Gynecologic Oncology Reports 29 (2019) 113–117

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case series

Patterns and duration of primary and recurrent treatment in ovarian cancer patients with germline *BRCA* mutations

Soledad Jorge[a,*], Elizabeth M. Swisher[a], Barbara M. Norquist[a], Kathryn P. Pennington[a], Heidi J. Gray[a], Renata R. Urban[a], Rochelle L. Garcia[b], Kemi M. Doll[a]

[a] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Washington School of Medicine, Seattle, WA 98195, USA
[b] Department of Pathology, University of Washington School of Medicine, Seattle, WA 98195, USA

ARTICLE INFO

Keywords:
Ovarian cancer
BRCA1 and *BRCA2* mutations
Disease course
Treatment
Long-term

ABSTRACT

The objectives of this study were to describe the patterns and duration of primary and recurrent treatment in patients with ovarian cancer (OC) harboring germline *BRCA1* and *BRCA2* (*BRCA*) mutations. A retrospective review of *BRCA* mutation carriers with advanced, high-grade OC diagnosed between 2004 and 2014 with at least 3 years of follow-up (or until death) was undertaken. Descriptive statistics were calculated and a Swimmer's Plot used to depict disease course. Forty *BRCA* mutation carriers (26 *BRCA1*, 14 *BRCA2*) were identified. Mean age was 54 (range 32–77). All had cytoreductive surgery and received platinum chemotherapy. Median platinum-free interval was 11.9 months (IQR 3.6–21.9). Among 28 patients who recurred, median number of treatment lines was 4 (IQR 3–6), with a median of 2 (IQR 2–3) platinum lines. On average, patients who recurred spent 32% (IQR 20–43%) of their time after diagnosis receiving cytotoxic chemotherapy and 54% (IQR 42–67%) of the time on some cancer-directed therapy, including maintenance. Median overall survival was 79.1 months from diagnosis and 25.4 months after first recurrence. In conclusion, beyond first-line therapy, there was treatment and outcome heterogeneity for *BRCA*-mutated OC. After OC diagnosis, patients spent close to half their life on treatment.

1. Introduction

Approximately 15% of epithelial ovarian cancers (OC) are associated with germline *BRCA1* and *BRCA2* (*BRCA*) mutations (Norquist et al., 2016). Patients with OC and germline *BRCA* mutations differ from sporadic cases in both tumor biology and treatment response. Women with *BRCA1* mutations present with OC at an earlier age (Alsop et al., 2012; Yang et al., 2011), and both *BRCA1* and *BRCA2* carriers usually have high-grade tumors (Norquist et al., 2016; Alsop et al., 2012). *BRCA* mutation carriers with OC, especially *BRCA2* carriers, have better five year survival rates than their counterparts without *BRCA* mutations (Norquist et al., 2016; Alsop et al., 2012; Yang et al., 2011; Bolton et al., 2012; Pennington et al., 2014; Tan et al., 2008; Ben David et al., 2002). This is in part due to increased platinum sensitivity and longer progression-free intervals (Alsop et al., 2012; Yang et al., 2011; Pennington et al., 2014). In addition, *BRCA* carriers have OCs that can be particularly sensitive to polyadenosine ribose polymerase (PARP) inhibitors (Fong et al., 2009). Despite these differences in tumor biology and clinical behavior, less is known about the long-term disease course (beyond five years) of OC patients with germline *BRCA* mutations. Chetrit et al. (Chetrit et al., 2008) demonstrated improved survival rates for women with *BRCA* mutations relative to wildtype controls with up to eight years of follow-up. However, recent studies suggest that the initial survival benefit seen in *BRCA* carriers disappears after ten years, though those data precede widespread access to PARP inhibitors (Kotsopoulos et al., 2016).

