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Real-world Outcomes Associated With Poly(ADP-ribose) Polymerase Inhibitor Monotherapy Maintenance in Patients With Primary Advanced Ovarian Cancer

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Objective: This study used real-world population data to assess the trends of first-line (1L) poly(ADP-ribose) polymerase inhibitor (PARPi) maintenance treatment uptake and outcomes in patients with primary advanced ovarian cancer (AOC).

Methods: Patients diagnosed with AOC between January 1, 2017, and June 30, 2021, who completed 1L chemotherapy were selected from a real-world database. Descriptive analyses were performed to evaluate patient demographics, clinicopathological characteristics, and 1L treatment patterns. Time to next treatment or death was used as a proxy for real-world progression-free survival (rwPFS). Kaplan-Meier methods and Cox models were used for statistical analyses.

Results: Of 705 patients who completed 1L chemotherapy, 166 received PARPi monotherapy and 539 underwent active surveillance (AS). Median follow-up was 10.9 months for PARPi monotherapy and 20.6 months for AS. PARPi monotherapy use increased from 6% in 2017 to 53% in 2021. Overall, patients receiving PARPi monotherapy had longer rwPFS than those who underwent AS (not reached vs 9.53 mo) respectively. rwPFS was also longer in patients who received PARPi monotherapy compared with AS in patients with *BRCA*-mutated disease (not reached vs 11.4 mo), *BRCA*–wild-type disease (13.5 vs 9.1 mo), homologous recombination-deficient tumors (not reached vs 10.2 mo), and homologous recombination-proficient or unknown status tumors (13.5 vs 9.3 mo).

Conclusions: Our real-world analysis suggested that 47% of patients with primary AOC did not receive PARPi maintenance in the year 2021. PARPi use was associated with significantly improved outcomes compared with AS.

Key Words: PARP inhibitor, advanced ovarian cancer, first-line, monotherapy, real-world

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With ~19,880 new cases and 12,810 deaths anticipated in 2022, ovarian cancer (OC) is the leading cause of gynecologic cancer death among women in the United States.[1,2] Although the survival rate of women with OC has been increasing, overall outcomes in patients with primary advanced OC (AOC) remain poor, with an estimated 5-year survival rate of ~31%.[1–3]

The preferred first-line (1L) treatment for primary AOC includes a combination of surgery plus platinum-based chemotherapy (PBCT), with or without antiangiogenic therapy.[4–6] For patients who achieve complete or partial response from 1L treatment, the AOC landscape has evolved in recent years to include maintenance therapies. Since 2018, the US Food and Drug Administration has approved 2 poly(ADP-ribose) polymerase (PARP)-inhibiting agents for 1L maintenance therapy for OC. Both niraparib and olaparib are PARP inhibitors (PARPi) that have demonstrated improved progression-free survival (PFS) compared with a placebo.[7,8] Niraparib monotherapy is indicated for all patients regardless of biomarker status in the 1L maintenance setting, whereas olaparib monotherapy is approved for patients with *BRCA*-mutated (*BRCA*m) tumors.[7–11] Olaparib in combination with bevacizumab is also approved in the 1L setting for patients with homologous recombination-deficient (HRd) tumors.[9]

Despite evidence for the benefit of PARPi maintenance therapy from clinical trials, many patients with complete or partial response to 1L PBCT continue to undergo active surveillance (AS) instead of receiving maintenance treatment. Thus, as the AOC treatment landscape continues to evolve, further evidence reflecting real-world practice is needed to characterize the outcomes of 1L PARPi maintenance therapy compared with AS. Such real-world evidence can help to support the outcomes observed in clinical trials to lend further evidence for clinical decision-making.

To address this real-world evidence gap, we conducted a retrospective observational study using deidentified patient-level electronic health record (EHR) data from the Flatiron Health EHR-derived database to evaluate trends in the adoption of 1L PARPi maintenance in primary AOC. We then compared the real-world PFS (rwPFS) of PARPi monotherapy maintenance therapy with AS.

METHODS

Study Design, Outcomes, and Data Source

This study was a real-world retrospective cohort study using the nationwide deidentified Flatiron Health EHR-derived database. The Flatiron Health EHR-derived database contains deidentified, longitudinal, patient-level data from ~280 cancer clinics (~800 sites of care) across the United States, including structured data (eg, laboratory values and prescribed drugs) and unstructured data collected through technology-enabled chart abstraction from physician's notes and other unstructured documents (eg, biomarker reports); of note, most patient data in the database originate from community oncology practices.[12,13] Although this study uses the Flatiron Health EHR-derived database, Flatiron Health was not involved in the study, its design, analysis, or interpretation, or in the drafting of this manuscript.

Patients with primary AOC (stage III or IV) who had completed 1L PBCT between January 1, 2017, and June 30, 2021, and received either PARPi monotherapy or AS in the 1L maintenance setting were included. The use of PARPi or AS was identified during a 120-day period after the last dose of 1L chemotherapy; the end of the 120-day 1L maintenance treatment identification period was defined as the index date (Fig. 1). Patient characteristics and rwPFS were evaluated and compared. Time to next treatment served as a proxy variable for rwPFS and was defined as the time from the index date to the earliest occurrence of second-line (2L) therapy start date (ie, initiation of a subsequent nonmaintenance line of therapy [either chemotherapy or a targeted therapy] after disease progression or recurrence) or death date. Those patients without an event indicating disease progression (ie, were alive and did not initiate a 2L therapy) were censored on the date of their last confirmed activity.

Participants

To identify patients eligible for inclusion in the study, women aged 18 years or older with an initial OC diagnosis between January 1, 2016, and June 30, 2021, were identified in the Flatiron Health EHR-derived database. Those patients with stage III or IV OC at initial diagnosis who had received 1L PBCT, had their last dose of 1L PBCT during the identification period (January 1, 2017, to June 30, 2021), and had received either PARPi monotherapy or AS as 1L maintenance during the 120-day period after the last dose of 1L PBCT were included in the study (Fig. 2). The period of January 1, 2017, to June 30, 2021, was chosen to align with the approvals of PARPi maintenance therapies.

