# Characteristics and real-world outcomes of patients with epithelial ovarian cancer who received niraparib plus bevacizumab first-line maintenance therapy in the COMB1NE study

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## ABSTRACT

**Objective** In the phase 2 OVARIO trial (NCT03326193) investigating niraparib-bevacizumab first-line maintenance, median progression-free survival was 14.2 months (95% confidence interval (CI) 8.6 to 16.8) for patients with homologous recombination (HR)–proficient (HRp) epithelial ovarian cancer, and 12.1 months (95% CI8.0–not evaluated) for patients with undefined HR status. However, real-world data are limited for patients who receive niraparib-bevacizumab first-line maintenance therapy. The COMB1NE study describes real-world clinical outcomes (time to treatment discontinuation; time to next treatment) in patients with epithelial ovarian cancer who received niraparib-bevacizumab first-line maintenance, regardless of first-line bevacizumab use.

**Methods** This real-world, retrospective study used a US nationwide electronic health record-derived deidentified database. Eligible patients were 18 years or older at initial epithelial ovarian cancer diagnosis and initiated niraparib-bevacizumab first-line maintenance (January 1, 2017–September 2, 2022) following first-line treatment. The index date was the start of first-line maintenance. Patients were followed until death, last clinical activity, or end of study, whichever occurred first. Time to treatment discontinuation and time to next treatment, a proxy for real-world progression-free survival, were estimated using the Kaplan–Meier method.

**Results** Among 59 included patients, the median age was 67 years (interquartile range (IQR) 61–76), and 81.4% had stage III/IV epithelial ovarian cancer at diagnosis. Overall, 83.1% of patients had *BRCA* wild-type with either HRp or HR status unknown disease. Median time to treatment discontinuation of first-line maintenance was 11.8 months (95% CI 8.7 to 13.5). Median time to next treatment was 14.1 months (95% CI 11.3 to 16.6). At 6 months after index, 77.9% of patients had not initiated second-line treatment; at 12 months, 61.3% had not.

**Conclusion** In this real-world study of patients receiving niraparib-bevacizumab first-line maintenance, the majority of whom had HRp/HR status unknown, the median time to next treatment was consistent with observed progression-free survival in patients with similar HR status in the OVARIO study.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Clinical trials have shown that, following first-line therapy with platinum-based chemotherapy with or without bevacizumab, first-line maintenance bevacizumab monotherapy and first-line maintenance niraparib monotherapy have both shown improved progression-free survival for patients with epithelial ovarian cancer, compared with active surveillance. In the single-arm, open-label, phase 2 OVARIO study, despite having a patient population at high risk for disease progression, first-line maintenance niraparib plus bevacizumab demonstrated a median progression-free survival of 19.6 months in the overall population of patients with epithelial ovarian cancer.

### WHAT THIS STUDY ADDS

⇒ Results from the COMB1NE study provide real-world outcomes for patients with epithelial ovarian cancer who received first-line maintenance niraparib plus bevacizumab, 83.1% of whom had *BRCA* wild-type with either HRp or HR status unknown disease. The estimated time to next treatment, a proxy for real-world progression-free survival, of 14.1 months supports the previous progression-free survival estimate for this treatment combination reported in OVARIO for patients with similar HR status.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The combination of niraparib plus bevacizumab may be a viable treatment option for patients with epithelial ovarian cancer in the first-line maintenance setting.

## INTRODUCTION

Ovarian cancer is the second most common gynecologic cancer in the US,[1] with a projected 19 680 new cases diagnosed and 12 740 deaths in 2024.[2] As over half of all patients present with advanced disease at diagnosis, survival remains low, with a 5-year overall survival rate of only 31.5%.[3]

For patients with advanced ovarian cancer, first-line treatment options include primary or interval

cytoreductive surgery and platinum-based chemotherapy with or without bevacizumab.[4] For patients who achieve a complete or partial response to first-line treatment, maintenance treatment is recommended to delay disease recurrence and prolong survival.[5] First-line maintenance with bevacizumab, following concurrent first-line platinum-based chemotherapy plus bevacizumab, has been shown to improve progression-free survival in patients with advanced epithelial ovarian cancer.[6] Niraparib, a poly(ADP-ribose) polymerase (PARP) inhibitor, was approved as first-line maintenance monotherapy for patients with advanced epithelial ovarian cancer responsive to first-line platinum-based chemotherapy, following the phase 3 PRIMA/ENGOT-OV26/GOG-3012 study, which showed significantly improved progression-free survival for patients who received niraparib versus patients who received placebo in first-line maintenance.[7] Although the current first-line maintenance approval is for niraparib monotherapy,[8] there is an interest in understanding the clinical benefit of first-line maintenance niraparib plus bevacizumab. The single-arm, unblinded, phase 2 OVARIO study evaluated first-line maintenance niraparib plus bevacizumab in patients with advanced epithelial ovarian cancer who received first-line platinum-based chemotherapy plus bevacizumab.[9] Overall, median progression-free survival was 19.6 months.[9] However, real-world data are limited on first-line maintenance niraparib plus bevacizumab use. The objective of the COMB1NE study was to describe real-world clinical outcomes in US patients with epithelial ovarian cancer who received first-line maintenance niraparib plus bevacizumab in the routine-care setting, irrespective of first-line bevacizumab use.

