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ORIGINAL ARTICLE

Olaparib as treatment for platinum-sensitive relapsed ovarian cancer by BRCA mutation and homologous recombination deficiency: Phase 2 LIGHT study final overall survival analysis

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Abstract

Background: LIGHT (oLaparib In HRD-Grouped Tumor types; NCT02983799) prospectively evaluated olaparib treatment in patients with platinum-sensitive relapsed ovarian cancer (PSROC) assigned to cohorts by known BRCA mutation (BRCAm) and homologous recombination deficiency (HRD) status: germline BRCAm (gBRCAm),

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somatic BRCAm (sBRCAm), HRD-positive non-BRCAm, and HRD-negative. At the primary analysis, olaparib treatment demonstrated activity across all cohorts, with greatest efficacy in terms of objective response rate and progression-free survival observed in the g/sBRCAm cohorts. The authors report final overall survival (OS).

Methods: In this phase 2, open-label, noncomparative study, patients with PSROC and one or more prior line of platinum-based chemotherapy were assigned to cohorts by BRCAm and HRD status. OS was a secondary end point. Tumors were analyzed using Myriad BRACAnalysis CDx and MyChoice CDx assays; HRD-positive tumors were defined using a genomic instability score of ≥42.

Results: Of 272 enrolled patients, 271 received olaparib and 270 met the inclusion criteria for the efficacy analysis. At data cutoff, 18-month OS rates in the gBRCAm, sBRCAm, HRD-positive non-BRCAm, and HRD-negative cohorts were 86.4%, 88.0%, 78.6%, and 59.6%, respectively. No new safety signals were observed. In a post hoc analysis, patients on treatment for >18 months were most frequently present in g/sBRCAm cohorts (31.0%).

Conclusions: Olaparib treatment continued to demonstrate benefit across all cohorts. Consistent with the primary analysis, the highest OS rates were observed in the BRCAm cohorts, regardless of g/sBRCAm. In patients without a BRCAm, a higher OS rate was observed in the HRD-positive non-BRCAm than the HRD-negative cohorts. These results highlight the importance of biomarker testing in this treatment setting.

Plain Language Summary

- The LIGHT (oLaparib In HRD-Grouped Tumor types; NCT02983799) study explored the use of olaparib therapy for women with relapsed ovarian cancer. Patients were grouped according to whether their tumor had a BRCA gene mutation (BRCAm) and other genetic changes that impaired the cancer cell's ability to repair DNA damage, known as homologous recombination deficiency (HRD).
- This final survival analysis showed that 18 months after start of olaparib, more patients with a BRCAm were alive than those without a BRCAm. For patients without a BRCAm, more patients who tested positive for HRD were alive 18 months after start of olaparib than patients who tested negative for HRD.

KEYWORDS
carcinoma, genomic instability, mutation, olaparib, ovarian epithelial, ovarian neoplasms, platinum, poly(ADP-ribose) polymerase inhibitors

INTRODUCTION

LIGHT (oLaparib In HRD-Grouped Tumor types; NCT02983799) was a prospective study of treatment with the poly(ADP-ribose) polymerase (PARP) inhibitor olaparib in patients with platinum-sensitive relapsed ovarian cancer (PSROC). Patients had known BRCA mutation (BRCAm) status and homologous recombination deficiency (HRD) status and one or more prior platinum-based chemotherapy line.[1] They were assigned to four cohorts based on their BRCAm and HRD status: germline BRCAm (gBRCAm), somatic BRCAm (sBRCAm), HRD-positive non-BRCAm, and HRD-negative.[1] At the primary analysis, olaparib treatment demonstrated activity across all cohorts.[1] Greatest efficacy was observed in patients with gBRCAm or sBRCAm, with objective response rates (ORRs; primary end point) of 69% and 64%, respectively. For patients without a BRCAm, higher response rate was observed in patients with HRD-positive than HRD-negative tumors (ORR 29% and 10%, respectively).[1] Median progression-free survival (PFS; secondary end point) was longer in patients with a gBRCAm and a sBRCAm (11 months) than in the HRD-positive non-BRCAm (7 months) and HRD-negative (5 months) cohorts.[1] There was a high disease control rate (DCR) of >75% across the cohorts. This suggested a wide range of patients with PSROC may benefit from PARP inhibitor treatment.[1]

In this final analysis, we report overall survival (OS), updated safety data, and explore clinical and molecular characteristics of patients with long-term and short-term treatment duration.

MATERIALS AND METHODS

Study design

LIGHT (NCT02983799) was a phase 2, open-label, nonrandomized, noncomparative, multicenter study in the United States and Canada.

The protocol was approved by ethics review committees at the participating institutions. The trial was performed in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and the AstraZeneca policy on bioethics.[2] All patients provided written informed consent.

Patients

Eligible patients ≥18 years old had relapsed ovarian, primary peritoneal, and/or fallopian tube cancer histologically confirmed as high-grade serous or endometrioid and measurable disease (per Response Evaluation Criteria in Solid Tumors version 1.1; ≥1 assessable lesion at baseline). A protocol amendment (October 10, 2017) reduced the number of prior platinum-based chemotherapy lines from two or more to one or more. Eligible patients had disease progression ≥6 months after the end of their last platinum-based chemotherapy regimen. No prior PARP inhibitors were permitted.

Patients were assigned to cohorts according to BRCAm and HRD status: Cohort 1, gBRCAm; Cohort 2, sBRCAm; Cohort 3, HRD-positive (genomic instability score ≥42) non-BRCAm; and Cohort 4, HRD-negative (genomic instability score <42).

The Myriad BRACAnalysis CDx® assay determined germline BRCA status and the Myriad MyChoice® CDx assay (formerly called MyChoice® HRD) determined tumor BRCA and HRD status (both assays: Myriad Genetics, Salt Lake City, Utah).

Trial procedures

Patients received olaparib tablets 300 mg twice daily until investigator-assessed disease progression, unacceptable toxicity, or other protocol-specified criteria. Patients without a Myriad test result were not assigned to a cohort but were permitted to receive study treatment.

