original reports

Randomized Phase II Trial of Nivolumab Versus Nivolumab and Ipilimumab for Recurrent or Persistent Ovarian Cancer: An NRG Oncology Study

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abstract

PURPOSE Single-agent PD-1 blockade exhibits limited efficacy in epithelial ovarian cancer (EOC). We evaluated ipilimumab plus nivolumab compared with nivolumab alone in women with persistent or recurrent EOC.

METHODS Eligibility criteria included measurable disease, 1-3 prior regimens, and platinum-free interval (PFI) < 12 months. Participants were randomly allocated to intravenous nivolumab (every 2 weeks) or induction with nivolumab plus ipilimumab for 4 doses (every 3 weeks), followed by every-2-week maintenance nivolumab for a maximum of 42 doses. The primary null hypothesis was equal probability of objective response within 6 months of random allocation in each arm.

RESULTS One hundred patients were allocated to receive either nivolumab (n = 49), or nivolumab plus ipilimumab (n = 51), with PFI of < 6 months in 62%. Six (12.2%) responses occurred within 6 months in the nivolumab group and 16 (31.4%) in the nivolumab plus ipilimumab group (odds ratio, 3.28; 85% CI, 1.54 to infinity; $P = .034$). The median progression-free survival (PFS) was 2 and 3.9 months in the nivolumab and nivolumab plus ipilimumab groups, respectively, with a PFI-stratified hazard ratio of 0.53 (95% CI, 0.34 to 0.82); the respective hazard ratio for death was 0.79 (95% CI, 0.44 to 1.42). Grade ≥ 3 related adverse events occurred in 33% of patients in the nivolumab group and 49% in the combination group, with no treatment-related deaths. PD-L1 expression was not significantly associated with response in either treatment group.

CONCLUSION Compared with nivolumab alone, the combination of nivolumab and ipilimumab in EOC resulted in superior response rate and longer, albeit limited, PFS, with toxicity of the combination regimen comparable to prior reports. Additional combination studies to enhance durability of the dual regimen are warranted.

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INTRODUCTION

The group of diseases commonly referred to as "ovarian cancer," including ovarian, primary peritoneal, and fallopian tube carcinomas, leads to 14,000 deaths in the United States annually. The 5-year cause-specific survival for the 65% of patients diagnosed with disease spread beyond the pelvis ranges from 20% to 41%.[1]

Patients with ovarian cancer may harbor endogenous cell-mediated immune mechanisms with the potential to eradicate tumor cells.[2-7] However, these processes tend to be suppressed, such as through checkpoints cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and programmed death 1 (PD-1) receptors, distinct negative regulators of T-cell function.[4] CTLA-4 is expressed on T cells early after antigen presentation in lymphoid organs, inhibiting the priming phase of the immune response; PD-1 is expressed during chronic antigen presentation in other sites, including tumor tissue, inhibiting the effector phase.[8]

Despite the initial promising activity of single-agent nivolumab in ovarian cancer,[9] the activity of therapies blocking PD-1 or its agonist, programmed death-ligand 1 (PD-L1), in the subsequent larger phase Ib and II trials for patients with recurrent or persistent ovarian cancer has been modest, with objective response proportions ranging from 8% to 10%, and with median progression-free survival (PFS) times just over 2 months.[10,11] Dual checkpoint inhibition targeting PD-1 and CTLA-4 has demonstrated enhanced preclinical antitumor activity compared with PD-1 inhibition alone,[12-14] and therapy with nivolumab and ipilimumab, human monoclonal antibodies neutralizing PD-1 and CTLA-4, respectively, has been approved for the treatment of advanced melanoma, renal cell carcinoma,

ASSOCIATED CONTENT

Data Supplement
Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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and mismatch repair–deficient colorectal carcinoma.[15] Therefore, we conducted a phase II randomized trial to investigate the relative efficacy and safety of nivolumab combined with ipilimumab compared with nivolumab alone in patients with recurrent or persistent ovarian cancer.

METHODS

Patients

Eligibility criteria included recurrent or persistent ovarian, primary peritoneal, or fallopian tube carcinoma of all histologic types except mucinous adenocarcinoma and carcinosarcoma; measurable disease according to RECIST, version 1.1[16]; history of primary platinum-based chemotherapy with a maximum of three prior cytotoxic regimens and with at least one regimen for recurrent disease containing a platinum or a taxane for those with three prior regimens; last platinum-free interval $<$ 12 months; an Eastern Cooperative Oncology Group performance status score of 0 (fully active) to 2 (ambulatory and capable of self-care but unable to work; up and about $>$ 50% of waking hours); and no history of autoimmune disease affecting vital organ function or requiring immunosuppressive treatment.

