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Prognostic Significance of Ethnicity and Age in Advanced Stage Epithelial Ovarian Cancer: An NRG Oncology/Gynecologic Oncology Group Study

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Study concept for design: Drs. duPont, Monk, Burger and Brady

Provision of materials or patients: Drs. Moxley, Walker, Rubin, Cosgrove, Bixel, Wahner Hendrickson, Fujiwara, Soper, Moore, Casey, Tewari, Thaker, Wahner-Hendrickson, Soper, Burger and Monk.

Acquisition of data: All

Analysis and interpretation of data: Drs. Enserro, Brady, duPont, Monk and Burger

Manuscript writing: Drs. duPont, Monk, Burger and Enserro

Critical review of manuscript: All

Final approval of manuscript: All

CONFLICTS OF INTEREST

Conflict of Interest Statement: This research was conducted by grant support from Roche-Genentech. Roche-Genentech provided support for GOG 218 with drug supply and funds to conduct the clinical trial.

Dr. Nefertiti duPont received a GOG Young Investigator Award from Genentech. She participated on a GSK gynecologic malignancy virtual advisory board, Sanara MedTech surgical advisory board, AstraZeneca and Merck advisory boards; HCA Houston Healthcare, Northwest Chief of Staff (2020) and Immediate Past Chief of Staff (current); SGO Ethics Committee Vice Chair (current), HCA Houston Healthcare, Northwest Credentials Committee, Chair (current).

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Dr. Robert Burger received consulting fees from Tesaro, Genentech, Agenus, Myriad and Merck. He also received support for attending meetings and/or travel from Tesaro and Genentech. He participated on a Data Safety Monitoring Board or Advisory Board from Morphotek. He has stock/stock options from Genentech when employed from 5/2020 to 11/2020 (relinquished upon resignation) and Mersana Therapeutics as an employee from 11/2020 to present, stock options only. He received other financial or non-financial interests from Genentech as an employee from 5/2020 to 11/2020 and also Mersana Therapeutics as employee from 11/2020 to present.

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Abstract

Background: Age and ethnicity are among several factors that influence overall survival (OS) in ovarian cancer. The study objective was to determine whether ethnicity and age were of prognostic significance in women enrolled in a clinical trial evaluating the addition of bevacizumab to front-line therapy.

Methods: Women with advanced stage ovarian, primary peritoneal, or fallopian tube cancer were enrolled in a phase III clinical trial. All women had surgical staging and received adjuvant chemotherapy with one of three regimens. Cox proportional hazards models were used to evaluate the relationship between OS with age and race/ethnicity among the study participants.

Results: One-thousand-eight-hundred-seventy-three women were enrolled in the study. There were 280 minority women and 328 women over the age of 70. Women age 70 and older had a 34% increase risk for death when compared to women under 60 (HR=1.34; 95% CI 1.16–1.54). Non-Hispanic Black women had a 54% decreased risk of death with the addition of maintenance bevacizumab (HR=0.46, 95% CI:0.26–0.83). Women of Asian descent had more hematologic grade 3 or greater adverse events and a 27% decrease risk of death when compared to non-Hispanic Whites (HR=0.73; 95% CI: 0.59-.90).

Conclusions: Non-Hispanic Black women showed a decreased risk of death with the addition of bevacizumab and patients of Asian ancestry had a lower death rate than all other minority groups, but despite these clinically meaningful improvements there was no statistically significant difference in OS among the groups.

Keywords

Minority populations; Asian women; African American women; elderly; ovarian cancer; bevacizumab

INTRODUCTION

Approximately 60% of women affected with epithelial ovarian cancer will present with advanced stage disease [1]. While much has been done to improve the treatment of this disease, overall survival (OS) for advanced stage disease is approximately 30% [1–3]. Prior studies have established age, stage, volume of residual disease, histology, and performance status as prognostic factors for epithelial ovarian cancer [4–6]. In addition to these prognostic factors, racial and ethnic disparities have been reported as an important factor in ovarian cancer survival [7–9]. When ovarian cancer survival data is examined from national databases OS is shorter among Black and Hispanic women when compared to White women [7–13]. These differences are due partly to the lack of access to high volume providers and insurance status [7–19]. However, several studies from large clinical trials show that when treatment factors are equal there is no difference in survival between Black and White women [15, 20–21]. The Gynecologic Oncology Group (GOG) published two similar retrospective analyses of six phase III clinical trials in White and Black patients [5, 22]. These two studies evaluated the same series of patients and categorized patients as Black, White, or other [5, 22]. Women in these trials received paclitaxel and a platinum-based regimen and no difference in OS was seen among these two racial groups [5, 22]. However, these studies limited their analyses to mainly Black and White patients [5, 22]. The purpose of the current study is to evaluate the prognostic significance of ethnicity and age in women enrolled in the context of a large phase III clinical trial.

Materials and Methods

Women with surgically staged epithelial ovarian, primary peritoneal, or fallopian tube cancer were enrolled in GOG-218, a phase III clinical trial, and randomized to one of three treatment regimens (Figure 1). Women in the control arm received adjuvant carboplatin and paclitaxel for 6 cycles followed by 16 cycles of placebo every 4 weeks. Women randomized to arm II received adjuvant carboplatin and paclitaxel for 6 cycles with the addition of bevacizumab starting with the second cycle of chemotherapy for a total of 5 cycles. Patients in arm II received placebo for an additional 16 cycles after the completion of primary therapy. Patients in arm III received the same chemotherapy as patients in arm II but with the addition of bevacizumab maintenance therapy for 16 cycles after the completion of primary therapy with carboplatin, paclitaxel, and bevacizumab. The details of the eligibility criteria and chemotherapy regimens have been previously published [23]. All patients gave written informed consent before enrollment.