Outcomes

Primary outcomes have previously been reported.[1] OS and safety were secondary end points. OS was defined as the time from the first dose of olaparib to death from any cause. Patients were contacted to assess survival every 12 weeks following disease progression until death, consent withdrawal, or study closure.

Homologous recombination repair (HRR) mutations (HRRm) were also assessed retrospectively using a research-only version of the Myriad MyChoice tumor tissue assay as a secondary end point. The panel of 16 HRR genes comprised *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCI*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*. This HRRm test was only conducted in patients assigned to the BRCA wild-type cohorts and was not used for cohort assignment.

Statistical analyses

The four cohorts were analyzed separately with no statistical comparison. The full analysis set included all enrolled patients. The efficacy analysis set included all patients who received one or more olaparib doses and had a baseline tumor assessment indicating measurable disease. The safety analysis set included all patients who received one or more doses of olaparib.

OS rates and 95% confidence intervals (CIs) were estimated using the Kaplan–Meier method. This final OS analysis (data cutoff; August 27, 2020) was conducted 12 months after the primary analysis and approximately 18 months after the last enrolled patient started study treatment.

A post hoc subgroup analysis at final data cutoff assessed clinical and molecular characteristics of patients with long-term (>18 months) and short-term (<3 months) treatment duration. For this analysis, Cohorts 1 and 2 (g/sBRCAm) were combined, resulting in three subgroups (Cohorts 1 and 2 [g/sBRCAm], Cohort 3 [HRD-positive non-BRCAm], and Cohort 4 [HRD-negative]).

RESULTS

Patients

From December 2016 to February 2019, 272 patients were enrolled (Figure 1; Table S1): 271 patients received at least one dose of olaparib (safety analysis set), of whom 270 patients had measurable disease at baseline (efficacy analysis set).

At final data cutoff, 27 (10.0%) patients were continuing treatment and 244 (90.0%) had discontinued treatment, mostly because of disease progression (n = 195 [72.0%]) (Figure 1). In total, 102 (37.5%) patients had died before withdrawal. Platinum-based chemotherapy was the most common subsequent cancer therapy (n = 117; 43.3%) (Table 1).

Survival

In the efficacy analysis set, overall median (range) follow-up among patients censored for OS was 26.3 (0.6–36.9) months. For the gBRCAm, sBRCAm, HRD-positive non-BRCAm, and HRD-negative cohorts, respectively, OS rates (95% CI) were 94.6% (86.3–97.9), 92.0% (71.6–97.9), 89.4% (79.1–94.8), and 71.9% (61.3–80.1) at 1 year, and 86.4% (76.2–92.4), 88.0% (67.3–96.0), 78.6% (66.6–86.8), and 59.6% (48.6–68.9) at 18 months (Figure 2).

