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Maintenance olaparib in patients with platinum-sensitive relapsed ovarian cancer: Outcomes by somatic and germline BRCA and other homologous recombination repair gene mutation status in the ORZORA trial

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HIGHLIGHTS

- Clinical activity of maintenance olaparib in platinum-sensitive relapsed ovarian cancer was seen with any BRCA mutation.
- This included activity in patients with somatic BRCA mutations.
- Activity was also seen in patients with non-BRCA homologous recombination repair mutations.
- Safety and tolerability were consistent with previous studies in this setting.

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ABSTRACT

Background. The open-label, single-arm, multicenter ORZORA trial (NCT02476968) evaluated the efficacy and safety of maintenance olaparib in patients with platinum-sensitive relapsed ovarian cancer (PSR OC) who had tumor BRCA mutations (BRCAm) of germline (g) or somatic (s) origin or non-BRCA homologous recombination repair mutations (HRRm) and were in response to their most recent platinum-based chemotherapy after ≥2 lines of treatment.

Methods. Patients received maintenance olaparib capsules (400 mg twice daily) until disease progression. Prospective central testing at screening determined tumor BRCAm status and subsequent testing determined gBRCAm or sBRCAm status. Patients with predefined non-BRCA HRRm were assigned to an exploratory cohort.

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Maintenance
BRCA mutation
HRR

The co-primary endpoints were investigator-assessed progression-free survival (PFS; modified Response Evaluation Criteria in Solid Tumors v1.1) in BRCAm and sBRCAm cohorts. Secondary endpoints included health-related quality of life (HRQoL) and tolerability.

Results. 177 patients received olaparib. At the primary data cut-off (17 April 2020), the median follow-up for PFS in the BRCAm cohort was 22.3 months. The median PFS (95% CI) in BRCAm, sBRCAm, gBRCAm and non-BRCA HRRm cohorts was 18.0 (14.3–22.1), 16.6 (12.4–22.2), 19.3 (14.3–27.6) and 16.4 (10.9–19.3) months, respectively. Most patients with BRCAm reported improvements (21.8%) or no change (68.7%) in HRQoL and the safety profile was as expected.

Conclusions. Maintenance olaparib had similar clinical activity in PSR OC patients with sBRCAm and those with any BRCAm. Activity was also observed in patients with a non-BRCA HRRm. ORZORA further supports use of maintenance olaparib in all patients with BRCA-mutated, including sBRCA-mutated, PSR OC.

1. Introduction

The major treatment goals for patients with relapsed ovarian cancer (OC) are to delay disease progression and prolong survival, while maintaining quality of life (QoL) [1]. Poly(ADP-ribose) polymerase (PARP) inhibitors, such as olaparib, are standard of care in relapsed platinum-sensitive OC. PARP inhibitors trap PARP at DNA single-strand breaks, preventing their repair and generating double-strand breaks that cannot be repaired accurately in tumors with defects in homologous recombination repair (HRR) (i.e. homologous recombination deficiency [HRD]) [2–4]. This leads to accumulated DNA damage and synthetic lethality in tumor cells. The most well-characterized HRD mechanisms are deleterious germline (g) or somatic (s) mutations in breast cancer genes *BRCA1/BRCA2* (BRCAm), although other mechanisms, including mutations in other genes associated with HRR (non-BRCA HRRm), are also implicated [5].

Olaparib is approved globally as maintenance therapy for patients with platinum-sensitive relapsed (PSR) OC irrespective of BRCAm or other biomarker status [6–9]. The phase II Study 19 trial (NCT00753545) showed significant progression-free survival (PFS) benefit versus placebo irrespective of BRCAm status in this setting (hazard ratio [HR] 0.35; 95% confidence interval [CI] 0.25–0.49) [10]. Subsequently, the phase III SOLO2 trial (NCT01874353) also demonstrated significant benefit for maintenance olaparib versus placebo, for patients with PSR OC and a gBRCAm (median PFS 19.1 vs 5.5 months, respectively; HR 0.30; 95% CI 0.22–0.41); no patients had a confirmed sBRCAm [11]. In Study 19, PFS benefit was retrospectively observed in a small sBRCAm cohort, consistent with that observed in the gBRCAm cohort, and the phase IIIb OPINION trial (NCT03402841) has also shown activity of maintenance olaparib in a small cohort ($n = 27$) with PSR OC and an sBRCAm (median PFS 16.4 months; 95% CI 12.8–not estimable) [12,13]. However, beyond this, data prospectively evaluating efficacy of olaparib in patients with sBRCAm are limited; therefore, ORZORA was designed as a confirmatory trial.

Evidence also exists for clinical benefit with PARP inhibitors in patients with HRD beyond BRCAm [14–17]. One approach to identifying these patients has been to develop sequencing-based biomarker tests to determine the mutation status of prespecified panels of HRR pathway associated genes which may cause HRD [18]. It has been hypothesized that tumor mutations in genes beyond *BRCA1/BRCA2* that are implicated in the DNA repair pathway of HRR may also be predictive of PARP inhibitor benefit in OC, although the relevance of individual mutations remains unclear [19].

