11-1-2021

Risk factors for progression or death after first-line platinum-based chemotherapy in real-world patients in the USA with ovarian cancer from 2011 to 2018

Shannon N Westin

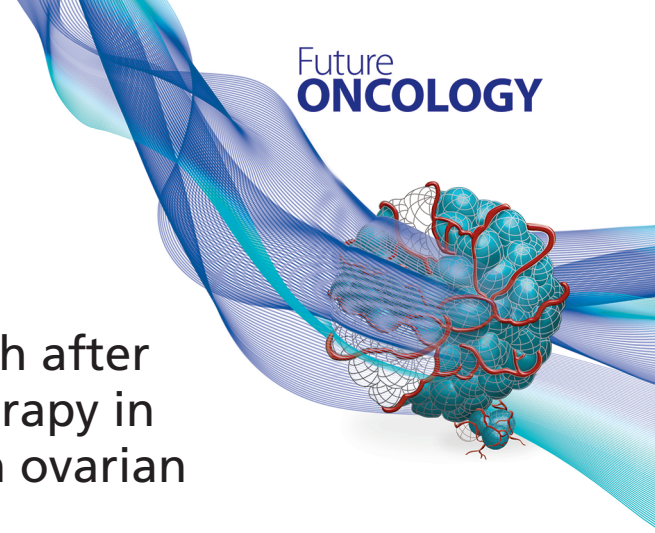
Melinda Louie-Gao

Divya Gupta

Premal H Thaker

Short Communication

For reprint orders, please contact: reprints@futuremedicine.com



Risk factors for progression or death after first-line platinum-based chemotherapy in real-world patients in the USA with ovarian cancer from 2011 to 2018

Shannon N Westin*[,1], Melinda Louie-Gao[2], Divya Gupta[3] & Premal H Thaker[4]

[1]Department of Gynecologic Oncology & Reproductive Medicine, University of Texas MD Anderson Cancer Center, Houston, TX 77230, USA

[2]Department of Statistics, GlaxoSmithKline, Waltham, MA 02451, USA

[3]Department of Clinical Development, GlaxoSmithKline, Waltham, MA 02451, USA

[4]Department of Obstetrics & Gynecology, Division of Gynecologic Oncology, Washington University School of Medicine, St Louis, MO 63110, USA

*Author for correspondence: Tel.: +1 713 794 4314; swestin@mdanderson.org

Aim: Patient chart data from the USA during the period of January 2011 through October 2018 were used to assess risk factors for progression in advanced ovarian cancer after response to first-line platinum-based chemotherapy. **Patients & methods:** Patients with stage III/IV ovarian cancer who completed first-line platinum-based chemotherapy after primary or interval debulking surgery were identified from the Flatiron Health database. Cox proportional hazards modeling was used to assess associations between baseline factors and time to next treatment (TTNT) or overall survival (OS). **Results:** Patients at stage IV or who received interval debulking surgery had shorter TTNT and OS than patients at stage III or who received primary debulking surgery, respectively. OS was worse in patients with residual disease and in *BRCA* wild-type. **Conclusion:** Multiple factors were associated with shorter TTNT or OS in this retrospective real-world analysis.

First draft submitted: 6 January 2021; Accepted for publication: 14 July 2021; Published online: 11 August 2021

Keywords: epithelial ovarian carcinoma • ovarian cancer • ovarian carcinoma • prognosis • risk factors

Ovarian cancer (OC) has the highest mortality of all gynecologic cancers in the USA, with an estimated 21,750 newly diagnosed cases and 13,940 deaths in 2020 [1]. Current standard of care for first-line treatment of OC is primary debulking surgery (PDS) followed by chemotherapy (platinum plus a taxane, with or without bevacizumab) or neoadjuvant chemotherapy (platinum plus a taxane, with or without bevacizumab) followed by interval debulking surgery (IDS) and further therapy. Poly(ADP-ribose) polymerase inhibitors (PARPi) have been approved for maintenance therapy in OC: niraparib is currently approved for all patients, olaparib is approved in patients with deleterious *BRCA* mutations, while combination therapy with bevacizumab and olaparib is approved in patients with homologous recombination deficient tumors.

Most patients respond to first-line treatment, but approximately 70% experience disease progression within 3 years [2]. Identifying prognostic factors that affect OC disease progression and survival is crucial to characterize OC populations at higher risk who may benefit from new treatment regimens. The American Joint Committee on Cancer (AJCC) recognizes International Federation of Gynecology and Obstetrics (FIGO) staging, histology and grade as prognostic factors for survival in patients with OC [3]. For patients with advanced disease, residual disease after primary cytoreduction is the most important prognostic factor for survival, with residual tumor size, number of residual sites and residual disease locations also recognized as prognostic factors [3,4]. Despite guidance regarding prognostic factors for survival, the AJCC does not assess prognostic factors for progression.

Data from electronic health records (EHR) are increasingly being used to augment results from clinical trials by providing valuable real-world information [5]. Clinical trials are often conducted with highly selected patient

populations with similar medical histories and are, therefore, limited in their generalizability to broader patient populations [6]. Real-world databases aggregate medical information at the point of care, allowing for data capture from a much larger, more diverse patient population. This is the first published study where we used the Flatiron Health database to identify prognostic factors associated with risk of disease progression or death in patients with advanced OC following response to first-line treatment.

Role of the funding source

The funder, GlaxoSmithKline, provided the data licensing and was involved in the study design, analysis, statistical support and funding for medical writing support. GlaxoSmithKline is the manufacturer of the PARPi niraparib.

The authors had access to relevant aggregated study data and other information required to understand and report research findings, such as study design, analytic plan and report, validated data tables and clinical study report. The authors take responsibility for the presentation and publication of the research findings, have been fully involved at all stages of publication and presentation development and are willing to take public responsibility for all aspects of the work. All individuals included as authors and contributors who made substantial intellectual contributions to the research, data analysis and publication or presentation development are listed appropriately. The role of the sponsor in the design, execution, analysis, reporting and funding is fully disclosed. The authors' personal interests, financial or nonfinancial, relating to this research and its publication have been disclosed.

