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Randomized, Double-Blind, Phase III Trial of Ipilimumab Versus Placebo in Asymptomatic or Minimally Symptomatic Patients With Metastatic Chemotherapy-Naive Castration-Resistant Prostate Cancer

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ABSTRACT

Purpose
Ipilimumab increases antitumor T-cell responses by binding to cytotoxic T-lymphocyte antigen 4. We evaluated treatment with ipilimumab in asymptomatic or minimally symptomatic patients with chemotherapy-naive metastatic castration-resistant prostate cancer without visceral metastases.

Patients and Methods
In this multicenter, double-blind, phase III trial, patients were randomly assigned (2:1) to ipilimumab 10 mg/kg or placebo every 3 weeks for up to four doses. Ipilimumab 10 mg/kg or placebo maintenance therapy was administered to nonprogressing patients every 3 months. The primary end point was overall survival (OS).

Results
Four hundred patients were randomly assigned to ipilimumab and 202 to placebo; 399 were treated with ipilimumab and 199 with placebo. Median OS was 28.7 (95% CI, 24.5 to 32.5) months in the ipilimumab arm versus 29.7 (95% CI, 26.1 to 34.2) months in the placebo arm (hazard ratio, 1.11; 95.87% CI, 0.88 to 1.39; $P = .3667$). Median progression-free survival was 5.6 months in the ipilimumab arm versus 3.8 with placebo arm (hazard ratio, 0.67; 95.87% CI, 0.55 to 0.81). Exploratory analyses showed a higher prostate-specific antigen response rate with ipilimumab (23%) than with placebo (8%). Diarrhea (15%) was the only grade 3 to 4 treatment-related adverse event (AE) reported in ≥ 10% of ipilimumab-treated patients. Nine (2%) deaths occurred in the ipilimumab arm due to treatment-related AEs; no deaths occurred in the placebo arm. Immune-related grade 3 to 4 AEs occurred in 31% and 2% of patients, respectively.

Conclusion
Ipilimumab did not improve OS in patients with metastatic castration-resistant prostate cancer. The observed increases in progression-free survival and prostate-specific antigen response rates suggest antitumor activity in a patient subset.

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INTRODUCTION

Prostate cancer is the second most frequently diagnosed malignancy in men, with > 1 million new cases and 307,500 deaths estimated worldwide.[1] Although significant treatment advances have been made recently with the introduction of novel therapeutic agents, such as enzalutamide, abiraterone acetate, cabazitaxel, and radium 223, prognosis and long-term outcomes for patients with castration-resistant prostate cancer (CRPC) need to be improved.[2-8]

The presence of inflammatory cells and T-cell infiltrates in prostate cancer tissues suggest that host inflammatory/immune effectors may reach these tumors and mediate antitumor responses.[9-11] Potential benefit from activation or reactivation of immune-mediated antitumor responses in patients with CRPC is further suggested by the results of preclinical studies in experimental prostate cancer models and by the

clinical activity of sipuleucel-T, a cellular immunotherapy based on ex vivo–activated peripheral mononuclear cells.[11-16]

Ipilimumab is a fully human monoclonal immunoglobulin G1 antibody that increases antitumor T-cell responses by binding to.[17-19] Blocking by ipilimumab of the T-cell negative regulator cytotoxic T-lymphocyte antigen-4 allows CD28 and B7 interactions, which result in T-cell activation; proliferation; tumor infiltration; and ultimately, cancer cell death. Treatment with ipilimumab, as a single agent or in combination with dacarbazine, provided significant survival benefit in two phase III trials of advanced melanoma. Of note, approximately 20% of ipilimumab-treated patients with melanoma experienced long-term survival.[17,18,20-26]

Results of a phase I/II dose-finding study of ipilimumab in 71 chemotherapy-naive or chemotherapy-pretreated patients with metastatic CRPC (mCRPC) showed antitumor activity in this clinical setting, with durable prostate-specific antigen (PSA) responses independent of prior chemotherapy, which supports further ipilimumab evaluation in phase III studies.[27] Treatment with single-agent ipilimumab 10 mg/kg after bone-directed radiotherapy (8 Gy in one fraction) in a randomized phase III trial (CA184-043) in patients with mCRPC, at least one bone metastasis, and disease progression after docetaxel therapy demonstrated antitumor activity (improvement in progression-free survival [PFS] and PSA responses), although the study did not meet its primary end point of improvement in overall survival (OS).[28] Exploratory and other post-hoc subgroup analyses of this trial have shown an improvement in OS with ipilimumab versus placebo in patients without visceral metastases, with non- or mildly elevated alkaline phosphatase levels and without anemia, which suggests a potential benefit in patients with mCRPC and favorable prognostic features.[28] The current randomized, double-blind, phase III trial (CA184-095) investigated efficacy and safety of ipilimumab versus placebo in the first-line treatment of patients with asymptomatic or minimally symptomatic mCRPC without visceral metastases.

