



Differences in presentation and survival of Asians compared to Caucasians with ovarian cancer: An NRG Oncology/GOG Ancillary study of 7914 patients[☆]

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HIGHLIGHTS

- Asians were younger at trial enrollment and had better performance status.
- Asians had improved 5-year disease-specific survival than Caucasians.
- Asian race remained significant prognostic factor in multivariate analysis.

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ABSTRACT

Purpose. To compare patient/tumor characteristics and outcomes of Asians to Caucasian patients with epithelial ovarian cancer.

Methods. Ancillary data were pooled and analyzed from ten prospective randomized front-line Gynecologic Oncology Group clinical trials from 1996 to 2011. Demographic, clinicopathologic features, disease-specific and all-cause survival were analyzed.

Results. Of 7914 patients, 7641 were Caucasian and 273 Asian. When compared to Caucasians, Asians were younger at trial enrollment, had a better performance status, earlier-stage cancers (17.2% vs. 8.1% with stage I; $p < 0.001$), and were more likely to be of clear cell (15.8% vs. 6.2%, $p < 0.001$) and mucinous (3.3% vs. 1.9%, $p < 0.001$) histology. Asians had an improved 5-year disease-specific survival of 54.1% compared to 46.1% for Caucasians, $p = 0.001$. In multivariate analysis, the Asian race remained a significant prognostic factor for all-cause survival (HR: 0.84; 95% CI: 0.72–0.99; $p = 0.04$). Other factors predictive of improved survival included younger age, better performance status, optimal cytoreduction, earlier stage, non-clear cell histology, and lower grade tumors.

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Conclusion. Asians enrolled into phase III ovarian cancer clinical trials were younger, with better performance status, earlier-stage of disease, and have a greater number of clear cell and mucinous tumors. After adjusting for these prognostic factors, Asians have a better survival compared to Caucasians.

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1. Introduction

Epithelial ovarian carcinoma is the leading cause of gynecologic cancer mortality in the United States with an estimate of 14,080 deaths in 2017 [1]. Although significant survival gains have been reported for epithelial ovarian cancer in the general population, these improvements have not been observed in all ethnic groups. For example, the 5-year survival rates have increased in Caucasians from 37 to 45% but have decreased in African-Americans from 43 to 37% during the years 1975 to 2006 [2]. However, there are few studies that have evaluated survival outcomes of Asians.

In a large population-based study using the National Cancer Institute Surveillance, Epidemiology, and End Results, Asians were found to have a higher 5-year disease-specific survival compared to Caucasians (59.1% vs. 47.3%, $p < 0.001$) [3]. Recently, a Kaiser Permanente cancer registry evaluation found that there was a trend towards improved all-cause mortality for Asians compared to Caucasians (HR 0.93, 95% CI 0.76–1.13) adjusted for age at diagnosis, stage, grade and histology [4]. However, population analyses are limited by the lack of central pathology review and standardization for surgery, chemotherapy and follow-up methods. Furthermore, it appears that there are survival differences in the various racial groups after treatment when comparing populations treated with similar regimens in clinical trials based in Japan, Europe and the United States [5–7]. For example, response to weekly chemotherapy was variable on different racial groups in recent trials from the Japanese Gynecologic Oncology Group [5] and GOG [6].

The objective of the current study was to compare the patient/tumor parameters at presentation and outcomes between Asians and Caucasians with primary ovarian, fallopian tube and peritoneal cancers using data from NRG/GOG, members of the NCI National Cancer Trials Network, prospective phase III randomized clinical trials over the last 20 years.

2. Methods

2.1. Demographic information

We included patients with epithelial ovarian, fallopian tube or peritoneal carcinoma treated on front-line NRG/Gynecologic Oncology Group clinical trials from 1986 to 2009. De-identified data from the Statistical and Data Center were collected. The demographic and clinical data elements included age, race (Asian and Caucasian), body mass index, performance status, extent of residual disease following surgical cytoreduction, stage, cell type, tumor grade, date of enrollment, date of last follow up and vital status. All patients provided written informed consent prior to enrollment after the study had been approved by the appropriate research ethics board for each participating center.