Trial Design and Interventions

The study (NRG GY003; CLinicalTrials.gov identifier: NCT02498600) was an open-label, randomized phase II trial. Patients were stratified by last platinum-free interval ($<$ 6 months *v* 6-12 months), then randomly allocated in a 1:1 ratio using permuted blocks within the strata to four intravenous infusions of nivolumab 3 mg/kg every 2 weeks (nivolumab) or nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks (nivolumab plus ipilimumab). Each induction regimen was followed by a common maintenance regimen: nivolumab 3 mg/kg every 2 weeks for a maximum of 42 doses. Treatment was discontinued at the onset of disease progression, an unacceptable adverse event, completion of all 42 doses of maintenance therapy, or withdrawal—whichever came first.

Disease was assessed with imaging of the chest, abdomen, and pelvis according to RECIST, version 1.1;[16] physical examination; and serum cancer antigen 125 (CA-125) level.[17] In the absence of disease progression or initiation of subsequent cancer therapy, disease assessment was continued, with imaging required every 8 weeks after the first study treatment of 8 months and then every 12 weeks, and both physical examination and CA-125 level within 7 days before each study treatment infusion. In the event of progression on the initial scan, patients were allowed to continue past the initial progression, provided they satisfied the criteria specified in the Data Supplement. The limits on the degree of radiographic progression allowed for post-progression treatment continuation were set to minimize the risk of clinical deterioration, which is frequently observed in this patient population.[18]

Patients were evaluated for adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0,[19] either until 100 days after treatment discontinuation or until resolution or stabilization of an unacceptable adverse event, whichever came later. Toxicity monitoring and treatment discontinuation criteria are outlined in detail in the Data Supplement.

Vital status after discontinuation of study treatment was assessed every 3 months for 2 years, then every 6 months for 3 years.

End Points and Statistical Analysis

The primary end point was objective tumor response (complete or partial) by RECIST, version 1.1,[16] within 6 months of enrollment. The targeted sample size was 96. The study was conducted in two stages, with accrual to the first stage held after enrollment of approximately 48 patients. Accrual to the second stage was contingent on the proportion of responses within 6 months of enrollment for the nivolumab plus ipilimumab group exceeding that of the nivolumab group and assessment by an independent data safety monitoring committee. The difference in response proportions within 6 months of enrollment between the two groups was evaluated using a modified Fisher's exact test,[20] with 80% statistical power to detect a 20% effect (ie, response probabilities being 20% in the nivolumab group and 40% in the nivolumab plus ipilimumab group) at a 15% (one-sided) level of significance.

Secondary end points included progression-free survival (PFS) and overall survival (OS), both stratified by last platinum-free interval, with relative hazard ratios estimated using the proportional-hazards model[21]; and severity of adverse events, with differences analyzed using an exact χ^2 test and P values $<$ .05 considered suggestive.[22] PFS was considered to have evented at the time of cancer progression as demonstrated by imaging or symptomatic deterioration according to RECIST, version 1.1[16] or death from any cause. For patients remaining free of documented progression at the time of last follow-up, data on duration of PFS were censored at the time of last radiographic assessment. Analyses of the impact of treatment within various subsets were conducted using the Cox model without stratifying on platinum sensitivity (event sizes were too small). Associations between treatment and factor levels were assessed using asymptotic methods with an interaction term.

End points related to efficacy were evaluated in all enrolled patients, and adverse events were evaluated only in patients who received any study treatment.

PD-L1 Immunohistochemistry

PD-L1 staining methods and statistical analyses are outlined in the Data Supplement.

RESULTS

Patients and Trial Interventions

Between June 29, 2015 and August 28, 2017, 100 patients were enrolled at 37 academic and community centers in the United States, with 49 and 51 patients randomly assigned to the nivolumab and nivolumab plus ipilimumab regimens, respectively (Fig 1; Table 1). Accrual to the first and second study stages was completed in approximately 14 weeks and 13 weeks, respectively, with a 20-month suspension between stages (Data Supplement). Baseline characteristics were generally well balanced between the treatment groups. Although the proportion of patients with 3 (versus 1) prior cytotoxic regimens appeared a bit greater for the nivolumab plus ipilimumab group, the difference in the distribution was not significant (Pearson chi-square $P = .34$). Of note, the last platinum-free interval was > 6 months in almost two-thirds of patients.

Patient disposition is shown in the Data Supplement. Treatment durations ranged widely, with medians of 1.1 and 3.0 months for the nivolumab and nivolumab plus ipilimumab regimens, respectively. Seventy-seven (77%) discontinued study treatment of disease progression, with 13% more in the nivolumab group than the nivolumab plus ipilimumab group. Eighteen (18%) discontinued study treatment of adverse events, with 11% more in the nivolumab plus ipilimumab group than the nivolumab group. Thirty-two (62.7%) patients received a total dose of at least 3.7 mg/kg of ipilimumab, translating into approximately 4 doses of induction. Two patients (in the nivolumab group) discontinued study treatment of completion of the regimen. Three patients (in the nivolumab plus ipilimumab group) remained on study treatment at the time of the database lock.

