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Real-World Outcomes Following First-Line Treatment in Patients with Advanced Ovarian Cancer with Multiple Risk Factors for Disease Progression who Received Maintenance Therapy or Active Surveillance

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ABSTRACT

Introduction: We evaluated real-world outcomes in patients with advanced ovarian cancer (AOC) based on their cumulative risk profile and maintenance therapy (MT) status following first-line (1L) treatment.

Methods: This retrospective observational study of a nationwide electronic health record-derived de-identified database included adult

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patients diagnosed with stage III/IV OC from January 1, 2011 to February 28, 2021, who received 1L therapy and had ≥ 12 weeks of follow-up after the index date (end of 1L therapy). Patients were grouped according to whether they received MT or active surveillance (AS) following 1L treatment and by the cumulative number of risk factors (RF) present (stage IV disease; no surgery/treated with neoadjuvant therapy and interval debulking surgery; had postoperative visible residual disease; and had *BRCA* wild-type disease/unknown *BRCA* status). Time to next treatment (TTNT) and overall survival (OS) were assessed with a cloning and inverse probability of censoring (IPC)-weighted Kaplan–Meier method.

Results: Among 1920 patients, 22.2% received MT and 77.8% received AS. Median IPC-weighted TTNT and OS were 13.3 months (95% CI 11.7–15.8) and 39.1 months (95% CI 32.5–48.6) in the MT cohort, respectively, and 8.6 months (95% CI 8.0–9.5) and 38.4 months (95% CI 36.4–41.0) in the AS cohort, respectively. Almost all patients had ≥ 1 RF (MT 95.3%; AS 96.7%). Median IPC-weighted TTNT was shorter among patients with more RF in both cohorts (MT: 1 RF, 19.3 months, 95% CI 13.5–37.8; 2 RF, 17.2 months, 95% CI 12.8–20.2; 3 RF, 11.0 months, 95% CI 8.2–13.8; 4 RF, 7.0 months, 95% CI 6.2–8.8; AS: 1 RF, 17.7 months, 95% CI 13.5–22.3; 2 RF, 10.2 months, 95% CI 9.1–11.5; 3 RF, 6.5 months, 95% CI 5.8–7.4; 4 RF, 4.1 months, 95% CI 3.5–4.5).

Conclusion: Regardless of RF number, MT was associated with longer TTNT in real-world patients with AOC.

Keywords: Electronic health records; Maintenance therapy; Ovarian cancer; Risk factors

Key Summary Points

Why carry out this study?

Patients with advanced ovarian cancer are at a high risk for disease progression or death and are typically managed with either maintenance therapy or active surveillance following first-line treatment.

Understanding real-world clinical outcomes in patients with advanced ovarian cancer by maintenance therapy status and by the number of high-risk factors for disease progression or death can help inform treatment decisions.

What was learned from the study?

Most patients had at least one high-risk factor for disease progression or death, and the distribution of patients by the total number of high-risk factors present was similar in patients who received maintenance therapy and those treated with active surveillance.

Maintenance therapy was associated with improved outcomes regardless of the number of high-risk factors present.

cancer cases are epithelial in origin, 70% of which present as high-grade serous tumors [3]. Moreover, approximately 70% of women with advanced stage ovarian cancer at diagnosis experience recurrence, and each successive line of treatment raises the likelihood of incurable ovarian cancer due to platinum-based chemotherapy resistance [4–7]. Patients with advanced disease at diagnosis are most commonly treated with a combination of surgery plus platinum-based chemotherapy with or without anti-angiogenic therapy [8–10]. To prolong progression-free survival (PFS) following first-line therapy, maintenance therapy with poly(ADP-ribose) polymerase (PARP) inhibitors is now an option for patients with primary advanced epithelial ovarian cancer following a complete or partial response to platinum-based chemotherapy [11–13].

Although the PFS benefit of first-line maintenance therapy has been well-established in clinical trials [12], further evidence is needed to fully characterize the outcomes associated with first-line maintenance therapy in clinical practice. In addition, it remains unknown how a patient's risk profile affects the efficacy of maintenance therapy. A greater understanding of maintenance therapy and whether patients with multiple high-risk factors experience different outcomes in a real-world setting could help inform clinical decision-making. In this retrospective real-world study, we describe the clinical characteristics and outcomes (i.e., disease progression and mortality) of patients with ovarian cancer, based on their risk category, who received first-line maintenance therapy or were under active surveillance following the completion of first-line treatment.

INTRODUCTION

Despite the slowly declining incidence over the past 20 years [1], ovarian cancer continues to be the leading cause of gynecological cancer death among women worldwide [2], with approximately 20,000 new diagnoses and more than 13,000 deaths attributed to the disease each year in the USA alone [1]. Up to 90% of ovarian

METHODS

Data Source

The Flatiron Health database is a longitudinal electronic health record (EHR)-derived database comprised of de-identified patient-level data from approximately 280 cancer clinics (ca. 800 sites of care) across the USA [14, 15]. The database includes both structured (e.g., laboratory

values, prescribed drugs) and unstructured patient-level data curated via technology-enabled chart abstraction from physicians' notes and other unstructured documents. The study was conducted using the Flatiron Health ovarian cancer database, which included women with a diagnosis of ovarian, fallopian tube, or peritoneal cancer (collectively referred to as ovarian cancer) as defined by International Classification of Diseases (ICD) codes 183x and 158x (ICD 9) and C56x, C57.0x, C48x (ICD-10) and at least two documented clinical visits between January 1, 2011 and February 28, 2021, hereafter referred to as the study period. Although this study used the Flatiron Health database, Flatiron Health was not involved in the study, its design, analysis, or interpretation, or in the drafting of this manuscript.