The open-label, single-arm, multicenter ORZORA trial (NCT02476968) evaluated efficacy and safety of maintenance olaparib in patients with PSR OC and in response to their most recent platinum-based chemotherapy after two or more lines of prior treatment, and who had a tumor BRCAm (tBRCAm) of germline or somatic origin or a non-BRCA HRRm.

2. Methods

2.1. Study design and patients

ORZORA is a prospective, open-label, multicenter, international study. Eligible patients had PSR, high-grade epithelial ovarian, primary peritoneal and/or fallopian tube cancer and a deleterious or suspected deleterious gBRCAm or sBRCAm, or a qualifying deleterious or suspected deleterious non-BRCA HRRm. Patients must have completed two or more prior lines of platinum-based therapy and been considered platinum-sensitive (disease progression ≥6 months after the last dose of their penultimate platinum-based chemotherapy regimen). Patients were also required to be in complete or partial response following platinum-based chemotherapy. Full eligibility criteria are in the Supplementary Material.

Eligible patients were screened to determine BRCAm and non-BRCA HRRm status (Fig. 1). In a subsequent study protocol version, patients with previously confirmed gBRCAm were excluded to limit their inclusion and ensure ≥50 patients with sBRCAm were recruited. Patients provided archival tumor samples for central tBRCAm testing and, if available, another sample for parallel non-BRCA HRRm testing. If central testing (myChoice® CDx, Myriad Genetic Laboratories, Inc., Salt Lake City, UT, USA) detected a BRCAm, patients were further categorized as sBRCAm or gBRCAm by central testing of blood samples (BRACAnalysis CDx®, Myriad Genetic Laboratories, Inc.), and entered the main study. Patients without tBRCAm (non-tBRCAm) were eligible for entry to the non-BRCA HRRm exploratory cohort if carrying one or more BRCA-independent qualifying mutations in genes involved in the HRR pathway (deleterious or suspected deleterious loss-of-function mutations in any of 13 predetermined genes [*ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D* and *RAD54L*], via FoundationOne® CDx Assay [Foundation Medicine, Inc., Cambridge, MA, USA]).

Patients initiated olaparib capsules 400 mg twice daily (bid) within 8 weeks after their last dose of platinum-containing chemotherapy and continued until investigator-assessed objective radiological disease progression (modified Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST v1.1]) or beyond if the investigator deemed the patient was benefitting and did not meet other discontinuation criteria (detailed in the Supplementary Material). Data collection continued for subsequent treatments, progression, overall survival (OS) and safety analyses.

2.2. Endpoints and assessments

The co-primary endpoints were investigator-assessed PFS (RECIST v1.1) or death in patients with any BRCAm, and in patients with an sBRCAm. Secondary endpoints in these cohorts were OS, time to investigator-assessed second progression or death (PFS2), time to first subsequent therapy or death (TFST), time to second