## METHODS

### Data Source

This retrospective, observational cohort study used data from the nationwide, US-based Flatiron Health database. This deidentified electronic health record-derived, longitudinal database captures data from approximately 280 cancer clinics, equivalent to an estimated 800 care sites.[10 11] This database contains both structured and unstructured data curated via technology-enabled abstraction from physician notes and other unstructured documents.[10 11] Data are subject to obligations to prevent reidentification and to protect patient confidentiality. Because no direct patient contact or individual patient data collection occurred, and because study results are presented as aggregate analyses only, no ethics committee or institutional review board approvals were required.

### Study Population

Patients aged 18 years or older who were diagnosed with ovarian cancer after January 1, 2011, were eligible for inclusion if they received first-line maintenance niraparib plus bevacizumab between January 1, 2017 (year of first niraparib approval in the US),[8] and September 2, 2022. The index date was defined as the first-line maintenance initiation date, defined as the earliest start date of niraparib or bevacizumab, in some instances occurring simultaneously, per predetermined oncologist-defined, rules-based lines of therapy. Additional inclusion criteria were evidence of epithelial histology (serous, clear cell, mucinous, endometrioid, transitional cell, epithelial not otherwise specified, or unknown) and ≥1 day of post-index follow-up (Figure 1). Patients were excluded if they had misclassified lines of therapy (ie, record of PARP inhibitor monotherapy in the first-line or second-line treatment setting). Follow-up was measured from index until death, last clinical activity, or study end (November 30, 2022), whichever occurred first.

### Key Variables

Patient demographics and clinical characteristics were assessed (described in Online supplemental appendix).

### Study Outcomes

Real-world clinical outcomes of interest were time to treatment discontinuation and time to next treatment (a proxy for real-world progression-free survival). Time to treatment discontinuation was measured from index to first-line maintenance discontinuation date or death, whichever occurred first. Time to treatment discontinuation was assessed for the overall duration of niraparib plus bevacizumab, and individually for the niraparib and bevacizumab components of first-line maintenance. For the overall duration, the first-line maintenance start date was defined as the earliest start date of niraparib or bevacizumab; the first-line maintenance discontinuation date was defined as the latest occurrence of the last dose of niraparib or administration of bevacizumab. Patients who did not discontinue first-line maintenance therapy or die were censored at last clinical activity or study end.

Time to next treatment was measured as the time from index to the start of second-line therapy or death, whichever occurred first. Patients who did not initiate second-line therapy or die were censored at last clinical activity or study end.

### Statistical Methods

Patient demographic and disease characteristics were summarized descriptively. Median time to treatment discontinuation and time to next treatment (and corresponding 95% CIs) were estimated using the Kaplan–Meier method. All analyses were conducted with SAS version 9.4 (SAS Institute, Cary, NC).

## RESULTS

Of 11 094 patients diagnosed with epithelial ovarian cancer during the study period, 59 patients met all eligibility criteria and were included in the analyses (Figure 1). The median age at index was 67 years (interquartile range (IQR), 61–76) (Table 1). Most patients were White (61.0%) and treated in a community-based oncology practice (98.3%). Approximately equal proportions of patients had stage III (42.4%) or stage IV (39.0%) disease at diagnosis, 10.2% of patients had no surgery, and 28.8% had visible residual disease. Fifty-three patients (89.8%) had an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0–1. A majority of patients (83.1%) had either *BRCA* wild-type with HR–proficient (HRp) disease or *BRCA* wild-type with HR status unknown disease. Most patients (81.4%) received a bevacizumab-containing regimen in the first-line induction treatment setting. Median follow-up time was 17.6 months (IQR, 10.6–25.7), and median time from end of first-line therapy to first-line maintenance initiation was 21.0 days (IQR, 14.0–35.9). The most frequently observed starting doses were 200 mg (45.8%) and 300 mg (28.8%) (Table 2). Twenty-nine patients (49.2%) initiated niraparib at an individualized starting dose based on weight and platelet count. Niraparib and bevacizumab were