An analysis of patients enrolled in GOG-218 was conducted to evaluate the prognostic significance of race and ethnicity, and age on treatment outcomes and OS. Follow-up data was frozen as of January 16, 2018.

The cumulative probability distributions of survival times were estimated with Kaplan-Meier procedures [24]. Differences in OS were assessed with the log-rank test. Duration of survival for each patient was calculated from the date of entry onto the study until the date of death, regardless of the cause of death. For those women who were alive at last contact, the time at risk of death was calculated up to the date of last contact. Cox proportional hazards

models were used to estimate the relative hazards of death for subgroups of patients [25]. Pearson's chi-squared test or Fisher's exact test were used to evaluate grade 3 toxicity by age and grade 3 toxicity by race/ethnicity. The Kruskal-Wallis rank test was used to compare patient subgroups with respect to age [26]. The presented p-values are nominal and do not account for testing multiple hypotheses. Finally, a test of interaction was used to assess for differences in treatment effect on OS in race/ethnicity groups and age groups.

RESULTS

One-thousand-eight-hundred-seventy-three women were enrolled in GOG-218 and 14.9% of the patients were of a racial or ethnic minority (Table 1). Three-hundred and twenty-eight women were age 70 or older and 32 women were age 80 or older. The characteristics of enrolled patients by age group are described in Table 2. Eighty-five percent of the patients enrolled had papillary serous histology. The distribution of age at diagnosis varied by primary site of cancer ($p<0.001$) with women diagnosed with primary peritoneal cancer (median age=64.6) being older than women with ovarian cancer (median age=59.1) or fallopian tube cancer (median age=61.3). Women diagnosed with a transitional cell carcinoma tended to be younger (median age=52.2) than women diagnosed with serous (median age=60.7) or endometrioid (median age=58.3) histology, $p<0.001$. Ninety-percent of women ages 70 or older had a GOG performance status of 0 or 1 compared to 95% of women who were <60 (Table 2). Therefore, increasing age correlated with a decrease in performance status ($p<0.001$). The distribution of age at diagnosis varied by race and ethnicity separately ($p<0.001$ for both).

OS curves by age group show increased risk of death with increasing age ($p<0.001$; Figure 2, Table 3). The hazard ratios (HR) for OS adjusted for stage and treatment showed that women who were 60 to 69 years of age had an 18% increase risk of death (HR=1.18; 95% CI: 1.05–1.32) and women age 70 or older had a 34% increase risk of death when compared to women under 60 (HR=1.34; 95% CI 1.16–1.54). Grade 3 or greater toxicities also varied by age with patient's age 70 years or older having more cardiac, musculoskeletal, metabolic, neurologic, and hematologic toxicities than other age groups (Table 4).

OS curves show a significant difference in OS among the race/ethnicity subgroups ($p=0.017$; Figure 3, Table 3). In particular, the HR for OS adjusted for stage and treatment show that women of Asian/PI ancestry had a 27% decrease risk of death as compared to non-Hispanic Whites (HR=0.73; 95% CI: 0.59–0.90). When toxicity was examined by race/ethnicity, women of Asian descent had more hematologic grade 3 or greater adverse events (Table 5). Interestingly, women of Asian descent were more likely to have a normal body mass index (BMI) than other racial groups (Table 1). Although not statistically significant, native Korean women had a median OS of 91.7 months compared to 55.9 months in Japanese women and 43.2 months for Asian women from the US (Figure 4, Table 3).

In terms of treatment effect with the addition of first-line or maintenance bevacizumab there was no difference among the three treatment arms in terms of age ($p=0.73$) and race/ethnicity ($p=0.16$) (Figure 5). However, non-Hispanic Black patients who were randomized to receive maintenance bevacizumab had a 54% decreased risk of death adjusted for stage

and performance status as compared to non-Hispanic Black patients in the control group (HR=0.46, 95% CI: 0.26–0.83) (Figure 5).

DISCUSSION

The goal of GOG-218 was to determine if front-line or maintenance bevacizumab impacted progression free survival (PFS) in women with surgically staged advanced ovarian cancer. The addition of upfront and maintenance bevacizumab to the standard regimen of intravenous carboplatin and paclitaxel offered patients a 3.8 month increase in PFS over placebo however, there was no improvement in OS [23,27]. The goal of this sub analysis was to determine if there was a difference in outcome in women of different ethnic or racial groups or in elderly women enrolled in GOG-218.

The results of this sub-analysis showed an improvement in survival in non-Hispanic Black women who received upfront and maintenance bevacizumab. These findings can be explained by the fact that non-Hispanic Black women enrolled in GOG-218 were more likely to have suboptimal debulking after primary surgery and 25% of these women had stage IV cancer. Therefore, the extended use of bevacizumab may have been beneficial to this high risk group of patients. The final results of GOG-218 showed that patients with stage IV cancer who received upfront and maintenance bevacizumab had a median OS advantage of 42.8 vs 32.6 months (27). Therefore, patients with suboptimal residual disease after primary surgery or stage IV disease may be the best patient population to offer upfront and maintenance bevacizumab with standard cytotoxic chemotherapy for the treatment of ovarian cancer (27).