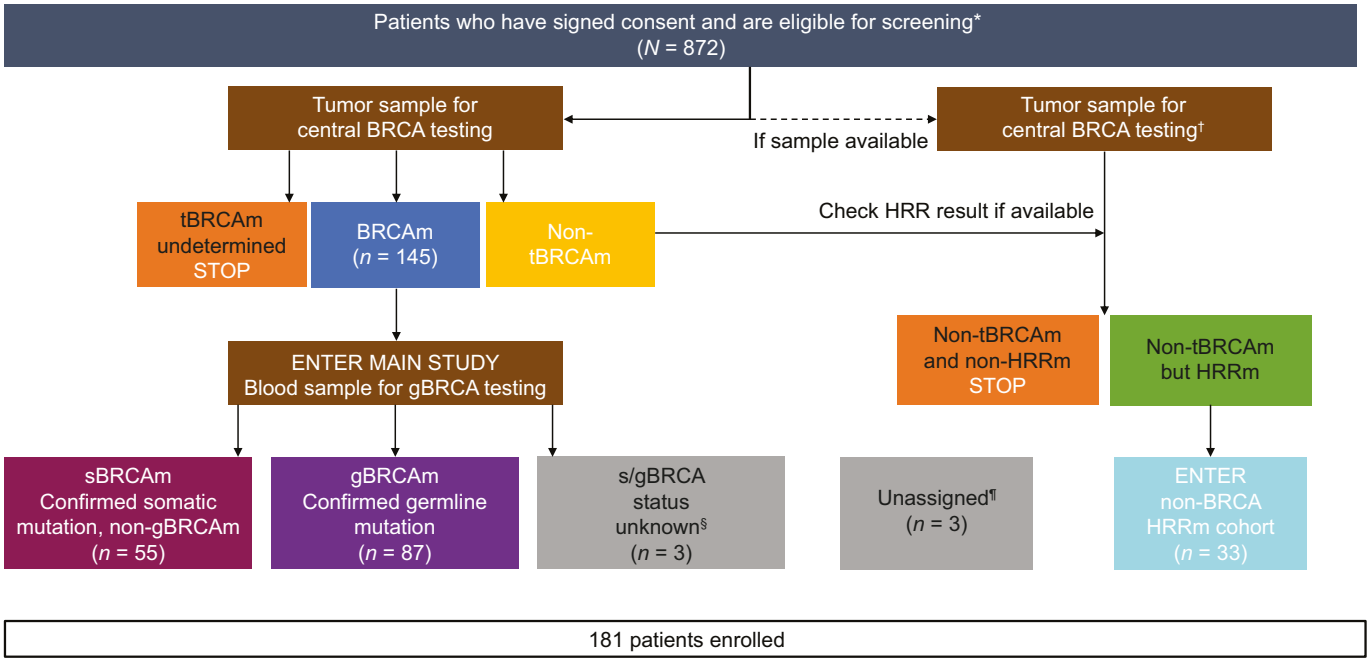

Fig. 1. Screening process. *After enrollment of 25 patients with gBRCAm, recruitment was restricted to those without previously confirmed gBRCAm to ensure that at least 50 patients with tBRCAm were included. †Prespecified non-BRCA HRR gene panel: *ATM*, *BRIP1*, *PALB2*, *RAD51C*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PPP2R2A*, *RAD51B*, *RAD51D*, *RAD54L*. ‡A minimum of 50 patients were to be recruited to the sBRCAm cohort. §s/gBRCA mutation status unknown: three patients had BRCAm but could not be classified as sBRCAm or gBRCAm. ¶Three patients enrolled without a BRCAm or HRRm were unassigned. BRCAm, BRCA mutation; g, germline; HRR, homologous recombination repair; HRRm, HRR mutation; s, somatic; t, tumor.

subsequent therapy or death, time to olaparib discontinuation or death, health-related quality of life (HRQoL; Functional Assessment of Cancer Therapy-Ovarian [FACT-O] Trial Outcome Index [TOI]), safety and tolerability.

Subgroup PFS analyses were performed in the BRCAm cohort by response to previous platinum-based chemotherapy, time to disease progression on penultimate platinum-based chemotherapy, measurable disease at baseline, BRCAm type, enrollment age, region, family history (ovarian or breast cancer), prior bevacizumab and number of prior chemotherapy lines. A key exploratory endpoint was PFS (RECIST v1.1) in patients with qualifying non-BRCA HRRm.

Tumor assessments were performed at baseline and every 12 weeks from enrollment date.

Treatment-emergent adverse events (TEAEs) were monitored throughout treatment and the 30-day safety follow-up period. Reporting of AEs of special interest (AESIs; myelodysplastic syndrome and/or acute myeloid leukemia [AML], new primary malignancies or pneumonitis) continued after this period.

2.3. Statistical analysis

No formal sample size calculation was provided. A sample size of ~250 patients was proposed, to allow recruitment of >50 patients with sBRCAm. The primary data cut was planned for 60% maturity, ~32 months after first subject enrollment. PFS (including median PFS and 12- and 24-month PFS rates and associated 95% CIs) was reported as Kaplan–Meier estimates in BRCAm, sBRCAm, gBRCAm and non-BRCA HRRm cohorts. All time-to-event endpoints were described as for PFS. A summary of PFS2, TFST and OS was produced, although data were immature. QoL data were analyzed using the TOI derived from the FACT-O questionnaire [20]. Efficacy data were reported using the full analysis set (all enrolled patients assigned to olaparib), and safety data using the safety analysis set (all patients who received ≥1 olaparib dose).

3. Results

3.1. Baseline patient characteristics

From September 2015 to October 2018, 872 patients were screened; 181 were enrolled and 177 received olaparib (Supplementary Table S1). Baseline characteristics are reported in Table 1. Following screening, 145 patients were classified as having a BRCAm: 87 and 55, respectively, with gBRCAm or sBRCAm, and three unclassified (Fig. 1). Thirty-three patients were classified as having a non-BRCA HRRm: two (6%) *ATM*, five (15%) *BRIP1*, 12 (36%) *CDK12* mutation, one (3%) *FANCL*, two (6%) *PALB2*, six (18%) *RAD51C*, four (12%) *RAD51D* and one co-occurring *CHEK2* and *RAD51C* (3%). Three enrolled patients were unassigned and had neither a BRCAm or non-BRCA HRRm. At the primary data cut-off (April 17, 2020), 59/177 patients (33%) were still receiving maintenance olaparib, including 51/143 (36%) with any BRCAm and 8/32 (25%) with a non-BRCA HRRm. Of 118 patients who discontinued, 87 (74%) discontinued because of disease progression. Patient characteristics were similar between cohorts.

3.2. Efficacy endpoints

In the any BRCAm cohort, the median duration of follow-up in patients censored for PFS was 22.3 months (range 0.0–52.2). There were 88 PFS events (61% maturity). The median PFS was 18.0 months (95% CI 14.3–22.1) and, based on Kaplan–Meier estimates, the 12- and 24-month PFS rate was 67% (95% CI 58.7–74.4) and 39% (95% CI 30.2–47.3), respectively (Fig. 2a).

Similarly, in the sBRCAm cohort, the median duration of follow-up in patients censored for PFS was 22.1 months (range 2.7–41.5). There were 35 PFS events (64% maturity). The median PFS was 16.6 months (95% CI 12.4–22.2), and the 12- and 24-month PFS rate was 65% (95% CI 50.4–75.8) and 33% (95% CI 19.4–46.9), respectively (Fig. 2b).