2.2. Clinical trials evaluated

This ancillary analysis incorporated pooled historical data from all patients enrolled on ten prospective randomized front-line GOG trials as de-identified data. The treatment protocols included intravenous (IV) chemotherapy alone (GOG 111 [8], 157 [9], 158 [10], 175 [11], 182 [12]), IV chemotherapy plus intraperitoneal (IP) chemotherapy (GOG 95 [13], 104 [14], 114 [15], 172 [16]), and IV chemotherapy plus biologic therapy (GOG 218 [17]). GOG 95 [13] enrolled stage I and II patients comparing ^{32}P vs. cyclophosphamide plus cisplatin. GOG 104 [14]

enrolled stage III patients and compared either IP cisplatin or IV cisplatin either combined with IV cyclophosphamide. GOG 111 [8] enrolled stage III and IV patients and compared either cyclophosphamide or paclitaxel, combined with cisplatin. GOG 114 [15] enrolled randomized stage III patients and compared IP cisplatin vs. IV cisplatin combined with paclitaxel. GOG 157 [9] enrolled stage IA grade 3 to stage II patients and compared 3 vs. 6 cycles of carboplatin and paclitaxel. GOG 158 [10] enrolled randomized stage III patients and compared cisplatin vs. carboplatin combined with paclitaxel. GOG 172 [16] enrolled stage III patients and compared IP cisplatin vs. IV cisplatin combined with paclitaxel. GOG 175 [11] randomized stage I and II patients and compared paclitaxel maintenance vs. observation combined with carboplatin and paclitaxel. GOG 182 [12] enrolled randomized stage III and IV patients and compared gemcitabine, pegylated liposomal doxorubicin, and topotecan vs. vehicle combined with carboplatin and paclitaxel. GOG 218 [17] enrolled stage III and IV patients and compared paclitaxel and carboplatin with or without bevacizumab.

2.3. Statistical methods

Pearson chi-square test, Wilcoxon-Mann-Whitney test and Cox proportional hazards model were used. The co-primary endpoints of our analysis were disease-specific survival and all cause survival. Patients who were lost to follow-up were censored at time of last follow-up. Kaplan-Meier estimates were used in plotting the survival probability. All statistical tests were two-tailed with the significance level set at $\alpha = 0.05$ and statistical analyses were performed using the R software (R Foundation for Statistical Computing, Vienna, Austria, 2013).

3. Results

3.1. Demographic and treatment information

Of 7914 patients in the study population, 7641 (96.6%) were Caucasian and 273 (3.4%) were Asian. The demographic and clinical characteristics of the study population are shown in Table 1 and Fig. 1. Asians were younger compared to Caucasians (median age: 54 vs. 59 years; $p < 0.001$) and had a lower body-mass index (BMI) and better performance status. Both groups had similar rates of optimal cytoreduction (defined per individual GOG trial) at 53% vs. 51% ($p = 0.63$). Asians were more likely to present with stage I disease (17% vs. 8%; $p < 0.001$) and clear cell cancers (16% vs. 6%, $p < 0.001$).

3.2. Survival based on race

Asians had a higher 5-year disease-specific survival (DSS) of 54% compared to 46% for Caucasians ($p = 0.001$) (Fig. 2 and Table 2). The higher survival in Asians was demonstrated after stratifying for age, performance status, stage of disease, serous histology and presence of gross residual disease (Supplemental Figs. 1A–E). Asians also had an improved survival when stratified by BMI (Table 2) and an improved all-cause survival of 51% compared to 43% in Caucasians ($p < 0.001$) (Table 3). On multivariate analysis for disease-specific survival, younger age, Asian race, better performance status, lower BMI, early stage, lower grade, non-clear cell subtype and no residual disease were all independent predictors for better survival (Table 4).

Table 1
Patient demographics and clinical characteristics (N = 7914).