Patients & methods

Data source

The Flatiron Health database is a longitudinal, demographically and geographically diverse database derived from EHR data in the USA [7]. It contains health information from more than 265 cancer clinics across approximately 800 sites of care, representing more than 2 million active US patients with cancer. The deidentified patient-level EHR data include structured data (e.g., laboratory values and prescribed drugs) in addition to unstructured data collected via technology-enabled chart abstraction from physician notes and other unstructured documents (e.g., biomarker reports). Rigorous quality control of structured and unstructured data is conducted to ensure that the data and information are a reliable and reasonable approximation of the truth (inclusive of the heterogeneous story of the real world). A real-time data mapping process is used to normalize structured data. For unstructured data, Flatiron developed a methodology of technology-enabled chart abstraction. The process enables efficient processing of large volumes of data, as well as centralized data quality and review, rapid reabstraction and incremental quality updates. Although this study utilizes the Flatiron Health database, Flatiron Health was not involved in the study, its design, analysis and interpretation or in the draft of this manuscript.

Study design & cohort definition

A retrospective observational study was designed to use real-world data to assess potential prognostic risk factors affecting outcomes in patients with OC who completed first-line platinum-based chemotherapy. The outcomes of interest were time to next treatment (TTNT), used as a surrogate for progression-free survival (PFS), and overall survival (OS). We identified all women in the Flatiron Health database who had a diagnosis of OC as defined by International Classification of Diseases (ICD) codes 183x, 158x (ICD-9) and C56x, C57.0x, C48x (ICD-10) and at least two documented clinical visits for ovarian, fallopian tube or peritoneal cancer between 1 January 2011 and 31 October 2018, a period which corresponded to contemporary data when the project began. Patients with stage III/IV OC who completed first-line platinum-based chemotherapy for five to ten cycles after PDS, two to ten cycles after IDS or four to ten cycles without surgery were included. In order to capture the natural history of OC progression on standard therapies prior to the introduction of PARPi to the market, patients who received any PARPi as first-line treatment or as maintenance therapy after first-line treatment were excluded. Only patients who started second-line treatment at least 2 months after completion of first-line treatment were selected and were considered to be in complete response or partial response to front-line platinum therapy. These criteria were designed to select patients who responded to first-line platinum therapy, regardless of whether the patient would ultimately be considered platinum sensitive or platinum resistant at the time of progression, and to exclude patients who were refractory to first-line platinum because patients with primary platinum-refractory disease are not reflective of the typical disease course for OC. Inclusion criteria for the Flatiron Health database OC cohort includes histology of one of the following: serous, mucinous, clear cell, transitional cell, endometrioid,

Table 1. Study attrition.

Attrition	Patients, n (%)
Ovarian cancer cohort (1 January 2011 to 31 October 2018)	5535 (100)
Patients had first-line treatment	4081 (74)
Patients had first-line platinum-based chemotherapy treatment	3499 (63)
Patients had stage III or IV disease	2314 (42)
Excluded patients with an unknown surgery date	2312 (42)
Platinum-based chemotherapy treatment criteria: a. Patients without surgery in the first line must have had ≥4 and ≤10 cycles of platinum-based therapy b. Patients treated with primary debulking surgery must have had ≥5 and ≤10 cycles of platinum-based therapy c. Patients must have had ≥2 and ≤10 postoperative cycles of platinum-based therapy after interval debulking surgery	1346 (24)
Patients naive to first-line PARP inhibitor treatment and PARP maintenance therapy after first-line treatment	1345 (24)
Patients who had active surveillance after first-line treatment	1217 (22)
Excluded patients who started second-line treatment within 2 months	1064 (19)
Sensitivity analysis	
Excluded patients who started second-line treatment within 3 months	1018 (18)

PARP: Poly(ADP-ribose) polymerase.

epithelial NOS, borderline or unknown/undocumented. The index date was defined as the last date of the first-line platinum-based chemotherapy treatment.

Analysis

The primary outcomes of interest were TTNT and OS. TTNT was used as a surrogate end point for PFS, which was defined as the time from the index date to the start date of second-line treatment or death or the date of a patient's last confirmed activity (last structured visit, laboratory test or medication administration), whichever occurred first. OS was defined as the time from the index date to death or the date of the patient's last confirmed activity (last structured visit, laboratory test, medication administration or abstracted end date for an oral span), whichever occurred first [8,9]. The following potential risk factors were included in the analysis to evaluate impact on patient prognosis: *BRCA* mutation status (identified as either somatic or germline mutation), history of neoadjuvant chemotherapy, stage of OC at initial diagnosis, presence of residual disease after PDS or IDS (if debulking surgery was described in the patient record as suboptimal or was unknown, patients were considered as having residual disease; if surgeries were described as optimal, patients were considered as having no residual disease), Eastern Cooperative Oncology Group (ECOG) performance status (using the most recent evaluation within the last 180 days), age (at index date), platelet count, hemoglobin and neutrophil count (using most recent values [within 28 days prior to index]). Potential risk factors were based on enrollment criteria for enrolling and ongoing trials in first-line OC when the analysis was designed.

First, we compared patient demographics and baseline characteristics by TTNT and OS status using descriptive statistics. Subsequently, the association between prognostic risk factors and disease progression in the real world was assessed using a multivariable model for all selected variables. A hazard ratio (HR) for each potential risk factor was calculated to assess its association with disease progression. Potential risk factors were selected based on literature, clinical experience and ongoing trials. In cases where the 90% CI excluded 1.0, risk factors were reported as significant. Finally, a stratified Kaplan–Meier analysis was performed to compare patient prognosis of some key risk factors (*BRCA* mutation status, history of neoadjuvant chemotherapy and disease stage at diagnosis). A sensitivity analysis was conducted that included patients who started second-line treatment at least 3 months after first-line treatment.