We present one of the first reports in ovarian cancer comparing native Asian women and US women of Asian ancestry to other racial groups receiving similar treatment [28]. While a statistically significant difference in OS among the different racial groups was not seen in this clinical trial, a clinically meaningful lower death rate was seen in all Asian women when compared to non-Hispanic White women. This difference is not believed to be treatment related due to the advantages of a randomized clinical trial but may have been related to the lower BMI seen in women of Asian ancestry and other factors that were not explored in this trial such as surgical aggressiveness and diet. The lower BMI seen in women of Asian ancestry may have led to the higher level of severe hematologic toxicities but also to the higher survival rates seen in this patient population since chemotherapy dosing may be more efficient in normal weight patients.

Zhang *et al.* studied the differences in the survival rate of patients with nine different cancers based upon race and ethnicity [29]. They used the SEER database to evaluate over 950,000 patients over a five-year period [29]. The authors showed that Black and Hispanic patients had lower cancer specific survival than Asian or White patients [29]. This study highlights the fact that more research is needed to understand all the factors that affect the cancer specific survival of minority populations with gynecologic malignancies. Other investigators have examined the outcome of ovarian cancer care in racial minorities, and they have shown that when treatment factors are equal, disparities are due to insurance status and differential

access to high volume hospitals and high-volume surgeons [7–11, 19, 21]. These factors may play a larger role in OS than race or ethnicity.

Older patients with ovarian cancer face outcome disparities due to their perceived frailty and co-morbidities and they are likely to experience lower rates of cytoreductive surgery in favor of conservative treatments [30–31]. In this report, patients 70 years and older had significant cardiac, musculoskeletal, metabolic, neurologic and hematologic toxicities than younger participants. Perri *et al.* evaluated a retrospective cohort of 169 patients with different gynecologic malignancies who were age 79 and older [31]. Twenty-six percent of their patient population had ovarian cancer [31]. Perri *et al.* showed that for all patients with suboptimal treatment the age and stage adjusted HR for death was 1.76 when compared to patients who had optimal treatment [31]. In the current study, women who were over 60 had an increased risk of death compared to women under 60 despite similar treatment. Therefore, as the US population ages finding ways to ameliorate this risk factor could improve care to the growing elderly patient population.

This study is a post-hoc analysis and was not powered to evaluate the prognostic significance of ethnicity and age, therefore, this is the main limitation of this study. Another limitation is the small number of minority and elderly women enrolled in this large, randomized phase III clinical trial. Women enrolled in clinical trials are commonly treated at academic medical centers while most adult cancer patients in the US receive care in non-academic community centers and therefore most clinical trials will have limitations on the generalizability of the study findings to the broader US population [32]. In addition, the number of women enrolled from Japan and Korea was small despite the data showing intriguing outcomes. Despite these limitations this study highlights the importance of increasing the number of elderly patients and racial/ethnic minorities in clinical trials so that our trials will be more representative of the patient population and when enrollment reflects the general cancer population our data will provide better personalization of cancer care.

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RESEARCH HIGHLIGHTS

- Black women were more likely to have suboptimal debulking but a decreased risk of death with extended bevacizumab
- A clinically meaningful lower death rate was seen in all Asian women when compared to non-Hispanic White women
- Native Asian women had a trend towards a longer median overall survival when compared to American women of Asian ancestry
- Enrolling more elderly and racial/ethnic minority patients is needed for better personalization of cancer care

RESEARCH HIGHLIGHTS

- Non-Hispanic black women had a decreased risk of death with upfront and maintenance bevacizumab
- Women of Asian ancestry had a decreased risk of death when compared to white women
- Native Asian women had a longer median overall survival rate when compared to American women of Asian ancestry

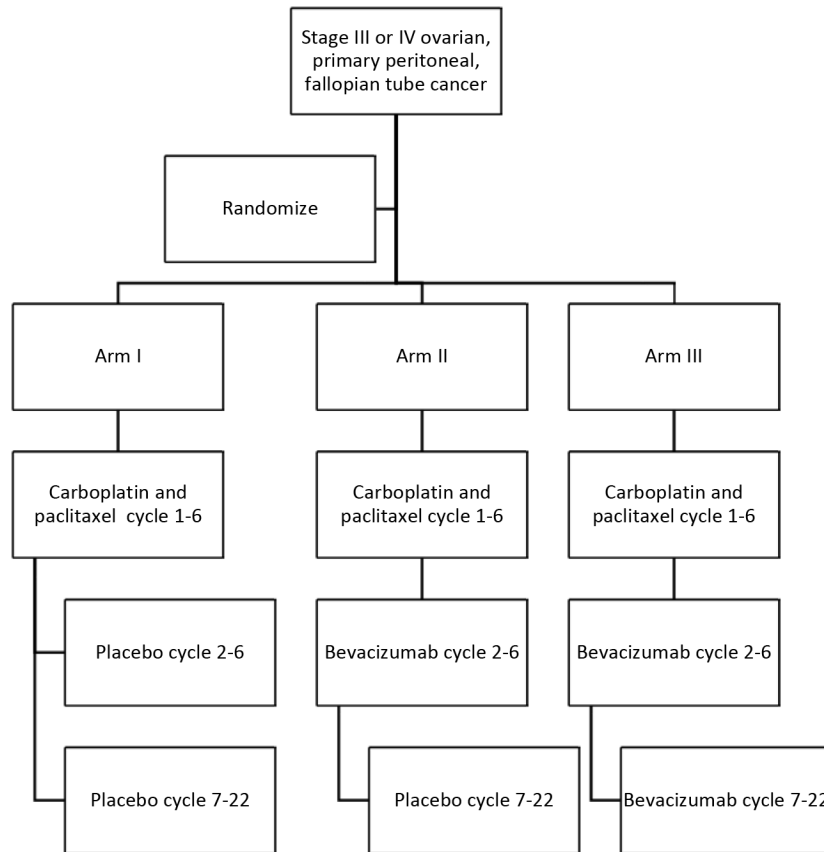


Figure 1. Schema for Gynecologic Oncology Group protocol 218.