Study Design, Patient Population, and Cohort Assignment

This retrospective observational cohort study included patients aged 18 years or older diagnosed with stage III or IV ovarian cancer during the study period, who received first-line therapy. The index date was defined as the end date of non-maintenance first-line treatment. Lines of therapy were oncologist-defined and rules-based according to the Flatiron Health database. Patients were required to have at least 12 weeks of follow-up after the index date to enable evaluation of the type of management used after first-line treatment (i.e., maintenance or active surveillance). Patients with incomplete or missing data regarding surgery type [i.e., primary debulking surgery (PDS), interval debulking surgery (IDS), or no surgery] and postoperative residual disease status (i.e., non-visible residual disease or visible residual disease) were excluded because this information was needed to determine each patient's risk profile. Additionally, patients who had gaps in their medical history after diagnosis were excluded because later treatments may have been mistakenly listed as earlier lines of therapy resulting in treatment line misclassification. For example, patients who received PARP inhibitor monotherapy first-line maintenance therapy

may have been misclassified as receiving first-line non-maintenance PARP inhibitor treatment because of missing data. Bevacizumab, PARP inhibitors (olaparib, rucaparib, niraparib), paclitaxel, and gemcitabine were all eligible to be considered maintenance therapies if given in the maintenance setting. Combination therapy with paclitaxel plus gemcitabine, bevacizumab plus a PARP inhibitor, and bevacizumab plus paclitaxel and/or gemcitabine were also eligible to be considered maintenance therapies if given in the maintenance setting. Patients were placed into either the maintenance therapy cohort or active surveillance cohorts based on whether or not they had received maintenance treatment within 120 days of the end of first-line therapy (index date). Patients were considered eligible for first-line PARP inhibitor maintenance therapy if they had received first-line platinum-based treatment containing cisplatin, carboplatin, or oxaliplatin and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. All patients were followed from their index date to the first occurrence of last clinical activity, or the end of the study period.

Four high-risk factors that have been reported in previous studies to increase the risk for disease progression and mortality among patients with ovarian cancer were used to define risk categories [16–18]. Patients were grouped according to the cumulative number of risk factors present that would place patients at moderate or high risk for disease progression. High-risk factors were (1) stage IV disease at initial diagnosis, (2) did not undergo surgery, or were treated with neoadjuvant therapy and IDS, (3) had visible residual disease following surgery, and (4) had *BRCA* wild-type (*BRCAwt*) disease or unknown *BRCA* status (Fig. S1 in the supplementary material). Patients who did not undergo debulking surgery were assumed to have visible residual disease. Patients were considered at moderate risk for disease progression if they had none of the high-risk factors and instead had all of the following: stage III disease, nonvisible residual disease following initial surgery, received PDS, and had *BRCA* mutated (*BRCAm*) disease.

Study Outcomes

Outcomes of interest included time to next treatment (TTNT) and overall survival (OS) assessed by treatment cohort (maintenance therapy or active surveillance) and by cumulative risk category. TTNT was used as a surrogate for PFS and defined as the time from the index date to the earliest occurrence of second-line therapy initiation or death; patients without an event indicating disease progression (i.e., initiation of second-line therapy or death) were censored at last activity. OS was defined as the time from index date to the date of death. Patients who did not have an event (i.e., death) were censored at the last activity or at the end of the study period. Patient demographic and clinical characteristics were defined on the basis of information from the time of diagnosis to the index date. The following index variables were described: age, weight, race, ethnicity, practice type, patient's region of residence, ECOG performance status, disease stage at diagnosis, tumor location, histology at diagnosis, *BRCA* mutation status, homologous recombination deficiency (HRD) status, therapy type (i.e., PDS with adjuvant therapy, IDS with neoadjuvant therapy, or no surgery), residual disease status following initial surgical treatment, hemoglobin level, neutrophil level, and platelet level. Full details on how variables were captured and/or derived from the database can be found in the supplemental methods.

Statistical Methods

Because treatments are not assigned at random in real-world clinical practice, rigorous methods were defined a priori and used to minimize biases and maximize the comparability of baseline characteristics across the two cohorts. To address any potential immortal time bias introduced by assessing treatments that occurred after the index date (i.e., maintenance therapy or active surveillance), a trial emulation cloning methodology was applied [19]. Additional details on the cloning methodology can be found in the supplemental methods. Potential selection bias associated with cohort assignment

was addressed using inverse probability of censoring (IPC) weighting (see supplemental methods for additional details). For each outcome of interest (TTNT, OS), survival curves for each cohort and risk group were estimated using an IPC-weighted non-parametric Kaplan–Meier estimator. For index characteristics, medians and interquartile ranges were reported for continuous variables and frequencies and percentages were reported for categorical variables prior to cloning the patient population.

Lastly, we conducted a series of sensitivity analyses. To assess the completeness of data, we required patients to have at least one confirmed clinical activity between 30 and 90 days post-index date. We also applied a grace period of 90 days to assign patients to first-line maintenance therapy or active surveillance groups and restricted the analysis to patients whose index date was on or after January 1, 2017, to align with PARP inhibitor commercial availability. All analyses were performed using SAS[®] 9.4 (SAS Institute Inc., Cary, NC).

Study Ethics

This study complied with all applicable laws regarding patient privacy. Institutional review board approval of the study protocol was obtained before study conduct and included a waiver of informed consent.

RESULTS

Participants

In total, 1920 patients with advanced ovarian cancer diagnosed between January 1, 2011 and February 28, 2021 and who met all eligibility criteria were included in the analysis (Fig. 1). Of these, 426 patients (22.2%) received maintenance therapy within 120 days of completing first-line treatment and were placed into the maintenance therapy cohort; 1494 patients (77.8%) did not receive maintenance therapy and were placed in the active surveillance cohort. Among the patients who received first-line maintenance therapy, 43.7% received

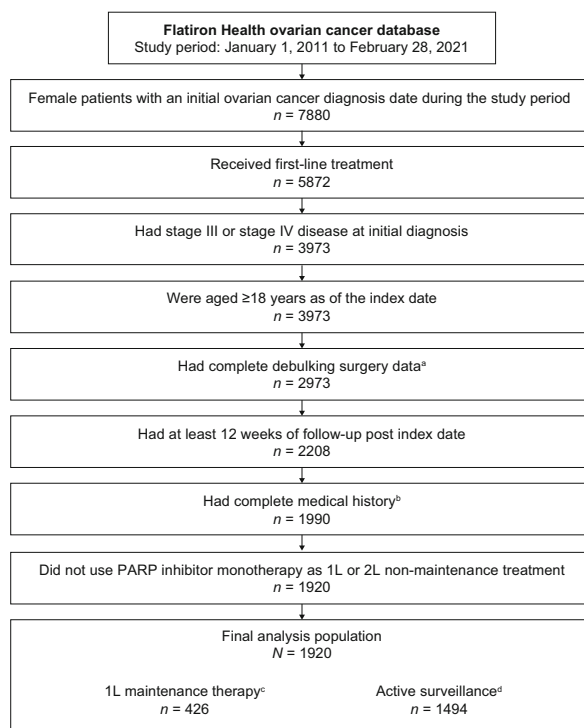


Fig. 1 Patient attrition chart for the selection of patients with advanced ovarian cancer who received first-line platinum-based chemotherapy prior to cloning and IPC weighting. ^aPatients who underwent debulking surgery and were missing either the surgical date or postoperative residual disease status were excluded. ^bPatients with incomplete medical history within 90 days of diagnosis or debulking surgery (no visit or non-cancelled medication order within 90 days of diagnosis or debulking surgery) were excluded. ^cPatients who received maintenance treatment within 120 days of the end of first-line therapy (index date). ^dPatients who did not receive maintenance treatment within 120 days of the end of first-line therapy (index date). 1L, first-line; 2L, second-line; IPC, inverse probability of censoring; PARP, poly(ADP-ribose) polymerase

