* nature of the updated and final PRIMA study PFS analysis should be considered when interpreting our findings. The data cutoff for the analysis was unplanned, and the database cleaning and data reconciliation were limited to the reported end-points. Additional limitations include investigator assessment rather than BICR assessment of disease progression and the relatively small number of patients with data at 4 years. OS data remained immature, limiting the ability to assess the long-term benefits of niraparib maintenance treatment. However, it is important to note that long-term PFS is likely a useful surrogate for long-term benefit in this population because it is not affected by the inevitable use of subsequent treatments over an extended duration of follow-up.

5. Conclusion

Taken together, these data indicate that niraparib first-line maintenance monotherapy treatment provided durable, long-term remission in women with newly diagnosed advanced OC who were at high risk for disease progression or death across all biomarker subgroups. TEAE findings were consistent with those of the primary analysis, with no new safety findings.

Data sharing statement

GSK is committed to sharing anonymized subject-level data from interventional trials as per GSK policies and as applicable. Requests for subject-level data should be done via the GSK link https://www.gsk-studyregister.com/en/.

CRediT authorship contribution statement

González-Martín: Conceptualisation, Investigation, Resources, Data curation, Visualisation, Writing – review & editing, Validation. **Pothuri**: Conceptualisation, Investigation, Resources, Data curation, Visualisation, Writing – review & editing, Validation. **Vergote**: Conceptualisation, Investigation, Resources, Data curation, Visualisation, Writing – review & editing, Validation. **Graybill**: Conceptualisation, Investigation, Resources, Data curation, Visualisation, Writing – review & editing, Validation. **Lorusso**: Conceptualisation, Investigation, Resources, Data curation, Visualisation, Writing – review & editing, Validation. **McCormick**: Conceptualisation, Investigation, Resources, Data curation, Visualisation, Writing – review & editing, Validation. **Freyer**: Conceptualisation, Investigation, Resources, Data curation, Visualisation, Writing – review & editing, Validation. **Backes**: Conceptualisation, Investigation, Resources, Data curation, Visualisation, Writing – review & editing, Validation. **Heitz**: Conceptualisation, Investigation, Resources, Data curation, Visualisation, Writing – review & editing, Validation. **Redondo**: Conceptualisation, Investigation, Resources, Data curation, Visualisation, Writing – review & editing, Validation. **Moore**: Conceptualisation, Investigation, Resources, Data curation, Visualisation, Writing – review & editing, Validation. **Vulsteke**: Conceptualisation, Investigation, Resources, Data curation, Visualisation, Writing – review & editing, Validation. **O'Cearbhaill**: Conceptualisation, Investigation, Resources, Data curation, Visualisation, Writing – review & editing, Validation. **Malinowska**: Conceptualisation, Project administration, Investigation, Resources, Data curation, Visualisation, Writing – original draft, Writing – review & editing. **Shtessel**: Conceptualisation, Project

administration, Investigation, Resources, Data curation, Visualisation, Writing – original draft, Writing – review & editing, Validation. **Compton**: Conceptualisation, Investigation, Resources, Data curation, Visualisation, Writing – original draft, Writing – review & editing, Validation. **Mirza**: Conceptualisation, Investigation, Resources, Data curation, Visualisation, Writing – review & editing, Validation. **Monk**: Conceptualisation, Investigation, Resources, Data curation, Visualisation, Writing – review & editing, Validation.