In the gBRCAm cohort, the median duration of follow-up in patients censored for PFS was 25.6 months (range 0.0–52.2). There were 52 PFS

Table 1
Patient demographic and disease characteristics at baseline (full analysis set).

Characteristic	BRCAm[a] ($n = 145$)	sBRCAm ($n = 55$)	gBRCAm ($n = 87$)	Non-BRCA HRRm ($n = 33$)
Patient age, years, median (range)[b]	61.5 (39–82)	67.0 (42–78)	56.0 (39–82)	64.0 (45–79)
Time from original diagnosis, years, median (range)	3.05 (1.4–25.3)	2.93 (1.5–25.3)	3.37 (1.4–15.3)	3.52 (1.7–9.4)
Primary tumor location, *n* (%)				
Ovary	124 (86)	43 (78)	78 (90)	27 (82)
Fallopian tubes	7 (5)	5 (9)	2 (2)	1 (3)
Primary peritoneal	14 (10)	7 (13)	7 (8)	5 (15)
Histology, *n* (%)				
Serous	131 (90)	52 (95)	76 (87)	29 (88)
Mucinous	2 (1)	1 (2)	1 (1)	0
Clear cell	2 (1)	0	2 (2)	2 (6)
Endometrioid	3 (2)	0	3 (3)	1 (3)
Undifferentiated	5 (3)	1 (2)	4 (5)	0
Mixed, epithelial	2 (1)	1 (2)	1 (1)	1 (3)
Tumor grade, *n* (%)				
High grade	144 (99)	54 (98)	87 (100)	33 (100)
Low grade	1 (1)	1 (2)	0	0
Prior lines of chemotherapy, *n* (%)				
2	80 (55)	34 (62)	45 (52)	18 (55)
3	41 (28)	12 (22)	28 (32)	11 (33)
≥4	23 (16)	9 (16)	14 (16)	4 (12)
Missing	1 (1)	0 (0)	0 (0)	(0)
Response to previous platinum-based chemotherapy, *n* (%)				
Complete response	75 (52)	30 (55)	44 (51)	11 (33)
Partial response	68 (47)	25 (45)	43 (49)	21 (64)
Missing	2 (1)	0 (0)	0 (0)	1 (3)
t*BRCA*m, *n* (%)[c]	124 (100)	55 (100)	66 (100)	0
BRCA1	81 (65)	36 (65)	42 (64)	0
BRCA2	42 (34)	19 (35)	23 (35)	0
Both	1 (1)	0	1 (2)	0

BRCAm, BRCA mutation; FIGO, International Federation of Gynecology and Obstetrics; g, germline; HRRm, homologous recombination repair mutation; s, somatic; t, tumor.
[a] BRCAm cohort includes three patients who reported a BRCAm but could not be classified as sBRCAm or gBRCAm.
[b] Patients for whom only year of birth was recorded (due to country restrictions) are excluded from this summary.
[c] Local or Myriad testing.

events (60% maturity). The median PFS was 19.3 months (95% CI 14.3–27.6), and the 12- and 24-month PFS rate was 70% (95% CI 58.6–78.4) and 43% (95% CI 31.6–53.3), respectively (Fig. 2c).

In the exploratory non-BRCA HRRm cohort, the median duration of follow-up in patients censored for PFS was 22.0 months (0.0–33.2). There were 22 PFS events (67% maturity). The median PFS was 16.4 months (95% CI 10.9–9.3), and the 12- and 24-month PFS rate was 68% (95% CI 48.4–81.2) and 26% (95% CI 12.0–43.2), respectively (Fig. 2d). Patient-level PFS varied across individual non-BRCA HRRm gene mutation (Fig. 3).

PFS2, TFST and OS are currently immature (data maturity: BRCAm cohort, 37%, 39% and 30%; sBRCAm cohort, 40%, 42% and 29%, respectively). In the BRCAm and sBRCAm cohorts, respectively, the 18-month PFS2 rate (95% CI) was 83% (75.2–88.7) and 84% (70.1–91.6); the first subsequent therapy-free survival rate (95% CI) was 71% (61.7–77.6) and 67% (51.9–77.8); and the OS rate (95% CI) was 91% (85.1–94.9) and 95% (83.8–98.2).

PFS was similar across BRCAm cohort subgroups (Supplementary Table S2).

3.3. HRQoL

One hundred and thirty-one patients with BRCAm had baseline evaluation and 125 had one or more subsequent questionnaire. HRQoL outcomes were similar in patients with any BRCAm, including sBRCAm, as assessed by best response in FACT-O TOI scores (Fig. 4). Overall, most patients with any BRCAm, or an sBRCAm, reported no change or improvement in HRQoL during maintenance therapy; only ~11% and 12% reported worsening as their best response, respectively.