bevacizumab-containing regimens, 35.0% received a PARP inhibitor, 5.4% received bevacizumab plus PARP inhibitor combination therapy, and 16.0% of patients received other agents. Focusing on PARP inhibitors, 13.1% (56/426) in the maintenance therapy cohort received niraparib monotherapy, 18.1% (77/426) received olaparib monotherapy, and 1.6% (7/426) received rucaparib monotherapy.

Overall, the majority of patients originated from a community practice (1685/1920, 87.8%). Demographic characteristics at index were generally similar across the maintenance therapy and active surveillance cohorts prior to cloning and IPC weighting (Table 1). However, the proportion of patients who had stage IV disease at diagnosis (40.4% and 31.7%), *BRCAM* disease (19.5% and 11.2%), ECOG performance status 0–1 (76.1% and 66.4%), and originated from a community practice (93.2% and 86.2%) was larger in the maintenance therapy cohort than in the active surveillance cohort.

In terms of timing, 70.7% of maintenance therapy patients (301/426) and 41.6% of active surveillance patients (622/1494) had an index date on or after January 1, 2017. Within the maintenance therapy cohort, 59.1% of patients (110/186) who received bevacizumab-containing regimens, 100% of patients who received PARP inhibitor monotherapy or bevacizumab plus PARP inhibitor combination therapy ($n = 172$), and 27.9% of patients (19/68) who received other agents had an index date on or after January 1, 2017. In terms of risk classification, almost all patients in the maintenance and active surveillance cohorts had at least one high-risk factor (95.3% and 96.7%, respectively). The distribution of patients by cumulative number of high-risk factors was similar across cohorts, with the highest proportion of patients having two high-risk factors (maintenance therapy, 32.4%; active surveillance, 34.2%; Fig. 2). The post-IPC-weighted key baseline characteristics were generally similar between the maintenance treatment and active surveillance cohorts (see supplemental methods and Figs. S2 and S3 for standardized mean differences).

TTNT and OS

By the end of follow-up, 59.6% (254/426) and 82.3% (1230/1494) of patients in the maintenance therapy and active surveillance cohorts, respectively, progressed to second-line therapy or died. The IPC-weighted median TTNT for patients in the maintenance therapy cohort was 13.3 months (95% CI 11.7–15.8) and

Table 1 Demographic and clinical characteristics at index by first-line maintenance therapy status prior to cloning ($N = 1920$)

Characteristic	Maintenance therapy ($n = 426$)	Active surveillance ($n = 1494$)
Median age (IQR), years	66.0 (58.0–74.0)	67.0 (58.0–75.0)
Age group, n (%)		
18–64 years	183 (43.0)	616 (41.2)
65–79 years	204 (47.9)	763 (51.1)
≥ 80 years	39 (9.2)	115 (7.7)
Weight, n (%)		
< 77 kg	311 (73.0)	1018 (68.1)
≥ 77 kg	114 (26.8)	451 (30.2)
Unknown	1 (0.2)	25 (1.7)
Race, n (%) ^a		
White	304 (71.4)	1094 (73.2)
Black	25 (5.9)	90 (6.0)
Asian	9 (2.1)	33 (2.2)
Other	61 (14.3)	177 (11.8)
Unknown	27 (6.3)	100 (6.7)
Ethnicity, n (%)		
Hispanic or Latino	39 (9.2)	82 (5.5)
Practice type, n (%)		
Academic	29 (6.8)	206 (13.8)
Community	397 (93.2)	1288 (86.2)
Region, n (%) ^b		
Northeast	54 (12.7)	170 (11.4)
Midwest	46 (10.8)	184 (12.3)
South	199 (46.7)	630 (42.2)
West	87 (20.4)	249 (16.7)
Unknown	40 (9.4)	261 (17.5)
ECOG performance status, n (%)		
0–1	324 (76.1)	992 (66.4)
2–4	36 (8.5)	146 (9.8)
Unknown	66 (15.5)	356 (23.8)
Disease stage at diagnosis, n (%)		
III	254 (59.6)	1021 (68.3)
IV	172 (40.4)	473 (31.7)

Table 1 continued

Characteristic	Maintenance therapy (<i>n</i> = 426)	Active surveillance (<i>n</i> = 1494)
Tumor location, <i>n</i> (%) ^c		
Ovary	356 (83.6)	1269 (84.9)
Fallopian tube	23 (5.4)	110 (7.4)
Primary peritoneal	46 (10.8)	178 (11.9)
Unknown	24 (5.6%)	52 (3.5)
Histology at diagnosis, <i>n</i> (%)		
Borderline, clear cell, endometrioid, mucinous, or transitional cell	19 (4.5)	95 (6.4)
Serous	341 (80.0)	1145 (76.6)
Epithelial NOS or unknown	66 (15.5)	254 (17.0)
<i>BRCA</i> status, <i>n</i> (%)		
<i>BRCA</i> mutated	83 (19.5)	167 (11.2)
<i>BRCA</i> wild-type	281 (66.0)	943 (63.1)
Unknown	62 (14.6)	384 (25.7)
HRD status, <i>n</i> (%)		
HRd	30 (7.0)	39 (2.6)
HRp	24 (5.6)	51 (3.4)
Unknown	372 (87.3)	1404 (94.0)
Therapy modality, <i>n</i> (%)		
PDS/adjuvant	186 (43.7)	781 (52.3)
IDS/neoadjuvant	163 (38.3)	483 (32.3)
No surgery	77 (18.1)	230 (15.4)
Residual disease, <i>n</i> (%) ^d		
NVRD	176 (41.3)	664 (44.4)
VRD	250 (58.7)	830 (55.6)
Hemoglobin, <i>n</i> (%)		
< 10 g/dL	136 (31.9)	492 (32.9)
≥ 10 g/dL	257 (60.3)	906 (60.6)
Unknown	33 (7.7)	96 (6.4)
Neutrophil level, <i>n</i> (%)		
< 1.5 × 10 ⁹ cells/L	43 (10.1)	175 (11.7)
≥ 1.5 × 10 ⁹ cells/L	259 (60.8)	883 (59.1)
Unknown	124 (29.1)	436 (29.2)