Activity

Objective responses were evaluated in both groups. Regarding the primary analysis, 6 (3 complete and 3 partial; 12.2%) and 16 (3 complete and 13 partial; 31.4%) responses occurred within 6 months of enrollment in the nivolumab and nivolumab plus ipilimumab groups, respectively. An additional 14 (29%) and 20 (39%) patients in the nivolumab and nivolumab plus ipilimumab group, respectively, had stable disease. The difference in response

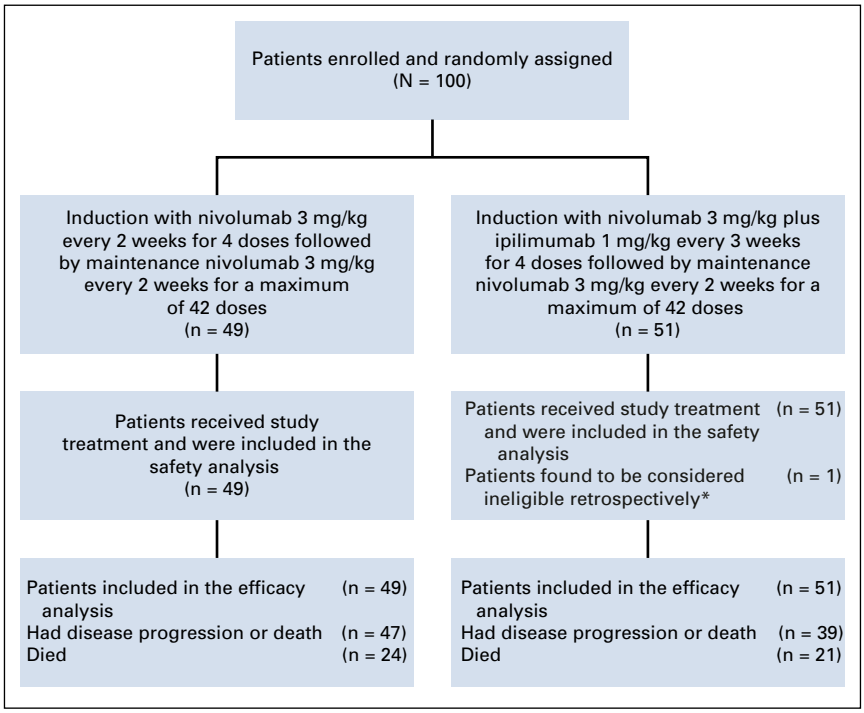

FIG 1. Eligibility, random allocation, and follow-up of the study patients. All patients who enrolled were included in the intention-to-treat analysis of efficacy end points. Patients were stratified by last platinum-free interval (< 6 months *v* 6-12 months), then randomly allocated in a 1:1 ratio to four intravenous infusions of the nivolumab or the nivolumab plus ipilimumab induction regimen: nivolumab 3 mg/kg every 2 weeks (nivolumab) or nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks (nivolumab plus ipilimumab). Each induction regimen was followed by a common maintenance regimen: nivolumab 3 mg/kg every 2 weeks for a maximum of 42 doses. The analysis of safety included all patients receiving at least one dose of study therapy. The date of data cutoff was September 3, 2018. (*) Pathology report from original diagnosis indicated coexisting superficially invasive endometrioid adenocarcinoma of the endometrium along with stage IIIb high-grade serous fallopian tube cancer.

TABLE 1. Baseline Characteristics of All Patients, According to Assigned Treatment Group

Characteristic	Nivolumab (n = 49)	Nivolumab and Ipilimumab (n = 51)
Age, years (range)	63 (37-87)	62 (38-92)
Body mass index, kg/m^2 (range)	26.2 (18.6-51.3)	27.5 (17.1-40.5)
Race or ethnic group[a]		
Non-Hispanic white	41 (83.7)	42 (82.4)
Non-Hispanic black	2 (4.1)	5 (9.8)
Asian	1 (2.0)	3 (5.9)
Hispanic	3 (6.1)	1 (2.0)
Other or unspecified	2 (4.1)	0 (0)
ECOG performance status score[b]		
0	33 (67.3)	37 (72.5)
1	14 (28.6)	12 (23.6)
2	2 (4.1)	2 (3.9)
Histologic type		
High-grade serous	42 (85.7)	42 (82.4)
Clear cell	6 (12.2)	6 (11.8)
High-grade endometrioid	0 (0.0)	2 (3.9)
Other	1 (2.0)	1 (2.0)
Most recent platinum-free interval, months		
< 6	31 (63.3)	31 (60.8)
6-12	18 (36.7)	20 (39.2)
No. of prior cytotoxic regimens		
1	14 (28.6)	10 (19.6)
2	23 (46.9)	22 (43.1)
3	12 (24.5)	19 (37.3)
Time since diagnosis to enrollment, months (range)	21.2 (0.6-68.8)	23.1 (4.7-116.6)