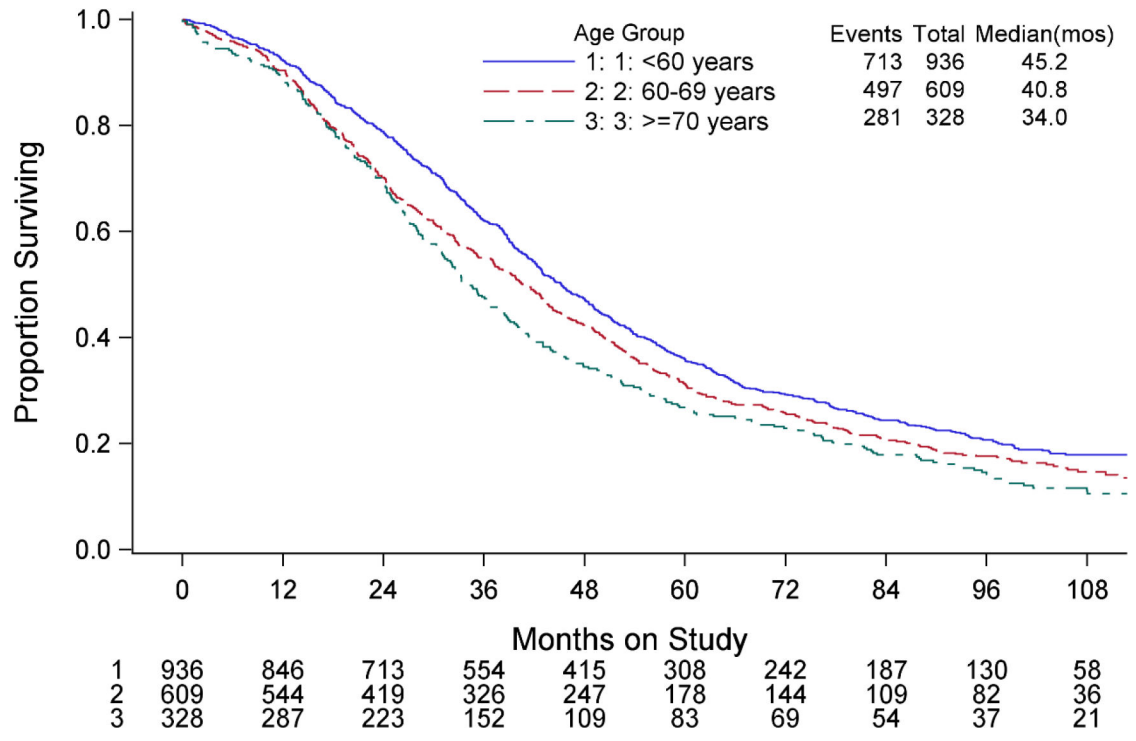


Figure 2.
Overall survival by age group.

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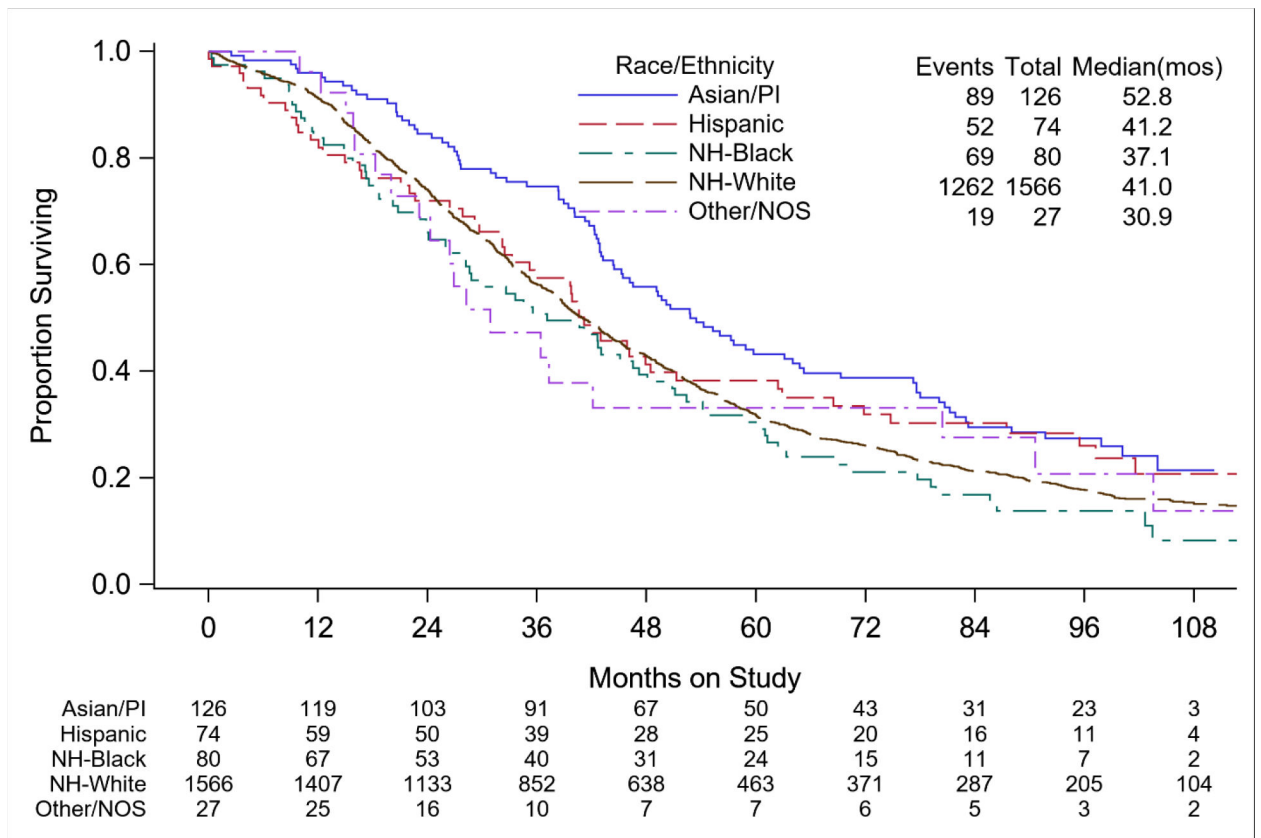