3.4. Safety endpoints

In the safety analysis set, the median (range) duration of maintenance therapy with olaparib was 17.7 months (0.0–53.8). TEAEs of any grade occurred in 94% of patients (most commonly nausea [54%], fatigue/asthenia [54%] and anemia [42%]), grade ≥3 TEAEs occurred in 35% (most commonly anemia [16%]), and serious AEs in 25%. TEAEs occurring in ≥10% of patients are given in Table 2. AEs leading to dose interruptions, reductions and discontinuations occurred in 49%, 28% and 5%, respectively. Two cases of AML, two new primary malignancies (papillary thyroid cancer and Burkitt's lymphoma) and no cases of pneumonitis were reported. The safety profile was similar by BRCAm and non-BRCA HRRm status (Supplementary Table S3).

4. Discussion

ORZORA was conducted to address an evidence gap for the use of maintenance olaparib in PSR OC patients with sBRCAm, and findings from this primary analysis of the study expand on limited results reported in previous studies. In ORZORA, maintenance olaparib demonstrated clinical activity, with good duration of follow-up, in patients with PSR OC with an sBRCAm, with similar median PFS of 18.0 and 16.6 months observed in the BRCAm cohort and the sBRCAm only cohort, respectively (co-primary endpoints), as well as median PFS of 19.3 months in the gBRCAm cohort.

The median PFS in these cohorts was consistent with that reported for maintenance olaparib in patients with PSR OC and a gBRCAm in SOLO2 (19.1 months), which was significantly greater than with placebo (5.5 months; HR 0.30) [11]. The similar PFS benefit observed in the ORZORA BRCAm, including sBRCAm, cohorts is also consistent with retrospective analysis from Study 19 showing that olaparib provided PFS benefit in a small sBRCAm cohort, similar to that observed in the gBRCAm cohort, and with primary results from OPINION demonstrating clinical activity for maintenance olaparib in a small sBRCAm cohort with PSR OC ($n = 27$; median PFS 16.4 months) [10,12,13].

Although PFS2, TFST and OS are currently immature in ORZORA, 18-month landmark data were consistent with SOLO2 (18-month PFS2, first subsequent therapy-free survival and OS rates of approximately 70% [11], 65% and 90% [21], respectively, in the olaparib group [estimates from Kaplan–Meier curves]) and supported the PFS outcome.

The exploratory non-BRCA HRRm cohort also showed clinical activity with maintenance olaparib in ORZORA, consistent with some previous studies in this setting [22,23]. This supports that tumor mutations in genes beyond *BRCA1*/*BRCA2* implicated in the DNA repair pathway of HRR may also be predictive of PARP inhibitor benefit in OC [19]. However, the relevance of individual HRR-associated genes has been challenging to determine. In the OPINION and PAOLA-1 trials, not all patients with a non-BRCA HRRm tumor were HRD-positive by Myriad genome instability score; in PAOLA-1, only 6/16 HRR genes analyzed had a median HRD-positive score (≥42; *BLM*, *BRIP1*, *RAD51C*, *PALB2*, *RAD51D*, *RAD51B*) [24,25]. In ORZORA, of eight patients who were progression-free and remained on treatment at data cut-off, five had a *RAD51* mutation (three *RAD51D*, two *RAD51C*), one *BRIP1*, one *PALB2* and one *ATM*. However, as in previous studies, the number of patients with mutations in any one non-BRCA HRR gene was too small to derive definitive conclusions, and further investigation is required to determine the relevance of specific biomarkers in the context of PARP inhibition in the PSR OC setting.

Most patients receiving maintenance olaparib reported improvements or no change in HRQoL. Maintenance olaparib was