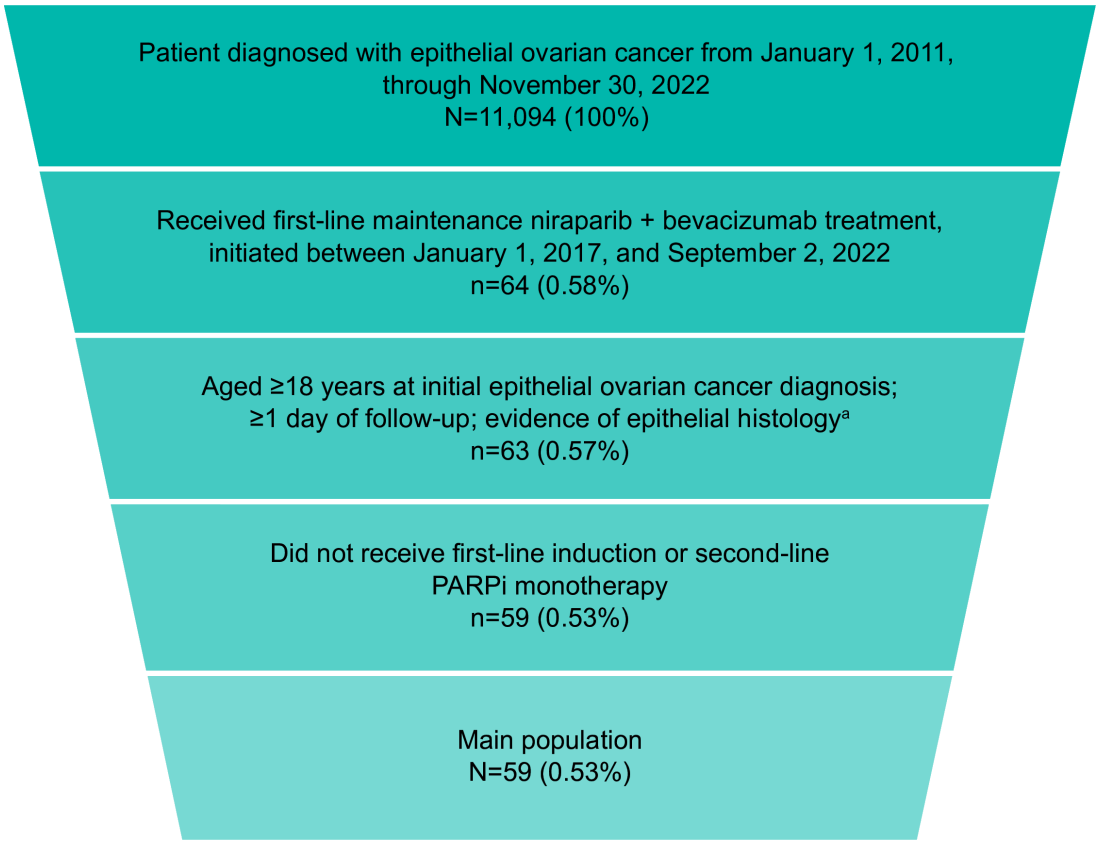


**Figure 1** Study population attrition. PARPi, poly(ADP-ribose) polymerase inhibitor. [a]May include serous, clear cell, mucinous, endometrioid, transitional cell, epithelial not otherwise specified, or unknown.

both discontinued for 45 patients (76.3%). Among 48 patients who discontinued niraparib, the reason was most commonly because of disease progression (n=24; 50.0%) and/or toxicity (n=22; 45.8%); reasons for bevacizumab discontinuation were unavailable (Table 2).

Among 59 patients, 33 (55.9%) started the bevacizumab component of the first-line maintenance regimen first, 19 (32.2%) started the niraparib component first, and 7 (11.9%) started both the niraparib and bevacizumab components on the same day. There was a median of 20.5 days (IQR, 11.0–63.0) between the start dates of the two components (bevacizumab and niraparib) in the first-line maintenance regimen. Median time to treatment discontinuation was 11.8 months (95% CI 8.7 to 13.5) for the first-line maintenance niraparib plus bevacizumab treatment regimen (Figure 2A). When assessed individually, median time to treatment discontinuation was 8.5 months (95% CI, 3.7 to 11.4) for patients discontinuing the niraparib component of the first-line maintenance regimen and 10.2 months (95% CI, 6.0 to 12.2) for patients discontinuing the bevacizumab component (Figure 2A,B).

Median time to next treatment was 14.1 months (95% CI 11.3 to 16.6) (Figure 3). At 6 months after index, 77.9% of patients had not initiated second-line treatment; at 12 months, 61.3% had not.

## DISCUSSION

### Summary of the Main Results

This retrospective, observational study of patients with epithelial ovarian cancer who received first-line maintenance niraparib plus bevacizumab provides useful real-world data for this first-line maintenance treatment combination. In the COMB1NE study, the median time to next treatment, a proxy for real-world progression-free survival,[12 13] was 14.1 months, and the overall median time to treatment discontinuation was 11.8 months. Reasons for bevacizumab discontinuation or for overall first-line maintenance discontinuation were not available in this data set, and niraparib discontinuations were primarily due to disease progression (50.0%) and/or to toxicity (45.8%). Additional information on adverse events, including severity or frequency of any adverse events, was not available.

### Results in the Context of Published Literature

In the phase 2 OVARIO study, which also investigated patients with advanced epithelial ovarian cancer who were treated with niraparib plus bevacizumab in the first-line maintenance setting, the median progression-free survival for the overall population was 19.6 months.[9] It should be noted that in the OVARIO study, 27.6% of patients had *BRCA*-mutated disease, whereas only 10.2% of patients from our study had *BRCA*-mutated disease. Among the 38 patients (36.2%) with HRp disease in OVARIO, median progression-free survival was 14.2 months. This is comparable to the median time to next treatment of 14.1 months reported in our study among a majority of patients who had *BRCA* wild-type/HRp or *BRCA* wild-type/HR unknown disease.[9] Among the 59 patients in our study, most patients had stage III (42.4%) or stage IV (39.0%) disease at diagnosis, 28.8% had visible residual disease, and 10.2% had no surgery, collectively indicating that patients included here may be