NOTE. Data presented as No. (%) unless otherwise indicated. Percentages may not sum to 100 because of rounding.
Abbreviation: ECOG, Eastern Cooperative Oncology Group.
[a]Race or ethnic group was self-reported.
[b]An ECOG performance status score of 0 indicates that the patient is fully active, 1 that the patient is restricted in physically strenuous activities but ambulatory, and 2 that the patient is ambulatory and capable of self-care but unable to work.

rates was statistically significant (odds ratio [OR], 3.28; 85% CI, 1.54 to infinity; $P = .034$). Four (8.2%) and 11 (21.6%) of these responses, respectively, were confirmed by radiologic disease assessment at least 4 weeks after initial criteria for response were met; the difference in confirmed response rate between arms remained statistically significant at the 15% level of significance (OR, 3.09; 85% CI, 1.38 to infinity; $P = .054$). After the 6-month evaluation period, one additional, unconfirmed partial response was reported in the nivolumab plus ipilimumab group, for a total response rate of 33%. Response durations of at least 6 months without evidence of new disease occurred in 4 (8.2%) and 8 (15.7%) patients, respectively (Figs 2A and 2B).

Follow-up was evenly distributed between the treatment groups, with a median of approximately 33 months for first-stage and 11 months for second-stage patients (Data Supplement). The median PFS was 2.0 and 3.9 months in the nivolumab group and nivolumab plus ipilimumab group, respectively (Fig 3A). Compared with the nivolumab group, the hazard of progression or death was significantly lower in the nivolumab plus ipilimumab group (hazard ratio, 0.528; 95% CI, 0.339 to 0.821; two-sided $P = .004$). The proportion with 6-month PFS was 16.3% in the nivolumab arm and 25.5% in the nivolumab plus ipilimumab arm (OR, 1.75; 95% CI, 0.59 to 5.43; $P = .19$).

Five patients (3 in the single-agent arm and 2 in the combination arm) met the criteria for treatment beyond progression at 8 weeks. Of these patients, 4 discontinued therapy at 16 weeks for confirmed progression, and 1 in the combination arm had disease stabilization and continued treatment until 34 weeks. The median OS was 21.8 and 28.1 months in the nivolumab group and nivolumab plus ipilimumab group, respectively (Fig 3B). Compared with