Figure 3. Overall survival by race and ethnicity.

PI=Pacific Islander, NH=Non-Hispanic, NOS=Not specified or unknown

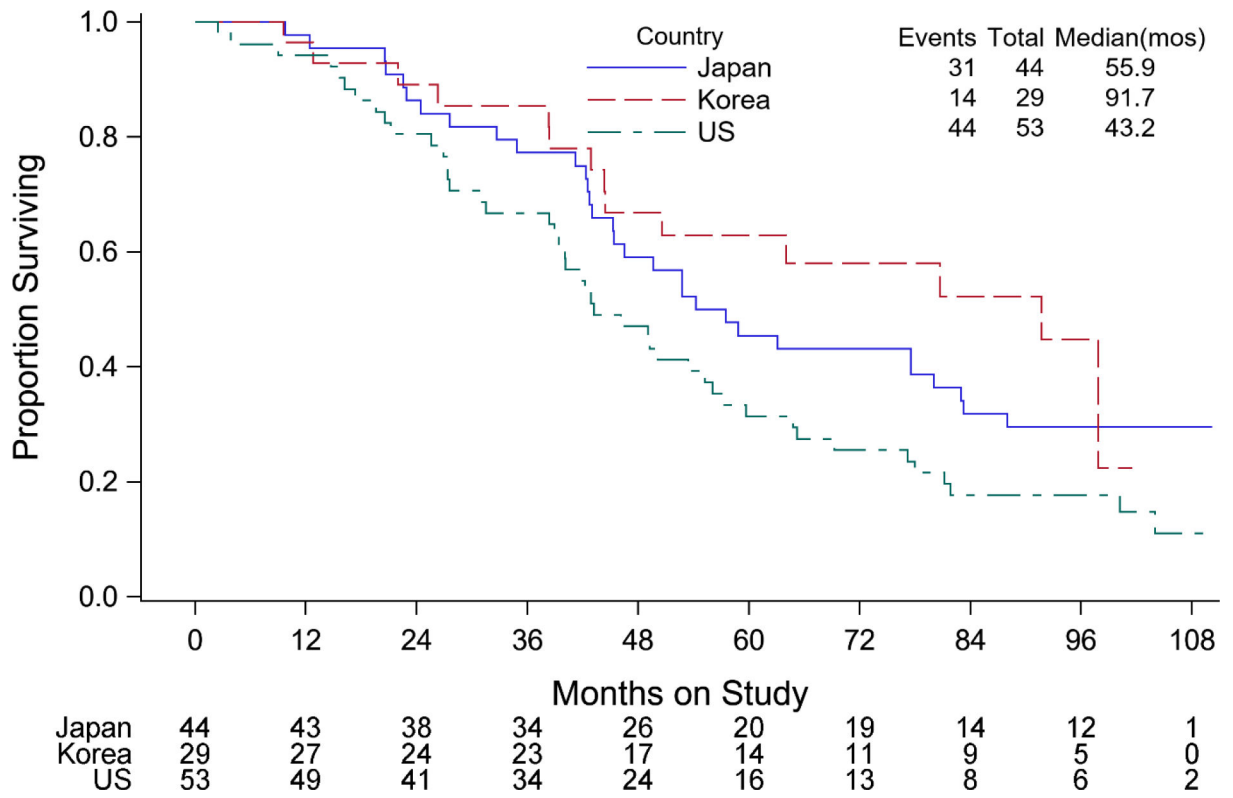


Figure 4. Overall survival for Asian patients by country of origin.