Due to the apparent unique features of germline *BRCA*-mutated OC, there is a need for information on the treatment patterns and outcomes over long-term periods of follow-up in this group. To our knowledge, there are no existing data on how much time women with *BRCA* mutations spend on treatment versus off treatment after an OC diagnosis and how many lines of therapy they typically receive, which reflect treatment burden. The objective of this study was thus to describe the disease course of a cohort of unselected OC patients with germline *BRCA* mutations, with an emphasis on treatment type, treatment duration, and disease status. Our goals are to present a comprehensive description of the natural history of germline *BRCA* mutation associated OC and provide information that can be useful for patient counseling. These baseline data are useful as women debate the merits of frontline or secondary maintenance therapy with PARP inhibitors, which is the

* Corresponding author at: Division of Gynecologic Oncology, Department of Obstetrics and Gynecologic, University of Washington, 1959 NE Pacific St, Box 356460, Seattle, WA 98195, USA.
E-mail address: sjorge@uw.edu (S. Jorge).

https://doi.org/10.1016/j.gore.2019.08.001
Received 20 June 2019; Received in revised form 3 August 2019; Accepted 6 August 2019
Available online 09 August 2019

new frontier of OC treatment for women with *BRCA* mutations (Moore et al., 2018; Pujade-Lauraine et al., 2017).

2. Methods

Patients with Stage II or higher, high-grade epithelial OC harboring germline *BRCA* mutations were retrospectively identified from an IRB-approved institutional tissue bank from 2004 to 2014. All patients in the tissue bank had provided informed consent. Banked DNA samples were sequenced using BROCA, a targeted capture, massively parallel sequencing test developed at the University of Washington, Seattle, as previously described (Walsh et al., 2010). Women were excluded if complete medical records and adequate follow-up (at least 3 years after diagnosis or until death) were not available, if they carried a *BRCA* variant of uncertain significance, or if they were diagnosed with an occult cancer at the time of risk-reducing salpingo-oophorectomy.

Demographic, pathological, treatment and outcome data were abstracted by review of medical records. Treatment information included use of neoadjuvant chemotherapy, debulking surgery, and adjuvant chemotherapy for all patients. For patients who recurred, date of recurrence and details of each subsequent treatment were collected. Operations performed by a gynecologic oncologist for the purpose of OC cytoreduction were considered debulking surgeries and were categorized as complete (no residual disease), optimal ($\leq$1 cm residual disease) or suboptimal ($>$ 1 cm residual disease). Women were considered to have received intraperitoneal chemotherapy if at least one cycle was administered intraperitoneally. Maintenance therapy was defined as the initiation or continuation of a chemotherapy agent after a complete or partial response was achieved.

Platinum free interval (PFI) was defined as the number of months elapsed from the last day of platinum chemotherapy for first-line treatment to the date of diagnosis of disease recurrence, or date of last follow-up if the patient did not recur during the study period. Patients were considered to have platinum-sensitive disease if the PFI was $\geq$ 6 months, platinum-resistant disease if the PFI was $<$ 6 months, and platinum-refractory disease if they did not respond at least partially to first-line platinum therapy. Median overall survival was calculated from date of diagnosis to date of death and censored at last patient contact, as well as from the date of first recurrence until date of death or last patient contact. The proportion of time on cytotoxic chemotherapy was calculated by adding each interval during which a patient received cytotoxic chemotherapy, and dividing this by the total amount of time elapsed from diagnosis to death or date of last contact. Similarly, the proportion of time spent on *any* cancer-directed therapy was calculated by adding each interval during which a patient had received any form of cancer-directed therapy and dividing this by the total amount of time. Cancer-directed therapy included any chemotherapy (neoadjuvant, adjuvant and maintenance), surgery and radiation, but excluded hospice and palliative-only care.

We calculated descriptive statistics as frequencies and proportions and compared characteristics between groups using *t*-tests for continuous data and chi-square tests or Fisher's exact tests for categorical data. Survival times were calculated using the Kaplan-Meier method and differences in median survival between *BRCA1* and *BRCA2* mutation carriers were compared using the log-rank test. *P*-values $<$ .05 were considered statistically significant. We created a Swimmer's Plot to depict individual disease timelines.

3. Results

Forty patients with Stage II-IV, high-grade epithelial OC and deleterious germline *BRCA* mutations (n = 26 *BRCA1*; 14 *BRCA2*) with complete medical records and adequate follow-up were available for review. The mean age at diagnosis was 54 years (range: 32–77) for the entire cohort and was younger for BRCA1 mutation carriers (52 years) compared to BRCA2 mutation carriers (57 years, *p*-value = .06). Most patients were white, had Stage IIIC disease, and had tumors with serous histology. Patient characteristics are summarized in Table 1.