Table 1 continued

Characteristic	Maintenance therapy (<i>n</i> = 426)	Active surveillance (<i>n</i> = 1494)
Platelet level, <i>n</i> (%)		
< 150 × 10 ⁹ platelets/L	106 (24.9)	399 (26.7)
≥ 150 × 10 ⁹ platelets/L	254 (59.6)	889 (59.5)
Unknown	66 (15.5)	206 (13.8)
Type of 1L maintenance therapy, <i>n</i> (%)		
Bevacizumab-containing regimen	186 (43.7)	NA
Bevacizumab + PARP inhibitor combination	23 (5.4)	NA
PARP inhibitor	149 (35.0)	NA
Other	68 (16.0)	NA
Median follow-up (IQR), months	16.2 (9.1–26.8)	24.0 (11.8–41.1)

1L first line, ECOG Eastern Cooperative Oncology Group, HRD homologous recombination deficiency, HRd homologous recombination deficient, HRp homologous recombination proficient, ICD International Classification of Diseases, IDS interval debulking surgery, IQR interquartile range, NA not applicable, NOS not otherwise specified, NVRD no visible residual disease, PARP poly(ADP-ribose) polymerase, PDS primary debulking surgery, VRD visible residual disease

^aHispanic/Latino is grouped into other

^bAcademic centers have unknown state. US territories are grouped into unknown

^cAn individual patient may have more than one tumor type (via ICD diagnosis code)

^dResidual disease status represents whether or not a patient had gross visible residual disease following all surgical treatment for their initial diagnosis of ovarian cancer, as determined through electronic health record chart abstraction. Patients who did not undergo debulking surgery were assumed to have visible residual disease

8.6 months (95% CI 8.0–9.5) in patients in the active surveillance cohort (Fig. 3a). Overall, 32.9% (140/426) of the maintenance cohort and 53.9% (805/1494) of the active surveillance cohort died during the study period. The IPC-weighted median OS in patients in the maintenance therapy cohort was 39.1 months (95% CI 32.5–48.6) and 38.4 months (95% CI 36.4–41.0) in patients in the active surveillance cohort (Fig. 3b). Sensitivity analyses results were consistent with the main analysis results.

TTNT and OS by Cumulative Risk

To assess whether there was an association with having multiple high-risk factors, TTNT and OS were evaluated by the cumulative number of high-risk factors in each cohort. Patients with more risk factors had shorter IPC-weighted median TTNT in both the maintenance and

active surveillance cohorts (Fig. 4a, b). For patients with moderate risk (no high-risk factors), the IPC-weighted median TTNT was not reached (95% CI 12.7–not reached) in patients who received maintenance therapy and 26.4 months (95% CI 16.4–49.2) in patients who received active surveillance. In patients with one risk factor, the IPC-weighted median TTNT in the maintenance group was 19.3 months (95% CI 13.5–37.8) and 17.7 months (95% CI 13.5–22.3) in the active surveillance group. In patients with two and three high-risk factors, respectively, the IPC-weighted median TTNT was 17.2 months (95% CI 12.8–20.2) and 11.0 months (95% CI 8.2–13.8) in maintenance therapy patients and 10.2 months (95% CI 9.1–11.5) and 6.5 months (95% CI 5.8–7.4) in active surveillance patients. Patients with all four high-risk factors had the shortest IPC-weighted median TTNT in both

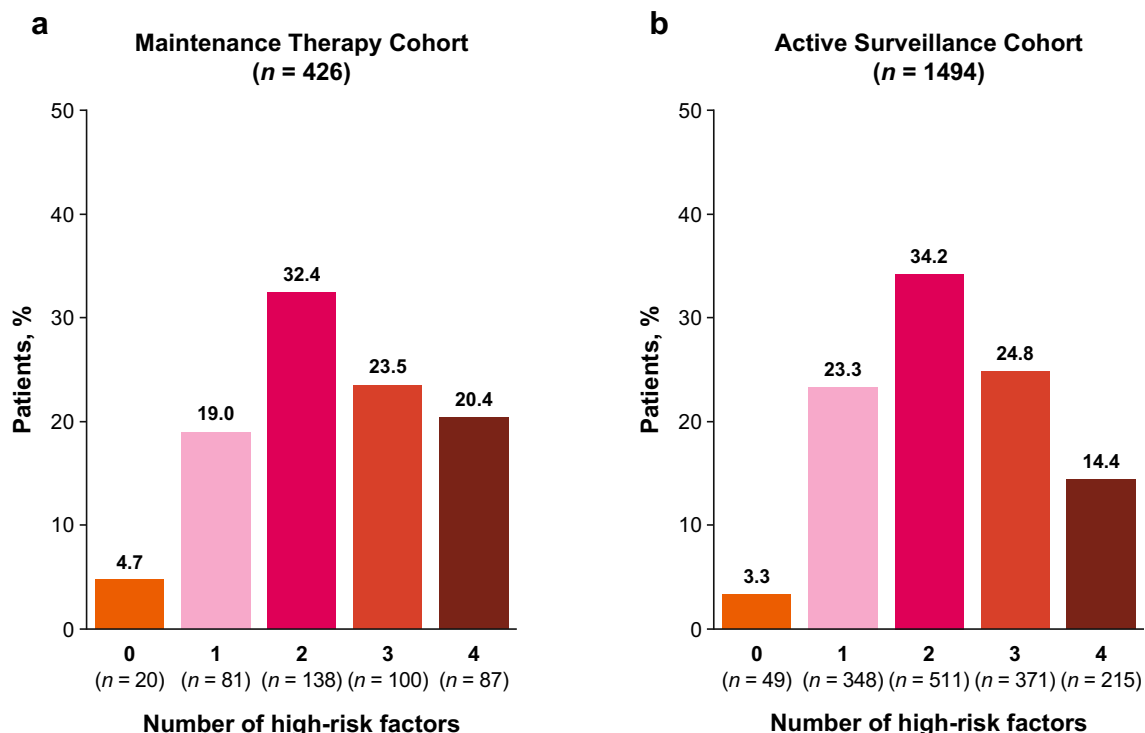


Fig. 2 Percentage of patients by cumulative number of high-risk factors prior to cloning. The percentage of patients by cumulative number of high-risk factors present

in the **a** maintenance therapy cohort and **b** active surveillance cohort. Patients who did not undergo debulking surgery were assumed to have visible residual disease

cohorts (maintenance therapy, 7.0 months, 95% CI 6.2–8.8; active surveillance, 4.1 months, 95% CI 3.5–4.5). In addition, patients with more risk factors had shorter IPC-weighted median OS in both cohorts (Fig. 4c, d).