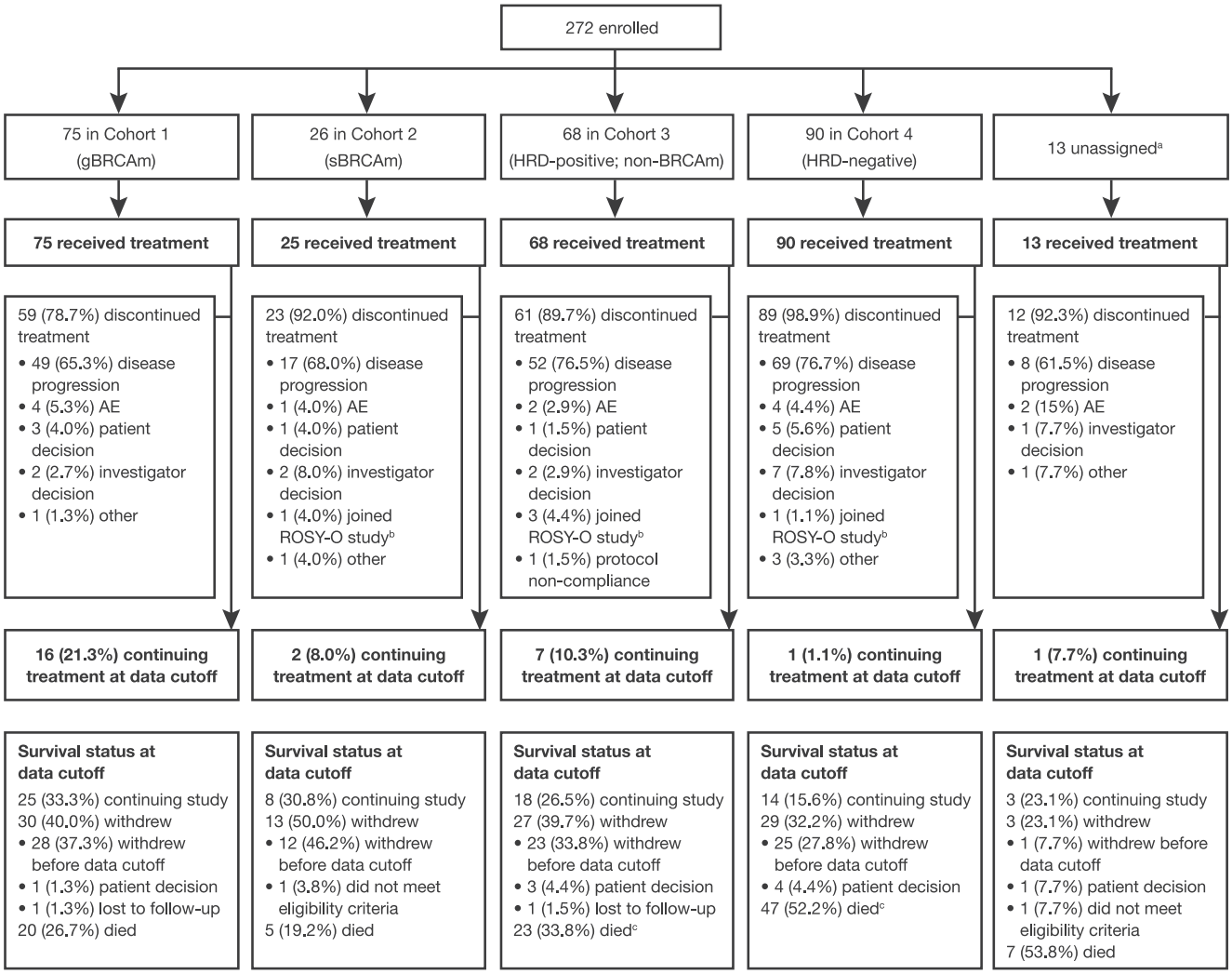


FIGURE 1 Patient disposition at final data cutoff (August 27, 2020). [a]Thirteen (5%) patients were unable to be assigned to a cohort as they had a failed or missing Myriad test result (one patient had missing gBRCAm status and 12 had a failed and/or missing genomic instability score). In patients where a genomic instability score failed, reasons contributing to failure mainly included low tumor content in samples, no tumor content in samples, or low tumor DNA content detected in samples. [b]ROSY-O (NCT04421963) is a phase 3, open-label, nonrandomized rollover study to continue to investigate the safety of olaparib in patients who have completed a previous oncology study with olaparib and are judged by the investigator to clinically benefit from continued treatment. [c]There is a small difference in the number of deaths reported in the disposition data in this figure, compared with the number of deaths in the overall survival data shown in Figure 2 (a difference of one in Cohort 3 and four in Cohort 4). The reason for this difference is because some patients were followed up after leaving the study, and these death records were added to the overall survival analysis at a later date than the analysis of the disposition data. Abbreviations: AE, adverse event; BRCAm, *BRCA1* and/or *BRCA2* mutation; gBRCAm, germline BRCA mutation; HRD, homologous recombination deficiency; sBRCAm, somatic BRCA mutation.

Safety

The most common treatment-emergent adverse events (TEAEs) from the primary analysis have been reported previously.[1]

In this final analysis, the median (range) total duration of treatment was 7.4 (0.5–30.6) months (Table 2). Most patients did not require dose modification. In total, 80 (29.5%) patients had a dose interruption and 73 (26.9%) patients had a dose reduction; these were due to adverse events in 71 (26.2%) and 59 (21.8%) patients, respectively (Table 2). A total of 14 patients (5.2%) discontinued olaparib because of TEAEs, most commonly fatigue/asthenia and nausea (each in two [0.7%] patients; all other TEAEs leading to discontinuation occurred in one [0.4%] patient only) (Table S2). Neuralgia and large intestinal obstruction were the only new TEAEs leading to discontinuation since the primary analysis (Table S2).

The most common treatment-related serious adverse events of any grade were anemia (three [1.1%] patients), pneumonia, and abdominal pain (each in two [0.7%] patients). For adverse events of special interest, one (0.4%) patient experienced grade 2 pneumonitis (57 days after the start of olaparib treatment) and another patient (0.4%) experienced grade 2 pulmonary fibrosis (110 days after the start of olaparib). In both cases, the events were considered causally

TABLE 1 Subsequent therapies: any radiotherapy or PARP inhibitor and type of systemic cancer therapies in ≥10% of patients (efficacy analysis set).

	Cohort 1 (gBRCAm) (*n* = 75)	Cohort 2 (sBRCAm) (*n* = 25)	Cohort 3 (HRD-positive non-BRCAm) (*n* = 68)	Cohort 4 (HRD-negative) (*n* = 89)	Unassigned[a] (*n* = 13)	Overall (*N* = 270)
Radiotherapy	4 (5.3)	1 (4.0)	5 (7.4)	3 (3.4)	0	13 (4.8)
Any systemic cancer therapy	27 (36.0)	8 (32.0)	38 (55.9)	50 (56.2)	5 (38.5)	128 (47.4)
Platinum-based chemotherapy	24 (32.0)	8 (32.0)	35 (51.5)	45 (50.6)	5 (38.5)	117 (43.3)
Carboplatin	23 (30.7)	6 (24.0)	33 (48.5)	43 (48.3)	4 (30.8)	109 (40.4)
Cisplatin	3 (4.0)	2 (8.0)	5 (7.4)	3 (3.4)	1 (7.7)	14 (5.2)
Anthracyclines[b]	12 (16.0)	4 (16.0)	24 (35.3)	30 (33.7)	3 (23.1)	73 (27.0)
Taxanes	15 (20.0)	2 (8.0)	17 (25.0)	16 (18.0)	2 (15.4)	52 (19.3)
Paclitaxel	15 (20.0)	2 (8.0)	17 (25.0)	14 (15.7)	2 (15.4)	50 (18.5)
Docetaxel	0	0	1 (1.5)	3 (3.4)	0	4 (1.5)
Bevacizumab	10 (13.3)	2 (8.0)	15 (22.1)	16 (18.0)	2 (15.4)	45 (16.7)
Gemcitabine	5 (6.7)	2 (8.0)	6 (8.8)	14 (15.7)	1 (7.7)	28 (10.4)
Antineoplastic agents[c]	2 (2.7)	1 (4.0)	4 (5.9)	5 (5.6)	0	12 (4.4)
PARP inhibitor	3 (4.0)	0	3 (4.4)	5 (5.6)	0	11 (4.1)
Niraparib	1 (1.3)	0	1 (1.5)	4 (4.5)	0	6 (2.2)
Olaparib	2 (2.7)	0	2 (2.9)	0	0	4 (1.5)
Rucaparib	0	0	1 (1.5)	1 (1.1)	0	2 (0.7)

Abbreviations: BRCAm, *BRCA1* and/or *BRCA2* mutation; gBRCAm, germline BRCAm; HRD, homologous recombination deficiency; PARP, poly (ADP-ribose) polymerase; sBRCAm, somatic BRCAm.

[a]Includes patients who were not assigned to a cohort because they had a Myriad test result of failed or missing.