Table 1
Baseline characteristics of 40 patients with OC and germline *BRCA* mutations. Percentages are calculated per column and may not add to 100% due to rounding.

	n (%)			
	All (n = 40)	BRCA1 (n = 26)	BRCA2 (n = 14)	p-value
Age				0.206
< 35	1 (2)	1 (4)	0 (0)	
35–40	3 (8)	3 (12)	0 (0)	
41–45	3 (8)	3 (12)	0 (0)	
> 45	33 (82)	19 (73)	14 (100)	
Race/ethnicity				0.950
White	32 (80)	19 (73)	13 (93)	
Black	1 (2)	1 (4)	0 (0)	
Hispanic (any race)	3 (8)	2 (8)	1 (7)	
Asian	1 (2)	1 (4)	0 (0)	
Native American	2 (5)	2 (8)	0 (0)	
Multiracial	1 (2)	1 (4)	0 (0)	
Year of diagnosis				0.763
2004–2008	17 (42)	12 (46)	5 (36)	
2009–2014	23 (57)	14 (54)	9 (64)	
Stage				0.594
Unstaged	1 (2)	1 (4)	0 (0)	
II	1 (2)	1 (4)	0 (0)	
IIIA-B	4 (10)	3 (12)	1 (7)	
IIIC	25 (62)	14 (54)	11 (79)	
IV	9 (22)	7 (27)	2 (14)	
Histology				0.401
Serous	30 (75)	21 (81)	9 (64)	
Endometrioid	2 (5)	1 (4)	1 (7)	
Mucinous	1 (2)	1 (4)	0 (0)	
Clear cell	7 (18)	3 (12)	4 (29)	

Number of treatment lines and treatment-duration are summarized in Table 2. Among all patients, median number of treatment lines was 3 (interquartile range (IQR) 1–6), and median number of platinum-containing lines was 2 (IQR 1–3). Among those who recurred, median number of treatment lines was 4 (IQR 3–6), and median number of platinum-containing lines was 2 (IQR 2–3). The decision to start a new line of chemotherapy was driven by disease recurrence or progression 83% of the time, whereas toxicity accounted for the remaining 17% of changes. On average, patients spent 20% (IQR 8–39%) of the time from diagnosis to death or date of last follow-up receiving cytotoxic chemotherapy, and 46% (IQR 14–65%) of the time on some form of cancer-directed therapy. For the subset of patients who recurred, the average amount of time spent receiving cytotoxic chemotherapy was higher at 32% (IQR 20–43%), and on any therapy it was 54% (IQR 41–67%).

Treatment modalities and chemotherapeutic agents utilized per treatment line are presented in Table 3. In the upfront setting, 15 patients (37%) received neoadjuvant chemotherapy, whereas 25 (62%) had a primary debulking surgery. Intraperitoneal chemotherapy was

Table 2
Number of treatment lines and treatment duration of patients with OC and germline BRCA mutations. In the first column, values are reported for all patients (n = 40), while in the second column values are presented for the subset of patients who recurred (n = 28). IQR = interquartile range.

	Median (IQR)	
	All patients (n = 40)	Patients who recurred (n = 28)
Number of treatment lines	3 (1–6)	4 (3–6)
Number of platinum lines	2 (1–3)	2 (2–3)
Percent of time on cytotoxic chemotherapy	20 (8–39)	32 (20–43)
Percent of time on any therapy[a]	46 (14–65)	54 (41–67)

[a] Includes all cytotoxic chemotherapy, bevacizumab, PARP inhibitors, other maintenance agents, and radiation.

Table 3
Treatment modalities and chemotherapeutic agents used per treatment line. Percentages for neoadjuvant chemotherapy and first-line treatment modalities are calculated based on all participants ($N = 40$) while percentages for second through tenth-line treatment modalities are calculated based on all patients who recurred during the study period ($N = 28$). For specific chemotherapeutic agents, percentages are calculated based on the number of patients who received a given treatment line.