PATIENTS AND METHODS

Study Design, Treatment, and Patients

In this randomized, multinational, double-blind, phase III trial, chemotherapy-naive patients with asymptomatic or minimally symptomatic mCRPC and no known visceral metastases were randomly assigned two to one to induction treatment with intravenous ipilimumab 10 mg/kg or placebo (normal saline or 5% dextrose infused at a matching volume [2 mL/kg] and frequency) every 3 weeks for up to four doses (weeks 1, 4, 7, and 10) followed by double-blind maintenance treatment with ipilimumab 10 mg/kg versus placebo every 12 weeks for eligible patients. Treatment was to be continued until unacceptable toxicity, clinical deterioration, or confirmed disease progression.

Study participants had confirmed CRPC, radiographic evidence of metastases, prior disease progression during hormonal treatment, discontinuation of prior antiandrogen therapy, Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, and testosterone levels $<$ 50 ng/dL. Patients were considered to have minimally symptomatic disease if they rated their 24-h worst pain as $\leq$ 4 on the Brief Pain Inventory-Short Form scale (1 to 10) in each of the 5 assessment days before random assignment and if they did not require opiate analgesic therapy for cancer-related pain. Patients were excluded from this study if they had liver, lung, or brain metastases; received prior immunotherapy or chemotherapy for mCRPC; had a history of autoimmune disease; had a HIV or hepatitis B or C infection; or received pelvic-targeted radiation therapy within 3 months of study entry.

Patients were randomly assigned to treatment with ipilimumab or placebo through an interactive voice response system that used a permuted block procedure to minimize the imbalance between treatment arms within the stratification factor levels. Patients were stratified by ECOG performance status (0 *v* 1), lactate dehydrogenase level ($<$ 200 *v* $\geq$ 200 International Units/L), pain (none *v* minimal), and region (United States/Canada *v* non–United States/Canada). The study was approved by the institutional review board or independent ethics committee of each participating center. It followed the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. All patients gave written informed consent.

The primary study end point was OS defined as time from random assignment to death from any cause in all patients. Secondary end points were PFS; time to subsequent systemic, cytotoxic therapy and to pain progression in all patients; and safety profile in treated patients. All time-dependent end points were measured from random assignment. Investigator-assessed PFS was defined as time to confirmed PSA or radiologic progression, clinical deterioration, or death. Time to pain progression was defined as time to an increase in average daily worst pain intensity of $\geq$ 2 points from baseline, maintained over two consecutive periods; initiation of opioid analgesic or palliative radiation therapy; or an increase from baseline in mean analgesic score (AS) $\geq$ 25% (for patients with baseline AS $>$ 10) or mean AS $\geq$ 10 points (for patients with baseline AS $\leq$ 10).

Planned enrollment was approximately 600 patients. The study was conducted in Europe, North and South America, and Australia.

Study Assessments

Tumor response was assessed by computed tomography scan or magnetic resonance imaging of the chest, abdomen, pelvis, and other soft tissues and by bone scans every 12 weeks until disease progression, start of subsequent therapy, or death. Disease progression was evaluated on the basis of the Prostate Cancer Clinical Trials Working Group 2 recommendations[29] and confirmed by a second scan performed $\geq$ 6 weeks after initial documentation at $\geq$ 12 weeks.

Serum PSA concentrations were determined every 6 weeks at a central laboratory. PSA response was defined as a 50% decrease from baseline confirmed by a second PSA value $\geq$ 6 weeks later. Disease progression by PSA required confirmation by two follow-up PSA values after initial documentation at $\geq$ 12 weeks. Pain intensity was evaluated every 12 weeks by daily patient report through the Analgesic Use Diary and the Brief Pain Inventory-Short Form for 5 consecutive days at each assessment point. Adverse events (AEs) were monitored until 90 days after last treatment dose (including maintenance therapy) or resolution/stabilization of ongoing AEs and graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

Statistical Analyses

Efficacy end points were analyzed in the intention-to-treat population (all randomly assigned patients) except for the PSA analyses (performed in PSA-evaluable patients defined as participants with a baseline and at least one on-study PSA measurement). Safety was evaluated in all patients who had received at least one dose of double-blind treatment.