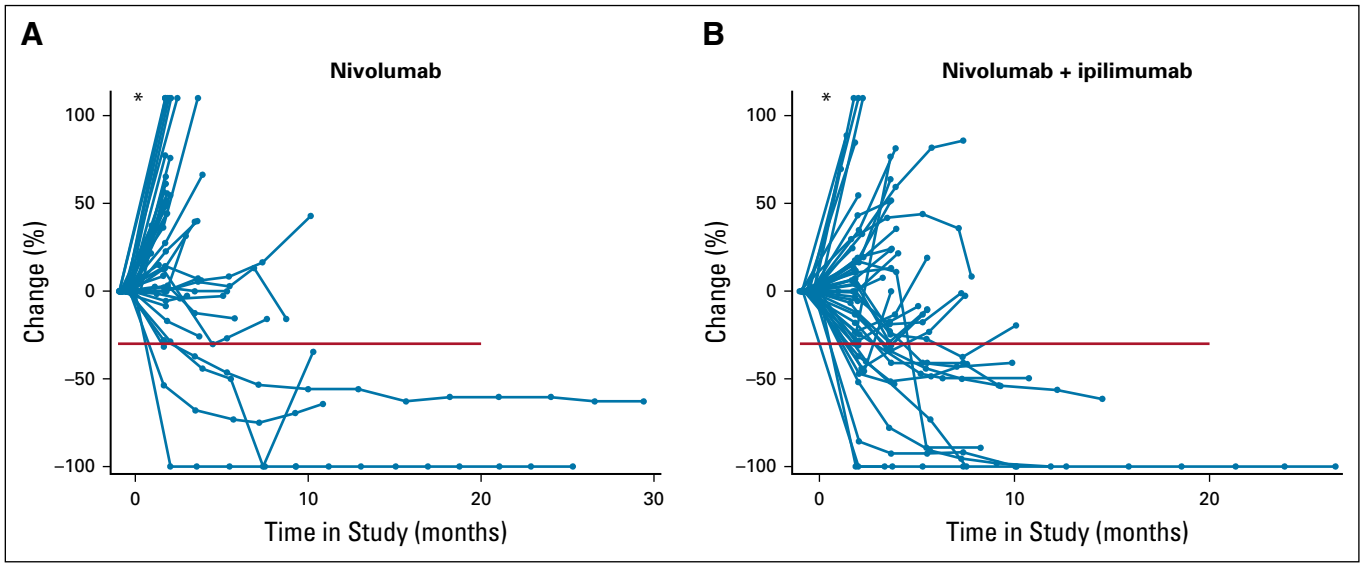

FIG 2. RECIST sum by time since enrollment, according to treatment group. The comparison of percentage change in RECIST sum across treatment groups over time is shown in these spider plots, where nodes below the red lines define objective response. Response durations of at least 6 months without evidence of new disease occurred in 4 (8.2%) and 8 (15.7%) patients in the (A) nivolumab and (B) nivolumab plus ipilimumab groups, respectively. (*) RECIST increase beyond 100%.

the nivolumab group, the hazard of death was 0.789 (95% CI, 0.439 to 1.418; two-sided $P = .43$).

An exploratory subset analysis adjusted for treatment group was performed to assess the association of age, performance status, number of prior cytotoxic regimens, platinum-free interval, and histologic type with outcomes (Data Supplement). There was a significant association between longer platinum-free interval and OS. Patients with clear cell carcinoma had an approximately fivefold odds of response compared with other types. An additional exploratory analysis was performed to determine whether any baseline characteristics favored combination therapy over the single-agent nivolumab. Overall, poor prognostic characteristics, such as inferior performance status, platinum

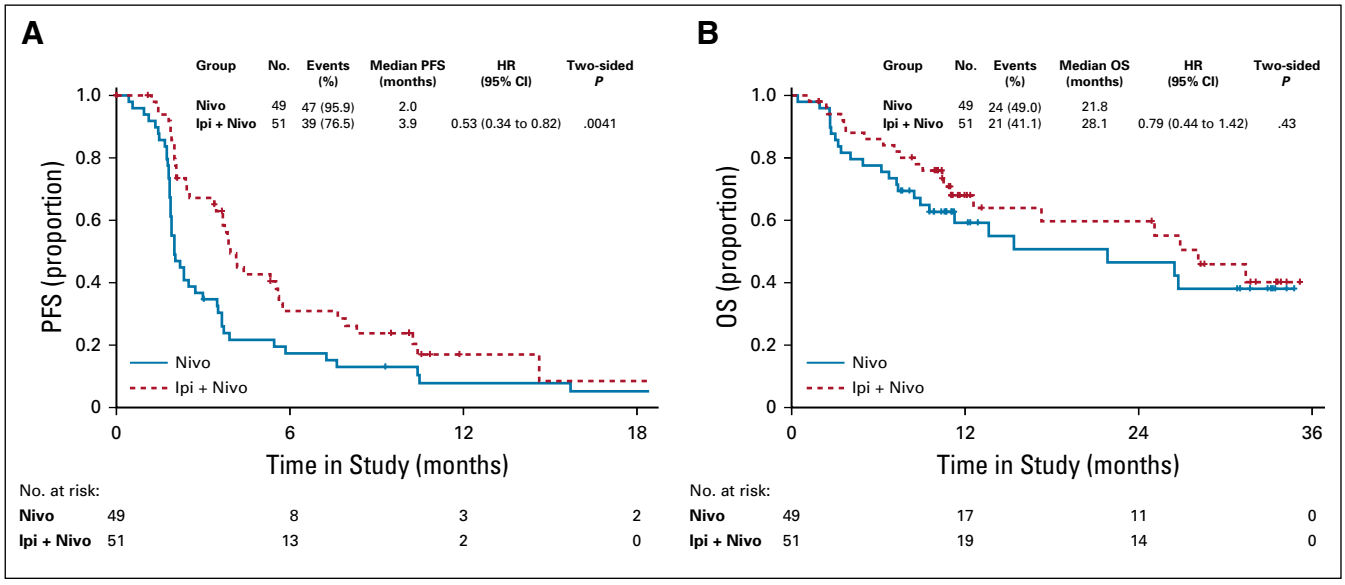

FIG 3. Analyses of progression-free survival (PFS) and overall survival (OS), according to treatment group. Analysis of (A) PFS and (B) OS, respectively, for all 100 patients randomly assigned to receive nivolumab induction followed by nivolumab maintenance therapy or nivolumab plus ipilimumab (Ipi) induction followed by nivolumab maintenance therapy, after stratification for the most recent platinum-free interval. Summary PFS and OS as well as hazard ratio (HR) and *P* value are presented in the respective tables. There was a significant, time-dependent decrease in the hazard of progression in the nivolumab plus ipilimumab group as compared with the nivolumab group (HR, 0.528; 95% CI, 0.339 to 0.821; $P = .0041$). As compared with the nivolumab group, the hazard of death was 0.789 for the nivolumab plus ipilimumab group (95% CI, 0.439 to 1.418; $P = .43$).

resistance, older age, higher prior number of therapies, larger baseline tumor burden, and obesity were favored in the combination arm, although older age was only suggestive, perhaps because of low patient numbers (Fig 4). Patients with clear cell carcinoma also appeared to benefit most from the combination, although only 12 patients on the study had this histologic subtype.