	n (%)										
	Upfront treatment (n = 40)		Recurrence treatment (n = 28)								
	Neoadjuvant	1st Line	2nd Line	3rd Line	4th Line	5th Line	6th Line	7th Line	8th Line	9th Line	10th Line
Chemotherapy	15 (37)	40 (100)	26 (93)	24 (86)	18 (64)	13 (46)	11 (39)	7 (25)	7 (25)	3 (11)	1 (4)
Cytoreduction	n/a	40 (100)	11 (39)	2 (7)	0	0	0	0	0	0	0
Complete (0 cm)	n/a	23 (57)	7 (25)	2 (7)	0	0	0	0	0	0	0
Optimal (≤1 cm)	n/a	13 (32)	1 (4)	0	0	0	0	0	0	0	0
Suboptimal (> 1 cm)	n/a	4 (10)	3 (11)	0	0	0	0	0	0	0	0
Intraperitoneal route	0	16 (40)	2 (7)	1 (4)	0	0	0	0	0	0	0
Clinical trial	0	8 (20)	5 (18)	2 (7)	2 (7)	0	0	0	0	0	0
Maintenance therapy	n/a	13 (32)	4 (14)	1 (4)	1 (4)	0	0	0	1 (4)	0	0
Radiation	0	0	1 (4)	1 (4)	0	1 (4)	1 (4)	1 (4)	0	0	0
Specific agents	*(N = 15)*	*(N = 40)*	*(N = 26)*	*(N = 24)*	*(N = 18)*	*(N = 13)*	*(N = 11)*	*(N = 7)*	*(N = 7)*	*(N = 3)*	*(N = 1)*
Platinum	15 (100)	40 (100)	18 (69)	11 (46)	7 (39)	3 (23)	1 (9)	2 (29)	1 (14)	1 (33)	1 (100)
Taxane	14 (93)	38 (95)	4 (15)	5 (21)	5 (28)	3 (23)	2 (18)	2 (29)	1 (14)	0	0
Liposomal doxorubicin	0	0	6 (23)	7 (29)	2 (11)	1 (8)	2 (18)	1 (14)	0	0	0
Gemcitabine	1 (7)	1 (3)	10 (38)	1 (4)	3 (17)	1 (8)	1 (9)	1 (14)	1 (14)	1 (33)	0
Topotecan	0	0	1 (4)	2 (8)	2 (11)	2 (15)	0	1 (14)	0	1 (33)	0
Bevacizumab	1 (7)	7 (18)	5 (19)	4 (17)	4 (22)	1 (8)	1 (9)	2 (29)	1 (14)	1 (33)	0
PARP inhibitor	0	0	3 (12)	2 (8)	2 (11)	2 (15)	2 (18)	0	1 (14)	0	0

given to 16 patients (40%). A maintenance regimen was given in 13 patients (32%) after completion of adjuvant treatment; 9 received bevacizumab, 1 carboplatin, 1 tamoxifen, and 2 experimental cancer vaccines. Among 28 patients (70%) who recurred, 11 (39%) had a secondary cytoreductive surgery, 2 (7%) had a tertiary cytoreductive surgery, 3 (11%) received intraperitoneal chemotherapy, and 5 (18%) received radiotherapy. Additionally, 7 patients (25%) went on to receive maintenance therapy after responding to subsequent-line treatment: 4 received bevacizumab and 3 a PARP inhibitor.

In terms of initial treatment response, median PFI was 11.9 months (IQR 3.6–21.9). Thirty-six patients (90%) had platinum-sensitive, 3 patients (7.5%) platinum-resistant and 2 patient (2.5%) platinum-refractory disease. With a median follow-up time of 49.3 months (IQR 33.7–85.4), median overall survival (OS) from diagnosis was 79.1 months. After first recurrence, OS was 25.4 months. There were no significant differences in survival between patients with *BRCA1* and *BRCA2* mutations (from diagnosis: OS 76.2 and 82.0 months, $p = .9$ and from first recurrence: OS 25.4 and 17.3 months, $p = .3$ for *BRCA1* and *BRCA2*, respectively). Twelve patients (30%) did not recur during follow-up. Six patients ($n = 4$ *BRCA1*; 2 *BRCA2*) (15%) had progression-free survivals longer than 5 years; one eventually recurred after 10 years. The characteristics of these 6 long-term responders did not differ significantly from the larger group with respect to age, stage, mutation (*BRCA1* or *BRCA2*), or residual disease after surgery. Conversely, 4 patients (10%) recurred < 6 months after treatment with a platinum agent and median overall survival for these patients was just 16.6 months from diagnosis to death.

Individual disease courses are depicted in a Swimmer's Plot (Fig. 1). The figure highlights the wide range of primary and secondary disease-free intervals; while some patients experienced prolonged remission, a few progressed during first-line therapy. Relatively long survival times after salvage treatment were notable for many women, and were associated with multiple lines of medications and a significant proportion of time spent on treatment.