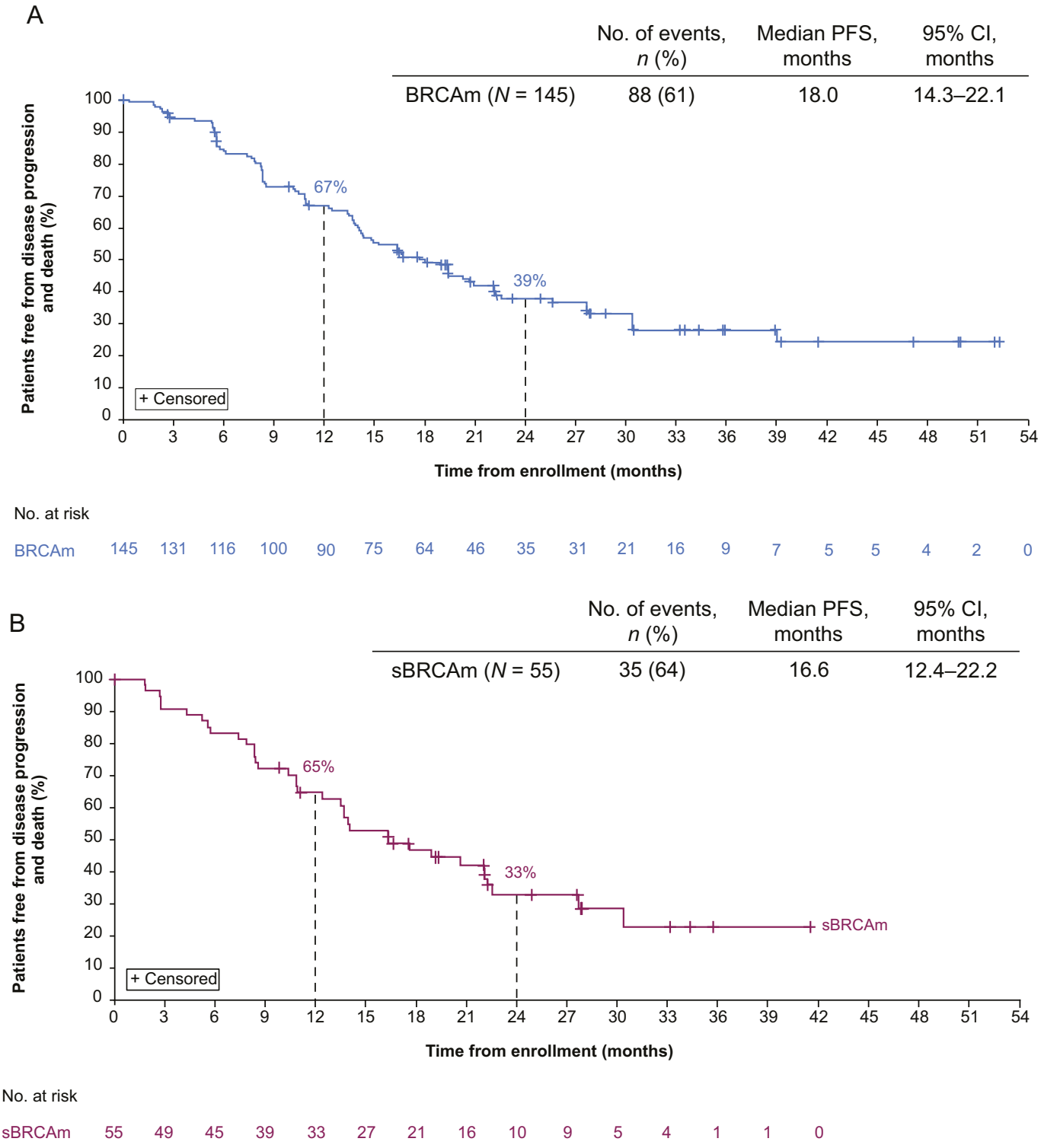

Fig. 2. Kaplan–Meier plot of progression-free survival in patients with ovarian cancer with (**A**) any BRCAm, (B) an sBRCAm, (C) a gBRCAm or (D) a non-BRCA HRRm. Tick mark indicates a censored observation. BRCAm, BRCA mutation; CI, confidence interval; g, germline; HRRm, homologous recombination repair mutation; PFS, progression-free survival; s, somatic.

generally well tolerated and its safety profile consistent with previous reports in this setting [11,13]. TEAEs were usually managed by dose interruption (seen in almost half of olaparib patients), with few requiring discontinuations. There was also a low incidence of AESIs. The safety profile was similar between the BRCAm, including sBRCAm, cohorts.

The main limitation of ORZORA was the lack of a comparator arm; however, such a design was not considered appropriate given the benefit patients were expected to derive from maintenance olaparib, as has been confirmed.

ORZORA used the capsule formulation (400 mg bid) of olaparib that was originally approved for maintenance treatment in the PSR OC setting