Cohort Assignment

Patients were assigned to 1 of the following 2 cohorts based on treatment received during the 120-day 1L maintenance treatment identification period. The PARPi monotherapy cohort included patients who received PARPi monotherapy as 1L maintenance after the last dose of PBCT and before receipt of any 2L therapy. The AS cohort included patients who did not receive 1L maintenance therapies after the last dose of PBCT and before receipt of any 2L therapy. Patient characteristics and clinical outcomes were evaluated and compared between these 2 cohorts.

In addition, subgroup analyses were performed that required stratification of patients by *BRCA* mutation status and homologous recombination deficiency status. Patients with *BRCA*1 and/or *BRCA*2 mutation or *BRCA* mutation not otherwise specified were included in the *BRCAm* subgroup. Patients with a genetic variant of unknown significance, genetic variant favoring polymorphism, or no *BRCA* mutation were included in the *BRCA* wild-type (*BRCA*wt) subgroup. For homologous recombination deficiency stratification, patients were classified as either HRd or homologous recombination-proficient (HRp)/homologous recombination status unknown (HRDunk).

Statistical Methods

Descriptive and statistical analysis of demographic and baseline clinical characteristics were evaluated and compared for the PARPi monotherapy maintenance and the AS cohort. Mean, standard deviation, median, and interquartile range were calculated for continuous variables, and count and percentage were calculated for categorical variables. Wilcoxon rank-sum

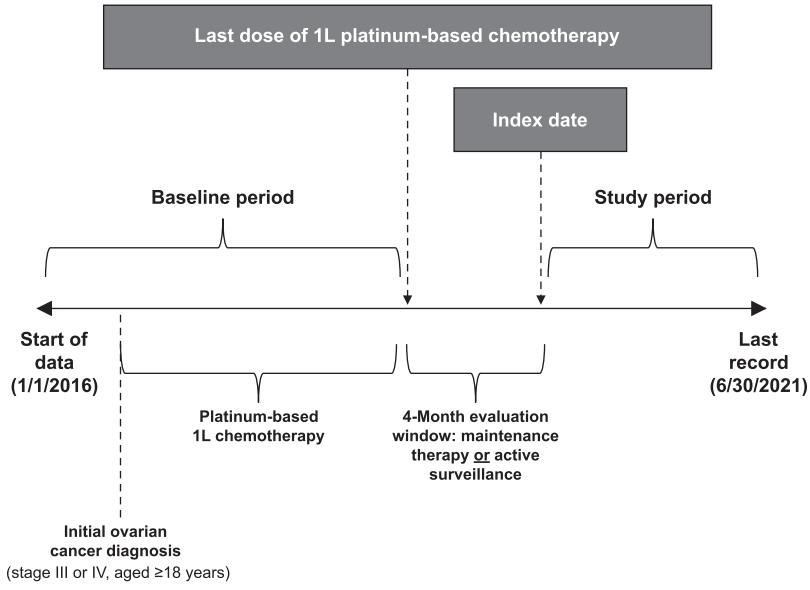


FIGURE 1. Study schematic. 1L indicates first-line.