4. Discussion

In this retrospective review, we investigated the disease courses of 40 *BRCA* mutation carriers with OC with long term follow up. Although *BRCA*-mutated OC is known to have high initial response rates to platinum therapy, we identified notable heterogeneity in secondary response and in overall disease course. Treatment duration was considerable, especially for women who recurred during the study period, who spent a third of their life after diagnosis receiving cytotoxic chemotherapy and half of their life on some form of cancer-directed therapy.

Our data describing successive lines of treatment are novel, given the scarcity of literature on the long-term treatment patterns of women with OC. A Dutch study by Houben et al. recently reported on the systemic treatments received by 261 patients with OC over multiple lines of therapy. They found that the median number of treatment lines was 2 (IQR 1–3) and identified 12 (5%) patients who received 8 or more lines. In keeping with our findings, they also noted significant variety in treatment patterns beyond second-line treatment (Houben et al., 2017). Our results provide additional details of treatment patterns, with an emphasis on treatment duration, and are the first to report specifically on patients with *BRCA* mutations.

Our estimates of overall survival correlate well to the published literature on *BRCA*-mutated OC, with prior estimates ranging from 53.4 to 100.8 months (Tan et al., 2008; Ben David et al., 2002; Chetrit et al., 2008). In spite of the generally favorable prognosis, it is interesting to note the range of responses seen in this cohort, with overall survival ranging from 14.8 to 139.2 months. While the small numbers available for this study precluded detecting significant differences in the characteristics of long-term responders and non-responders, our data challenge the notion that all *BRCA*-mutated carcinoma portends a better prognosis, and may reflect the presence of effect modification by other biological or treatment factors. For example, it would be interesting to consider if platinum non-responders have somatic reversions of the *BRCA* alleles to wildtype (Norquist et al., 2011). A strength of this study is that women with *BRCA* mutations were identified from a OC cohort enrolled at diagnosis in which all patients were tested for *BRCA* mutations, reducing genetic testing selection bias present in many studies of survival in *BRCA*-mutated OC.

This study has several limitations. It is a small, retrospective cohort of patients treated at a single institution, an academic center, where practice patterns may differ from community settings, thereby reducing generalizability. Additionally, our metrics of treatment duration (proportion of time spent on cytotoxic and on any cancer-directed therapy) is just one consideration when debating the merits of different treatment strategies, including maintenance therapy. Other factors, such as