**Table 1** Patient demographic and clinical characteristics

| Characteristic | Patients (n=59)* |
|---|---|
| Age | |
| Median (IQR), years | 67 (61–76) |
| <75 years, n (%) | 41 (69.5) |
| ≥75 years, n (%) | 18 (30.5) |
| Race, n (%) | |
| White | 36 (61.0) |
| Other | 13 (22.0) |
| Missing | 10 (16.9) |
| Ethnicity, n (%) | |
| Not Hispanic or Latino | 40 (67.8) |
| Hispanic, Latino, or Unknown | 19 (32.2) |
| Region of residence, n (%)† | |
| Midwest | 6 (10.2) |
| South | 31 (52.5) |
| West | 6 (10.2) |
| Northeast | 10 (16.9) |
| Other/unknown | 6 (10.2) |
| Practice type, n (%)‡ | |
| Community | 58 (98.3) |
| Academic | 6 (10.2) |
| Body weight, n (%) | |
| <77 kg | 44 (74.6) |
| ≥77 kg | 15 (25.4) |
| Platelet count, n (%) | |
| <1 50 000/µL | 19 (32.2) |
| ≥1 50 000/µL | 33 (55.9) |
| Unknown | 7 (11.9) |
| Hypertension, n (%)§ | 4 (6.8) |
| Systolic blood pressure, mean (SD), mm Hg¶ | 136.6 (21.2) |
| Diastolic blood pressure, mean (SD), mm Hg¶ | 79.4 (9.6) |
| Type of cytoreductive surgery, n (%) | |
| Primary cytoreductive surgery | 24 (40.7) |
| Interval cytoreductive surgery | 29 (49.2) |
| No surgery | 6 (10.2) |
| First-line treatment regimen, n (%) | |
| Platinum-based chemotherapy without bevacizumab | 11 (18.6) |
| Platinum-based chemotherapy with bevacizumab | 44 (74.6) |
| Other** | 4 (6.8) |
| Residual disease status, n (%) | |
| No visible residual disease | 23 (39.0) |
| Visible residual disease | 17 (28.8) |
| No surgery | 6 (10.2) |
| Unknown | 13 (22.0) |
| ECOG PS score, n (%) | |
| 0–1 | 53 (89.8) |
| 2–4 | 6 (10.2) |
| Stage at initial diagnosis, n (%) | |
| I/II | 3 (5.1) |
| III | 25 (42.4) |
| IV | 23 (39.0) |
| Unknown | 8 (13.6) |
| Epithelial histology, n (%) | |
| Serous | 47 (79.7) |
| Other/unknown†† | 12 (20.3) |
| *BRCA*/HRD biomarker status, n (%) | |
| HRd | 7 (11.9) |
| *BRCA* mutated‡‡ | 6 (10.2) |
| *BRCA* wild-type‡‡ | 1 (1.7) |
| *BRCA* wild-type/HRp or *BRCA* wild-type/HRunk | 49 (83.1) |
| *BRCA* status unknown and HRunk | 3 (5.1) |
| Follow-up time, median (IQR), months | 17.6 (10.6–25.7) |
| Duration of first-line therapy, median (IQR), months | 5.1 (3.7–6.8) |
| Time from end of first-line to start of first-line maintenance, median (IQR), days | 21.0 (14.0–35.9) |

*Because of rounding, percentages for some categories may not equal 100%.
†Patients from academic practices have "unknown" geographic region. Patients in Puerto Rico were grouped into "other/unknown" because of low numbers.
‡Patients with records in academic and community practices are counted in both categories; therefore, patient counts may sum to more than 100%. Academic may include both university and non-university academic settings.
§Defined as yes/no, via International Classification of Diseases (ICD) 9 and 10 codes.
¶One patient was missing systolic and diastolic blood pressure and is not included.
**Other includes bevacizumab monotherapy or combinations with non–platinum-based chemotherapy.
††Includes endometrioid/epithelial not otherwise specified.
‡‡*BRCA*-mutated and *BRCA* wild-type are subcategories of HRd.
ECOG PS, Eastern Cooperative Oncology Group performance status; HRd, homologous recombination–deficient; HRD, homologous recombination deficiency; HRp, homologous recombination–proficient; HRunk, homologous recombination status unknown; IQR, interquartile range; SD, standard deviation.

at higher risk of relapse. These patient characteristics are similar to those in the OVARIO trial, where among 105 enrolled patients, all patients had stage III/IV disease, and 26.7% had visible residual disease (all patients received surgery).[9] In our study, 45.8% of patients (22 of 48) who discontinued niraparib did so due to toxicity.

**Table 2** Dosing characteristics and discontinuation

| Characteristic, n (%) | Patients (n=59)* |
|---|---|
| Niraparib starting dose | |
| 100 mg | 10 (16.9) |
| 200 mg | 27 (45.8) |
| 300 mg | 17 (28.8) |
| Unknown | 5 (8.5) |
| Starting dose status | |
| Individualized starting dose† | 29 (49.2) |
| Lower than individualized starting dose | 12 (20.3) |
| Higher than individualized starting dose | 11 (18.6) |
| Unknown | 7 (11.9) |
| Dose modification of niraparib | |
| Yes | 28 (47.5) |
| No | 18 (30.5) |
| Unknown | 13 (22.0) |
| Type of dose modification of niraparib‡ | |
| Increase | 3 (10.7) |
| Decrease | 17 (60.7) |
| Both | 8 (28.6) |
| Number of dose modifications‡ | |
| 1 | 19 (67.9) |
| 2 | 2 (7.1) |
| ≥3 | 7 (25.0) |
| Discontinued niraparib | |
| Yes | 48 (81.4) |
| No | 11 (18.6) |
| Reasons for discontinuation of niraparib§ | |
| Disease progression | 24 (50.0) |
| Toxicity | 22 (45.8) |
| Other/unknown¶ | 6 (12.5) |