Results

We retrospectively identified 5535 patients diagnosed with OC between January 2011 and November 2018 (Table 1). Of these, 1064 patients met the inclusion criteria for the study. For OC, 87% of patients in the database were from community practices and 13% of patients were from academic centers. Demographics and baseline characteristics of patients included in the TTNT and OS analyses are shown in Tables 2 & 3. In the Flatiron Health database OC cohort, 76% of the patients had serous histology, as shown in Tables 2 & 3.

Table 2. Patient demographics and baseline characteristics for time to next treatment.

Characteristic	Time to next treatment		p-value
	Event (n = 645), n (%)	No event (n = 419), n (%)	
Age (years)			0.94
18–65	297 (46)	192 (46)	
≥66	348 (54)	227 (54)	
Race			0.20
White	489 (76)	320 (76)	
Black	33 (5)	18 (4)	
Asian	22 (3)	10 (2)	
Hispanic/Latino	1 (<1)	0 (0)	
Other	65 (10)	34 (8)	
Unknown	35 (5)	37 (9)	
Tumor *BRCA* status			0.42
*BRCA*mut[†]	90 (14)	54 (13)	
*BRCA*wt	292 (45)	177 (42)	
BRCA unknown	263 (41)	188 (45)	
Therapy type			0.34
Adjuvant	393 (61)	274 (65)	
Neoadjuvant	165 (26)	96 (23)	
No surgery	87 (13)	49 (12)	
Stage of disease at initial diagnosis			0.003
III	449 (70)	326 (78)	
IV	196 (30)	93 (22)	
Residual disease after PDS/IDS			0.92
No visible gross	292 (45)	191 (46)	
Visible gross	353 (55)	228 (54)	
ECOG performance status			0.08
0–1	323 (50)	239 (57)	
2–4	50 (8)	30 (7)	
Missing	272 (42)	150 (36)	
Platelet count ($\times 10^9$/l)			0.003
<150	150 (23)	90 (21)	
≥150	326 (51)	179 (43)	
Missing	169 (26)	150 (36)	
Hemoglobin (g/dl)			0.48
<10	78 (12)	41 (10)	
≥10	536 (83)	359 (86)	
Missing	31 (5)	19 (5)	
Neutrophil count ($\times 10^9$/l)			0.01
<1.5	57 (9)	38 (9)	
≥1.5	223 (35)	183 (44)	
Missing	365 (57)	198 (47)	
Tumor site			
Ovarian	560 (87)	366 (87)	0.80
Fallopian tube	43 (7)	37 (9)	0.19
Primary peritoneal	64 (10)	46 (11)	0.58
Histology			0.93
Serous	488 (76)	316 (75)	
Borderline, mucinous or transitional cell	15 (2)	9 (2)	
Clear cell	12 (2)	9 (2)	

[†]Approximately 3% of *BRCA* results were genetic variants of unknown significance or favored polymorphism grouped as *BRCA*mut.
*BRCA*mut: *BRCA* mutated; *BRCA*wt: *BRCA* wild-type; ECOG: Eastern Cooperative Oncology Group; IDS: Interval debulking surgery; PDS: Primary debulking surgery.

Table 2. Patient demographics and baseline characteristics for time to next treatment (cont.).

Characteristic	Time to next treatment		p-value
	Event (n = 645), n (%)	No event (n = 419), n (%)	
Endometrioid	16 (2)	15 (4)	
Epithelial NOS	100 (16)	62 (15)	
Unknown/not documented	14 (2)	8 (2)	

[†]Approximately 3% of *BRCA* results were genetic variants of unknown significance or favored polymorphism grouped as *BRCA*mut.
*BRCA*mut: *BRCA* mutated; *BRCA*wt: *BRCA* wild-type; ECOG: Eastern Cooperative Oncology Group; IDS: Interval debulking surgery; PDS: Primary debulking surgery.