[b]Includes doxorubicin, liposomal doxorubicin hydrochloride, pegylated liposomal doxorubicin, and pegylated liposomal doxorubicin hydrochloride.

[c]Includes investigational antineoplastic agents in seven (2.6%) patients in Cohorts 1–4, and topotecan in five (1.9%) patients in Cohorts 3 (*n* = 2) and 4 (*n* = 3).

related to olaparib by the investigator. One (0.4%) patient experienced grade 4 acute myeloid leukemia (711 days after the start of olaparib treatment), considered unrelated to olaparib; this patient had not received subsequent anticancer therapy.

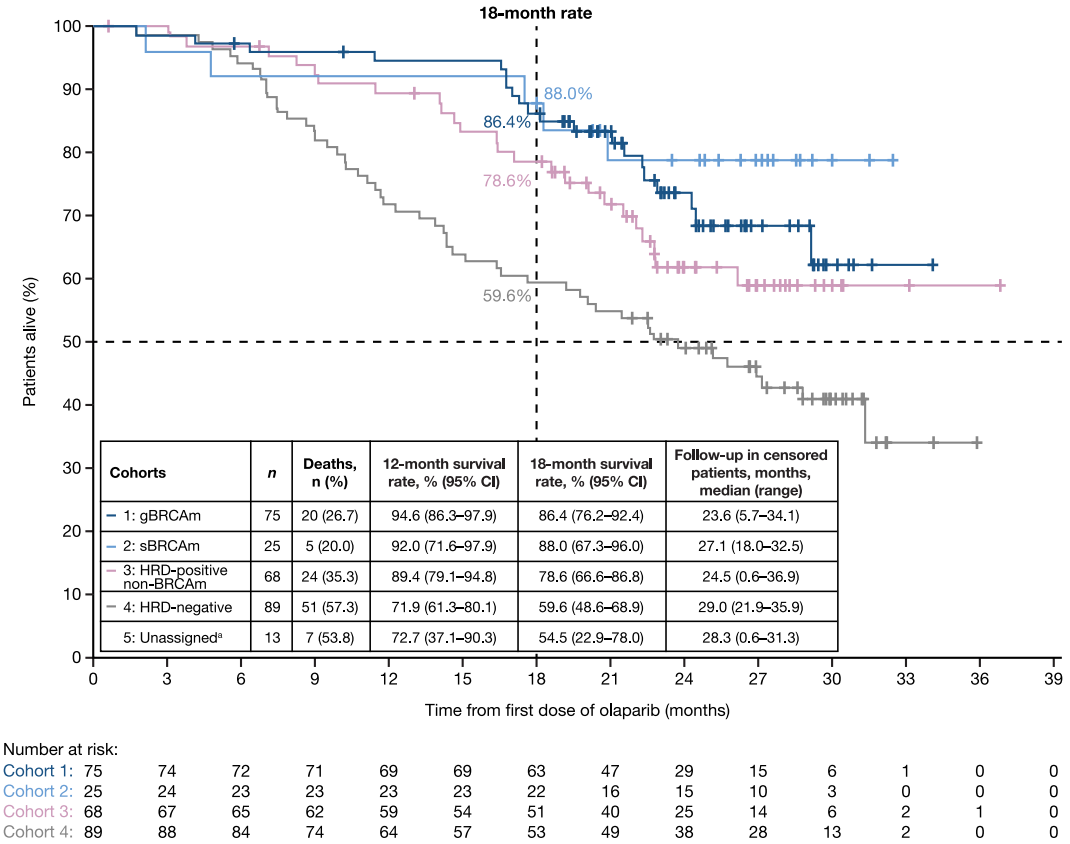
Two (0.7%) patients died due to adverse events, both of which were considered unrelated to olaparib: one (0.4%) patient (sBRCAm cohort) died as a result of atrial fibrillation, which occurred on treatment (46 days after the first dose of olaparib), and one (0.4%) patient (cohort unassigned) died due to intestinal perforation, which occurred during the survival follow-up period (192 days and 32 days after the first and last dose of olaparib, respectively).

Treatment duration subgroup analysis

BRCAm and HRD status was available for 258 of 271 (95.2%) patients (Figure 3A). Patients with long-term treatment duration (*n* = 45) were present in all cohorts but were more frequently observed in Cohorts 1 and 2 (g/sBRCAm *n* = 31/100; 31.0%) followed by Cohort 3 (HRD-positive non-BRCAm; *n* = 11/68; 16.2%) (Figure 3B). Patients with short-term treatment duration (*n* = 48) were most frequently observed in Cohort 4 (HRD-negative *n* = 25/90; 27.8%; Figure 3B).

Few patients (9/93; 9.7%) with long-term or short-term treatment duration had non-BRCA HRRm (Figure 4). In patients with long-term treatment duration, a non-BRCA HRRm (*RAD51D*) was detected in only one (*n* = 1/45; 2.2%) patient (Figure 4). Non-BRCA HRRm were detected in eight of 48 (16.7%) patients with short-term treatment duration, gene alterations observed were *BRIP1* (*n* = 3/48; 6.3%), *CDK12* (*n* = 1/48; 2.1%), *ATM* (*n* = 1/48; 2.1%), *FANCL* (*n* = 1/48; 2.1%), *RAD51B* (*n* = 1/48; 2.1%), and *PPP2R2A* (*n* = 1/48; 2.1%) (Figure 4).

In terms of baseline characteristics, the overall, median (range) time since primary diagnosis was 36.2 (9.7–146.4) months and 29.1 (8.0–98.4) months in patients with long-term and short-term treatment duration, respectively. A higher proportion of patients with long-term treatment duration had better performance status and fewer lines of prior chemotherapy than those with short-term treatment duration (Figure 3C).