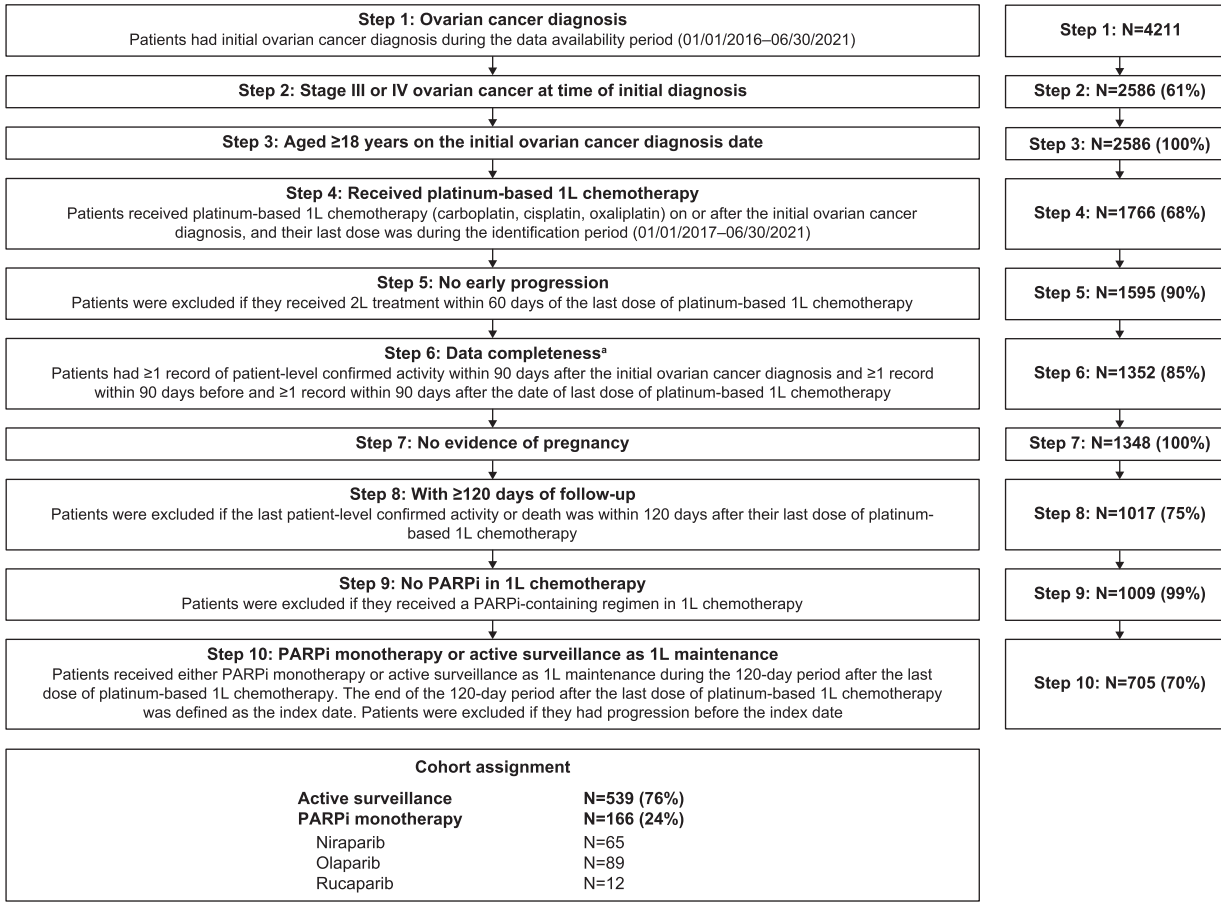


FIGURE 2. Patient selection flowchart. Patient-level confirmed activity included patient visits (medication administrations, vital sign assessments, or laboratory tests) and abstracted treatment information (oral abstractions and other abstracted drug episodes). Pregnant patients were identified through the International Classification of Disease, 9th and 10th revisions, and Clinical Modification codes. 1L indicates first-line; 2L, second-line; PARPi, poly(ADP-ribose) polymerase inhibitor.

tests were used to compare continuous variables; χ^2 or Fisher exact tests were used to compare categorical variables.

The clinical outcome of rwPFS was summarized and compared between the PARPi monotherapy cohort and the AS cohort based on Kaplan-Meier analyses. Median time to event (95% CI), number of patients with the event, and rates at discrete time points (eg, 1, 3, 6, and 12 mo) were reported. Unadjusted hazard ratios (HRs) were reported using Cox regression analysis.

To adjust for potential confounding factors, adjusted Cox regression analyses were conducted, with the variables included selected using a forward stepwise approach, with a cutoff point at the statistical significance level of P <0.10. Baseline characteristics for stepwise selection included: age at index (years), race, region, practice type, body mass index, Eastern Cooperative Oncology Group performance status, group stage at initial diagnosis, receipt of debulking surgery before index, residual disease status, disease duration before index, histology (serous, other, and unknown), *BRCA* status, platelet count, hemoglobin count, neutrophil count, bevacizumab-based 1L treatment, and number of chemotherapy cycles.

Study Ethics

This study complied with all applicable laws regarding patient privacy. The study had no direct patient contact, and no primary collection of individual patient data or identification occurred. Results are in tabular form, presented as aggregate analyses only, omitting patient identification; therefore, informed consent, ethics committee, or Institutional Review Board approval was not required. Institutional Review Board approval of the study protocol for data collection from the real-world cohort was obtained before the study was conducted and included a waiver of informed consent.

RESULTS

Participants

Of the 4211 patients identified as being diagnosed with AOC between January 1, 2016, and June 30, 2021, 705 patients were included in the study (Fig. 2). The demographic, clinicopathologic, and primary treatment characteristics of the PARPi monotherapy and AS cohorts are shown in Table 1. After completion of 1L chemotherapy, 166 patients (23.5%) received PARPi maintenance and 539 patients (76.5%) had AS. Of the 103 *BRCA*wt patients receiving PARPi monotherapy, 53.4% received niraparib, 38.8% received olaparib, and 7.8% received rucaparib.

Those patients in the PARPi monotherapy cohort were younger at the index date than those in the AS cohort, with median ages of 65.0 and 68.0 years, respectively (P < 0.01;

TABLE 1. Baseline Demographic and Clinical Characteristics of Patients on 1L PARPi Monotherapy Maintenance Versus Patients Under AS

	AS (n = 539); n (%)	PARPi monotherapy (n = 166); n (%)	P*
Follow-up			
Duration of follow-up (mo)			**< 0.001**
Median	20.6	10.9	—
IQR	(9.6–34.0)	(5.0–21.0)	—
Demographics			
Age at index (y)			**< 0.01**
Median	68.0	65.0	—
IQR	(59.0–75.0)	(56.0–72.8)	—
Age category at index (y)			0.098
18–44	25 (4.6)	10 (6.0)	—
45–54	56 (10.4)	25 (15.1)	—
55–64	121 (22.4)	45 (27.1)	—
65–74	187 (34.7)	54 (32.5)	—
75–84	150 (27.8)	32 (19.3)	—
Index date during COVID-19 pandemic			**< 0.001**
Yes	96 (17.8)	84 (50.6)	—
No, before pandemic	443 (82.2)	82 (49.4)	—
Index year			**< 0.001**
2017	117 (21.7)	8 (4.8)	—
2018	180 (33.4)	16 (9.6)	—
2019	129 (23.9)	43 (25.9)	—
2020	84 (15.6)	66 (39.8)	—
2021	29 (5.4)	33 (19.9)	—
Initial diagnosis year			**< 0.001**
2016	85 (15.8)	4 (2.4)	—
2017	183 (34.0)	18 (10.8)	—
2018	136 (25.2)	37 (22.3)	—
2019	87 (16.1)	62 (37.3)	—
2020	48 (8.9)	45 (27.1)	—
Race			0.752
Black or African American	30 (5.6)	8 (4.8)	—
White	364 (67.5)	111 (66.9)	—
Other race†	97 (18.0)	35 (21.1)	—
Unknown	48 (8.9)	12 (7.2)	—
Hispanic or Latino	34 (6.3)	14 (8.4)	0.439
Region			0.136
Midwest	69 (12.8)	27 (16.3)	—
Northeast	60 (11.1)	14 (8.4)	—
South	228 (42.3)	69 (41.6)	—
West	96 (17.8)	39 (23.5)	—
Unknown/other	86 (16.0)	17 (10.2)	—
Practice type			0.03
Academic	67 (12.6)	11 (6.6)	—
Community	471 (87.4)	155 (93.4)	—
Clinical characteristics			
Weight (kg)			0.575
Mean (SD)	71.5 (18.9)	72.3 (17.9)	—
Median	67.9	68.8	—
IQR	(58.2–81.2)	(58.4–81.0)	—
BMI			0.206
Mean (SD)	27.3 (7.0)	27.9 (6.5)	—
Median	26.0	26.8	—
IQR	(22.5–31.3)	(23.6–31.2)	—
ECOG-PS			0.131
0–1	390 (72.4)	133 (80.1)	—
2–4	49 (9.1)	10 (6.0)	—
Unknown	100 (18.6)	23 (13.9)	—
Group stage at initial diagnosis			**< 0.05**
III	383 (71.1)	103 (62.0)	—
IV	156 (28.9)	63 (38.0)	—
Receipt of debulking surgery before index			0.655
Yes	492 (91.3)	154 (92.8)	—
No/unknown	47 (8.7)	12 (7.2)	—
Residual disease status after debulking surgery			0.495
No residual disease	245 (45.5)	78 (47.0)	—
Residual disease	150 (27.8)	51 (30.7)	—
Unknown	144 (26.7)	37 (22.3)	—
Disease duration before index date (mo)			**< 0.05**
Median	9.4	9.7	—
IQR	(8.7–10.4)	(8.9–10.9)	—