Safety

Grade 3 or greater adverse events (regardless of attribution) occurred in 27 (55.1%) and 34 (66.7%) patients in the nivolumab group and nivolumab plus ipilimumab group, respectively (Data Supplement). The difference in the frequency of grade 3 or greater adverse events overall ($P = .31$) and for each system between the treatment groups was not significant. Overall grade 5 events occurred in 2 (4%) and 4 (8%) in the nivolumab group and nivolumab plus ipilimumab group, respectively, with an OR of 2.0 (95% CI, 0.27 to 23.08; $P = .68$); there were no treatment-related deaths. Of the 6 deaths in the study (4 in the nivolumab group and 2 in the ipilimumab/nivolumab group), 4 patients died as a result of cancer progression. One patient in the nivolumab group with history of extensive pulmonary emboli developed sudden shortness of breath and cardiac arrest believed to be related to recurrent pulmonary embolism. One patient in the ipilimumab/nivolumab group died as a result of aspiration pneumonia related to underlying achalasia.

Table 2 shows the frequency of adverse events at least grade 2 in severity and considered at least possibly related to nivolumab or ipilimumab. Overall frequency of grade 3 or higher related adverse events was 16 in the nivolumab group and 25 in the nivolumab and ipilimumab group. The most commonly reported grade 3 or higher adverse events in the combination group were asymptomatic elevation in pancreatic enzymes (16%), elevation in liver enzymes (8%), anemia (8%), and colitis or diarrhea (6%). Although the overall frequencies of related grade 2-4 events between treatment groups were not statistically different, the nivolumab plus ipilimumab group trended toward a greater incidence of colitis or diarrhea (16% *v* 4%; $P = .09$), anemia with or without hemolysis (16% *v* 4%; $P = .09$), and rash (14% *v* 4%; $P = .16$).