Patients Eligible for First-Line PARP Inhibitor Maintenance Therapy

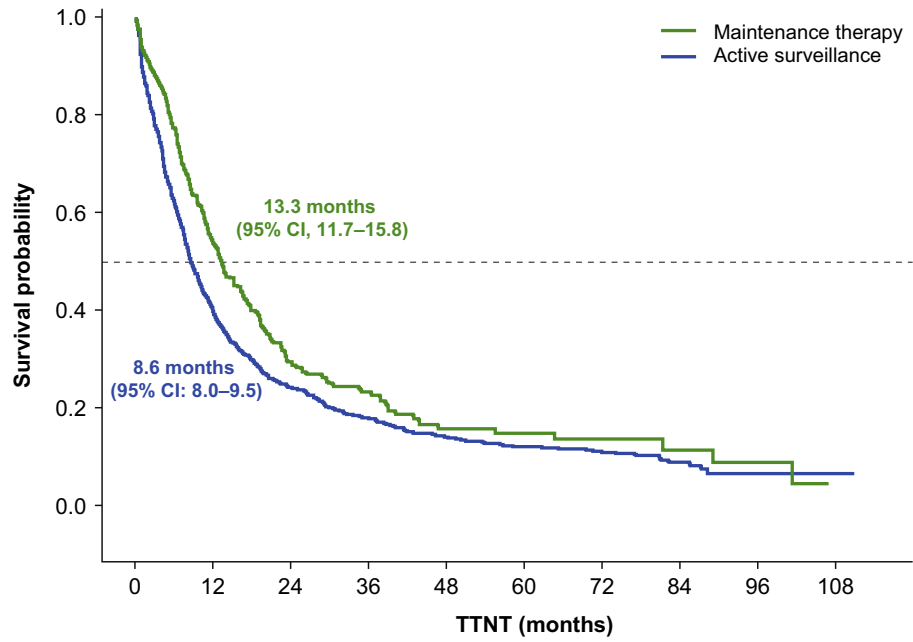
Because first-line PARP inhibitor maintenance therapy is recommended for patients with advanced ovarian cancer who had a complete or partial response to chemotherapy, outcomes were also evaluated in the 1251 patients who were considered eligible for first-line PARP inhibitor maintenance therapy. Within this subpopulation, 323 (25.8%) patients received first-line maintenance therapy and 928 (74.2%) of patients were treated with active surveillance prior to cloning and IPC weights. Demographic and clinical characteristics in this subpopulation were generally similar to the overall

population (Table S1 in the supplementary material). Similar to the overall population, the IPC-weighted median durations of TTNT and OS were longer in the maintenance therapy cohort than in the active surveillance cohort in patients who were considered eligible for first-line PARP inhibitor maintenance therapy (Table S2 in the supplementary material). The trends for shorter IPC-weighted median TTNT and OS among patients with more high-risk factors were also observed in PARP inhibitor eligible patients in both cohorts (Table S2).

DISCUSSION

In this retrospective analysis of real-world patients with stage III or IV ovarian cancer at diagnosis who received first-line therapy, almost all patients (ca. 96%) had at least one high-risk factor for disease progression or death. The individual high-risk factors for disease

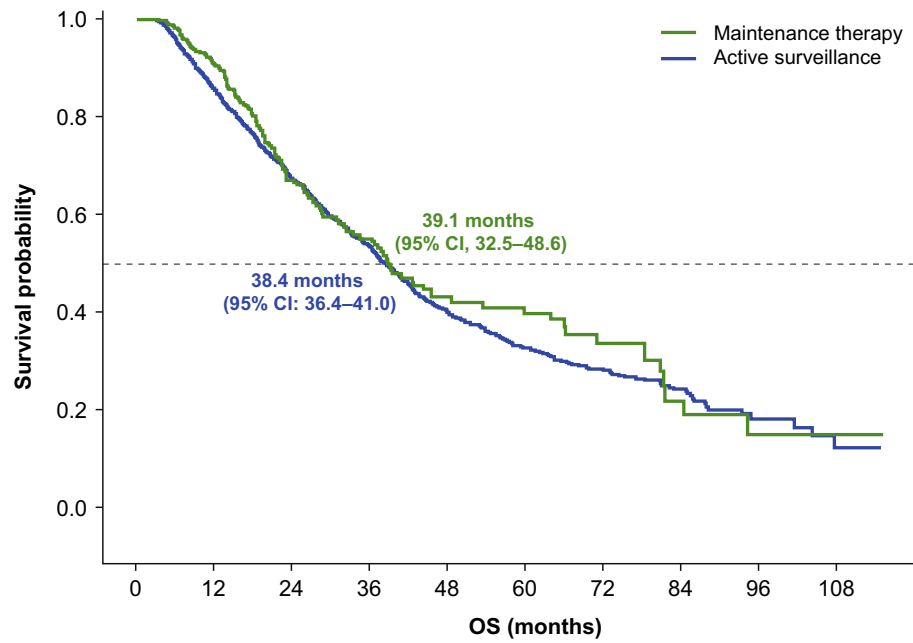
a



Patients at risk (weighted)

Maintenance therapy	3491	129	34	15	6
Active surveillance	2420	356	136	55	6

b



Patients at risk (weighted)

Maintenance therapy	4206	288	94	35	8
Active surveillance	2414	1025	388	141	25

Fig. 3 Kaplan–Meier survival curves for TTNT and OS based on IPC-weighted cloning ($N = 1920$). Kaplan–Meier estimated **a** TTNT and **b** OS using IPC-weighted cloning method. IPC, inverse probability of censoring; TTNT, time to next treatment; OS, overall survival