Cohorts	n	Deaths, n (%)	12-month survival rate, % (95% CI)	18-month survival rate, % (95% CI)	Follow-up in censored patients, months, median (range)
1: gBRCAm	75	20 (26.7)	94.6 (86.3–97.9)	86.4 (76.2–92.4)	23.6 (5.7–34.1)
2: sBRCAm	25	5 (20.0)	92.0 (71.6–97.9)	88.0 (67.3–96.0)	27.1 (18.0–32.5)
3: HRD-positive non-BRCAm	68	24 (35.3)	89.4 (79.1–94.8)	78.6 (66.6–86.8)	24.5 (0.6–36.9)
4: HRD-negative	89	51 (57.3)	71.9 (61.3–80.1)	59.6 (48.6–68.9)	29.0 (21.9–35.9)
5: Unassigned[a]	13	7 (53.8)	72.7 (37.1–90.3)	54.5 (22.9–78.0)	28.3 (0.6–31.3)

FIGURE 2 Kaplan–Meier plot of overall survival (efficacy analysis set) *The unassigned group includes patients who were not assigned to a cohort as they had a Myriad test result of failed or missing and is not shown on the Kaplan–Meier graph due to small patient numbers. Abbreviations: BRCAm, *BRCA1* and/or *BRCA2* mutation; CI, confidence interval; gBRCAm, germline BRCA mutation; HRD, homologous recombination deficiency; sBRCAm, somatic BRCA mutation.

TABLE 2 Safety summary (safety analysis set).

	Cohort 1 (gBRCAm) (*n* = 75)	Cohort 2 (sBRCAm) (*n* = 25)	Cohort 3 (HRD-positive non-BRCAm) (*n* = 68)	Cohort 4 (HRD-negative) (*n* = 90)	Unassigned[a] (*n* = 13)	Overall (*N* = 271)
Median (range) treatment duration, months	11.1 (1.7–29.2)	11.8 (1.5–29.5)	6.1 (0.6–30.6)	4.7 (0.5–29.4)	6.2 (0.6–27.9)	7.4 (0.5–30.6)
Serious TEAE	13 (17.3)	8 (32.0)	7 (10.3)	35 (38.9)	6 (46.2)	69 (25.5)
Treatment-related serious TEAE	5 (6.7)	5 (20.0)	1 (1.5)	9 (10.0)	1 (7.7)	21 (7.7)
Dose interruption due to TEAE	17 (22.7)	12 (48.0)	15 (22.1)	22 (24.4)	5 (38.5)	71 (26.2)
Dose reduction due to TEAE	14 (18.7)	10 (40.0)	15 (22.1)	16 (17.8)	4 (30.8)	59 (21.8)
Discontinuation due to TEAE	5 (6.7)	1 (4.0)	2 (2.9)	4 (4.4)	2 (15.4)	14 (5.2)
Discontinuation due to treatment-related TEAE	2 (2.7)	1 (4.0)	2 (2.9)	4 (4.4)	1 (7.7)	10 (3.7)

Note: Data are number (%) of patients unless stated otherwise. Only data for deaths, serious adverse events, adverse events of special interest, and adverse events leading to discontinuation were actively reported after the data cutoff for the primary analysis. TEAEs were defined as new or worsening of prior adverse events following the first dose of study treatment through to 30 days after the last dose of study treatment. Adverse events were coded to preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.1, with adverse event severity graded using CTCAE version 4.03.

Abbreviations: BRCAm, *BRCA1* and/or *BRCA2* mutation; CTCAE, Common Terminology Criteria for Adverse Events; gBRCAm, germline BRCAm; HRD, homologous recombination deficiency; sBRCAm, somatic BRCAm; TEAE, treatment-emergent adverse event.

[a]Includes patients who were not assigned to a cohort because they had a Myriad test result of failed or missing.