TABLE 1. (*continued*)

	AS (n = 539); n (%)	PARPi monotherapy (n = 166); n (%)	*P**
Histology			0.790
Borderline	12 (2.2)	1 (0.6)	—
Clear cell	14 (2.6)	2 (1.2)	—
Endometrioid	15 (2.8)	3 (1.8)	—
Mucinous	5 (0.9)	1 (0.6)	—
Serous	419 (77.7)	134 (80.7)	—
Transitional cell	1 (0.2)	0	—
Epithelial NOS	71 (13.2)	25 (15.1)	—
Unknown	2 (0.4)	0	—
BRCA status			**< 0.001**
*BRCA*m	41 (7.6)	52 (31.3)	—
*BRCA*wt	361 (67.0)	103 (62.0)	—
Unknown	137 (25.4)	11 (6.6)	—
HRD status			**< 0.001**
HRd	54 (10.0)	72 (43.4)	—
HRp	28 (5.2)	7 (4.2)	—
HRDunk	457 (84.8)	87 (52.4)	—
Platelet count (cells/μL)			0.908
≥ 150,000	405 (75.1)	122 (73.5)	—
< 150,000	78 (14.5)	26 (15.7)	—
Unknown	56 (10.4)	18 (10.8)	—
Hemoglobin count (g/dL)			0.165
≥ 10	451 (83.7)	140 (84.3)	—
< 10	80 (14.8)	20 (12.0)	—
Unknown	8 (1.5)	6 (3.6)	—
Neutrophil count (cells/μL)			0.489
≥ 1500	430 (79.8)	127 (76.5)	—
< 1500	29 (5.4)	8 (4.8)	—
Unknown	80 (14.8)	31 (18.7)	—
Platelet count (cells/μL)			0.483
Median	211,000.0	208,000.0	—
IQR	(167,000.0–263,500.0)	(166,750.0–257,000.0)	—
Hemoglobin count (g/dL)			0.958
Median	11.6	11.7	—
IQR	(10.6–12.5)	(10.8–12.3)	—
Neutrophil count (cells/μL)			**< 0.01**
Median	3100.0	2800.0	—
IQR	(2237.5–4295.0)	(2200.0–3410.0)	—
1L treatment			—
1L chemotherapy	—	—	0.604
Carboplatin based	523 (97.0)	164 (98.8)	—
Cisplatin based	13 (2.4)	2 (1.2)	—
Oxaliplatin based	3 (0.6)	0	—
Bevacizumab-based 1L treatment	53 (9.8)	29 (17.5)	**< 0.05**
Time to 1L chemotherapy (d)			0.087
Mean (SD)	39.7 (55.5)	35.9 (37.0)	—
Median	31.0	28.0	—
IQR	(20.0–47.0)	(16.0–42.8)	—
No. chemotherapy cycles			**< 0.001**
Median	6.0	6.0	—
IQR	(6.0–6.0)	(6.0–7.0)	—
Time to maintenance therapy (d)			—
Median	—	48.5	—
IQR	—	(35.0–69.8)	—
1L maintenance treatment			1.000
Niraparib	—	65 (39.2)	—
Olaparib	—	89 (53.6)	—
Rucaparib	—	12 (7.2)	—

*A statistically significant *P* value <0.05 was denoted by bold values. Wilcoxon rank-sum tests were used to compare continuous variables, and χ^2 tests were used to compare categorical variables.

†Patients with "other" race included those with Asian, Hispanic or Latino, or "other race" (as classified by Flatiron).

AS indicates active surveillance; BMI, body mass index; *BRCA*m, *BRCA*-mutated; *BRCA*wt, *BRCA* wild-type; COVID-19, coronavirus disease 2019; ECOG-PS, Eastern Cooperative Oncology Group performance status; HRD, homologous recombination deficiency; HRd, homologous recombination-deficient; HRDunk, homologous recombination deficiency unknown; HRp, homologous recombination-proficient; IQR, interquartile range; 1L, first-line; NOS, not otherwise specified; PARPi, poly(ADP-ribose) polymerase.