The study was powered for analysis of OS. A two-sided log-rank test, stratified by ECOG performance status (0 *v* 1), lactate dehydrogenase level ($<$ 200 *v* $\geq$ 200 International Units/L), pain (none versus minimal), and region (United States/Canada versus non–United States/Canada), was used for the comparison of OS between the two study arms. The superiority boundary was α = .0413, which adjusted for α spent for the interim analysis. Interim and final OS analyses were to occur after 304 and 379

deaths, respectively, to give a 90% power to detect an increase in median OS from 21.7 to 31 months (hazard ratio [HR], 0.7). The secondary efficacy end points were tested in hierarchical order: PFS > time to subsequent nonhormonal cytotoxic therapy > time to pain progression. If the comparison for the primary or a secondary efficacy end point showed $P > .05$, no further P values would be determined for any end point that followed in the hierarchal order. Statistical analyses were performed with SAS 8.2 software (SAS Institute, Cary, NC).

RESULTS

Patients

The trial was initiated on July 28, 2010 (first patient, first visit), and the database was locked on August 28, 2015, with a total of 380 OS events reported. After screening 837 patients, 602 were randomly assigned, with 400 to the ipilimumab arm and 202 to the placebo arm; 399 patients were treated with ipilimumab and 199 with placebo (Fig 1). F1

The median number of study drug doses was 4.0 (range, 1 to 17) in the ipilimumab arm and 4.0 (range, 1 to 16) in the placebo arm (Appendix Table A1, online only). Thirty-seven percent of patients in the ipilimumab arm versus 12% in the placebo arm stopped treatment before the fourth dose. The majority of patients discontinued treatment due to confirmed radiographic or PSA progression (ipilimumab arm, 197 [49%]; placebo arm, 156 [78%]). In the ipilimumab arm, 114 (29%) and 29 (7%) patients discontinued because of a treatment-related and non–treatment-related AEs, respectively, versus five (3%) and 13 (7%), respectively, in the placebo arm (Fig 1). Additional reasons for treatment discontinuation were withdrawal of consent, patient request, death, obtained maximum clinical benefit, poor compliance with treatment, not meeting inclusion criteria after random assignment, and other or not reported. At the end of the study, one patient still received treatment with ipilimumab and one with placebo.

Patient demographics and baseline disease characteristics were balanced between treatment groups (Table 1). Median age was T1
69.5 (range, 44 to 91) years in the ipilimumab arm and 69 (range, 42 to 92) years in the placebo arm. The majority of patients were 65 years of age or older (74% *v* 68%) and had an ECOG performance status of 0 (75% in both arms) and bone metastases (78% *v* 79%). Approximately one half of the patients (48% and 45% in the ipilimumab and placebo arms, respectively) had a Gleason score ≥ 8. Median PSA levels were 41.2 (range, 0 to 4,956) μg/L in the