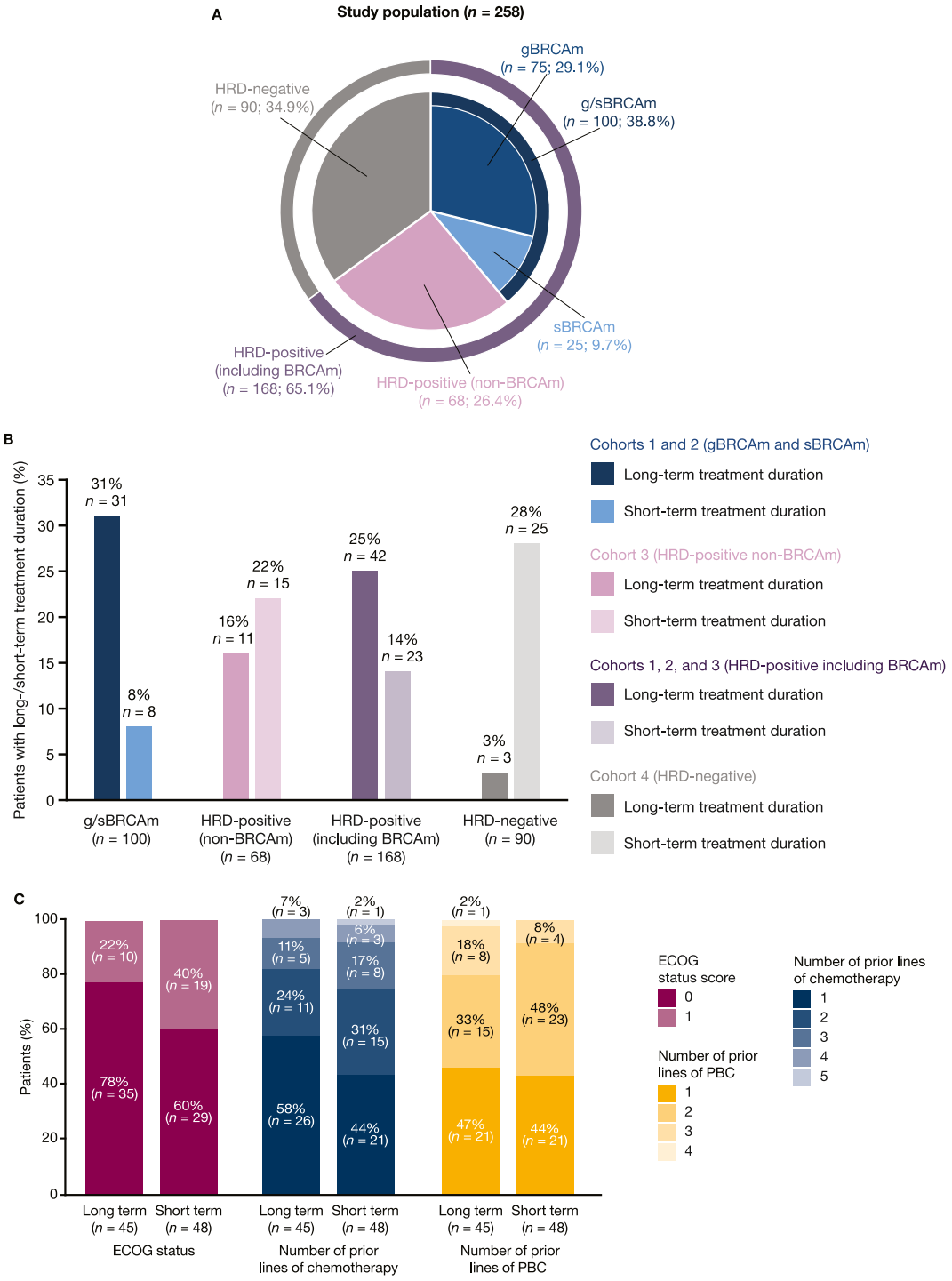


FIGURE 3 Biomarker subgroup analysis: (A) baseline biomarker status of all treated patients with BRCAm/HRD status[a]; (B) long-term or short-term treatment duration split by BRCAm/HRD status; and (C) baseline characteristics of patients with long-term and short-term treatment duration. Percentages may not total 100 because of rounding. In (A) and (B), germline BRCA status was determined using the Myriad BRACAnalysis CDx assay; tumor BRCA status and HRD status were determined using the Myriad MyChoice CDx assay (both assays from Myriad Genetics, Salt Lake City, Utah). [a]Biomarker status was available for 258 of the 271 enrolled patients who received olaparib. [b]"Other" included nonevaluable, not applicable, and missing best response to last platinum-based chemotherapy data. Abbreviations: BRCAm, *BRCA1* and/or *BRCA2* mutation; ECOG, Eastern Cooperative Oncology Group; gBRCAm, germline BRCA mutation; HRD, homologous recombination deficiency; PBC, platinum-based chemotherapy; sBRCAm, somatic BRCA mutation.

Although the frequency of dose interruptions was similar between treatment duration subgroups, more patients with long-term than short-term treatment duration experienced dose reductions (40.0% vs. 16.7%) (Table S3). In both subgroups, adverse events were the most common reason for dose modification and disease progression was the most common reason for discontinuing olaparib