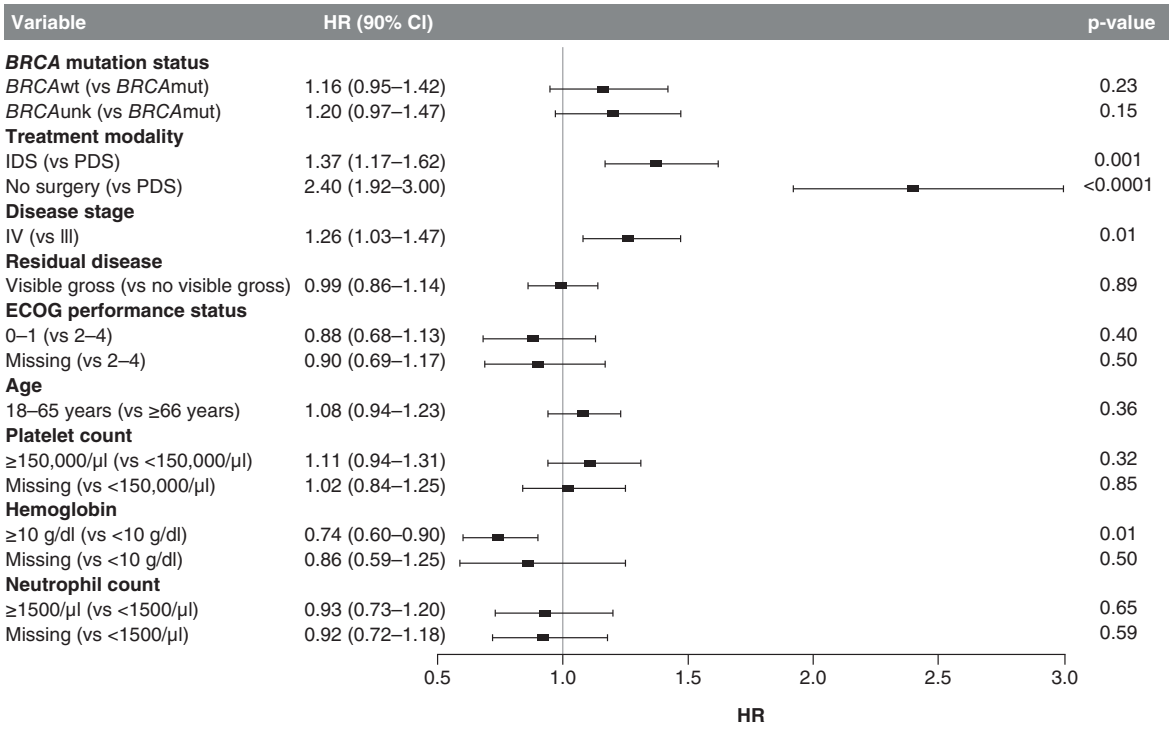


Figure 1. Cox proportional hazards model analysis of time to next treatment. The multivariable model adjusted for all variables shown in the forest plot. An HR greater than 1.0 indicates a shorter time to next treatment.
*BRCA*mut: *BRCA* mutated; *BRCA*unk: *BRCA* unknown; *BRCA*wt: *BRCA* wild-type; ECOG: Eastern Cooperative Oncology Group; HR: Hazard ratio; IDS: Interval debulking surgery; PDS: Primary debulking surgery.

Time to next treatment

Patients who received neoadjuvant chemotherapy (as defined by receiving IDS) had a shorter TTNT than those who received PDS, after adjusting for other covariates (IDS vs PDS: HR: 1.37, 90% CI: 1.17–1.62) (Figure 1). Patients who received no surgery also had a shorter TTNT (no surgery vs PDS: HR: 2.40, 90% CI: 1.92–3.00). Patients with stage IV disease had a shorter TTNT than patients with stage III disease, after adjusting for other covariates (stage IV vs stage III: HR: 1.26, 90% CI: 1.08–1.47) (Figure 1).

The median TTNT was 13.8 months for patients who received PDS and 10.2 months for patients who received IDS (Figure 2C). The median TTNT was 12.9 months for patients with stage III disease and 8.9 months for patients with stage IV disease (Figure 2B).

Overall survival

Consistent with TTNT results, patients who received IDS had a shorter OS than those who received PDS (IDS vs PDS: HR: 1.64, 90% CI: 1.31–2.04), after adjusting for other covariates (Figure 3). Patients who received no surgery had a shorter OS than those who received PDS (no surgery vs PDS: HR: 2.88, 90% CI: 2.19–3.80). Patients with stage IV disease had a shorter OS than patients with stage III disease (stage IV vs stage III: HR: 1.24, 90% CI: 1.01–1.51).

Table 3. Patient demographics and baseline characteristics for overall survival.

Characteristic	Overall survival		p-value
	Event (n = 372), n (%)	No event (n = 692), n (%)	
Age (years)			0.04
18–65	155 (42)	334 (48)	
≥66	217 (58)	358 (52)	
Race			0.36
White	289 (78)	520 (75)	
Black	20 (5)	31 (4)	
Asian	10 (3)	22 (3)	
Hispanic/Latino	0 (0)	1 (<1)	
Other	36 (10)	63 (9)	
Unknown	17 (5)	55 (8)	
Tumor *BRCA* status			<0.0001
*BRCA*mut†	35 (9)	109 (16)	
*BRCA*wt	148 (40)	321 (46)	
BRCA unknown	189 (51)	262 (38)	
Therapy type			<0.0001
Adjuvant	206 (55)	461 (67)	
Neoadjuvant	94 (25)	167 (24)	
No surgery	72 (19)	64 (9)	
Stage of disease at initial diagnosis			<0.0001
III	242 (65)	533 (77)	
IV	130 (35)	159 (23)	
Residual disease after PDS/IDS			0.001
No visible gross	144 (39)	339 (49)	
Visible gross	228 (61)	353 (51)	
ECOG performance status			0.004
0–1	171 (46)	391 (57)	
2–4	34 (9)	46 (7)	
Missing	167 (45)	255 (37)	
Platelet count ($\times 10^9$/l)			0.002
<150	87 (23)	153 (22)	
≥150	198 (53)	307 (44)	
Missing	87 (23)	232 (34)	
Hemoglobin (g/dl)			0.22
<10	43 (12)	76 (11)	
≥10	306 (82)	589 (85)	
Missing	23 (6)	27 (4)	
Neutrophil count ($\times 10^9$/l)			0.01
<1.5	25 (7)	70 (10)	
≥1.5	129 (35)	277 (40)	
Missing	218 (59)	345 (50)	
Tumor site			
Ovarian	326 (88)	600 (87)	0.67
Fallopian tube	23 (6)	57 (8)	0.23
Primary peritoneal	37 (10)	73 (11)	0.76
Histology			0.0069
Serous	269 (72)	535 (77)	
Borderline, mucinous or transitional cell	11 (3)	13 (2)	

†Approximately 3% of *BRCA* results were genetic variants of unknown significance or favored polymorphism grouped as *BRCA*mut.
*BRCA*mut: *BRCA* mutated; *BRCA*wt: *BRCA* wild-type; ECOG: Eastern Cooperative Oncology Group; IDS: Interval debulking surgery; PDS: Primary debulking surgery.

Table 3. Patient demographics and baseline characteristics for overall survival (cont.).

Characteristic	Overall survival		p-value
	Event (n = 372), n (%)	No event (n = 692), n (%)	
Clear cell	8 (2)	13 (2)	
Endometrioid	4 (1)	27 (4)	
Epithelial NOS	68 (18)	94 (14)	
Unknown/not documented	12 (3)	10 (1)	

† Approximately 3% of *BRCA* results were genetic variants of unknown significance or favored polymorphism grouped as *BRCA*mut.
*BRCA*mut: *BRCA* mutated; *BRCA*wt: *BRCA* wild-type; ECOG: Eastern Cooperative Oncology Group; IDS: Interval debulking surgery; PDS: Primary debulking surgery.