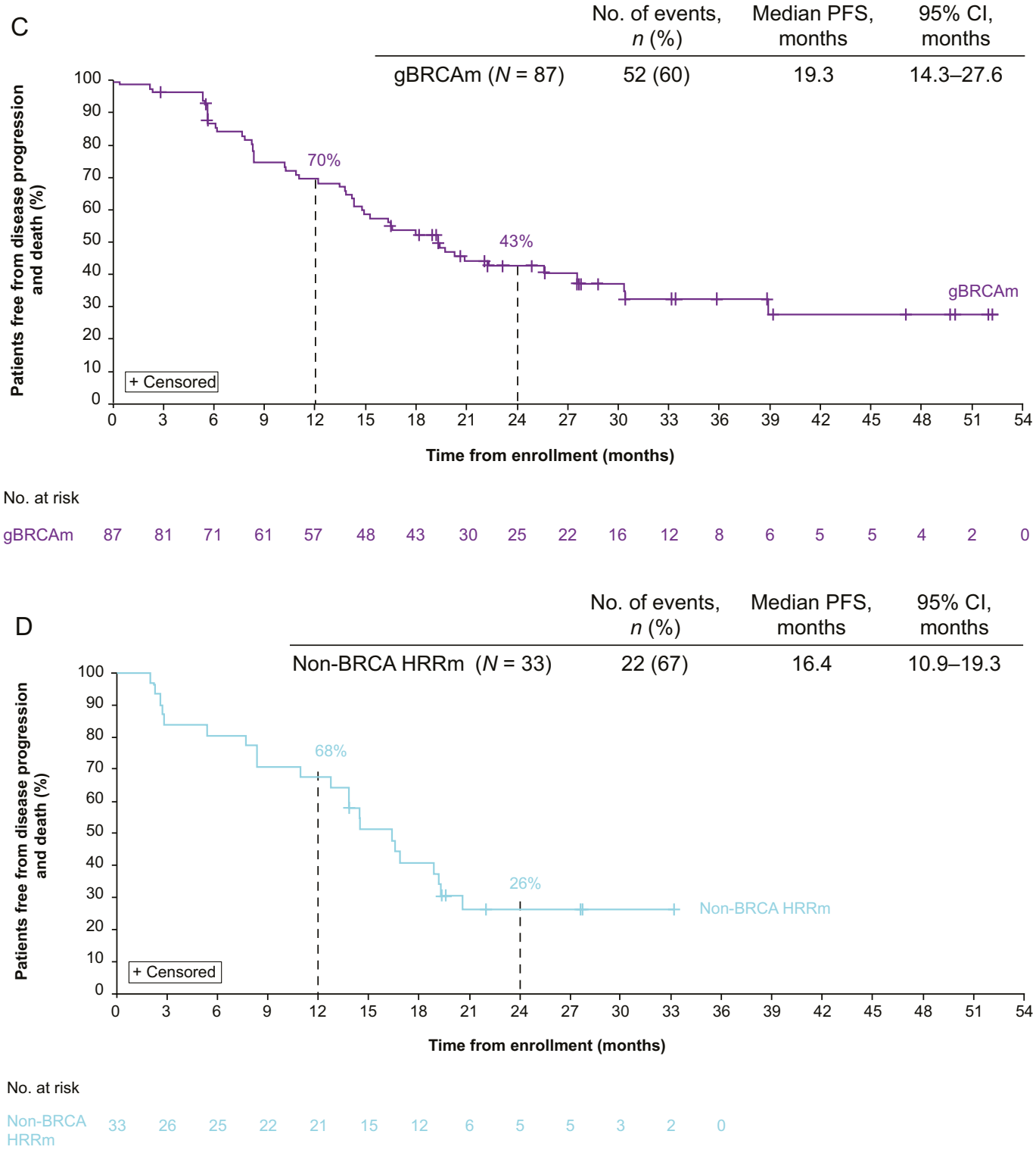

Fig. 2 (*continued*).

and was standard at the time of study conception [10,26]. Capsules have since been superseded by tablets (300 mg bid), which have similar olaparib exposure with reduced pill burden (two tablets bid vs eight capsules bid) and were confirmed to significantly prolong PFS in patients with PSR OC in SOLO2 [6,11,27]. With this caveat, findings from ORZORA remain relevant given the similar efficacy of the different formulations.

5. Conclusions

In ORZORA, maintenance olaparib demonstrated clinical activity in patients with PSR OC and a BRCAm, including those with an sBRCAm, consistent with benefit reported in other studies. Maintenance olaparib also showed activity in the exploratory cohort of patients with a non-BRCA HRRm. As the largest prospective cohort to show a benefit in