Declaration of Competing Interest

Dr. González-Martín reports support for the manuscript funding from GSK; grants or contracts from GSK and Roche; consulting fees from Alkermes, Amgen, AstraZeneca, Clovis Oncology, Genmab, GSK, ImmunoGen, Merck Sharp & Dohme, MacroGenics, Novartis, Oncoinvent, Pfizer/Merck, PharmaMar, Roche, Sotio, and Sutro; honoraria fees from AstraZeneca, Clovis, GSK, PharmaMar, and Roche; and support for attending meetings from AstraZeneca, GSK, PharmaMar, and Roche. Dr. Pothuri reports institutional grant support from AstraZeneca, Celsion, Genentech/Roche, Karyopharm, Merck, Mersana, GSK, Sutro, Toray, Incyte, Imab, Onconova, VBL Therapeutics, and Clovis Oncology; consulting fees from AstraZeneca, GSK, SeaGen, and Merck; advisory board fees from Eisai, Lily, Merck, Sutro Biopharma, Tesaro/GSK, Astra Zeneca, and GOG Foundation. Dr. Vergote reports institutional payments for corporate sponsorship research from Amgen and Roche and contracted research from Genmab and Oncoinvent AS; institutional consulting fee payments from Amgen (Europe) GmbH, AstraZeneca, Carrick Therapeutics, Clovis Oncology Inc, Deciphera Pharmaceuticals, Elevar Therapeutics, F. Hoffmann–La Roche Ltd, Genmab, GSK, Immunogen Inc, Mersana, Millennium Pharmaceuticals, MSD, Novocure, Oncoinvent AS, Octimet Oncology, Sotio, Verastem Oncology, and Zentalis; consulting fees from Deciphera Pharmaceuticals, Jazz Pharmaceuticals, and Oncoinvent AS; honoraria payments from Agenus, Aksebio, AstraZeneca, Bristol Myers Squibb, Deciphera Pharmaceuticals, Eisai, F. Hoffmann–La Roche Ltd, Genmab, GSK, Immunogen Inc, Jazz Pharmaceuticals, Karyopharm, MSD, Novartis, Novocure, Oncoinvent AS, Seagen, and Sotio; institutional travel support from Amgen, AstraZeneca, MSD, Roche, and Tesaro; advisory board fees from Agenus, AstraZeneca, Bristol Myers Squibb, Deciphera Pharmaceuticals (2021), Eisai, F. Hoffmann–La Roche Ltd, Genmab, GSK, Immunogen Inc, MSD, Novartis, Novocure, Seagen (2021), and Sotio. Dr. Graybill reports advisory board and speaker fees from GSK. Dr. Lorusso reports personal fees from Amgen, AstraZeneca, Clovis Oncology, Genmab, Immunogen, Merck, and PharmaMar; and grants from Merck and PharmaMar. Dr. McCormick reports advisory role fees from AstraZeneca, Clovis, GSK, ImmunoGen, and Merck. Dr. Freyer reports personal fees from AstraZeneca, Biogaran, Bristol Myers Squibb, Clovis Oncology, MSD, Novartis, Pfizer Inc., Roche Holding AG, S.A.S., and Tesaro; grants from AstraZeneca, Mylan, and Roche Holding AG. Dr. Backes reports personal fees from Agenus, CEC Oncology, Clovis, Eisai, Merck, AstraZeneca and GSK. ImmunoGen, Myriad; grants from Clovis, Eisai, Immunogen, and Merck, Beigene, Natera. Dr. Heitz reports honoraria from Roche, AstraZeneca, GSK, NovoCure, and PharmaMar; advisory board fees from NovoCure; and leadership role with AGO study group. Dr. Redondo reports institutional grants from Eisai, PharmaMar, and Roche; honoraria fees from AstraZeneca, MSD, Clovis, GSK, PharmaMar, and Eisai; advisory board roles at AstraZeneca, MSD, Clovis, GSK, PharmaMar, and Eisai; and travel support from AstraZeneca, GSK, and PharmaMar. Dr. Moore reports personal fees from Abcodia Inc, Fujirebio Diagnostics Inc, and Humphries Pharmaceutical; and institutional grants from Angle Plc. Dr. Vulsteke reports medical writing support to GSK; consulting fees from Atheneum Partners, Bristol Myers Squibb, GSK, Janssen-Cilag, Leo-Pharma, Merck Sharp & Dohme, and Roche; advisory board fees from AstraZeneca, Bayer, GSK, Janssen-Cilag, Leo Pharma, Merck Sharp & Dohme; and travel support from Pfizer and Roche. Dr. O'Cearbhaill reports participating in advisory boards with 2seventy bio, Bayer, Carina Biotech, Fresenius Kabi, Immunogen, GSK, Miltenyi Biotec, Regeneron, and Seattle Genetics; personal fees from GOG Foundation; travel fees from Hitech Health and Gathering Around Cancer, Ireland; service as a non-compensated steering committee member for the PRIMA and Moonstone (niraparib) and DUO-O (olaparib) studies; institutional research support grants from Acrivon Therapeutics, AstraZeneca/Merck, Atara Biotherapeutics/Bayer, Genentech, Genmab, GSK, Gynecologic Oncology Group Foundation, Juno Therapeutics, Kite/Gilead, Ludwig Institute for Cancer Research, Lyell Immunopharma, Regeneron, Sellas Life Sciences, StemcentRx, Syndax, TapImmune Inc, and TCR2 Therapeutics. Drs. Malinowska and Shtessel are employees of GSK. Ms. Compton is a former employee of GSK and currently receiving consulting fees from GSK. Dr. Mirza reports consulting and advisory role fees from AstraZeneca, Biocad, GSK, Karyopharm,

Merck, Roche, and Zai Lab; speakers' bureau fees from AstraZeneca and GSK; institutional research funding from Apexigen, AstraZeneca, Deciphera (trial chair), GSK, and Ultimovacs; and personal financial interest in Karyopharm (stocks/shares, member of board of directors). Dr. Monk reports consulting fees from Agenus, Akeso Bio, Amgen, Aravive, Bayer, Elevar, EMD Merck, Genmab/Seagen, GOG Foundation, Gradalis, ImmunoGen, Iovance, Karyopharm, Macrogenics, Mersana, Myriad, Novocure, Novartis, Pfizer, Puma, Regeneron, Sorrento, US Oncology Research, and VBL; and speakers' bureau honoraria from AstraZeneca, Clovis, Eisai, Merck, Roche/Genentech, and Tesaro/GSK.

Acknowledgements

The authors thank Klaus Baumann, MD, for his contributions to the initial presentation of the data at the European Society for Medical Oncology (ESMO) Congress 2022, September 9–13, 2022, and his feedback on the manuscript outline. Medical writing and editorial assistance, funded by GSK (Waltham, MA) and coordinated by Hasan Jamal, MSc, and Prudence Roaf, MPH, of GSK, were provided by Betsy C. Taylor, PhD, CMPP, and Mary C. Wiggin of Ashfield MedComms, an Inizio company.

Funding

This study (NCT02655016) was supported by GSK.

Clinical trial information

NCT02655016

Prior Presentation

Portions of these data were previously presented at the European Society for Medical Oncology (ESMO) Congress 2022, September 9–13, 2022, and the International Gynecologic Cancer Society 2022 Annual Global Meeting, September 29–October 1, 2022. Additional encore presentations of the data are planned for the 12th International Charité Mayo Conference 2023, April 26–29, 2023, the Nordic Society of Gynaecological Oncology 2023 Annual Meeting, June 14–16, 2023, and the British Gynaecological Cancer Society Annual Scientific Meeting 2023, June 28–30, 2023.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.04.024.

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