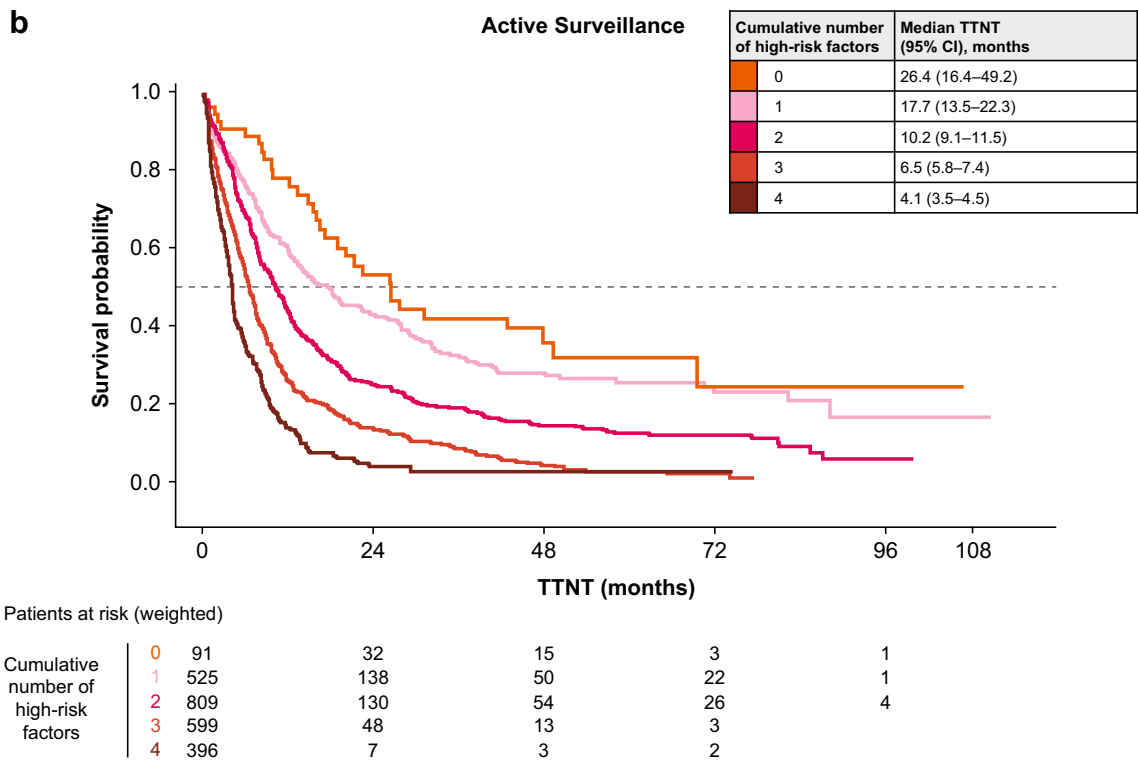
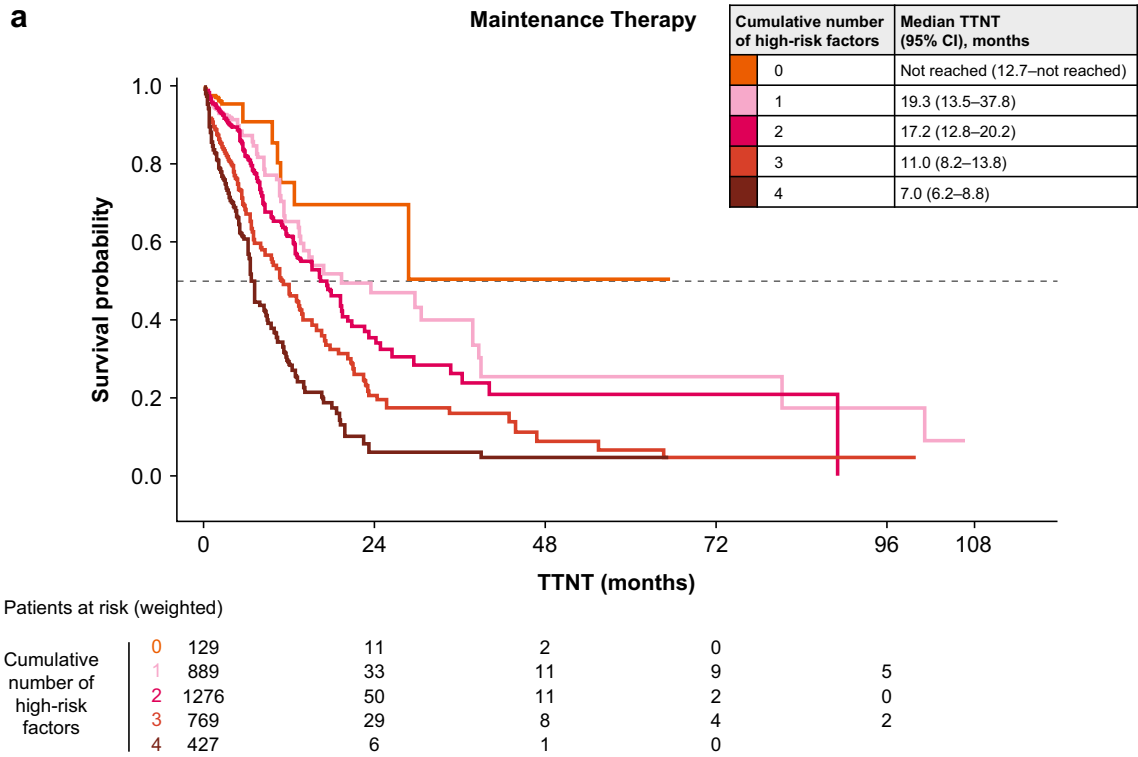
progression or death of stage IV disease at diagnosis, *BRCA*wt or unknown *BRCA* status, IDS, and visible residual disease, are well known, and have been studied using both clinical trial and real-world data [2, 16–18, 20, 21]. Patients with advanced ovarian cancer are generally considered at high risk for disease progression or death, with a 5-year survival rate of patients with distant disease at diagnosis of approximately 30% [2]. Interestingly, the percentage of patients with high-risk factors was similar across the maintenance therapy and active surveillance cohorts. Because most patients (77.8%) in this study did not receive maintenance therapy, this suggests that in clinical practice a high percentage of patients who were at risk for recurrence did not receive maintenance therapy.

Additionally, the study results also showed that patients who received maintenance therapy had both longer IPC-weighted median TTNT and OS than those who received active surveillance. This result is consistent with those of the PRIMA/ENGOT-OV26 [22], OVARIO [23], SOLO-1 [24], and PAOLA-1/ENGOT-OV25 [25] clinical trials that demonstrated the benefit of PARP inhibitor monotherapy or PARP inhibitor plus bevacizumab first-line maintenance therapy in patients with advanced ovarian cancer. The observed difference in outcomes between patients receiving maintenance therapy and active surveillance was more pronounced in the TTNT than OS results.