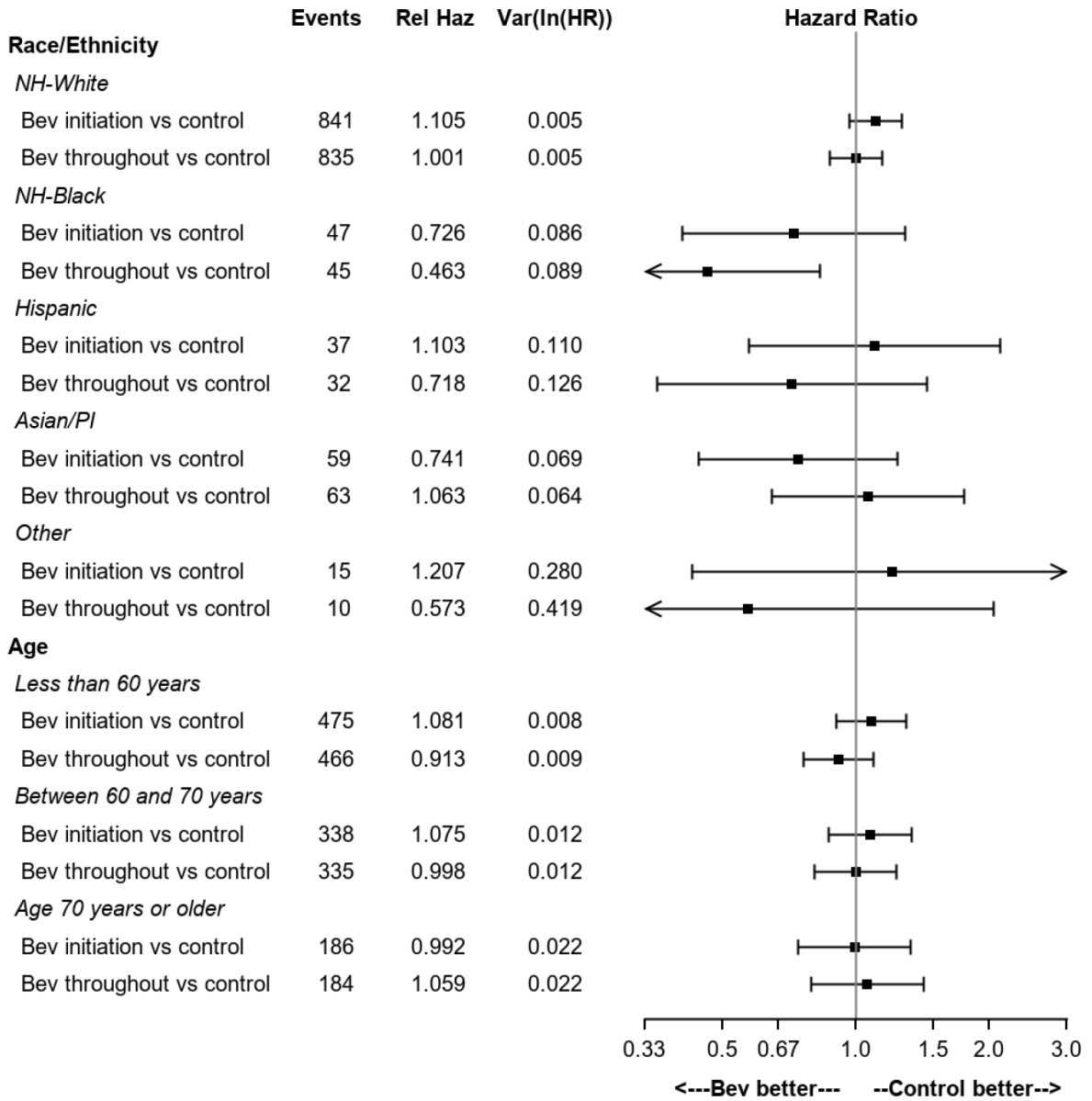


Figure 5. Treatment effect on overall survival by race/ethnicity and age.
 The treatment regimens were carboplatin, paclitaxel and placebo for cycles 1–6 followed by placebo for cycles 7–22 (CTP->Placebo); carboplatin, paclitaxel for cycles 1–6 and bevacizumab for cycles 2–6 followed by placebo for cycles 7–22 (CTB->Placebo); carboplatin, paclitaxel for cycles 1–6 and bevacizumab for cycles 2–6 followed by bevacizumab for cycles 7–22 (CTB->Bevacizumab). PI=Pacific Islander, NH=Non-Hispanic.

Table 1

Patient characteristics by race and ethnicity.

Patient characteristic		NH-White n %	NH-Black n %	Hispanic n %	Asian/Pacific Islander n %	Other n %	Total
Treatment	CTP- > Placebo	526 (33.6)	25 (31.3)	21 (28.4)	46 (36.5)	7 (25.9)	625
	CTB- > Placebo	519 (33.1)	28 (35.0)	28 (37.5)	39 (31.0)	11 (40.7)	625
	CTB- > Bevacimmab	521 (33.3)	27 (33.8)	25 (33.5)	41 (32.5)	9 (33.3)	623
Age Cioup	<60 years	752 (48.0)	38 (47.5)	51 (68.9)	80 (63.5)	14 (51.9)	935
	60–69 years	518 (33.1)	32 (40.0)	14 (18.5)	38 (30.2)	8 (29.6)	610
	70 years	296 (18.9)	10 (12.5)	9 (12.2)	8 (6.3)	5 (18.5)	328
Performance Status	0	761 (48.6)	41 (51.3)	37 (50.0)	81 (64.3)	11 (40.7)	931
	1	697 (44.5)	31 (38.8)	32 (43.2)	38 (30.2)	11 (40.7)	809
	2	108 (6.9)	8 (10.0)	5 (6.5)	7 (5.6)	5 (18.5)	133
Primary Site	Ovary	1300 (83.0)	73 (91.3)	63 (85.1)	109 (86.5)	18 (66.7)	1563
	Fallopian tube	30 (1.9)	0 (0.0)	3 (4.1)	2 (1.6)	1 (3.7)	36
	Primary peritoneum	236 (15.1)	7 (8.8)	8 (10.8)	15 (11.9)	8 (29.6)	274
Histology	Papillaiy serous	1342 (85.7)	67 (83.8)	58 (78.4)	96 (76.2)	22 (81.5)	1585
	Endometrioid	45 (3.1)	4 (5.0)	1 (1.4)	6 (4.8)	0 (0.0)	59
	Clear cell	40 (2.6)	1 (1.3)	4 (5.4)	7 (5.6)	3 (11.1)	55
	Mucinous	15 (1.0)	1 (1.3)	1 (1.4)	1 (0.8)	1 (3.7)	19
	Adenocarcinoma, not specified	20 (1.3)	0 (0.0)	0 (0.0)	4 (3.2)	0 (0.0)	24
	Transitional cell	10 (0.6)	2 (2.5)	0 (0.0)	4 (3.2)	0 (0.0)	16
	Mixed adenocarcinoma	64 (4.1)	5 (6.3)	9 (12.2)	6 (4.8)	1 (3.7)	85
	Undifferentiated carcinoma	20 (1.3)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	21
	Other	7 (0.4)	0 (0.0)	0 (0.0)	2 (1.6)	0 (0.0)	9
Stage, Residual size	III-optimal	537 (34.3)	22 (27.5)	25 (33.5)	46 (36.5)	10 (37.0)	640
	III-subofstimal	629 (40.2)	38 (47.5)	24 (32.4)	51 (40.5)	10 (37.0)	752
	IV	400 (25.5)	20 (25.0)	25 (33.5)	29 (23.0)	7 (25.9)	481
BMI	<25	703 (44.9)	22 (27.5)	34 (45.9)	100 (79.4)	8 (29.6)	867
	25–29.9	424 (27.1)	18 (22.5)	22 (29.7)	21 (16.7)	7 (25.9)	492
	230	439 (28.0)	40 (50.0)	18 (24.3)	5 (4.0)	12 (44.4)	514
Total		1566	80	74	126	27	1873