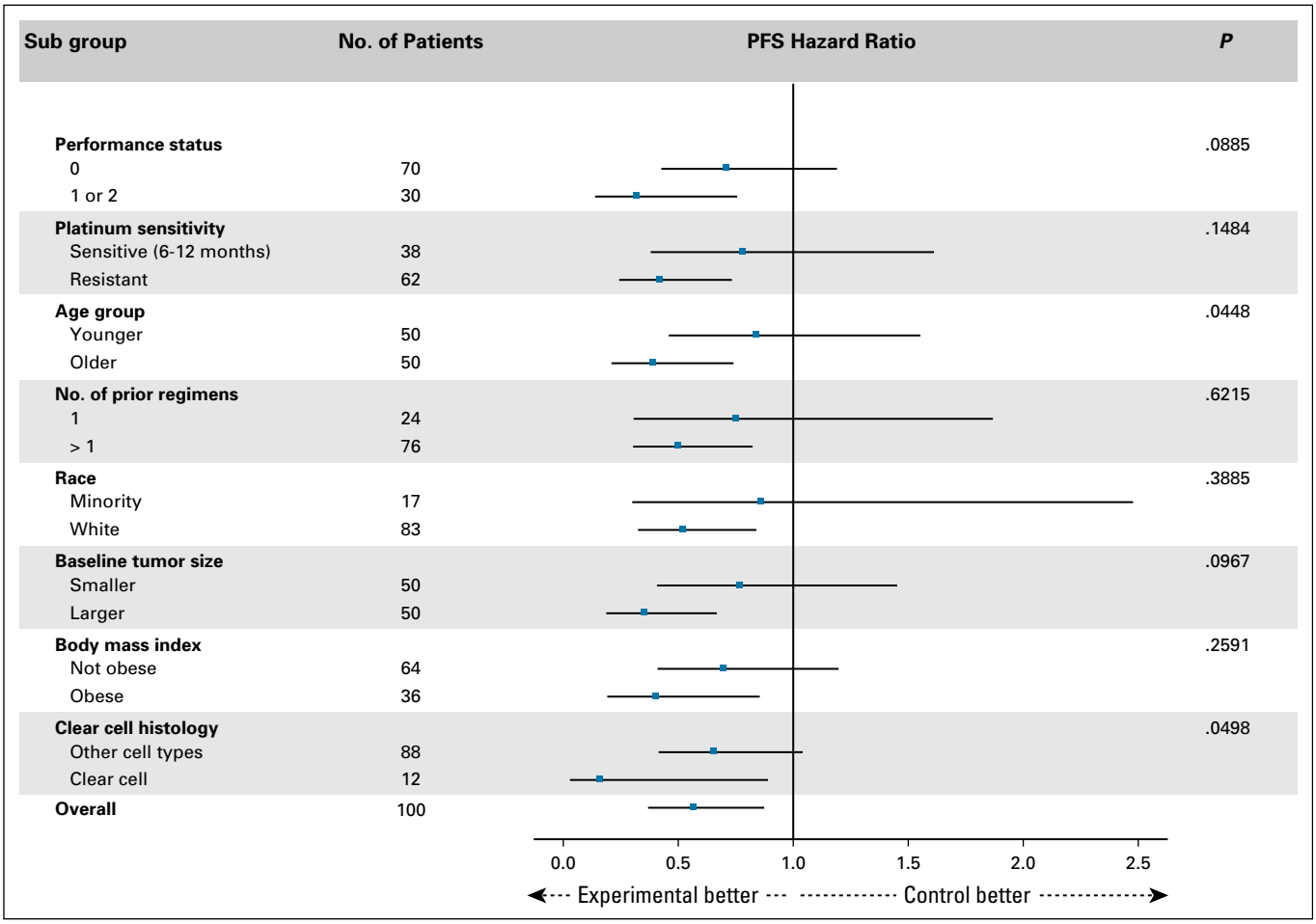

FIG 4. Forest plot for selected baseline characteristics. Associations are determined with asymptotic methods. Because the number of events in some sets is small, the associated *P* value may be inaccurate. Control, nivolumab arm; Experimental, nivolumab plus ipilimumab arm; PFS, progression-free survival.

TABLE 2. Adverse Events at Least Possibly Related to Nivolumab or Ipilimumab, by Treatment Group

System	Event	Maximum Grade						
		Nivolumab (n = 49)			Nivolumab and Ipilimumab (n = 51)			
		2	3	4	2	3	4	χ^2 P^a
General	Fatigue	3 (6)	4 (8)	0 (0)	11 (22)	1 (2)	0 (0)	.31
	Fever	1 (2)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	.62
GI	Colitis or diarrhea	0 (0)	2 (4)	0 (0)	5 (10)	3 (6)	0 (0)	.09
	Nausea with or without emesis	2 (4)	1 (2)	0 (0)	4 (8)	0 (0)	0 (0)	1.00
	Pancreatitis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1.00
	Liver enzyme elevation	1 (2)	2 (4)	0 (0)	3 (6)	3 (6)	1 (2)	.32
	Pancreatic enzyme elevation	1 (2)	1 (2)	2 (4)	0 (0)	5 (10)	3 (6)	.36
Hematologic	Anemia with or without hemolysis	1 (2)	1 (2)	0 (0)	4 (8)	3 (6)	1 (2)	.09
	Neutropenia	0 (0)	1 (2)	0 (0)	0 (0)	2 (4)	0 (0)	1.00
	Thrombocytopenia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1.00
Dermatologic	Rash	0 (0)	2 (4)	0 (0)	5 (10)	2 (4)	0 (0)	.16
Endocrine	Hypothyroidism	0 (0)	0 (0)	0 (0)	3 (6)	0 (0)	0 (0)	.24
	Hyperthyroidism	2 (4)	0 (0)	0 (0)	2 (4)	0 (0)	0 (0)	1.00
	Adrenal insufficiency	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	.50
	Hyperglycemia	1 (2)	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	.61
	Other	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	.49
Musculoskeletal	Arthritis or arthralgia	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	1.00
Respiratory	Dyspnea	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)	.50
	Pneumonitis	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	1.00
	Hypoxia	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	1.00
Renal	Acute kidney injury	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	1 (2)	.50
Neurologic	Encephalopathy	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	1.00

NOTE. Data presented as No. (%). Adverse events were those with onset between enrollment and 100 days after last treatment.
[a]Analysis of grade 2 or greater adverse events between treatment groups.

PD-L1 Biomarker Analysis

Tissue suitable for PD-L1 testing was available from 52 patients. Although presence of detectable PD-L1 stain in tumor cells appeared to enrich for responders in both treatment cohorts, the difference was not significant (Data Supplement). Similarly, presence of PD-L1 staining in tumor-infiltrating immune cells was more common in patients with response in both treatment cohorts, but the difference was also not significant (Data Supplement). Finally, there was no significant association observed between PFS and PD-L1 positivity at any cutoff (Data Supplement), although the power of these analyses was limited because of small sample size.