*Because of rounding, the percentages for some categories may not equal 100%.
†Individualized starting dose was a derived variable based on body weight and platelet count at the closest visit to index. Patients weighing ≥77 kg and with a platelet count ≥150 000/µL were indicated for a 300 mg dose; patients weighing <77 kg or with a platelet count <150 000/µL were indicated for a 200 mg dose.
‡Among the 28 patients who had a niraparib dose modification.
§Among the 48 patients who discontinued niraparib. Patients who discontinued niraparib may have had ≥1 reason for discontinuation, so categories are not mutually exclusive, and percentages may exceed 100%.
¶"Other" may include financial reasons, patient request, disease-related symptom not specific to therapy, other (including death), lack of evidence of disease, unknown, and completed treatment.

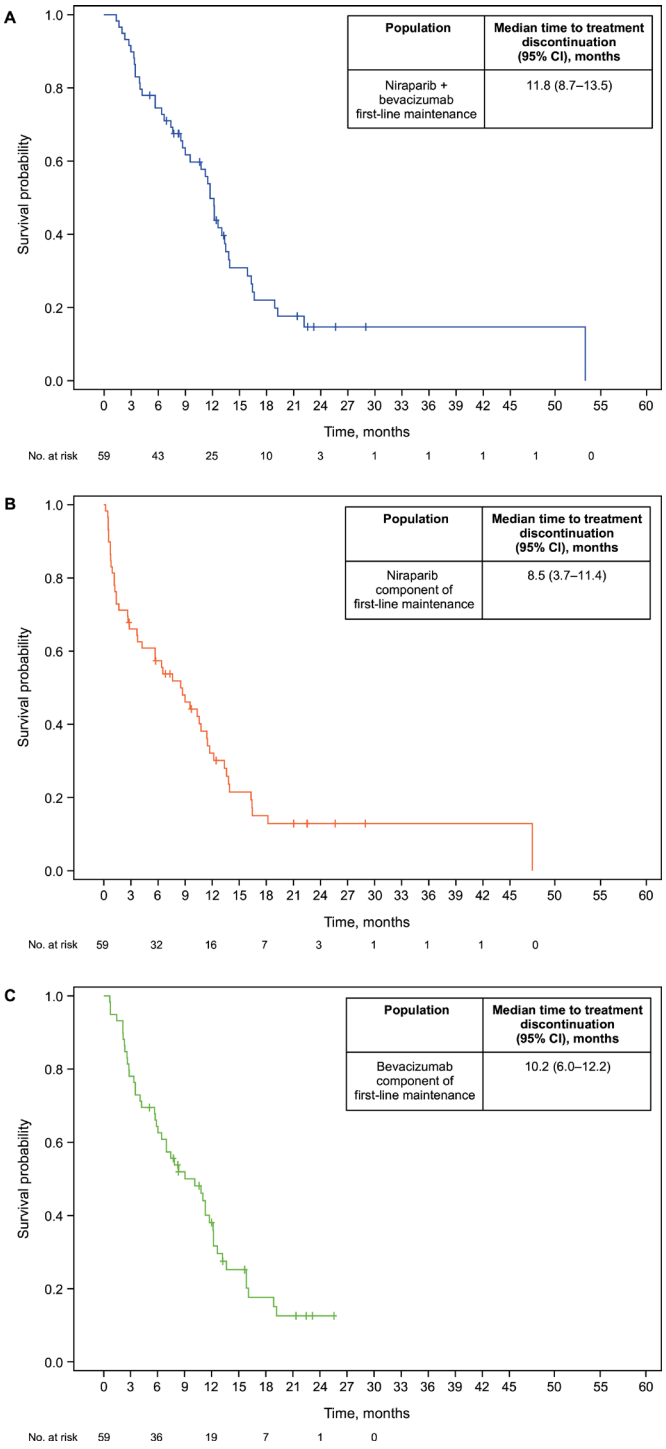


**Figure 2** Real-world time to treatment discontinuation for the overall first-line maintenance treatment regimen of niraparib plus bevacizumab* (A), the niraparib component of first-line maintenance† (B), and the bevacizumab component of first-line maintenance‡ (C) *For the overall first-line maintenance treatment regimen of niraparib plus bevacizumab, 45 patients (76.3%) discontinued both drugs, and 14 patients (23.7%) did not. †For the niraparib component of first-line maintenance, 48 patients (81.4%) discontinued niraparib, and 11 (18.6%) did not. ‡For the bevacizumab component of first-line maintenance, 46 patients (78.0%) discontinued bevacizumab, and 13 (22.0%) did not.