	N	Asian N = 273 (%)	Caucasian N = 7641 (%)	p-Value
Age (mean years) (range)	7914	54 (48–62)	59 (51–67)	<0.001
Age (years)				
<59		178 (65)	3779 (50)	
≥59		95 (35)	3862 (50)	
BMI kg/m ² (range)	6764	22 (20–25)	25 (22–29)	<0.001
Performance status	7914			=0.008
0		185 (68)	4523 (59)	
1		72 (26)	2708 (35)	
2/3		16 (6)	410 (5)	
FIGO stage	7914			<0.001
I		47 (17)	617 (8)	
II		9 (3)	266 (3)	
III		176 (65)	5777 (76)	
IV		41 (15)	981 (13)	
Histology	7914			<0.001
Serous		179 (66)	5630 (74)	
Clear-cell		43 (16)	473 (6)	
Endometrioid		18 (7)	613 (8)	
Mucinous		9 (3)	147 (2)	
Adenocarcinoma, NOS		3 (1)	119 (2)	
Mixed epithelial		15 (5)	472 (6)	
Other		6 (2)	187 (2)	
Tumor grade (differentiation)	7914			<0.001
1		15 (5)	579 (8)	
2		69 (25)	2309 [30]	
3		146 (54)	4355 (57)	
Ungraded		43 (16)	398 (5)	
Gross residual disease	7914			=0.63
Yes		129 (47)	3725 (49)	
No		144 (53)	3916 (51)	
Treatment	7914			<0.001
³² p		0 (0)	88 (1)	
CDDP + cyclophosphamide		9 (3)	377 (5)	
CDDP (IP) + cyclophosphamide		2 (1)	61 (1)	
CDDP + paclitaxel		19 (7)	910 (12)	
CDDP (IP) + paclitaxel		3 (1)	185 (2)	
Carboplatin + paclitaxel		117 (43)	2397 [31]	
Carboplatin + paclitaxel + other		50 (18)	2676 (35)	
Carboplatin + paclitaxel + bevacizumab		73 (27)	947 (12)	
GOG Protocol ^a	7914			<0.001
GOG-0095		2 (0.7)	182 (2.4)	
GOG-0104		3 (1.1)	120 (1.6)	
GOG-0111		4 (1.5)	343 (4.5)	
GOG-0114		7 (2.6)	467 (6.1)	
GOG-0157		9 (3.3)	270 (3.5)	
GOG-0158		17 (6.2)	681 (8.9)	
GOG Protocol (Con't)				
GOG-0172		12 (4.4)	372 (4.9)	
GOG-0175		45 (16.5)	431 (5.6)	
GOG-0182		63 (23.1)	3337 (43.7)	
GOG-0218		111 (40.7)	1438 (18.8)	

BMI = Body Mass Index.

CDDP = Cisplatin.

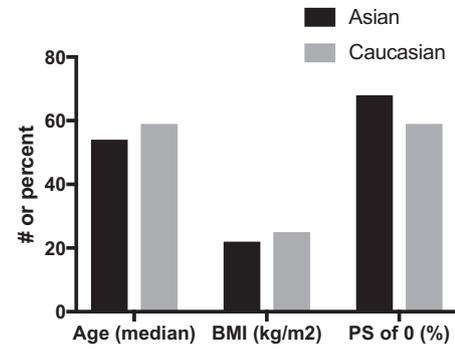
IP = Intraperitoneal.

^a Study period GOG-0095: 1986-1994 GOG-0104: 6/1986-7/1992 GOG-111: – GOG-114: 8/1992-4/1995 GOG-157: 3/1995-5/1998 GOG-158: – GOG-172: 3/1998-1/2001 GOG-175: 9/1998-12/2006 GOG-182: 1/2001-9/2004 GOG-218: 10/2005-6/2009.

4. Discussion

In this current study, we found that Asians were younger, had lower BMIs, and better performance status when compared to Caucasians. Even after adjusting for these factors, Asians still had better survival outcomes. Prior studies have shown that patients from Asia, Europe and the United States have different survival outcomes despite similar treatments with weekly chemotherapies [5–7]. Nevertheless, there may be

A.



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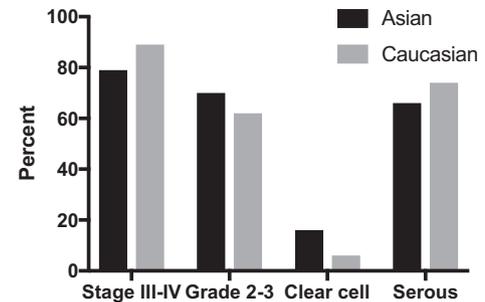


Fig. 1. Clinical and demographic information on study population. A) Age, BMI, Performance status (PS), B) Stage, grade, clear cell, serous histology compared between Asians and Caucasians.

differences in the extent of surgery, relative dose intensity and post recurrence treatments across these clinical trials. In this current report, the extent of cytoreductive surgery was comparable between Asians and Caucasians. Asians have been found to have fewer polymorphisms in drug metabolizing enzymes that can lead to decreased activity for paclitaxel such as CYP2C8*3 (9.5–17% in Caucasians vs 0% in Asians), CYP3A5*3, *6, *7 (85–98% in Caucasians vs 60–77% in Asians) [18]. Additionally, Asians have been found to receive a higher relative dose intensity of chemotherapy which may contribute to the improved survival [4]. Further translational studies are needed to correlate the genomic data with chemotherapy tolerance of Asian and other racial groups to demonstrate whether these genetic variations may result in better survival for Asians.