Furthermore, the study found that across both cohorts, TTNT and OS outcomes were shorter among patients with more high-risk factors (stage IV disease at initial diagnosis; no surgery or treated with neoadjuvant therapy and IDS; had visible residual disease following surgery; and *BRCA*wt disease or unknown *BRCA* status). Importantly, the IPC-weighted median TTNT in patients in the maintenance therapy

cohort was consistently longer than in patients in the active surveillance cohort regardless of the cumulative number of risk factors present. Even among patients with all four high-risk factors who had the shortest outcomes, the IPC-weighted median TTNT was longer among patients treated with maintenance therapy than in patients who received active surveillance. These data are generally consistent with findings from clinical trials showing that patients benefited from first-line maintenance therapy regardless of whether they were classified as being at a “low” or “high” risk for progression [26].

However, IPC-weighted median OS was similar between the maintenance and active surveillance cohorts. In part, this could have been because some of the patients in the active surveillance cohort may have gone on to receive maintenance therapy after subsequent lines of treatment. Additionally, the duration of follow-up for the study population was relatively short (median 16.2 months for the maintenance therapy cohort and 24.0 months for the active surveillance cohort) to evaluate OS. IPC-weighted median OS in both cohorts was shorter with multiple risk factors, with the shortest OS seen among patients with a total of four high-risk factors. Dissimilarities in the IPC-weighted median OS in the maintenance therapy and active surveillance cohorts were inconsistent across risk groups. In this study, most patients received active surveillance (ca. 80%) instead of maintenance therapy of any kind. This analysis included patients with ovarian cancer diagnosed between January 1, 2011 and February 28, 2021. During this time, the treatment landscape for first-line maintenance therapy evolved significantly, with the US Food and Drug Administration (FDA) approval of PARP inhibitors alone and in combination with bevacizumab [11]. The bulk of these treatment options were not widely available until the later portion of the study period, which could have contributed to the low percentage of patients who received maintenance therapy. In addition, approvals for different first-line maintenance therapies vary on the basis of *BRCA* and HRD status. Among patients who received first-line maintenance therapy, bevacizumab and



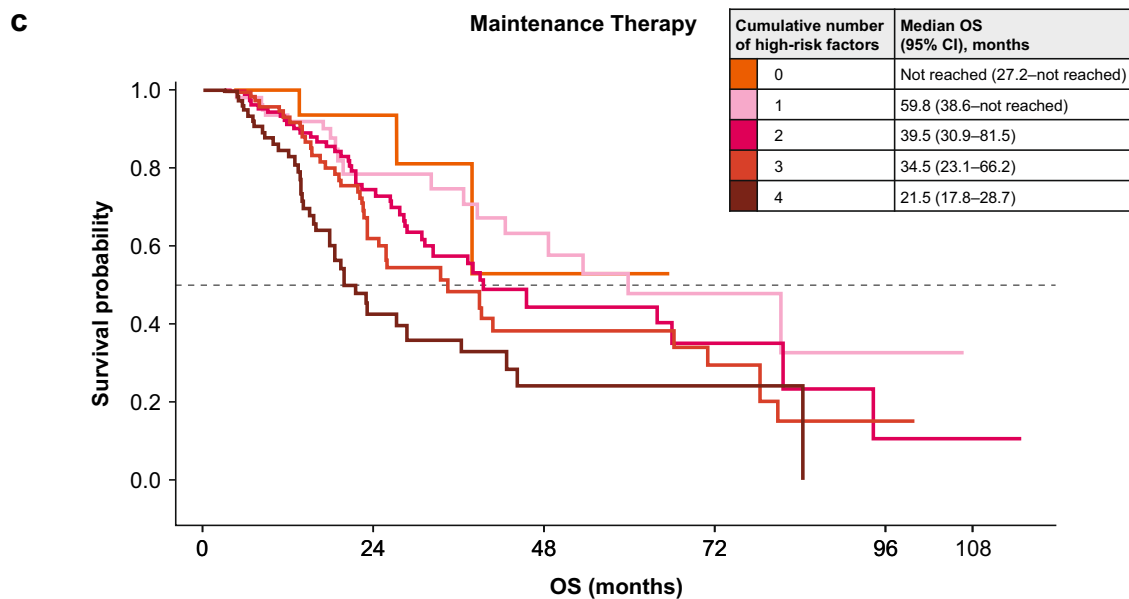
◀**Fig. 4** IPC-weighted Kaplan–Meier survival curves for TTNT and OS by risk category ($N = 1920$). Kaplan–Meier estimated TTNT and OS by cohort and cumulative number of high-risk factors using IPC-weighted cloning method. IPC-weighted TTNT in **a** patients who received maintenance therapy and **b** patients who were treated with active surveillance. IPC-weighted OS in **c** patients who received maintenance therapy and **d** patients who were treated with active surveillance. Patients who did not undergo debulking surgery were assumed to have visible residual disease. IPC, inverse probability of censoring; OS, overall survival; TTNT, time to next treatment

PARP inhibitors were most commonly used, with only a small percentage (ca. 5%) of patients receiving bevacizumab plus PARP inhibitor combination therapy. In a European survey-based study conducted between September 2013 and March 2016, less than half (ca. 45%) of patients with primary epithelial ovarian cancer were aware that maintenance therapy was an option; in these patients, most (ca. 70%) were made aware of the option by doctors [27]. In terms of patient preference, extended OS and PFS were strong motivating factors for choosing maintenance therapy [27, 28]. In a discrete choice experiment, patients with ovarian cancer expected a PFS and OS benefit with maintenance therapy to offset treatment-related side effects; of note, the magnitude of the expected PFS benefit increased in relation to the expected severity of the queried adverse event [28]. Analysis of two online community events for patients with ovarian cancer promoted to US audiences reported patient interest in side effects, expectations of benefit, information on the relationship between genetic mutations and PARP inhibitors, and a desire for more information regarding clinical trial results [29]. Although it is expected that the level of awareness about maintenance therapy has increased over time since the initial approvals, results from these previous studies and our findings suggest that additional work may be needed to increase patient awareness of maintenance therapy options and their potential benefits and risks.