However, detailed data on reasons for bevacizumab discontinuation and on adverse events were not available here, so comparisons to the OVARIO trial or other clinical trials were not made, which is a limitation of our study. The percentage of patients who experienced

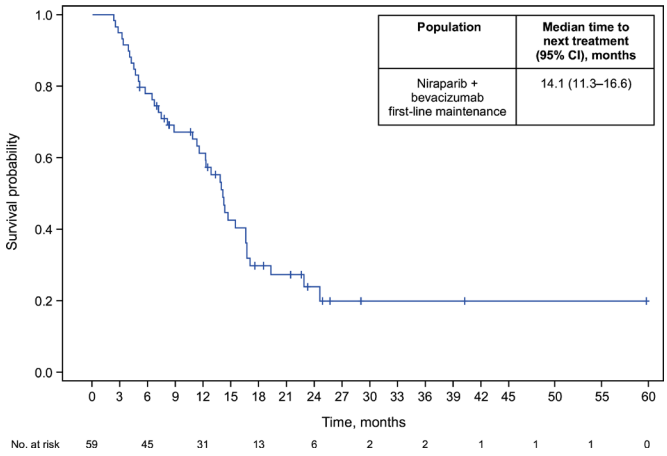


**Figure 3** Real-world time to next treatment* for patients who received first-line maintenance niraparib plus bevacizumab. *For the overall first-line maintenance treatment regimen of niraparib plus bevacizumab, there were 40 (67.8%) time to next treatment events.

hypertension was extremely low in our study (6.8%), but this finding likely reflects the difficulty in capturing comorbidity data from International Classification of Diseases codes in a real-world oncology electronic health record-derived data set, which is not comprehensive of all clinical care.[14] However, systolic and diastolic blood pressure values were available for a larger number of patients, and mean (standard deviation [SD]) values were within the normal range (systolic, 136.6 [21.2] mm Hg; diastolic, 79.4 [9.6] mm Hg), supporting the diagnosis of hypertension. In the ongoing phase 3 AGO-OVAR 28/ENGOT-ov57 trial (NCT05009082), the combination of niraparib plus bevacizumab (vs niraparib alone) is also being investigated in patients with newly diagnosed advanced ovarian cancer who received chemotherapy with or without bevacizumab in the first-line induction setting; results are expected in 2028.[15]

In PRIMA, median progression-free survival for patients in the overall population who received first-line maintenance niraparib monotherapy was 13.8 months vs 8.2 months for placebo (hazard ratio 0.62; 95% CI 0.50 to 0.76).[7] The effects were more pronounced among patients in the HRd subgroup, in which median progression-free survival was 21.9 months for niraparib vs 10.4 months for placebo (hazard ratio, 0.43; 95% CI 0.31 to 0.59); among patients in the HRp subgroup, median progression-free survival was 8.1 months for niraparib vs 5.4 months for placebo (hazard ratio, 0.68; 95% CI 0.49 to 0.94). Median time to next treatment in this COMB1NE study (14.1 months; 95% CI 11.3 to 16.6 ) was longer than the median progression-free survival for patients in the overall population and in the HRp subgroup of PRIMA. It is important to note that PRIMA excluded patients who were at lower risk for disease progression (stage III with no visible residual disease after primary cytoreductive surgery), while our study did not.

Other clinical trials have also investigated bevacizumab-containing combination therapies. In the GOG-0218 study, first-line induction bevacizumab plus chemotherapy followed by bevacizumab maintenance was investigated in patients with epithelial ovarian cancer.[6] The median progression-free survival for patients who received chemotherapy alone was 10.3 months; for chemotherapy plus bevacizumab, 11.2 months. The median progression-free survival was 14.1 months for patients who received induction chemotherapy plus bevacizumab, followed by continued bevacizumab.[6] However, because of the study design of GOG-0218, progression-free survival was measured from time of enrollment, vs in our study, where it was measured from start of first-line maintenance. In the overall population (n=806) of the PAOLA-1/ENGOT-ov25 study, median progression-free survival was significantly prolonged for olaparib plus bevacizumab (22.1 months) compared with bevacizumab monotherapy (16.6 months; hazard ratio, 0.59; 95% CI 0.49 to 0.72).[16] The association was stronger among 387 patients with HRd tumors (olaparib plus bevacizumab, 37.2 months vs bevacizumab monotherapy, 17.7 months; hazard ratio, 0.33; 95% CI 0.25 to 0.45). Among 419 patients with HRp tumors or who had unknown HR status, median progression-free survival was 16.9 months for olaparib plus bevacizumab compared with 16.0 months for bevacizumab monotherapy (hazard ratio, 0.92; 95% CI 0.72 to 1.17). Findings by HRD subgroup remained consistent after 5 years of follow-up,[17] even after stratifying by risk factors for disease progression.[18] Notably, the PAOLA-1 study population was restricted to patients with ECOG PS of 0 or 1, who experienced complete or partial response following first-line platinum-based chemotherapy plus bevacizumab. These restrictions were not applied to this real-world study.