Additionally, germline mutations such as BRCA1 or BRCA2 have been found to be higher in certain Asian subgroups compared to Caucasians. For example, Wu et al. reported a 28.5% incidence of BRCA1 or BRCA2 germline mutations in Chinese ovarian cancer patients [19]. This is compared to an incidence of 15% of 1915 ovarian cancer patients identified from the University of Washington of gynecologic phase III clinical trials GOG 218 and 262, of which approximately 88% of the patients were non-Hispanic whites [21]. Higher response to cisplatin and overall survival has been reported in patients with BRCA mutations [22]. Similarly, improved outcomes have been reported for BRCA patients treated with PARP inhibitors [23]. These findings could, in part, help explain the better survival in Asians with ovarian cancer and can be studied in subsequent trials in which race/ethnicity and mutational status is controlled.

Similarly, improved overall survival in Asians compared to Caucasians has also been documented in lung cancer with the trend continuing to be seen when adjusting for risk factors such as surgical treatment (HR = 0.82; 95% CI: 0.79–0.86) [24] as well as in colorectal and breast cancer [25–27]. For example, the risk of death for patients with colorectal cancer was significantly lower for Asians than Caucasians (HR = 0.80; CI: 0.70–0.92) [25]. In the recent Annual Report to the Nation on the Status of Cancer, Jemal et al. noted that Asians had lower adjusted risk of cancer deaths for 12 out of 20 cancers [2]. The 5-year cause-

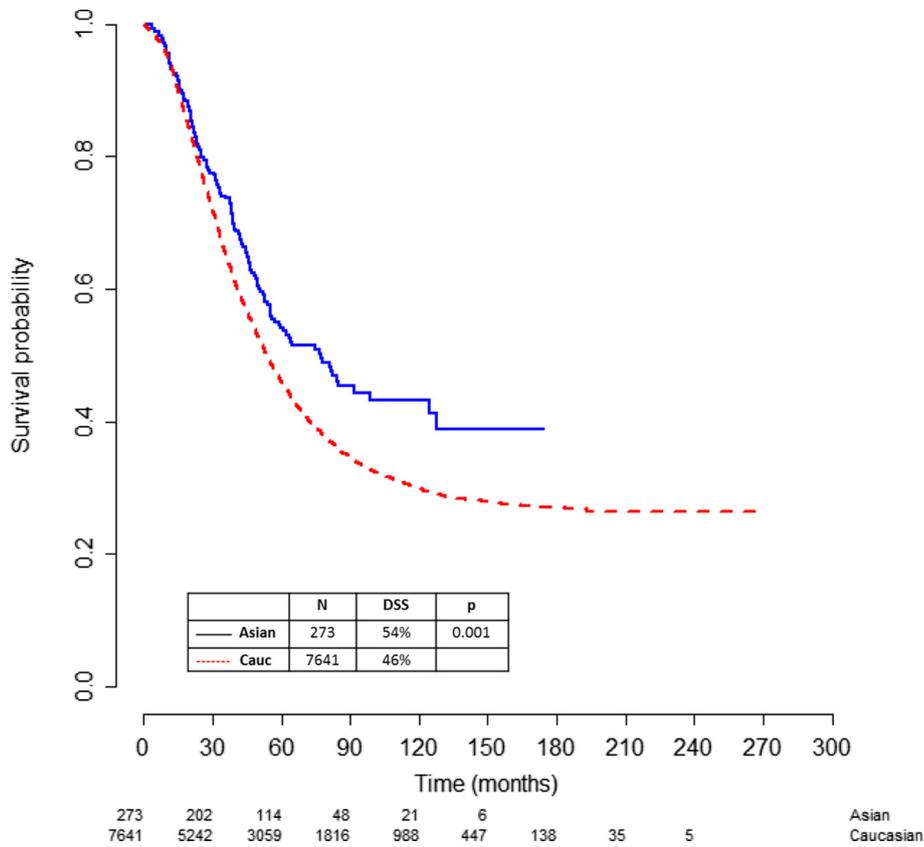


Fig. 2. 5-year disease-specific survival (DSS) of Asians compared to Caucasians. Asians had an improved 5-year DSS of 54% compared to 46% for Caucasians (p = 0.001).