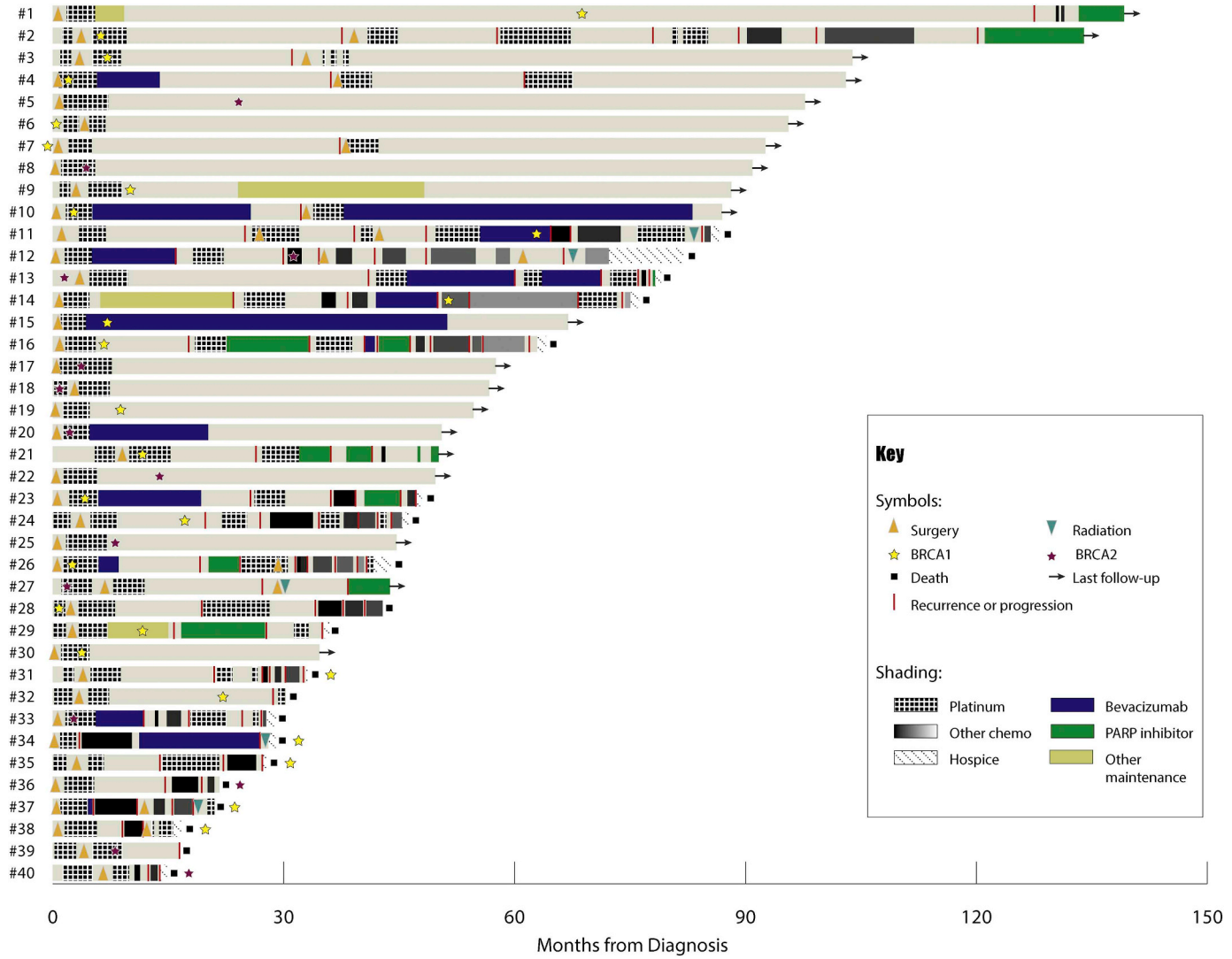

Fig. 1. Swimmer Plot depicting time course of OC from diagnosis to death or date of last follow-up in women with germline *BRCA* mutations. Filled blocks represent times patients spent in treatment (details provided in key), while blank portions represent treatment-free intervals. Red lines mark times when disease progression was diagnosed (by imaging if done or CA-125 otherwise). Times in between red lines represent progression-free intervals where patients either had no evidence of disease (complete responses), partial responses, or stable disease. Cytoreductive surgeries, radiation therapy, and date of clinical *BRCA* mutation testing are denoted by specific symbols (details provided in key). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

patient-reported quality of life, performance status, and rates of adverse events are clearly important. Nonetheless, even if a treatment is relatively well tolerated, it exacts substantial time and expense, and thus treatment duration remains relevant to patient-centered care. Given the paucity of detailed data on treatment-related burden for OC, these data represent a unique contribution, and may be particularly relevant for *BRCA*-mutated OC, where the availability of targeted maintenance regimens may further extend treatment durations.

Importantly, given the period of study (2004–2014), many patients did not receive PARP inhibitors. Current standard of care for *BRCA*-mutated recurrent OC is to use PARP inhibitors as stand-alone therapy or as maintenance therapy following response to platinum (Pujade-Lauraine et al., 2017), and PARP inhibitors will increasingly play a role as upfront maintenance therapy for *BRCA* carriers following the recent publication of the SOLO1 trial (Moore et al., 2018). As patients wrestle with the decision of whether to take on the toxicity of long-term PARP inhibitor following primary treatment, our data provide insight into the disease course in the absence of PARP inhibitor therapy. The large amount of time spent on active therapy and relatively low rate (15%) of 5-year disease free interval would argue favorably for the use of PARP inhibitor maintenance therapy in considering overall quality of life. It will be important to await data from the SOLO1 trial to assess whether the improvement in disease-progression at three years observed with olaparib maintenance after upfront treatment translates into durable responses and even cures. If this is the case, two years of maintenance PARP inhibitors may significantly reduce treatment duration in the long-run.

Author contribution

Conception and design: Kemi Doll, Heidi Gray, Soledad Jorge, Elizabeth Swisher, Renata Urban.

Collection and assembly of data: Rochelle Garcia, Soledad Jorge, Barbara Norquist, Kathryn Pennington, Elizabeth Swisher.

Data analysis and interpretation: Kemi Doll, Soledad Jorge, Elizabeth Swisher.

Manuscript writing and editing: All authors.

Final approval: All authors.

Accountable for all aspects of work: All authors.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

Acknowledgments

Research reported in this publication was supported by the National Institutes of Health under award number T32CA009515.

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