Real-world studies investigating niraparib plus bevacizumab in the first-line maintenance setting were not available for comparison. However, in an abstract reporting the real-world use of niraparib monotherapy, median time to treatment discontinuation from index was 9.3 months (95% CI 6.0 to 11.3), and median time to next treatment from end of first-line was 12.9 months (95% CI 11.5 to 19.0),[19] which align with the results we report here. Of note, the median age of patients included in our study was high at 67 years. This age is consistent with the median age of the 93 patients included in the real-world study of niraparib monotherapy.[19] In a separate US-based real-world study looking at the use of PARP inhibitors in any setting, the median age of 303 patients taking olaparib was 59.0 years (IQR, 11.0); of 348 patients taking niraparib, 59.0 years (IQR, 11.0); and of 162 patients taking rucaparib, 59.0 years (IQR, 11.0).[20] However, the data source used insurance data, including patients who were insured commercially through their employers, which could have led to an underrepresentation of older patients who have retired. In comparison, the data set used in our study is derived from electronic health records and not limited by insurance coverage. The high median age may also be a result of a majority of patients having HRp/HR unknown status, as we know patients with *BRCA* mutations are more likely to be diagnosed at a younger age.[21]

## Strengths and Weaknesses

These results should be considered within the context of study strengths and limitations. The database contained robust clinical and demographic data, allowing a detailed description of the patient population. Furthermore, the database includes a sample of patients from all geographic regions of the US. Finally, patients included here had a high median age of 67 years, demonstrating this treatment combination is effective in an older patient population. Limitations should also be considered, including a relatively small sample size. This may be reflective of the limited real-world use of combination niraparib plus bevacizumab first-line maintenance therapy when this study was conducted. Furthermore, these

results were derived from an electronic health record-derived database of patients who were mostly White and primarily received their care in a community-based setting, and as such, may not fully represent the overall epithelial ovarian cancer population. All analyses were limited to available data, which did not include some variables of interest. Though at least some biomarker data (HRD and/or *BRCA* status) were available for 94.9% of patients, given the strong association with biomarker status and outcomes for patients with ovarian cancer, it would have been useful to have more complete biomarker data. However, this may be reflective of real-world community-based practice, where HRD testing may not be as frequent (in this study, only 13 patients (22.0%) had available HRD status vs 56 (94.9%) with available *BRCA* status). Data on dose holds or reasons for bevacizumab discontinuation were also not available. Time to treatment discontinuation was measured by administration date for bevacizumab, but for niraparib was measured by the abstracted start and end date for the oral drug. This difference was due to bevacizumab being administered intravenously (in a healthcare setting) and niraparib being taken orally (including at-home administration). This makes it difficult for a clinician to capture the exact dates niraparib was received, and may have led to the numerical differences in time to treatment discontinuation for each medication. However, in practice, continuation maintenance therapy with bevacizumab may be captured as patients starting bevacizumab prior to niraparib. Data here support this, as 55.9% of patients started the bevacizumab component first, whereas 11.9% started both agents simultaneously, and 32.2% started niraparib first. When assessing median time to treatment discontinuation, data also show patients had a longer duration on bevacizumab than niraparib. Finally, patients may have sought care outside of the network from which these data were collected, which may have contributed to missing or incomplete data or loss to follow-up. Despite these limitations, these data provide useful real-world outcomes for patients with epithelial ovarian cancer who received first-line maintenance niraparib plus bevacizumab.

### Implications for Practice and Future Research

To our knowledge, this is the first-real world study reporting on first-line maintenance niraparib plus bevacizumab use for patients from a nationwide US database, and these data provide useful real-world outcomes for these patients. Given the results reported here, the treatment combination of niraparib plus bevacizumab may be a viable treatment option for patients with epithelial ovarian cancer in the first-line maintenance setting. Future studies should continue to investigate this treatment combination to confirm these results. Given the limited safety data available, future studies should also investigate real-world clinical events of interest in this patient population in more detail.

## CONCLUSION

In summary, these results offer real-world insight into the use of niraparib plus bevacizumab as first-line maintenance therapy in patients with epithelial ovarian cancer, most of whom had HRp/HR status unknown. The median time to next treatment, a proxy for real-world progression-free survival, was 14.1 months and generally aligned with the progression-free survival estimated in a clinical trial examining the same first-line maintenance treatment combination of niraparib plus bevacizumab, suggesting this combination may be a viable treatment option for patients with epithelial ovarian cancer.

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## REFERENCES

1 Center for Disease Control and Prevention. Ovarian cancer statistics. Available: https://www.cdc.gov/cancer/ovarian/statistics/ [Accessed 9 Sep 2023].