specific survivals were 45.4% for the whites vs. 57.6% for Asian and Pacific Islanders. It is possible that social or economic differences, such as access to healthcare, may play a role in survival differences seen

Table 2
Kaplan-Meier 5-year disease-specific survival (N = 7914).

Variable	Total (%)	Asian (%)	Caucasian (%)	Log rank
Overall	46.4	54.1	46.1	0.001
Age				
≥59	42.3	47.3	42.2	0.050
BMI (n = 6764)				
<25	44.5	49.4	44.2	0.024
≥25	43.6	65.6	43.2	0.004
Performance status				
0	51.4	55.9	51.3	0.047
1	40.5	51.8	40.2	0.02
2/3	27.8	40.7	27.4	0.77
FIGO stage				
I	89.0	89.1	89.0	0.69
II	80.7	63.5	81.2	0.48
III	43.4	47.9	43.2	0.18
IV	25.5	36.9	25.0	0.045
Histology				
Serous	41.6	50.5	41.3	0.006
Clear-cell	59.9	61.3	59.8	0.64
Endometrioid	67.3	64.9	67.3	0.77
Mucinous	55.8	77.8	54.4	0.34
Adenocarcinoma	66.7	100.0	65.8	0.25
NOS mixed	52.8	33.3	53.5	0.09
Epithelial other	49.3	66.7	48.8	0.21
Tumor grade (differentiation)				
1	61.7	73.3	61.4	0.38
2	43.1	41.3	43.2	0.98
3	44.5	53.8	44.2	0.007
Ungraded	64.1	68.3	63.6	0.42
Gross residual disease				
Yes	32.9	41.6	32.5	0.02
No	58.9	64.9	58.7	0.03

Table 3
Kaplan-Meier 5-year all-cause survival (N = 7914).

Variable	Total (%)	Asian (%)	Caucasian (%)	Log rank
Overall	43.1	51.1	42.8	<0.001
Age				
<59	48.1	56.3	47.7	0.02
≥59	38.2	41.6%	38.1	0.046
BMI (n = 6764)				
<25.0	41.9	46.7	41.6	0.01
≥25.0	40.6	65.6	40.2	0.001
Performance status				
0	48.1	53.2	47.9	0.01
1	37.7	48.4	37.4	0.01
2/3	24.0	36.7	23.5	0.73
I	87.0	89.1	86.8	0.21
II	77.4	55.6	78.1	0.31
III	40.0	44.5	39.9	0.1
IV	23.6	34.4	23.1	0.04
Histology				
Serous	38.7	46.8	38.4	0.01
Clear-cell	56.8	61.3	56.4	0.34
Endometrioid	64.1	58.4	64.3	0.81
Mucinous	50.2	77.8	48.5	0.14
Adenocarcinoma.	47.0	100.0	45.8	0.13
NOS mixed	49.2	33.3	49.8	0.19
Epithelial other	47.8%	66.7	47.2	0.16
FIGO stage (range)				
I	87.0	89.1	86.8	0.21
II	77.4	55.6	78.1	0.31
III	40.0	44.5	39.9	0.1
IV	23.6	34.4	23.1	0.04
Tumor grade (differentiation)				
1	59.0	73.3	58.7	0.25
2	40.8	39.7	40.8	0.95
3	41.6	51.3	41.2	0.003
Ungraded	50.3	60.9	49.2	0.03
Yes	29.8	37.4	29.6	0.014
No	55.8%	62.3%	55.5%	0.009

Table 4
Multivariate disease-specific survival analysis (N = 7914).