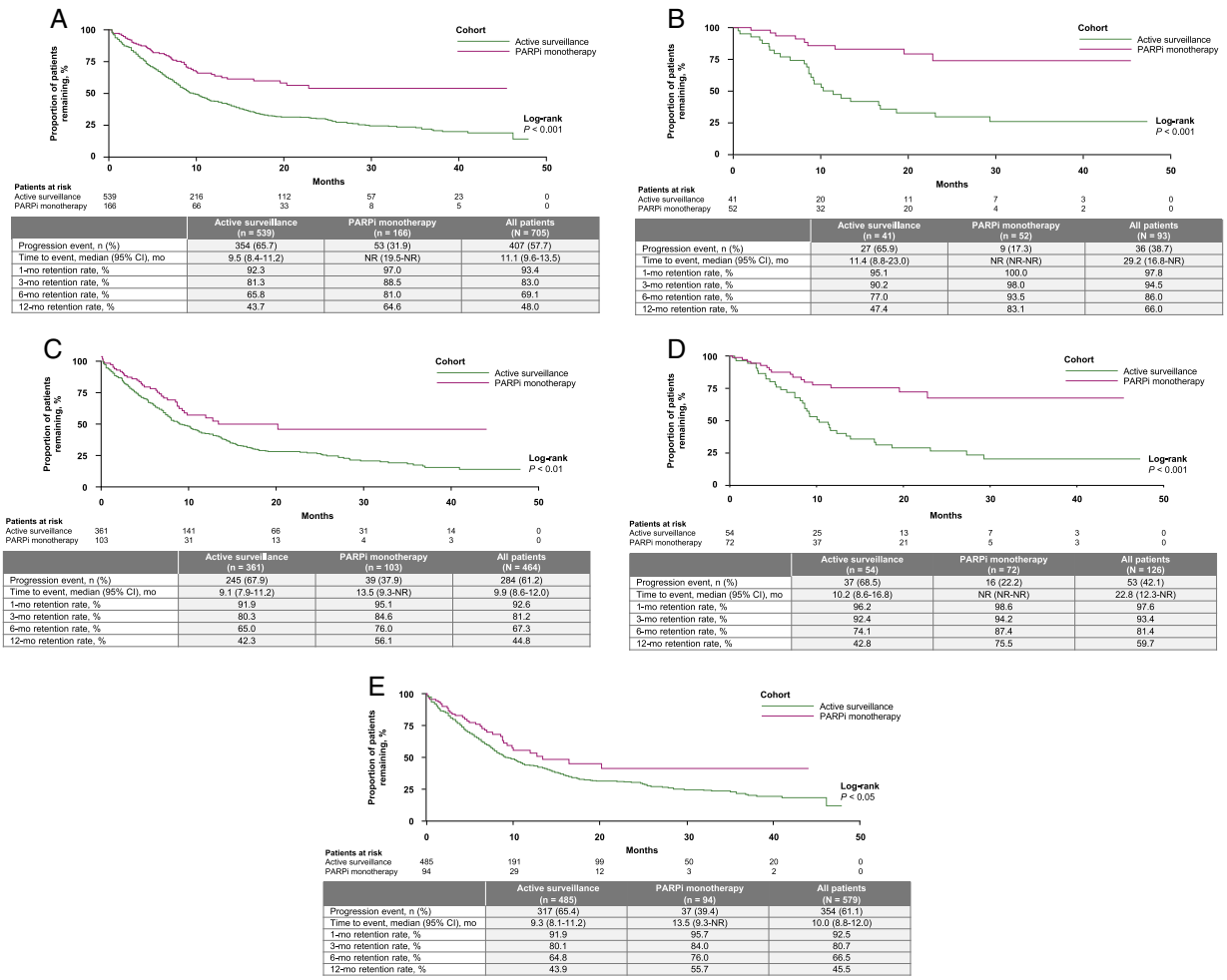
Table 1). In addition, at initial diagnosis, most patients in both cohorts were white as compared with other races (66.9% for PARPi monotherapy, 67.5% for AS), and were treated at a community practice (93.4% for PARPi monotherapy, 87.4% for AS; Table 1). Patients in the PARPi monotherapy cohort were less likely to have stage III disease at diagnosis (71.1% vs 62.0%; $P < 0.05$), while being more likely to have an index date during the coronavirus disease 2019 pandemic (50.6% vs 17.8%; $P < 0.001$) and have a shorter follow-up (13.7 vs 21.8 mo; $P < 0.001$). In the PARPi monotherapy cohort, 31.3% of patients had *BRCA*m tumors and 43.4% had HRd tumors, compared with 7.6% and 10.0% of patients, respectively, in the AS cohort (both $P < 0.001$). Trend analysis over the 4-year study period showed PARPi monotherapy use increased from 6.4% in 2017 to 8.1% in 2018, 25.0% in 2019, 44.0% in 2020, and 53.2% in 2021.

Clinical Outcomes

In the PARPi monotherapy cohort, 166 patients (31.9%) progressed to 2L or died, whereas, at a median follow-up of 20.6 months, 354 of 539 patients (65.7%) in the AS cohort progressed to 2L or died. Median rwPFS was not reached (95% CI: 19.53 to not reached) for patients in the PARPi monotherapy cohort compared with 9.5 months (95% CI: 8.37-11.23) for the AS cohort ($P < 0.001$; Fig. 3A). The 12-month rwPFS rate was 64.6% for the PARPi monotherapy cohort and 43.7% for the AS cohort.

Maintenance treatment with PARPi was an independent predictor for improved rwPFS when compared with AS (adjusted HR, 0.47; 95% CI: 0.34-0.63; $P < 0.001$). Patient characteristics that were associated with poorer rwPFS in all patients included stage IV disease at diagnosis, no debulking surgery, residual disease after debulking surgery, *BRCA*wt tumor status, and 1L bevacizumab use (Fig. 4A).