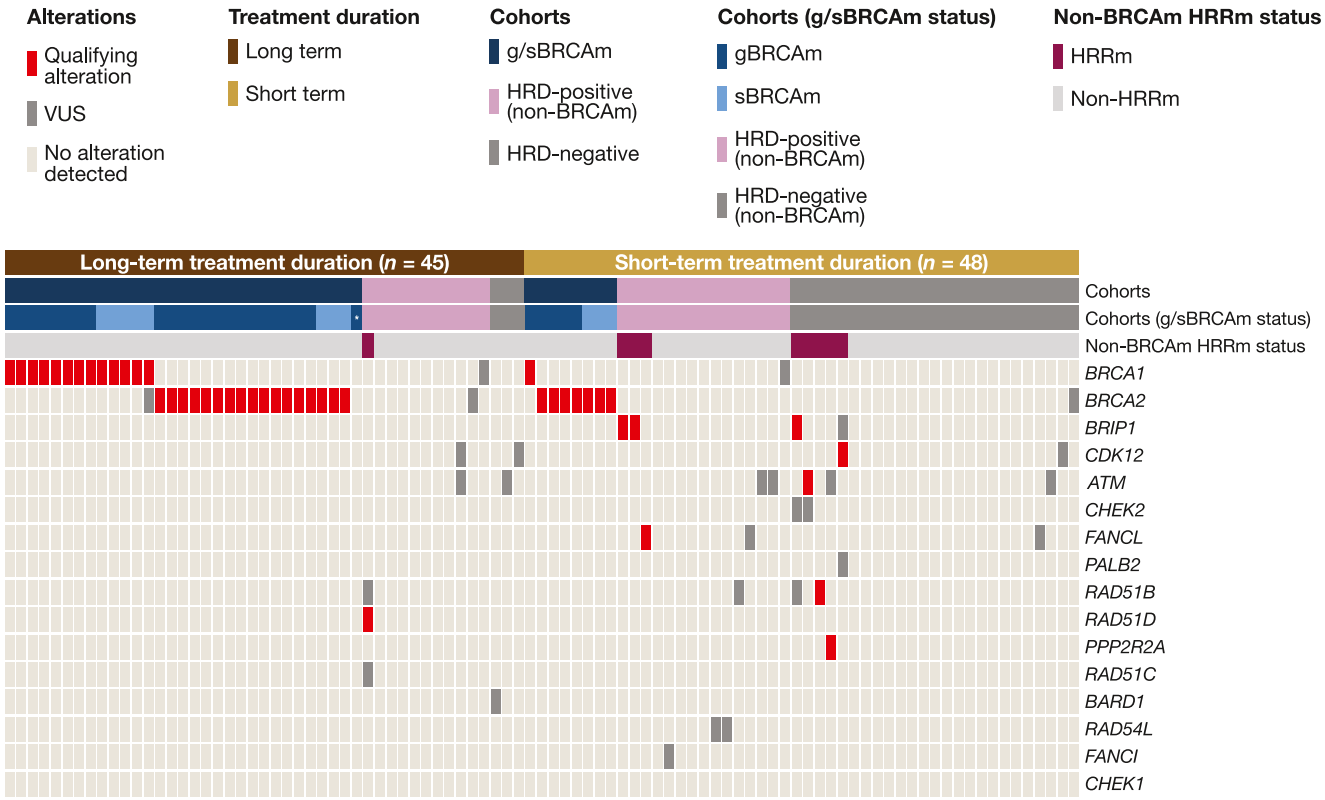


FIGURE 4 OncoPrint of alterations detected in patients with long-term and short-term treatment duration. Patients ordered by long-term/short-term treatment duration, cohorts used in the long-term/short-term treatment duration analysis, non-BRCA HRRm status (genes ordered by *BRCA1*, *BRCA2*, and then prevalence of other non-BRCA HRR genes mutated in LIGHT), and best response to last prior platinum-based chemotherapy. One patient was assigned to Cohort 1 (gBRCAm) using a historical Myriad BRCA report, indicating gBRCAm positive, and is indicated by the * in the "Cohort" bar. HRR genes assessed were *BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *ATM*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51D*, *PPP2R2A*, *RAD51C*, *BARD1*, *RAD54L*, *FANCI*, and *CHEK1*. Qualifying alteration was defined as a deleterious or suspected deleterious mutation associated with loss-of-function of the encoded protein. VUS was defined as an alteration for which clinical significance has not yet been determined. Abbreviations: BRCAm, *BRCA1* and/or *BRCA2* mutation; gBRCAm, germline BRCA mutation; HRD, homologous recombination deficiency; HRRm, homologous recombination repair mutation; sBRCAm, somatic BRCA mutation; VUS, variant of uncertain significance.

(Table S3). Longer treatment duration was not associated with a greater frequency of grade 3 or higher adverse events, or serious adverse events (Table S3).

DISCUSSION

Consistent with the LIGHT study primary analysis,[1] the highest OS rates with olaparib treatment at the final OS analysis were observed in the BRCAm cohorts, regardless of gBRCAm or sBRCAm status. Among patients without a BRCAm, a higher OS rate was observed in patients with HRD-positive tumors than those with HRD-negative tumors. A similar pattern of relative benefit between cohorts was observed when patients were stratified by number of prior chemotherapy regimens (one and two or more). No new safety signals were observed at the final LIGHT OS analysis compared with the primary analysis and prior olaparib studies.[1,3–5]

Our data are consistent with findings from the OPINION study of maintenance olaparib in patients with PSROC without a gBRCAm and two or more prior lines of platinum chemotherapy. Final OS results showed that higher 30-month OS rates were observed in patients with HRD-positive tumors including sBRCAm (66.7% [95% CI, 57.5–74.3]) than those with HRD-negative tumors (38.9% [95% CI, 29.9–47.8]).[4]

Other studies have investigated PARP inhibitors as treatment in this setting. ARIEL4 assessed rucaparib treatment in patients with relapsed OC, g/sBRCAm, and two or more prior chemotherapy lines.[6] The results suggested a possible detrimental effect on OS with rucaparib treatment versus chemotherapy (hazard ratio [HR] 1.31; 95% CI, 1.00–1.73; $p = .05$; median OS 19.4 vs. 25.4 months, respectively).[7] Although no statistically significant difference in OS was observed between treatment groups in platinum-sensitive patients (HR, 1.07; 95% CI, 0.71–1.62; $p = .54$), the indication for rucaparib treatment for patients with platinum-sensitive BRCA-mutated ovarian cancer after two or more platinum-based chemotherapy lines was voluntarily withdrawn.[7] Olaparib was approved in the United States for the treatment of patients with advanced ovarian cancer, a gBRCAm, and three or more prior chemotherapy

lines. The confirmatory phase 3 trial, SOLO3, in patients with PSROC, a gBRCAm, and two or more prior lines of platinum-based chemotherapy demonstrated statistically significant and clinically relevant improvements in ORR and PFS with olaparib as treatment versus single-agent nonplatinum chemotherapy.[3] Final OS in SOLO3 was similar with olaparib treatment compared with single-agent nonplatinum chemotherapy (HR, 1.07; 95% CI, 0.76–1.49; $p = .71$; median 34.9 and 32.9 months, respectively).[8] Following the ARIEL4 results, SOLO3 post hoc analyses revealed that in patients with two prior chemotherapy lines, OS favored olaparib treatment versus chemotherapy (HR, 0.83; 95% CI, 0.51–1.38; median OS 37.9 vs. 28.8 months, respectively), but in patients with three or more prior chemotherapy lines, there was a potentially detrimental effect on OS (HR, 1.33; 95% CI, 0.84–2.18; median OS 29.9 vs. 39.4 months, respectively).[9] Therefore, the indication for olaparib treatment for gBRCAm ovarian cancer after three or more prior chemotherapy lines was voluntarily withdrawn.[10,11] Similarly, the niraparib treatment indication for HRD-positive ovarian cancer after three or more prior chemotherapy regimens, which was based on the single-arm QUADRA study, was voluntarily withdrawn, citing ARIEL4 and SOLO3 results.[12,13] As a result, currently there are no approvals of PARP inhibitors in the ovarian cancer treatment (nonmaintenance) setting.

The OS achieved by patients in LIGHT may be related to the earlier treatment setting, as patients had only received one or more prior platinum-based chemotherapy lines. Similarly, in SOLO3, earlier line patients did better than later lines in the post hoc analysis described above.[9] This observation is supported by OS benefits in the newly diagnosed setting. In SOLO1, maintenance olaparib demonstrated a clinically meaningful improvement in the 7-year OS rate versus placebo (67.0% vs. 46.5%, respectively; HR, 0.55; 95% CI, 0.40–0.76) in patients with BRCAm ovarian cancer.[14] In PAOLA-1, maintenance olaparib plus bevacizumab showed clinically meaningful improvement in the 5-year OS rate versus bevacizumab alone (65.5% vs. 48.4%, respectively; HR, 0.62; 95% CI, 0.45–0.85) in patients with HRD-positive tumors (defined as tumor BRCAm and/or genomic instability).[15] Olaparib was the first PARP inhibitor to show a clinically meaningful OS benefit in the newly diagnosed setting. Based on the SOLO1 and PAOLA-1 results, maintenance olaparib was approved for patients with BRCAm ovarian cancer in the newly diagnosed setting, and maintenance olaparib plus bevacizumab was approved for HRD-positive ovarian cancer in the newly diagnosed setting, respectively. [11] These findings indicate the importance of starting maintenance PARP inhibitor in the newly diagnosed setting.