This study provides new data showing how the risk of disease progression and mortality

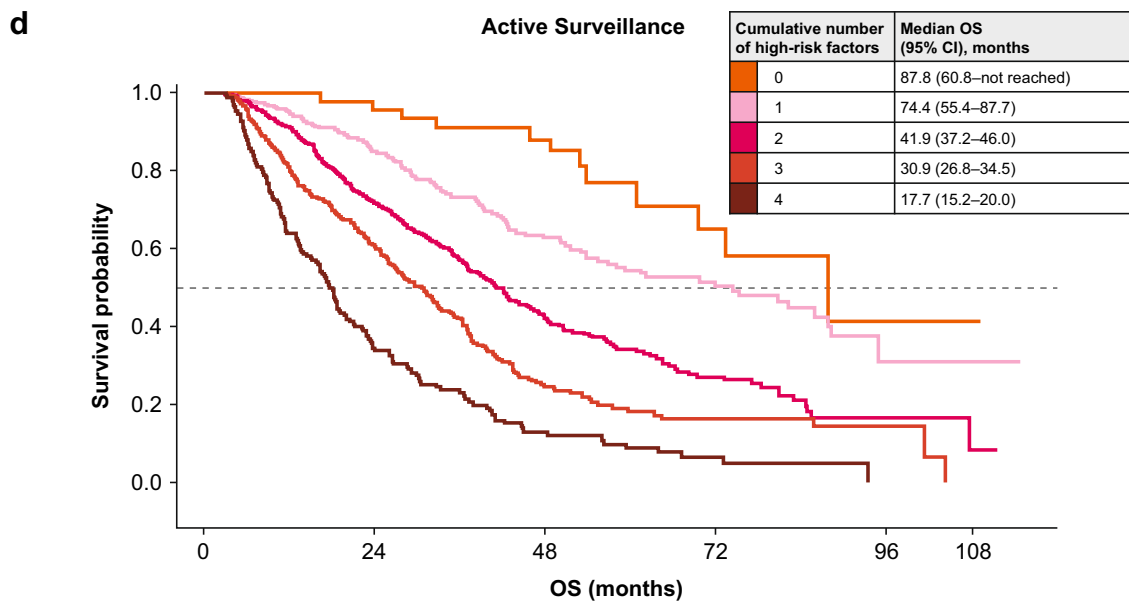
varies by the overall risk profile of patients, which should be considered when making treatment decisions. Previous studies have only evaluated the impact of individual risk factors on patient outcomes. To our knowledge, no other studies have assessed outcomes in patients with multiple risk factors by the type of disease management received after first-line treatment (i.e., maintenance therapy and active surveillance). Clinical trials are often conducted with highly selected patient populations with similar medical histories, thereby providing results that are limited in their generalizability to broader patient populations [30]. Data from EHRs are increasingly being used to augment results from clinical trials by providing valuable real-world information [30, 31]. This study used real-world data that aggregates medical information at the point of care, allowing for data capture from a much larger, more diverse patient population.

Some methodological limitations must be taken into consideration when interpreting the findings from this retrospective analysis. The Flatiron Health population may not be representative of the overall population of patients with ovarian cancer in the USA. In particular, because the database is focused primarily on patients cared for in US community-based practice, it may not be fully representative of patients treated in academic center practices. Therefore, the study results may not be generalizable to all ovarian cancer populations. In addition, as an EHR database, the Flatiron Health database is subject to data entry errors and missing data. Further, as the database does not uniformly capture health visits and treatments outside of the Flatiron Health Network, incomplete medical histories may have occurred, contributing to missing data for some of the study variables. There were several factors that may have also impacted the TTNT and OS estimates. Some patients may have initiated second-line treatment during the grace period, and accordingly would not have been eligible for maintenance therapy for the remainder of the grace period. However, this additional person-time contributed to both cohorts as both clones were not censored during the grace period.



Patients at risk (weighted)

Cumulative number of high-risk factors	0	24	48	72	96	108
0	134	17	2	0		
1	1000	57	28	9	5	
2	1473	117	35	11	2	
3	1005	67	21	13	2	
4	595	30	9	2	0	



Patients at risk (weighted)

Cumulative number of high-risk factors	0	24	48	72	96	108
0	91	56	38	13	4	
1	524	286	123	56	7	
2	803	377	145	46	10	
3	599	230	60	19	4	
4	397	76	23	5	0	

Fig. 4 continued

Within the USA, first-line PARP inhibitor maintenance therapy is indicated for use in patients with a complete or partial response to first-line platinum-based treatment [32, 33]. Because response to first-line treatment was not available in the database, it is likely that not all patients in the analysis were eligible for maintenance therapy. The cloning approach with IPC weighting ensured that the baseline characteristics between the two cohorts (i.e., maintenance therapy and active surveillance) were similar by accounting for differences in the factors that may have affected treatment assignment and resulted in informative censoring during the grace period. For risk factor assessment, patients who had no documented information on surgery were assumed to have visible residual disease, resulting in these patients having a minimum of two high-risk factors (IDS/no surgery and visible residual disease), which could have led to the misclassification of the risk profile for some patients. However, there was a similar proportion of patients who did not undergo surgery in both cohorts (18.1% maintenance, 15.4% active surveillance), likely resulting in minimal bias. Also, data were not adjusted for future therapies that could have affected the outcomes of interest, particularly OS. Finally, results stratified by cumulative risk factors should be interpreted with caution because of the small sample size prior to the cloned analysis, particularly in the moderate risk and PARP inhibitor maintenance therapy eligible group. In the future, risk level assignment in this patient population should be validated in the context of clinical studies. In addition, as the first-line maintenance therapy landscape has shifted in recent years, it will be important to evaluate maintenance therapy treatment patterns and outcomes over time as maintenance therapies have become more widely available.

CONCLUSIONS

The findings from this study contribute to real-world evidence on longer IPC-weighted clinical outcomes in patients with advanced ovarian cancer who received first-line maintenance

therapy than in patients monitored with active surveillance, especially among those grouped as high risk. In addition, the results provide important information about the clinical outcomes of patients with advanced ovarian cancer with multiple risk factors in the real world.

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Compliance with Ethics Guidelines. This study complied with all applicable laws regarding patient privacy. Institutional review board approval of the study protocol was obtained prior to study conduct and included a waiver of informed consent.

Data Availability. The data that support the findings of this study have been originated by Flatiron Health, Inc. These de-identified data may be made available upon request and are subject to a license agreement with Flatiron Health; interested researchers should contact <DataAccess@flatiron.com> to determine licensing terms.

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