The treatment regimens were carboplatin, paclitaxel and placebo for cycles 1–6 followed by placebo for cycles 7–22 (CTP->Placebo); carboplatin, paclitaxel for cycles 1–6 and bevacizumab for cycles 2–6 followed by placebo for cycles 7–22 (CTB->Placebo); carboplatin, paclitaxel for cycles 1–6 and bevacizumab for cycles 2–6 followed by bevacizumab for cycles 7–22 (CTB->Bevacizumab). Twenty-seven patients were listed in the other category and this group comprised seven American Indian/Alaskan native patients and twenty patients who did not specify a racial or ethnic group. NH=Non-Hispanic.

Table 2

Pattern characteristics by age group (on-line only).

Patient characteristics		Age Group (years)			Total
		<60 n(%)	60–69 n(%)	70 n(%)	
Study Regimen	CTP- > Placebo	307 (32.8)	214 (35.1)	104 (31.7)	625
	CTB- > Placebo	307 (32.8)	201 (33.0)	117 (35.7)	625
	CIB- > Bevacmrnub	321 (34.3)	195 (32.0)	107 (32.6)	623
Performance status	0	504 (53.9)	296 (48.5)	131 (39.9)	931
	1	381 (40.7)	263 (43.1)	165 (50.3)	809
	2	50 (5.3)	51 (8.4)	32 (9.8)	133
Primary site	Ovary	835 (89.3)	477 (78.2)	251 (76.5)	1563
	Fallopian tube	16 (1.7)	15 (2.5)	5 (1.5)	36
	Primary peritoneum	84 (9.0)	118 (19.3)	72 (22.0)	274
Histologic type	Papillary serous	760 (81.3)	528 (86.6)	297 (90.5)	1585
	Endometrioid	35 (3.7)	17 (2.8)	7 (2.1)	59
	Clear cell	37 (4.0)	15 (2.5)	3 (0.9)	55
	Mucinous	12 (1.3)	6 (1.0)	1 (0.3)	19
	Transitional	16 (1.7)	0 (0.0)	0 (0.0)	16
	Other	75 (8.0)	44 (7.2)	20 (6.1)	139
Total		935	610	328	1873

The treatment regimens were carboplatin, paclitaxel and placebo for cycles 1–6 followed by placebo for cycles 7–22 (CTP->Placebo); carboplatin, paclitaxel for cycles 1-6 and bevacizumab for cycles 2–6 followed by placebo for cycles 7–22 (CTB->Placebo); carboplatin, paclitaxel for cycles 1–6 and bevacizumab for cycles 2–6 followed by bevacizumab for cycles 7–22 (CTB->Bevacizumab).

Table 3

Kaplan-Meier overall Survival estimates.

		Events / At-risk	Median (95% CI), montlis
Age Group	<60 yews	713 / 936	452 (42.5–48.5)
	60–69 years	497 / 609	408 (37.1–43.7)
	70 yews	281 / 328	34.0(31.0–38.4)
Race & Ethnicity	Asian/PI	89 / 126	528(44.4–64.8)
	Hispanic	52/74	412(32.4–51.3)
	NH-Black	69/80	37.1 (28.1–472)
	NH-White	1262 / 1566	41.0 (39.0–43.0)
	Other/NOS	19 / 27	30.9(23.1–80.4)
Asian/Pi by country of origin	Japan	31 / 44	559(43.0–83.0)
	Korea	14 / 29	91.7(44.3 – undefined 1
	US.	44 / 53	432 (38.9–56.0)

PI=Pacific Islander, NH=Non-Hispanic, NOS=Not specified or unknown Twenty-seven patients were listed in NOS category and this group comprised seven American Indian/Alaskan native patients and twenty patients who did not specify a racial or ethnic group.