DISCUSSION

Results of this trial justify ongoing investigation of T-cell–targeted immunotherapy for patients with ovarian cancer. They also support the general hypothesis that for this disease, as has been observed for other solid tumors,[23-25] combined PD-1 and CTLA-4 inhibition as an induction regimen before sustained anti–PD-1 therapy enhances antitumor activity compared with PD1 inhibition alone. The efficacy results were internally consistent with respect to primary and secondary end points. There was a significantly greater rate of response within 6 months of enrollment (31.4% *v* 12.2%), supported by a significant prolongation of PFS (median, 3.9 months *v* 2.0 months; hazard ratio, 0.528) and a greater number of patients remaining progression free at 6 months. The response rate in the nivolumab group reflects that observed for single-agent anti–PD-1 and anti–PD-L1 therapy trials in similar patient populations.[26,27] These findings highlight, however, that in the majority of patients clinical benefit is not durable and that additional exploration of the ipilimumab plus nivolumab regimen, possibly in combination with other agents, is warranted.

The exploratory analysis of activity outcomes for all enrolled patients, adjusted for treatment group (for response) and for both treatment group and platinum-free interval (for PFS

and OS), suggested that the antitumor effect of both regimens was independent of age, performance status, and number of prior cytotoxic regimens. Interestingly, clinical characteristics typically associated with worse prognosis, such as worse performance status, platinum resistance, older age, greater number of prior therapies, and larger baseline tumor burden, seem to favor the combination arm. Consistent with other ovarian cancer trials evaluating PD-1 and PD-L1–targeted agents, this analysis indicated potentially greater antitumor activity for patients with clear cell tumors,[9,28] on the basis of a fivefold odds of response compared with patients with other histologic types. However, because patients with clear cell carcinomas represented only 12% of the study population, this finding should be interpreted with caution.

The frequency and severity of immune-related adverse events (Table 2) were also similar to previous trials leading to the approval of similar dosing of nivolumab-ipilimumab induction followed by nivolumab maintenance therapy for nongynecologic malignancies.[23-25,29,30] Similar to the prior studies, a large proportion of grade 3 or higher adverse events were accounted for by asymptomatic elevation in pancreatic enzymes without evidence of pancreatitis. As noted in other trials comparing these regimens, nivolumab-ipilimumab treatment trended toward greater incidence of toxicity, such as colitis and diarrhea, requiring treatment delay or discontinuation. The relative degree of toxicity observed in trials evaluating the combination of nivolumab and ipilimumab appears to be combination dose related, with the induction regimen in the current trial and pivotal trials for advanced or metastatic renal cell carcinoma[30] and colorectal carcinoma[24] (nivolumab at 3 mg/kg and ipilimumab at 1 mg/kg) better tolerated than that for advanced and metastatic melanoma[25] (nivolumab at 1 mg/kg and ipilimumab at 3 mg/kg). Referring to diarrhea and colitis as an example, in the melanoma trial using ipilimumab at 3 mg/kg, the combined rate of grade 3-4 diarrhea and colitis was 17%,[25] whereas the studies in non–small cell lung cancer, renal cell carcinoma, and colorectal carcinoma using lower doses of ipilimumab reported the overall incidence of grade 3 or 4 diarrhea or colitis of 1.6%-4%.[24,29,30]

At present, genomic and microenvironment biomarkers predictive of response to nivolumab or nivolumab in combination with ipilimumab remain unknown, which is a limitation of this report. Similar to previous studies of immune checkpoint inhibitors in ovarian cancer, in this study, PD-L1 expression was found to be of limited predictive value, although these analyses were limited by overall small sample size.[10,11] Studies in different cancers highlighted several additional biomarkers predictive of response to immune checkpoint blockade. These include tumor mutational burden,[31] expression of PD-L1,[32] presence of tumor-infiltrating lymphocytes,[33] IFNγ transcriptional signature,[34] and intratumoral and peripheral TCR clonality.[33,35] The predictive value of these biomarkers for immunotherapy response in ovarian cancer remains unknown, and studies evaluating tumor microenvironment and genomic parameters as baseline and on-treatment predictors of clinical benefit in the current trial are presently ongoing.

In conclusion, the combination of nivolumab and ipilimumab induction followed by nivolumab maintenance in ovarian cancer resulted in superior response rate and improvement in PFS when compared with nivolumab alone, and toxicities were manageable. The relatively improved response rate observed in the combination therapy group, however, must be balanced by the lack of benefit for the majority of patients enrolled as well as limited duration of PFS observed in the study. These findings highlight the need to build on this experience for the greater good, likely through additional combinations incorporating the dual regimen.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Randomized Phase II Trial of Nivolumab Versus Nivolumab and Ipilimumab for Recurrent or Persistent Ovarian Cancer: An NRG Oncology Study

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