Of the 93 patients with *BRCA*m disease, 52 received PARPi monotherapy maintenance, and 41 had AS. The median time to progression or death was not reached for PARPi monotherapy versus 11.4 months (95% CI: 8.83-23.03 mo) on AS ($P < 0.001$; Fig. 3B). The 12-month rwPFS was 83.1% for the PARPi monotherapy cohort and 47.4% for the AS cohort. The use of 1L PARPi monotherapy maintenance was associated with significantly better rwPFS than AS (adjusted HR, 0.17; 95% CI: 0.07-0.41; $P < 0.001$; Fig. 4B).



	Active surveillance (n = 539)	PARPi monotherapy (n = 166)	All patients (N = 705)
Progression event, n (%)	354 (65.7)	53 (31.9)	407 (57.7)
Time to event, median (95% CI), mo	9.5 (8.4-11.2)	NR (19.5-NR)	11.1 (9.6-13.5)
1-mo retention rate, %	92.3	97.0	93.4
3-mo retention rate, %	81.3	88.5	83.0
6-mo retention rate, %	65.8	81.0	69.1
12-mo retention rate, %	43.7	64.6	48.0

	Active surveillance (n = 41)	PARPi monotherapy (n = 52)	All patients (N = 93)
Progression event, n (%)	27 (65.9)	9 (17.3)	36 (38.7)
Time to event, median (95% CI), mo	11.4 (8.8-23.0)	NR (NR-NR)	29.2 (16.8-NR)
1-mo retention rate, %	95.1	100.0	97.8
3-mo retention rate, %	90.2	98.0	94.5
6-mo retention rate, %	77.0	93.5	86.0
12-mo retention rate, %	47.4	83.1	66.0

	Active surveillance (n = 361)	PARPi monotherapy (n = 103)	All patients (N = 464)
Progression event, n (%)	245 (67.9)	39 (37.9)	284 (61.2)
Time to event, median (95% CI), mo	9.1 (7.9-11.2)	13.5 (9.3-NR)	9.9 (8.6-12.0)
1-mo retention rate, %	91.9	95.1	92.6
3-mo retention rate, %	80.3	84.6	81.2
6-mo retention rate, %	65.0	76.0	67.3
12-mo retention rate, %	42.3	56.1	44.8

	Active surveillance (n = 54)	PARPi monotherapy (n = 72)	All patients (N = 126)
Progression event, n (%)	37 (68.5)	16 (22.2)	53 (42.1)
Time to event, median (95% CI), mo	10.2 (8.6-16.8)	NR (NR-NR)	22.8 (12.3-NR)
1-mo retention rate, %	96.2	98.6	97.6
3-mo retention rate, %	92.4	94.2	93.4
6-mo retention rate, %	74.1	87.4	81.4
12-mo retention rate, %	42.8	75.5	59.7

	Active surveillance (n = 485)	PARPi monotherapy (n = 94)	All patients (N = 579)
Progression event, n (%)	317 (65.4)	37 (39.4)	354 (61.1)
Time to event, median (95% CI), mo	9.3 (8.1-11.2)	13.5 (9.3-NR)	10.0 (8.8-12.0)
1-mo retention rate, %	91.9	95.7	92.5
3-mo retention rate, %	80.1	84.0	80.7
6-mo retention rate, %	64.8	76.0	66.5
12-mo retention rate, %	43.9	55.7	45.5

FIGURE 3. Kaplan-Meier curves for real-world PFS for the (A) overall population and the (B) *BRCA*m, (C) *BRCA*wt, (D) HRd, and (E) HRp/HRDunk subgroups. *BRCA*m indicates *BRCA*-mutated; *BRCA*wt, *BRCA* wild-type; HRd, homologous recombination-deficient; HRDunk, homologous recombination deficiency unknown; HRp, homologous recombination-proficient; PARPi, poly(ADP-ribose) polymerase inhibitor; PFS, progression-free survival. full color online