Table 4

Severe patient toxicities (grade 3) by age (on-line only).

System Organ Class	<60 years (n = 935)	60–69 years (n = 610)	170 years (n=32S)	Pearson Chi-squared P-value
Auditory/Eat	1 (0.1)	2 (0.3)	1 (0.3)	0.51*
Allergy/Immunology	39 (4.2)	17 (2.3)	6 (1.3)	0.08
Coagulation	8 (0.9)	7 (1.1)	6 (1.3)	0.35
Constitutional Symptoms	96 (10.3)	75 (12.3)	41 (12.5)	0.36
Cardiac	46 (4.9)	56 (9.2)	46 (14.0)	<0.001
Dermatology/Skin	29 (3.1)	17 (2.3)	3 (0.5)	0.10
Death	7 (0.7)	11 (1.5)	5 (1.5)	0.16
Endocrine	7 (0.7)	3 (0.5)	0 (0.3)	0.36*
Gastrointestinal	154 (16.5)	118 (19.3)	59 (18.3)	0.35
Renal/Genitourinary	14 (1.5)	10 (1.3)	5 (1.5)	0.57
Hemorrhage/Bleeding	15 (1.6)	11 (1.3)	4 (1.2)	0.79
Hematologic/Toxicity	810 (86.6)	554 (90.8)	298 (90.9)	0.016
Hepatobiliary/Pancreas	4 (0.4)	1 (0.2)	1 (0.3)	0.86*
Infection	111 (11.5)	84 (13.8)	50 (15.2)	0.25
Lymphatics	3 (0.3)	4 (0.7)	3 (0.5)	0.33*
Secondary Malignancy	2 (0.2)	0 (0.0)	0 (0.3)	0.67*
Musculoskeletal/Soft Tissue	18 (1.5)	13 (2.1)	22 (6.7)	<0.001
Metabolic/Laboratory	119 (12.7)	98 (13.1)	66 (20.1)	0.004
Neurology	70 (7.5)	67 (11.0)	73 (22.3)	<0.001
Ocular/Visual	2 (0.3)	3 (0.5)	4 (1.2)	0.07*
Pulmonary/Upper Respiratory	41 (4.4)	31 (5.1)	25 (7.6)	0.07
Pain	141 (15.1)	81 (13.3)	35 (10.7)	0.13
Sexual Reproductive Function	1 (0.1)	0 (0.0)	0 (0.3)	1.00*
Vascular	46 (4.5)	37 (6.1)	25 (7.6)	0.18

Adverse events graded with CTCAE version 3.

* Denotes p-value from Fisher's exact test.

Table 5

Severe patient toxicities (grade 3) by race/ethnicity (on-line only).

System Organ Class	NH-White (n = 1566)	NH-Black (n = 80)	Hispanic (n = 74)	Asian/PI (n = 126)	Other (n = 27)	Pearson Chi-squared P-value*
Auditory/Ear	3 (0.2)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0.51*
Allergy/Immunology	53 (3.4)	3 (3.8)	1 (1.4)	4 (3.2)	1 (3.7)	0.90*
Coagulation	21 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.66*
Constitutional Symptoms	183 (11.7)	9 (11.3)	10 (13.5)	8 (6.3)	2 (7.4)	0.40
Cardiac	125 (8.0)	6 (7.5)	6 (8.1)	8 (6.3)	3 (11.1)	0.93
Dermatology/Skin	40 (2.6)	2 (2.5)	1 (1.4)	4 (3.2)	2 (7.4)	0.44*
Death	21 (1.3)	0 (0.0)	2 (2.7)	0 (0.0)	0 (0.0)	0.39*
Endocrine	10 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.00*
Gastrointestinal	286 (18.3)	15 (18.8)	9 (12.2)	14 (11.1)	7 (25.9)	0.14
Renal/Cenitourinary	27 (1.7)	1 (1.3)	1 (1.4)	0 (0.0)	0 (0.0)	0.67*
H emorrhage/Bleeding	29 (1.9)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0.72*
Hematologic Toxicity	1394 (89.0)	66 (82.5)	58 (78.4)	121 (96.0)	23 (85.2)	0.001
Hepatobiliary/Pancreas	3 (0.2)	0 (0.0)	1 (1.4)	1 (0.8)	1 (3.7)	0.025*
Infection	213 (13.6)	9 (11.3)	6 (8.1)	12 (9.5)	5 (18.5)	0.36
Lymphatics	9(0.6)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0.83*
Secondary Malignancy	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.00*
Musculoskeletal/Soft Tissue	42 (2.7)	4 (5.0)	3 (4.1)	4 (3.2)	0 (0.0)	0.54*
Metabolic/Laboratory	230 (14.7)	18 (22.5)	12 (16.2)	17 (13.5)	6 (22.2)	0.29
Neurology	180 (11.5)	5 (6.3)	12 (16.2)	8 (6.3)	5 (18.5)	0.08
Ocular/Visual	8 (0.5)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0.66*
Pulmonary/Upper Respiratory	87 (5.6)	5 (6.3)	3 (4.1)	2 (1.6)	0 (0.0)	0.25*
Pain	220 (14.0)	9 (11.3)	10 (13.5)	11 (8.7)	7 (25.9)	0.16
Sexual/Reproductive Function	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.00*
Vascular	99 (6.3)	3 (3.8)	3(4.1)	1 (0.8)	2 (7.4)	0.05*

Adverse events graded with CTCAE version 3. NH=Non-Hispanic, PI=Pacific Islander.

* Denotes p-value from Fisher's exact test.