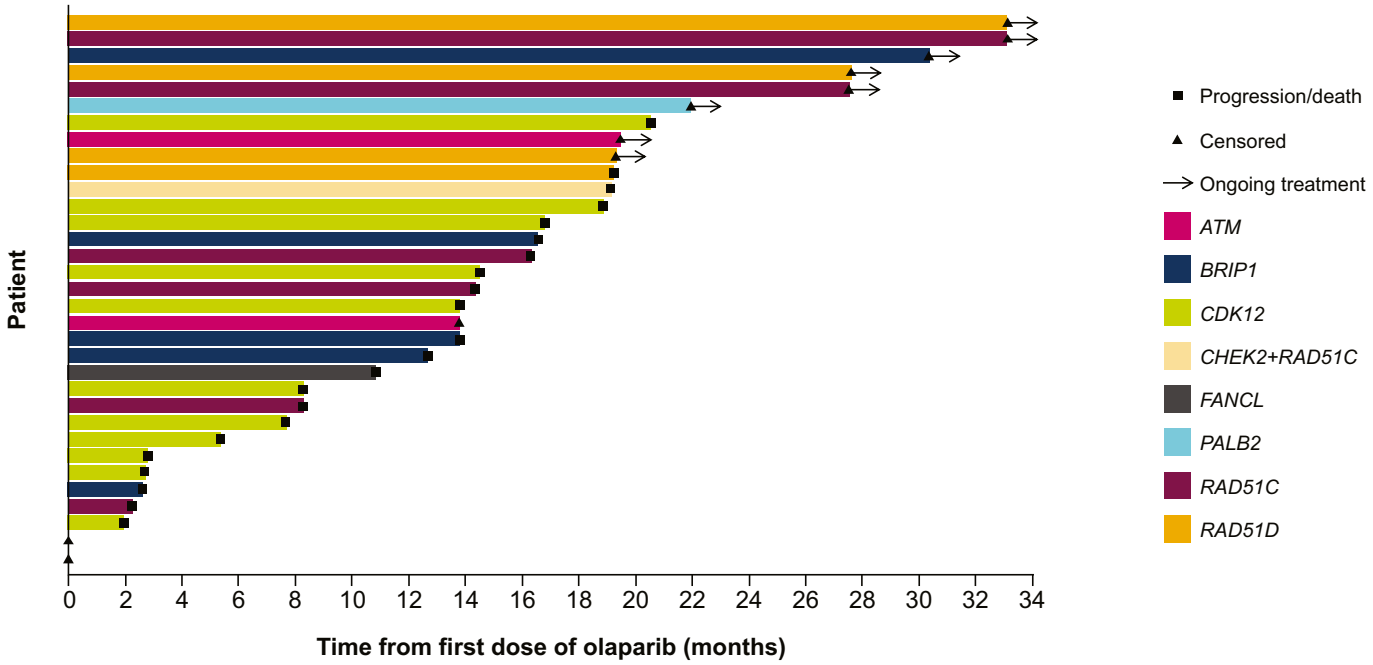

Fig. 3. Swimmer plot of patient-level PFS in the non-BRCA HRRm cohort. Two patients censored at day 1 had *PALB2* and *CDK12* mutations, respectively. HRRm, homologous recombination repair mutation; PFS, progression-free survival.

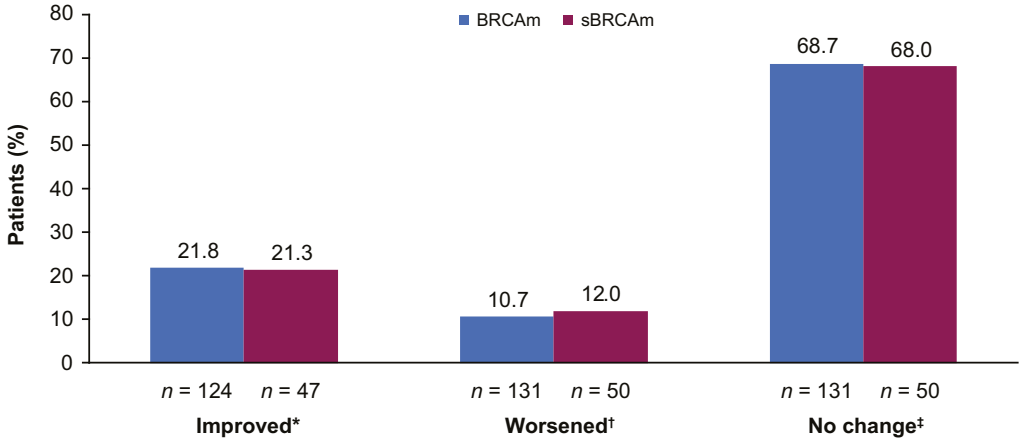

Fig. 4. Best response in FACT-O TOI scores in patients with any BRCAm, or an sBRCAm. TOI scores range from 0 to 100, with higher scores indicating better HRQoL. *Improved: defined as an increase from baseline of ≥10 points. Two visit responses of 'improved' were required a minimum of 28 days apart, without an intervening visit response of 'worsened'. All patients with a baseline score of ≤90 were included. †Worsened: defined as a decrease from baseline of ≥10 points. A visit response of 'worsened' was required without a response of improved' or 'no change' within 28 days. All patients with a baseline score ≥10 were included (no patient with a baseline score was excluded, as none had a baseline score <10). ‡No change: two visit responses of either 'no change' or 'improved' and 'no change' were required a minimum of 28 days apart without an intervening visit response of 'worsened'. All patients with baseline score were included. BRCAm, BRCA mutation; FACT-O, Functional Assessment of Cancer Therapy-Ovarian; HRQoL, health-related quality of life; s, somatic; TOI, Trial Outcome Index.

patients with an sBRCAm, the primary analysis of ORZORA further supports the use of maintenance olaparib in all BRCAm patients with PSR OC including those with a BRCAm of somatic origin.

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CRediT authorship contribution statement

Sandro Pignata: Conceptualization, Methodology, Investigation, Resources, Writing – original draft, Writing – review & editing. **Amit Oza:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Geoff Hall:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Beatriz Pardo:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Radoslaw Madry:** Investigation, Resources, Writing – original draft, Writing – review & editing. **David Cibula:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Jaroslav Klat:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Ana Montes:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Rosalind Glasspool:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Nicoletta Colombo:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Imre Pete:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Ana Herrero Ibáñez:** Investigation, Resources, Writing

Table 2
Summary of TEAEs occurring in ≥10% of patients (safety analysis set, $n = 177$).

TEAE	All grades, *n* (%)	CTCAE grade ≥3, *n* (%)
Nausea	95 (54)	2 (1)
Fatigue/asthenia[a]	95 (54)	4 (2)
Anemia[a]	75 (42)	28 (16)
Neutropenia[a]	25 (14)	2 (1)
Vomiting	49 (28)	2 (1)
Dyspepsia	28 (16)	0
Abdominal pain	30 (17)	1 (1)
Diarrhea	31 (18)	2 (1)
Decreased appetite	22 (12)	1 (1)
Headache	19 (11)	0
Dyspnea	18 (10)	0
Cough	18 (10)	0
Thrombocytopenia[a]	17 (10)	3 (2)
Urinary tract infection	17 (10)	1 (1)

The TEAEs were graded using CTCAE version 4.0 and coded to preferred terms using the *Medical Dictionary for Regulatory Activities* coding dictionary version 23.0.
CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.
[a] Grouped term data.

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Appendix A. Supplementary data

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