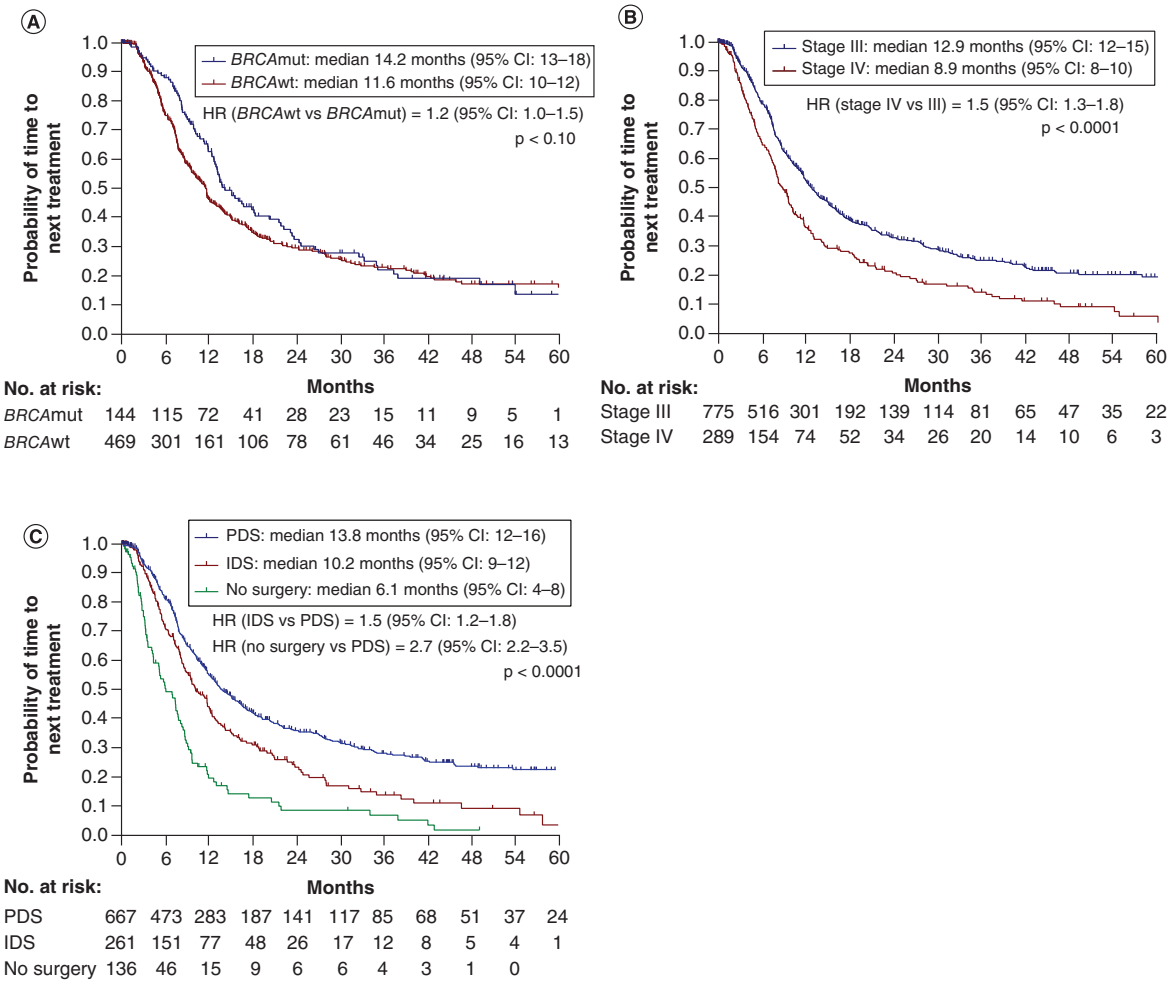


Figure 2. Kaplan–Meier analysis of time to next treatment. (A) By *BRCA* mutation status. **(B)** By disease stage. **(C)** By treatment modality.
*BRCA*mut: *BRCA* mutated; *BRCA*wt: *BRCA* wild-type; HR: Hazard ratio; IDS: Interval debulking surgery; PDS: Primary debulking surgery; TTNT: Time to next treatment.

Median OS was 49 months in patients who received PDS and 32 months in patients who received IDS (Figure 4C). Median OS was 43 and 29 months in patients with stage III and stage IV disease, respectively (Figure 4B).

In addition to risk factors for progression, we identified prognostic factors that affected OS. Patients with residual disease after debulking surgery had a shorter OS than those without residual disease (visible gross residual disease vs no visible gross residual disease: HR: 1.27, 90% CI: 1.05–1.55) (Figure 3). Patients with *BRCA* wild-type (*BRCA*wt) disease had a worse OS than patients with *BRCA* mutated (*BRCA*mut) disease (*BRCA*wt vs *BRCA*mut:

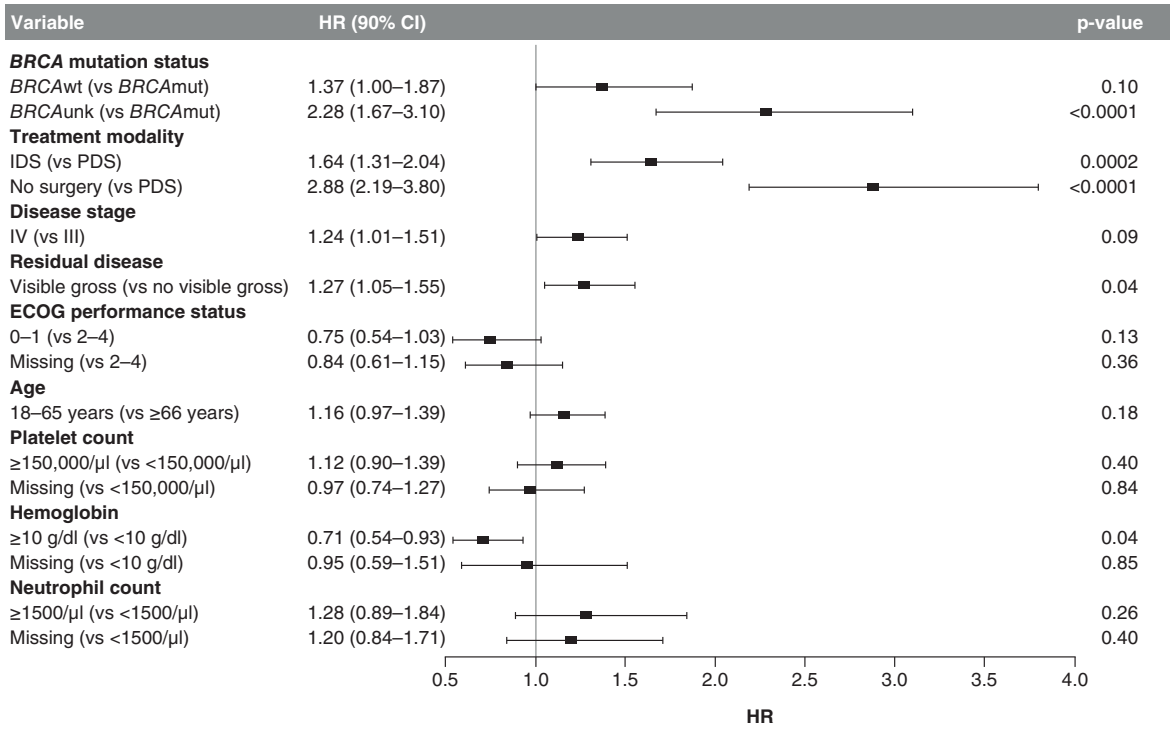


Figure 3. Cox proportional hazards model analysis of overall survival. The multivariable model adjusted for all variables shown in the forest plot. An HR greater than 1.0 indicates a shorter OS.
*BRCA*mut: *BRCA* mutated; *BRCA*wt: *BRCA* wild-type; *BRCA*unk: *BRCA* unknown; ECOG: Eastern Cooperative Oncology Group; HR: Hazard ratio; IDS: Interval debulking surgery; OS: Overall survival; PDS: Primary debulking surgery.

HR: 1.37, 90% CI: 1.00–1.87) (Figure 3). Median OS was not reached in patients with a *BRCA*mut and was 43 months in patients with *BRCA*wt tumors (Figure 4A).

A sensitivity analysis of TTNT and OS excluded 46 patients from the main analysis who received second-line treatment within 3 months of finishing first-line treatment (data not shown). The results of the sensitivity analysis were similar to the results of the main analysis for the 1018 patients who met the inclusion criteria after this exclusion.

Discussion

In this retrospective analysis of a real-world dataset, prognostic factors for disease progression and overall survival in patients with advanced ovarian cancer were evaluated. By excluding patients who received a PARPi as first-line treatment or maintenance therapy after first-line treatment, we were able to view the association between *BRCA*mut and *BRCA*wt status and TTNT, which is a surrogate for PFS and OS. *BRCA*wt status was associated with a decrease in OS. Receipt of neoadjuvant chemotherapy, higher FIGO disease stage at diagnosis and presence of residual disease after surgery were also associated with a shorter TTNT or OS. These real-world data confirm prognostic factors for survival that have been previously identified in meta-analyses of clinical trials [10,11], as well as those recognized by the AJCC [3].

By including TTNT as a surrogate for PFS, data from the present analysis expand on previous findings in identifying prognostic factors for disease recurrence – an important factor in OC given that approximately 70% of patients in this analysis experienced disease recurrence at 3 years (median time to recurrence: 14.2 months in *BRCA*mut; 11.6 months in *BRCA*wt) and that OC is considered incurable after recurrence [2]. Patients with *BRCA*mut tend to have a longer window of platinum sensitivity than patients with *BRCA*wt, which is believed to drive the longer OS seen in the *BRCA*mut population. The present analysis demonstrates a 3-month difference in median TTNT between *BRCA*mut and *BRCA*wt, which is small but reflects that a greater percentage of *BRCA*mut patients will be classified as platinum sensitive to their last platinum regimen.