In LIGHT, post hoc analysis of the clinical and molecular characteristics of patients with long-term (>18 months) and short-term (<3 months) treatment duration showed that patients with long-term treatment duration were present in all four cohorts; however, they were more frequently observed in the g/sBRCAm cohort (31.0%) followed by the HRD-positive non-BRCAm cohort (16.2%). Of the key baseline characteristics examined, patients with long-term treatment duration had characteristics associated with better prognosis, such as better performance status, and fewer lines of prior chemotherapy than patients with short-term treatment duration. Exploratory analysis from the OPINION study showed that patients with long-term PFS (>18 months) in OPINION more commonly had HRD-positive tumors, with or without a BRCAm, than patients with short-term PFS (<4 months).[16] This supports our observation in LIGHT that long-term response is observed in all biomarker subgroups but is more prominent among patients with BRCAm and HRD-positive, including BRCAm, tumors.

Our analysis revealed few patients with long-term or short-term treatment duration had non-BRCA HRRm and, because of this low occurrence, it was not possible to assess the association of non-BRCA HRRm with treatment duration in this PSROC setting. A similar mutational analysis of patients treated with rucaparib in ARIEL2 also reported few HRRm.[17] In the ARIEL2 analysis almost all responders with a non-BRCA HRRm had a *RAD51C/D* mutation; the response rate in patients with *RAD51C/D* mutations was 71.4% ($n = 5/7$).[17] In our analysis, only one patient with long-term treatment duration had a non-BRCA HRRm, which was *RAD51D*. Analysis from the ARIEL3 study of maintenance rucaparib also showed that BRCAm and molecular markers of HRD (*RAD51C/D* alterations and genome-wide loss of heterozygosity) were statistically significantly associated with PFS benefit from rucaparib.[18] Although the patient numbers are small, it is interesting to note that in LIGHT three patients with *BRIP1* mutations exhibited short term treatment duration; this observation is consistent with a recent study suggesting heterogeneity in the HRD phenotype within this HRRm group.[19] In the PSROC setting in the ORZORA and OPINION studies, exploratory analysis demonstrated that olaparib activity in patients harboring non-BRCA HRRm was similar to the observed activity for patients with BRCAm.[20–22] In ORZORA, median PFS (95% CI) in the 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.[20] In OPINION, median PFS (95% CI) was 16.4 (12.8 to not evaluable)[21] and 14.8 (10.8 to not evaluable)[22] months for the sBRCAm cohort and for patients harboring non-BRCA HRRm, respectively. Further studies of PARP inhibitor use in *BRIP1* and other rare genomic subgroups would be needed to guide therapy.

Limitations of the LIGHT study have been previously reported[1] and include lack of a comparator arm, lack of randomization, and a lower proportion of patients in the HRD-negative cohort with one prior line of therapy following a protocol amendment that reduced the required number of prior lines of platinum-based chemotherapy from two or more to one or more. Patients with prior PARP inhibitor therapy were not eligible to participate in the LIGHT study, which may also limit interpretation of this study given the increasing likelihood of prior PARP inhibitor exposure for PSROC. There are limited data on PARP inhibitor retreatment (after previous PARP inhibitor treatment). Analyses have suggested some patients may derive benefit from PARP inhibitor retreatment,[23–25] and the phase 3 OReO study showed a PFS benefit with olaparib rechallenge over placebo in the maintenance setting, with no unexpected safety findings.[26] However, additional data on PARP inhibitor rechallenge are needed. Specific to the LIGHT analysis, the median duration of follow-up for

OS was relatively short at 26 months and precluded the estimation of median survival. Although we provide data on subsequent treatments, we do not have granular data on response rates and time on treatment, and this should be explored in future studies. Genomic data were collected from archival tissue only and were not collected from pretreatment biopsies before LIGHT study entry, and a targeted, rather than whole genome, analysis was performed. In addition, low numbers of patients with non-BRCA HRRm limit interpretation of these data. Finally, although few patients with g/sBRCAm had short-term treatment duration, future studies should investigate biomarkers of poor response in this population including location of mutation (as investigated in the PAOLA-1 study),[27] to optimize the survival benefit in the frontline setting.

In conclusion, final OS analysis of the LIGHT study of olaparib treatment in PSROC showed that the highest OS rates were observed in the g/sBRCAm cohorts. Among patients without a BRCAm, OS rates were highest in the HRD-positive cohort. Subgroup analysis indicated that patients could achieve long-term treatment duration regardless of baseline clinical or molecular factors; however, long-term response was most prominent among patients with characteristics associated with better prognosis, and those with HRD-positive tumors (including BRCAm).

AUTHOR CONTRIBUTIONS

Ying L. Liu: Resources and writing–review and editing. **Cara A. Mathews**: Resources and writing–review and editing. **Fiona Simpkins**: Resources and writing–review and editing. **Karen A. Cadoo**: Conceptualization, methodology, resources, and writing–review and editing. **Diane Provencher**: Resources and writing–review and editing. **Colleen C. McCormick**: Resources and writing–review and editing. **Adam C. ElNaggar**: Resources and writing–review and editing. **Alon D. Altman**: Resources and writing–review and editing. **Lucy Gilbert**: Resources and writing–review and editing. **Destin Black**: Resources and writing–review and editing. **Nashwa Kabil**: Writing–review and editing. **Rosie N. Taylor**: Writing–review and editing. **Alan Barnicle**: Writing–review and editing, data curation, and visualization. **Jiefen Y. Munley**: Writing–review and editing. **Carol Aghajanian**: Conceptualization, methodology, resources, and writing–review and editing.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. The AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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