2 American Cancer Society. Key statistics for ovarian cancer. 2024. Available: https://www.cancer.org/cancer/types/ovarian-cancer/about/key-statistics.html
3 National Cancer Institute. Cancer stat facts: ovarian cancer. 2023. Available: https://seer.cancer.gov/statfacts/html/ovary.html
4 DiSilvestro P, Alvarez Secord A. Maintenance treatment of recurrent ovarian cancer: Is it ready for prime time? *Cancer Treat Rev* 2018;69:52–65.
5 Ray-Coquard I, Mirza MR, Pignata S, *et al*. Therapeutic options following second-line platinum-based chemotherapy in patients with recurrent ovarian cancer: Comparison of active surveillance and maintenance treatment. *Cancer Treat Rev* 2020;90:102107.
6 Burger RA, Brady MF, Bookman MA, *et al*. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med* 2011;365:2473–83.
7 González-Martín A, Pothuri B, Vergote I, *et al*. Niraparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med* 2019;381:2391–402.
8 Zejula. Prescribing information. 2023. Available: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208447s015s017lbledt.pdf
9 Hardesty MM, Krivak TC, Wright GS, *et al*. OVARIO phase II trial of combination niraparib plus bevacizumab maintenance therapy in advanced ovarian cancer following first-line platinum-based chemotherapy with bevacizumab. *Gynecol Oncol* 2022;166:219–29.
10 Birnbaum B, Nussbaum N, Seidl-Rathkopf K, *et al*. Model-assisted cohort selection with bias analysis for generating large-scale cohorts from the EHR for oncology research. *arXiv* Preprint posted online January 13, 2020.
11 Ma X, Lura L, Moon S, *et al*. Comparison of population characteristics in real-world clinical oncology databases in the US: Flatiron Health, SEER, and NPCR. *medRxiv* Preprint posted online June 7, 2023.
12 Walker B, Boyd M, Aguilar K, *et al*. Comparisons of real-world time-to-event end points in oncology research. *JCO Clin Cancer Inform* 2021;5:45–6.
13 Blumenthal GM, Gong Y, Kehl K, *et al*. Analysis of time-to-treatment discontinuation of targeted therapy, immunotherapy, and chemotherapy in clinical trials of patients with non-small-cell lung cancer. *Ann Oncol* 2019;30:830–8.
14 Parrinello CM, Seidl-Rathkopf KN, Bourla AB, *et al*. Comparison of structured versus abstracted comorbidities using oncology EHR data from cancer patients in the Flatiron Health Network. *Value Health* 2018;21:S14.
15 Heitz F, Marth C, Henry S, *et al*. AGO-OVAR 28/ENGOT-ov57. Niraparib alone versus niraparib in combination with bevacizumab in patients with carboplatin-taxane-based chemotherapy in advanced ovarian cancer: a multicenter randomized phase III trial. *Int J Gynecol Cancer* 2023;33:1966–9.
16 Ray-Coquard I, Pautier P, Pignata S, *et al*. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. *N Engl J Med* 2019;381:2416–28.
17 Ray-Coquard I, Leary A, Pignata S, *et al*. Olaparib plus bevacizumab first-line maintenance in ovarian cancer: final overall survival results from the PAOLA-1/ENGOT-ov25 trial. *Ann Oncol* 2023;34:681–92.
18 Lorusso D, Mouret-Reynier M-A, Harter P, *et al*. Updated progression-free survival and final overall survival with maintenance olaparib plus bevacizumab according to clinical risk in patients with newly diagnosed advanced ovarian cancer in the phase III PAOLA-1/ENGOT-ov25 trial. *Int J Gynecol Cancer* 2024;34:550–8.
19 Rimel BJ, Boyle TAC, Perhanidis J, *et al*. Real-world (RW) use of niraparib (Nir) monotherapy (mono) as first-line (1L) switch maintenance (1LSM) therapy following chemotherapy (CT) plus bevacizumab (bev) induction treatment in patients (pts) with epithelial ovarian cancer (EOC) in the SW1TCH study. *JCO Oncol Pract* 2023;19:536.
20 Arend RC, O'Malley DM, Banerjee S, *et al*. Utilization of poly(ADP-ribose) polymerase inhibitors in ovarian cancer: a retrospective cohort study of US healthcare claims data. *Adv Ther* 2022;39:328–45.
21 Moschetta M, George A, Kaye SB, *et al*. BRCA somatic mutations and epigenetic BRCA modifications in serous ovarian cancer. *Ann Oncol* 2016;27:1449–55.

**Supplementary Appendix**

Supplementary material has been provided by the authors to provide more detailed methods.

**Supplement to:** Characteristics and real-world outcomes of patients with epithelial ovarian cancer who received niraparib plus bevacizumab first-line maintenance therapy in the COMB1NE study

**Supplemental Methods**

**Key Variables**

Patient demographics and clinical characteristics were assessed. Specifically, age, race, ethnicity, geographic region, practice type, year of initial ovarian cancer diagnosis, year of end of first-line therapy, duration of first-line therapy, prior primary or interval cytoreductive surgery, first-line treatment regimen, second-line treatment regimen, residual disease status, body height and weight, platelet count, hypertension diagnosis (defined as yes/no, via International Classification of Diseases [ICD] 9 and 10 codes), systolic and diastolic blood pressure, Eastern Cooperative Oncology Group performance status (ECOG PS) score, histology at ovarian cancer diagnosis, stage at initial diagnosis, and BRCA and homologous recombination (HR) deficiency (HRD) biomarker status were assessed. Dosing characteristics for first-line maintenance niraparib monotherapy were also collected. The individualized starting dose was determined based on the patient's weight and platelet count. Patients weighing <77 kg or with a platelet count of <150,000/μL were indicated for a 200-mg starting dose. Patients weighing ≥77 kg and with a platelet count ≥150,000/μL were indicated for a 300-mg starting dose. If patient weight and/or platelet count data were missing, the individualized starting dose was recorded as unknown. Starting dose status was a categorical variable defined as individualized starting dose (a patient started at the dose indicated by individualized starting dose calculation), received a dose lower than individualized starting dose (e.g., indicated for 300 mg but had a starting dose of 200 mg or 100 mg), or received a dose higher than individualized starting dose (e.g., indicated for 200 mg but had a starting dose of 300 mg); patients with missing data for any of these variables had a starting dose status classified as "other or unknown."



Thaker PH, *et al. Int J Gynecol Cancer* 2024;0:1–8. doi: 10.1136/ijgc-2024-005611