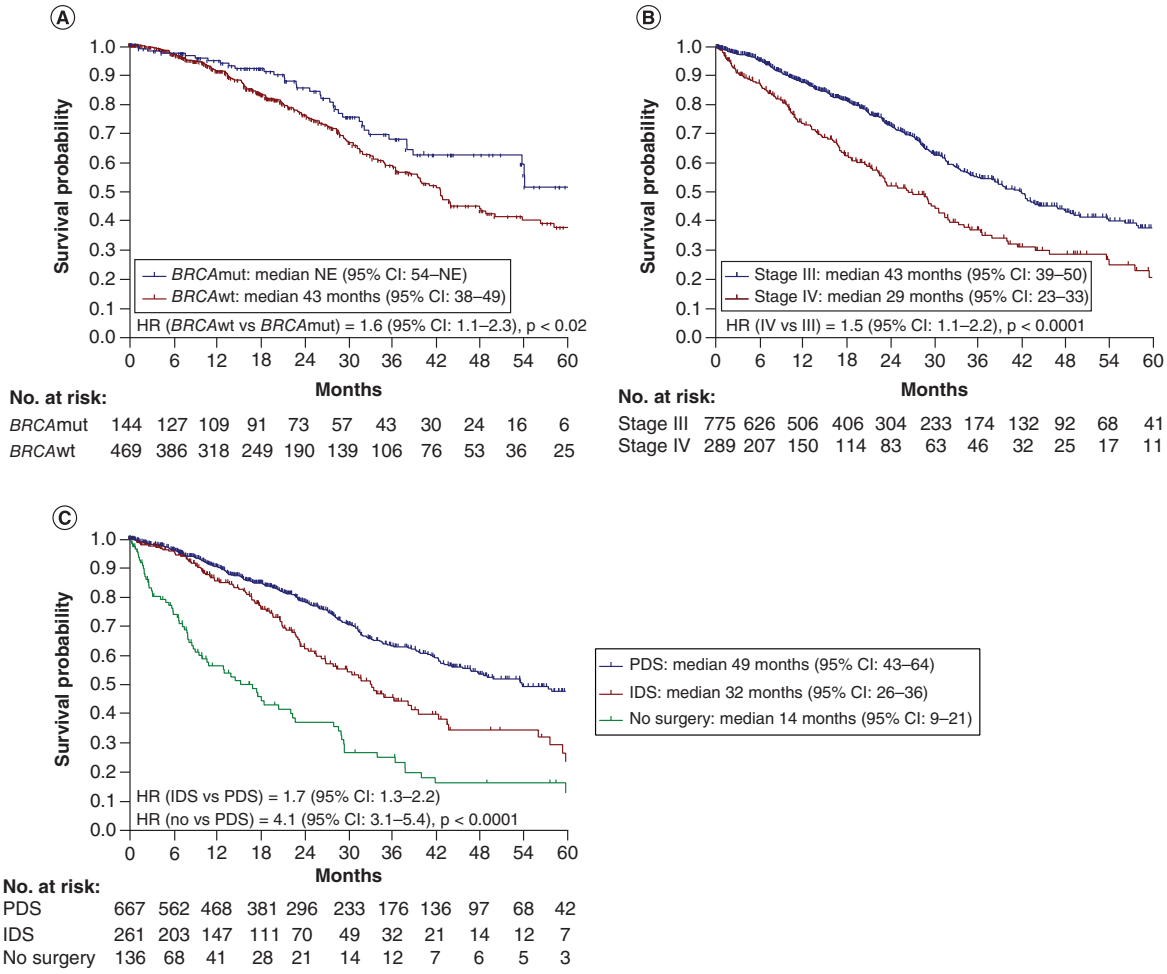


Figure 4. Kaplan–Meier analysis of overall survival. (A) By *BRCA* mutation status. **(B)** By disease stage. **(C)** By treatment modality.
*BRCA*mut: *BRCA* mutated; *BRCA*wt: *BRCA* wild-type; HR: Hazard ratio; IDS: Interval debulking surgery; NE: Not evaluable; PDS: Primary debulking surgery.

This study also provides novel insights into the OC population in real-world clinical practice settings rather than as a more selected clinical trial population. Clinical trial and real-world data cannot be directly compared. However, the present analysis indicates concordance between prognostic factors identified in analyses of clinical trials and real-world practice. As such, this analysis provides useful insight into how clinical trial data are representative of patients in a real-world setting.

Real-world databases have limitations related to the type of data collected and the quality control of data within the network. Here, it was necessary to use TTNT as a proxy for PFS because of inherent limitations in data capture within the Flatiron Health database. TTNT has been used previously as a proxy for PFS in real-world analyses of patients with multiple myeloma [12,13]. In addition, patients in the database might seek care outside the Flatiron Health network, making complete patient histories difficult to capture. During the period of this analysis, many large Phase III clinical trials were enrolling patients, particularly trials with PARPi. Bias in the population of patients receiving treatment in Flatiron-participating centers versus those being recruited to clinical trials may exist, since patients in this analysis were less likely to meet the inclusion criteria for highly selected clinical trial patient populations. This study is also limited in that the Flatiron Health database is representative of US patients only; therefore, these results may not apply to global populations where patient demographics or first-line treatments may differ considerably. One further limitation is the percentage of patients included in the study who had unknown tumor *BRCA* status (42% of all patients) and/or missing ECOG status (40% of all patients). Although unavoidable due to the study design, this limitation may impact the association of those risk factors with TTNT or OS.

Despite the limitations, real-world data from EHR provide a useful supplement to clinical trial data by allowing for large retrospective analyses that are not possible within a clinical trial setting. Based on the selection criteria used, patients from this real-world dataset should be similar to those in the placebo arm of the SOLO1 and PRIMA trials of maintenance treatment after response to first-line platinum-based chemotherapy in patients with OC [14].

In the PRIMA trial, median PFS for the placebo arm was 8.2 months, whereas in the SOLO1 trial, median PFS for the placebo arm was 13.8 months [14,15]. However, the populations of the two trials had distinct differences. All patients enrolled in the SOLO1 trial had deleterious germline or somatic *BRCA1/2* mutation. In addition, those patients with stage IV disease had undergone either biopsy or up-front or interval cytoreductive surgery [14]. The PRIMA trial, in contrast, did not require *BRCA1/2* mutation for enrollment and furthermore, was open to patients with any stage IV disease, which led to the PRIMA trial enrolling patients at high risk for progression [15].

Because of the differences in these trial populations, not only is it impossible to directly compare SOLO1 with PRIMA, it is also impossible to directly compare these two trials to the real-world data presented in this analysis. As PARPi usage and approvals in the first-line therapy setting increase, we hope to assess the utility of these additional prognostic factors derived from real-world data.

Conclusion

In this real-world analysis from the Flatiron Healthcare database of patients identified with stage III/IV OC who completed first-line platinum-based chemotherapy after surgery, IDS, disease stage at diagnosis, residual disease after PDS or IDS and *BRCA*wt were associated with a shorter TTNT or OS.

Summary points

- Most patients with ovarian cancer (OC) respond to first-line treatment, but approximately 70% experience disease progression within 3 years.
- Although there is guidance regarding prognostic factors for survival in patients with OC, there is no guidance regarding prognostic factors for progression, which is crucial to identify patients who are at higher risk of progression and may benefit from new treatment regimens.
- Real-world databases allow for data capture from a much larger and more diverse patient population than clinical studies.
- In a real-world dataset, patients with OC receiving interval debulking surgery had a shorter time to next treatment (TTNT) or overall survival than patients with OC who received primary debulking surgery.
- Patients with stage IV OC had a shorter TTNT and OS than patients with stage III OC in the real-world dataset.
- In this dataset, *BRCA*wt status was associated with a decrease in OS in ovarian cancer.
- Higher FIGO (International Federation of Gynecology and Obstetrics) stage, neoadjuvant chemotherapy, and residual disease after surgery were associated with shorter TTNT/OS in OC in the dataset.
- Real-world data confirmed prognostic factors for survival in OC that had been previously identified in clinical trials.