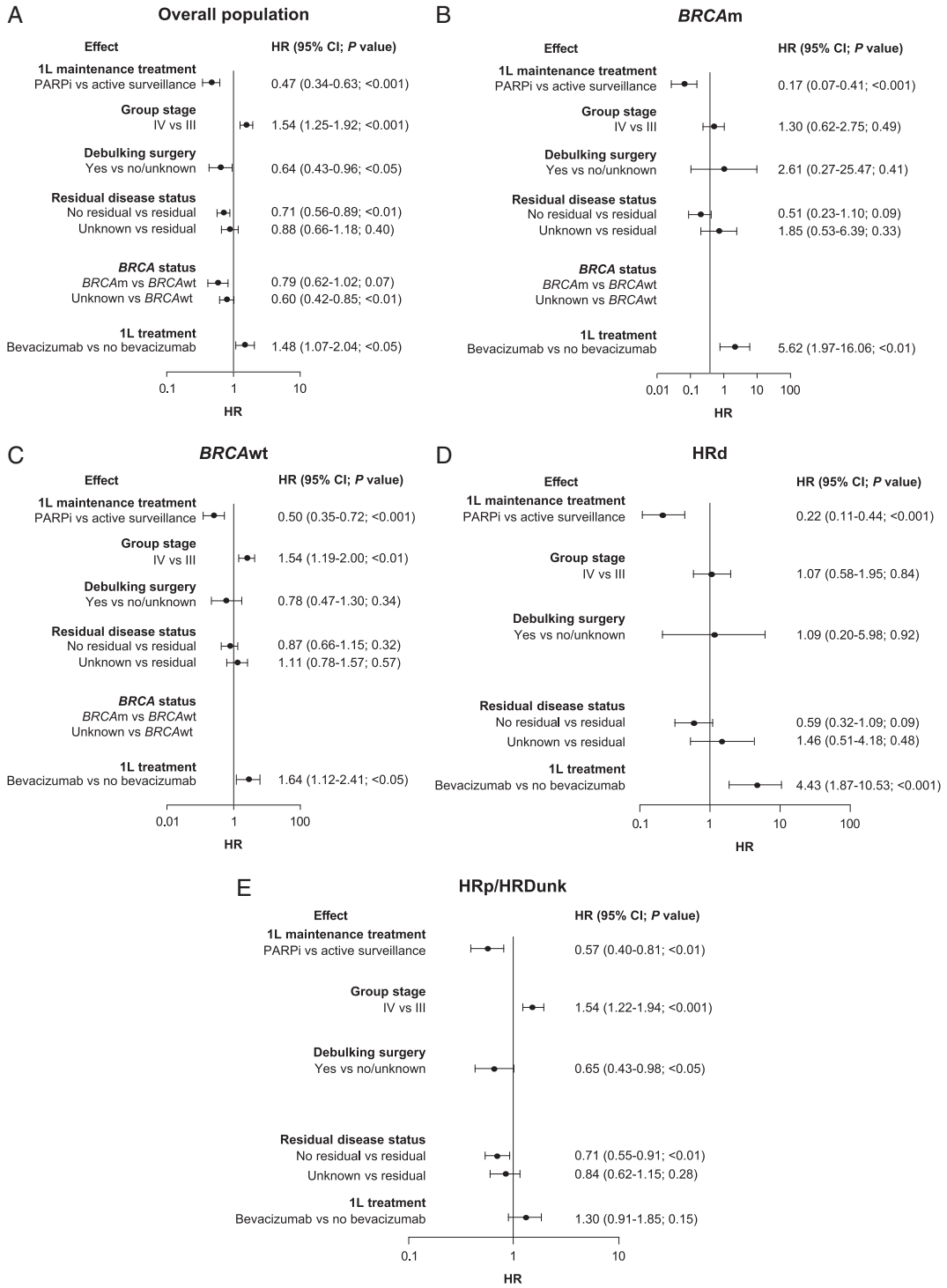


FIGURE 4. Multivariate Cox regression analysis for the (A) overall population and the (B) *BRCA*m, (C) *BRCA*wt, (D) HRd, and (E) HRp/HRDunk subgroups. *BRCA*m indicates *BRCA*-mutated; *BRCA*wt, *BRCA* wild-type; HR, hazard ratio; HRd, homologous recombination-deficient; HRDunk, homologous recombination deficiency unknown; HRp, homologous recombination-proficient; 1L, first-line; PARPi, poly(ADP-ribose) polymerase inhibitor.

Among the 464 patients with *BRCA*wt disease, 103 patients received 1L PARPi maintenance, and 361 patients were on AS. Median time to progression to 2L or death was 13.5 months (95% CI: 9.33 mo to not reached) and 9.1 months (95% CI: 7.90-11.23 mo) in the PARPi monotherapy and AS cohorts, respectively ($P < 0.01$; Fig. 3C). The 12-month rwPFS was 56.1% versus 42.3% for the PARPi monotherapy and the AS cohorts, respectively. rwPFS remained significantly better

with PARPi monotherapy versus AS ($P < 0.01$; adjusted HR, 0.50; 95% CI: 0.35-0.72; $P < 0.001$; Fig. 4C). For patients in both the *BRCA*m and *BRCA*wt subgroups, stage IV disease at initial diagnosis, no receipt of debulking surgery, residual disease after surgery, and receipt of bevacizumab during 1L treatment were associated with poorer rwPFS (Figs. 4B and C).

Among the 126 patients with HRd tumors, 72 patients received PARPi maintenance, and 54 were on AS. The median time to progression or death was not reached for PARPi monotherapy versus 10.2 months (95% CI: 8.60-16.77 mo) on AS ($P < 0.001$; Fig. 3D), and the 12-month rwPFS was 75.5% and 42.8%, respectively. In the HRp/HRDunk subgroup, 35 patients had HRp tumors, and 544 had HRDunk tumors. The median time to progression or death was 13.5 months (95% CI: 9.33 mo to not reached) for PARPi monotherapy versus 9.3 months (95% CI: 8.10-11.23 mo) on AS ($P < 0.05$; Fig. 3E), and the 12-month rwPFS was 55.7% and 44.9%, respectively. Using covariates selected for all patients, adjusted rwPFS remained significantly better in the HRd subgroup for patients on PARPi monotherapy maintenance than for those on AS (adjusted HR, 0.22; 95% CI: 0.11-0.44; $P < 0.001$; Fig. 4D), with similar results seen in the HRp/HRDunk subgroup (adjusted HR, 0.57; 95% CI: 0.40-0.81; $P < 0.01$; Fig. 4E).

DISCUSSION

The aim of this retrospective study was to describe real-world clinical outcomes associated with PARPi monotherapies for 1L maintenance compared with AS among patients in the United States with newly diagnosed AOC to confirm the benefits observed in clinical trials. Our data suggest that maintenance with PARPi monotherapies was associated with a 53% reduced risk of progression in all patients regardless of biomarker status. In addition, we found that the use of a PARPi in the maintenance setting has significantly increased over our study period, with more than 50% of patients with primary OC receiving PARPi maintenance in the year 2021. However, 47% of patients with primary AOC were still not receiving any PARPi maintenance in the 1L setting. Given the established benefit of PARPi monotherapies as 1L maintenance in both clinical trials and real-world settings, outreach strategies should be considered to improve access to receipt of PARPi maintenance therapies.