	HR	95 CI	Log rank	
Age ≥59	1.01	1.01	−1.02	0.032
Asian (Caucasian)	0.78	0.64	−0.96	0.017
Body Mass Index (>25)	1.01	1.002221g1.01	−1.01	<0.001
Performance Status of 2 or 3 (0)	1.49	1.33	−1.67	<0.001
Stage III (Stage 1)	7.83	6.29	−9.75	<0.001
Stage IV (Stage 1)	11.46	9.09	−14.4	<0.001
Clear-cell histology (serous)	2.04	1.72	−2.43	<0.001
Grade 3 (Grade 1)	1.38	1.22	−1.57	<0.001
No residual disease (residual)	0.65	0.61	−0.70	<0.001

among ethnicities. These findings support our data showing that for cancer patients there may be underlying treatment and biologic differences that contribute to the better outcome with treatment.

Our current data analysis supports that, in a clinically well-annotated study, Asians continued to have an improved disease-specific survival compared with Caucasians. Bandera et al. [4] showed improved outcome for Asians vs Caucasians although, in their study, the differences were not statistically significant. The differences in surgery, varying chemotherapy regimens, lack of adjustment for extent of gross residual disease and potential differences in Asian subgroups in our GOG cohorts compared to those in the Bandera et al. may in part explain the differences in our findings [4]. Our prior study using the National Cancer Institute SEER data was limited by lack of standardized staging, extent of cytoreduction, type of treatment, surveillance and central pathology review. The use of prospectively collected data from cooperative group randomized trials on uniform protocols helps to minimize some of these deficits since enrollment for the GOG trials have standardized staging, performance status and comorbidity exclusion criteria. The strengths of the study are the following: offers the first large-scale study with central pathology review, standardized treatment by gynecologic oncologists and well-documented clinical follow-up. Unique to this study, we were able to address differences in Asians versus Caucasians on performance status, BMI, residual disease and treatment regimens particularly in all patients who received a platinum-based regimen.

Our study was limited by the small sample size of Asians for ovarian trials [30] and we did not undertake additional analyses based on Asian subgroups or on patients' immigration status and duration of living in USA prior to diagnosis. We are also limited in knowing how many of the Asian women in this study were from Asia. The recommended dose and received dose by the patient were not evaluated. It is possible that Asians tolerated more cycles of chemotherapy, which may have biased their improved survival [4]. Given the small numbers of Asians receiving particular treatment regimens, such subsets for intraperitoneal chemotherapy versus bevacizumab-containing regimens, a sub-analysis to determine whether Asians had an improved survival due to particular treatment regimens was not feasible. A prior study from our group showed that immigration affected survival [3]. Additionally, there were proportionally fewer Asians enrolling on clinical trials than based on the population, this may have been due to a cultural barrier and additional patient navigation resources could be useful.

In this first analysis evaluating clinico-demographic, clinical outcomes and survival differences in Asians and Caucasians from the clinically, well-annotated NRG/GOG database of 10 prospective, randomized clinical trials, we found that Asian patients were younger, had better GOG performance status and lower body-mass index at diagnosis. Asian race was found to be an independent predictor for disease-specific survival. Future international collaborative projects comparing demographic, socioeconomic, environment, genetic and pharmacogenomics of Asian vs. Caucasian patients treated with similar regimens may help us better understand racial differences in ovarian cancer survival.

Author contributions

All authors provided data, were involved in writing, revision, and approved the final manuscript. Dr. Java performed the statistical analyses of this study.

Declaration of Competing Interest

The authors have no conflicts of interest with the exception of Dr. Java who reports an immediate family member serving as a consultant and receiving honoraria from Merck KGaA. Dr. Chan reports receiving honoraria from AstraZeneca, Clovis, Roche and Tesaro and serving as a consultant for these companies. Dr. Chan also participates in the Speakers' bureau and has received travel, accommodations or reimbursement for such. Dr. Burger reports receiving personal fees from Genentech outside of the submitted work. Maurie Markman reports that he is employed as the President, Medicine and Science for Cancer Treatment Centers and he has received honoraria from Astra-Zeneca, Clovis, Genentech and Tesaro and participates in the Speakers bureau for these companies. Dr. Markman has served as a consultant for Celgene, Merck and Delmar Pharmaceuticals. Dr. Ozols serves as an advisor on DSMB's and IDMC's for Pfizer, Johnson & Johnson, Clovis, Astra Zeneca, Gradalis and Syndax.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ygyno.2019.05.013>.

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