Author contributions

SN Westin, M Louie-Gao, D Gupta and PH Thaker designed the study. M Louie-Gao compiled the data and did statistical analysis. SN Westin, M Louie-Gao, D Gupta and PH Thaker prepared the manuscript.

Financial & competing interests disclosure

This study was supported by GlaxoSmithKline. SN Westin funding: NIH SPORE for Ovarian Cancer (P50 CA083639), Andrew Sabin Family Fellowship (no grant number), GOG Foundation Scholar Investigator Award (no grant number), NCI (CA217685 and CA16672). SN Westin reports personal fees from Agenus, GlaxoSmithKline, AstraZeneca, Circulogene, Roche/Genentech, Medscape, Clovis Oncology, Watermark Research Partners, Gerson Lehrman Group, Vaniam Group, Merck, Pfizer, BioAscend, Novartis, Takeda, Zentalis, Eisai; research support outside the submitted work from ArQule, AstraZeneca, Novartis, Bayer, GlaxoSmithKline, Cotinga Pharmaceuticals, Clovis Oncology, Roche/Genentech. PH Thaker reports personal fees and other from Stryker; personal fees from Celsion, GlaxoSmithKline, Clovis, AstraZeneca, AbbVie, Iovance Biotherapeutics, Genentech, Immunogen, Merck; research support from Merck and GlaxoSmithKline outside the submitted work. M Louie-Gao and D Gupta are current or former employees of GlaxoSmithKline. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Medical writing and editorial assistance, funded by GlaxoSmithKline (MA, USA) and coordinated by H Ostendorff-Bach of GlaxoSmithKline, were provided by N Renner and M Kacillas of Ashfield Healthcare Communications (CT, USA) and AM Schreiber of GlaxoSmithKline.

Ethical conduct of research

This study used a deidentified dataset provided by Flatiron Health. The data remained deidentified throughout the analyses to protect patient confidentiality. Provisions were in place to prevent re-identification of deidentified data to ensure patient confidentiality.

Open access

References

Papers of special note have been highlighted as: • of interest

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J. Clin.* 70(1), 7–30 (2020).
2. Ledermann JA, Raja FA, Fotopoulou C *et al.* Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* 24(Suppl. 6), vi24–vi32 (2013).
3. American Joint Committee on Cancer (AJCC). *Ovary, Fallopian Tube, and Primary Peritoneal Carcinoma.* 8th Edition. AJCC, IL, USA (2017).
4. Polterauer S, Vergote I, Concin N *et al.* Prognostic value of residual tumor size in patients with epithelial ovarian cancer FIGO stages IIA-IV: analysis of the OVCAD data. *Int. J. Gynecol. Cancer.* 22(3), 380–385 (2012).

• **Demonstrates that the size of residual disease after cytoreduction is a crucial prognostic indicator in ovarian cancer.**

5. Berger ML, Curtis MD, Smith G, Harnett J, Abernethy AP. Opportunities and challenges in leveraging electronic health record data in oncology. *Future Oncol.* 12(10), 1261–1274 (2016).

• **Discusses the challenges of using electronic health record data to obtain information in clinical research in oncology.**

6. Sox HC, Greenfield S. Comparative effectiveness research: a report from the Institute of Medicine. *Ann. Intern. Med.* 151(3), 203–205 (2009).
7. Flatiron. Flatiron Health EHR-derived database. https://flatiron.com/real-world-evidence/
8. Curtis MD, Griffith SD, Tucker M *et al.* Development and validation of a high-quality composite real-world mortality endpoint. *Health Serv. Res.* 53(6), 4460–4476 (2018).

• **Discusses how data quality and completeness in electronic health databases impact the ability of the data to yield reliable real-world evidence.**

9. Zhang Q, Gossai A, Monroe S, Nussbaum NC, Parrinello CM. Validation analysis of a composite real-world mortality endpoint for US cancer patients. *Presented at: 111th Annual Meeting of the American Association for Cancer Research.* Philadelphia, PA, USA (22 June–24 June 2020). Abstract nr 5772. https://www.abstractsonline.com/pp8/#!/9045/presentations/5772/1

• **Looked at the sensitivity, specificity and date accuracy of the composite mortality variable across cancer types in the Flatiron Health database.**

10. Bristow RE, Chi DS. Platinum-based neoadjuvant chemotherapy and interval surgical cytoreduction for advanced ovarian cancer: a meta-analysis. *Gynecol. Oncol.* 103(3), 1070–1076 (2006).
11. Bristow RE, Eisenhauer EL, Santillan A, Chi DS. Delaying the primary surgical effort for advanced ovarian cancer: a systematic review of neoadjuvant chemotherapy and interval cytoreduction. *Gynecol. Oncol.* 104(2), 480–490 (2007).
12. Chen CC, Parikh K, Abouzaid S *et al.* Real-world treatment patterns, time to next treatment, and economic outcomes in relapsed or refractory multiple myeloma patients treated with pomalidomide or carfilzomib. *J. Manag. Care Spec. Pharm.* 23(2), 236–246 (2017).
13. Rifkin RM, Medhekar R, Amirian ES *et al.* A real-world comparative analysis of carfilzomib and other systemic multiple myeloma chemotherapies in a US community oncology setting. *Ther. Adv. Hematol.* 10, (2019). https://doi.org/10.1177/2040620718816699

• **Demonstrates the feasibilty of estimating a time to next treatment through the use of electronic health records and comparing it to the progression-free survival observed in a clinical trial. The study looks at patients receiving carfilzomib for multiple myeloma and the Phase III ASPIRE trial.**

14. Moore K, Colombo N, Scambia G *et al.* Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. *N. Engl. J. Med.* 379(26), 2495–2505 (2018).

• **Demonstrates that the use of maintenance olaparib provided a benefit to progression-free survival in women with newly diagnosed advanced ovarian cancer and a *BRCA1/2* mutation.**

15. González-Martín A, Pothuri B, Vergote I *et al.* Niraparib in patients with newly diagnosed advanced ovarian cancer. *N. Engl. J. Med.* 381(25), 2391–2402 (2019).