The OC landscape has evolved since 2018, with the approval of 1L PARPi maintenance therapies. Evidence from clinical trials points to the well-demonstrated clinical benefit of PARPi monotherapies.[7,8] Niraparib monotherapy has been the only approved treatment for 1L maintenance in otherwise eligible patients regardless of biomarker status and in the PRIMA/ENGOT-OV26/GOG-3012 trial, was associated with a PFS benefit compared with placebo.[7] Moreover, in the subgroup of patients with *BRCA*m disease, the benefit of PARPi monotherapy demonstrated by both niraparib and olaparib in clinical trials was more prominent, with 60% to 70% reduced risk of progression.[7,8] However, clinical trials often contain narrowly defined populations not reflective of real-world cancer patient populations.[14–17]

In the AOC population, a lack of real-world studies has been identified, particularly in the areas of population uptake and survival outcomes.[14,18] Although PARPi monotherapy maintenance treatments have been introduced into the clinical landscape of AOC, there is little insight into their real-world uptake and the associated outcomes. Because of the potential differences between the clinical trial populations and the real-world AOC populations, including but not limited to the possibility of differences in age, race, comorbidities, and clinical practice locations, it is important to examine real-world evidence of PARPi monotherapy maintenance treatment outcomes.[14–18]

Although in some cases there may be differences between the conclusions drawn from real-world data and clinical study findings, the results found in this study align with those seen in both the PRIMA trial and the PRIME trial, in which PFS benefit was shown with PARPi monotherapy in the overall intention-to-treat trial population.[7,19] In PRIMA, the overall median duration of PFS was 13.8 months with niraparib and 8.2 months with placebo (HR, 0.62; 95% CI: 0.50-0.76; $P < 0.001$), whereas, in the PRIME trial, the overall median duration of PFS was 24.8 months with niraparib and 8.3 months with placebo (HR, 0.45; 95% CI: 0.34-0.60; $P < 0.001$).[7,19] Of note, the PRIME trial comprised a Chinese population and had slightly different enrollment criteria, which may contribute to the differences seen in the PFS of the intention-to-treat population of the 2 trials.[19] Our real-world data were consistent with those of the clinical studies as the overall median rwPFS was not reached for patients receiving PAPRi monotherapy and was 9.53 months for patients on AS ($P < 0.001$), thus providing further evidence for the benefit of PARPi monotherapy maintenance use, regardless of biomarker status.

Some methodological limitations intrinsic to real-world retrospective database analysis, other than the limited sample size, must be considered. First, although the Flatiron Health EHR-derived population is highly representative of patients cared for in US community-based practices, it may not be fully generalizable to the population of patients with AOC in the United States. Although the Flatiron Health EHR-derived population is mainly representative of community-based practices, it is not representative of academic centers, which care for a sizable number of patients with AOC in the United States. This may lead to differences in treatment patterns, patient socioeconomic conditions, and patient health insurance/Medicaid rates. Second, there are limitations in the capture of death data in EHR databases, and as such, mortality data may be incomplete in structured EHR databases,[20,21] and death date data may lack day-level precision for some patients. However, a validation analysis conducted by Flatiron Health indicated that the accuracy of the death date was 96% to 98%.[22]

The Flatiron Health database is built by data abstraction from patient charts, which could contain errors in data entry. The database is also not a closed system; hence, prescriptions and encounters outside of the Flatiron Health network were not able to be captured in the database. Moreover, imaging information is not available to confirm progression, necessitating the initiation of 2L or death as a proxy for progression, which is a widely acknowledged approach in real-world studies when progression data are not available. Flatiron also takes measures to corroborate abstracted data with structured information (eg, office visits, treatment administrations, or orders) before generating combined data sets, which mitigates the risk of data error.

In addition to the limitations of the Flatiron Health database, several aspects of the study design should also be considered when interpreting these results. The PARPi monotherapy patient population may have been impacted by the enrollment period, which began before the US approvals of olaparib and niraparib for 1L maintenance therapy. Patients who received PARPi maintenance therapy before approval may have had a more advanced disease or had other risk factors placing them at high risk for progression. Also, the study excluded patients whose last patient-level confirmed

activity was within 4 months (120 d) of the last dose of 1L PBCT regimens. Therefore, all patients included in the study must have lived for at least 4 months after completing 1L chemotherapy. Consequently, patients with more aggressive diseases (ie, patients who died within 120 d of the last dose of 1L chemotherapy) were excluded, which may have led to an overestimation of the rwPFS. However, the index date was defined as 120 days after the last dose of 1L chemotherapy, which may have resulted in the underestimation of median rwPFS for PARPi monotherapies. In addition, based on the Flatiron Health database rules, treatment was considered to be continuous until a gap of >120 days between prescriptions was observed. In our study, patients remained in the maintenance cohort until the end of the follow-up period. Consequently, patients who discontinued PARPi treatment before the end of the study may have been included in the PFS analyses. Nonetheless, the impact of these potential biases is expected to be small because of the long median PFS associated with PARPi monotherapies. The wide variability in the duration of follow-up may also have affected the rwPFS results. Because almost 60% of patients in the PARPi monotherapy cohort had an index date in 2019 or 2020, the duration of follow-up in the PARPi monotherapy cohort was approximately half as long as that for patients in the AS cohort.

Our study focused on assessing outcomes in patients who received PARPi monotherapy as maintenance treatment. As such, patients who received combination maintenance therapy with PARPi and bevacizumab or other novel targeted agents were excluded from our analyses. Future studies that include PARPi combination maintenance therapy regimens may provide a better understanding of potential synergistic effects and additive toxicities with combination therapies.

Despite these limitations, data from EHRs based on real-world outcomes are highly valuable for confirming evidence from clinical trials.[20,21] Because they are often conducted with highly selected patient populations with similar medical histories, clinical trials provide data that are limited in their generalizability to broader patient populations;[21] however, real-world databases aggregate medical information at the point of care, allowing for data capture from a potentially larger, more diverse patient population.

CONCLUSIONS

The findings from this study contribute real-world evidence for PARPi monotherapy as 1L maintenance therapy. We found that compared with AS, maintenance with PARPi monotherapy was associated with significantly improved rwPFS in patients with AOC who achieved response to 1L chemotherapy. The clinical benefit was more prominent in patients with *BRCA*m or HRd status, although the benefit was still noteworthy in patients with *BRCA*wt AOC status. Results of our real-world analysis suggested that 47% of patients with primary AOC were not receiving PARPi maintenance in the year 2021, reflecting a need for further PARPi maintenance adoption in AOC.

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