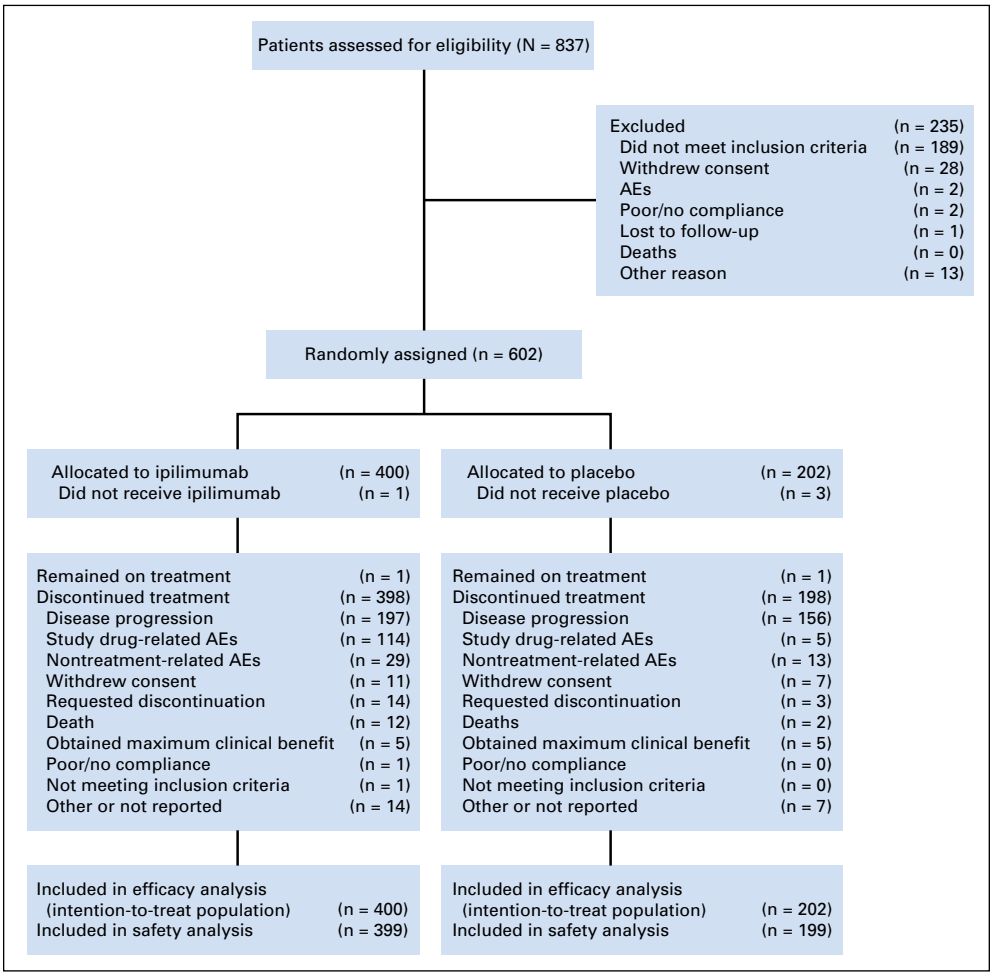

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Fig 1. Patient flow. AE, adverse event.

Table 1. Demographic and Baseline Patient Characteristics

Characteristic	Ipilimumab, No. (%)	Placebo, No. (%)
No. of patients	400	202
Median age, years (range)	70 (44-91)	69 (42-92)
Age-group		
< 65 years	104 (26)	65 (32)
≥ 65 years	296 (74)	137 (68)
Race		
White	361 (90)	185 (92)
Black	20 (5)	11 (5)
Asian	4 (1)	2 (1)
American Indian/Alaskan	2 (< 1)	1 (< 1)
Native Hawaiian/Pacific Islander	1 (< 1)	0
Other	12 (3)	3 (2)
Region		
United States/Canada	136 (34)	70 (35)
Not United States/Canada	264 (66)	132 (65)
ECOG performance status		
0	299 (75)	151 (75)
1	100 (25)	51 (25)
2	1 (< 1)	0
Lactate dehydrogenase level		
< 200 IU/L	250 (63)	130 (64)
≥ 200 IU/L	149 (37)	72(36)
Not reported	1 (< 1)	0
Hemoglobin concentration		
< 11 g/dL	31 (8)	14 (7)
≥ 11 g/dL	364 (91)	183 (91)
Not reported	5 (1)	5 (3)
Measurable disease		
Yes	169 (42)	96 (48)
No	228 (57)	102 (51)
Not reported	3 (< 1)	4 (2)
Alkaline phosphatase level		
< 1.5 × ULN	327 (82)	176 (87)
≥ 1.5 × ULN	72 (18)	26 (13)
Not reported	1 (< 1)	0
Gleason score		
≤ 7	189 (47)	103 (51)
≥ 8	192 (48)	91 (45)
Not reported	19 (5)	8 (4)
PSA		
Patients with available PSA data	393	197
Median (range), μg/L	41.2 (0.05-4,956)	49.5 (0.01-9,297)
Bone metastases		
Yes	312 (78)	159 (79)
No	85 (21)	39 (19)
Not reported	3 (< 1)	4 (2)
Average daily worst bone pain intensity score		
None	215 (54)	109 (54)
Minimal	179 (45)	90 (45)
Not reported	6 (< 2)	3 (2)
Bisphosphonate use		
Yes	99 (25)	62 (31)
No	301 (75)	140 (69)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IU, International Units; PSA, prostate-specific antigen; ULN, upper limit of normal.

ipilimumab arm and 49.5 (0 to 9,297) μg/L in the placebo arm. Two hundred sixty-eight (67%) and 158 (79%) patients in the ipilimumab and placebo arms, respectively, received subsequent systemic treatment with chemotherapy, hormonal therapy, and/or immunotherapy, with no imbalance between study arms (Appendix Table A2, online only).

Efficacy

At the time of the primary OS analysis, all patients had been followed for 2 years, 85% for 3 years, and 26% for 4 years. No significant difference in OS was observed between study arms. Median OS was 28.7 (95% CI, 24.5 to 32.5) months in the ipilimumab arm and 29.7 (95% CI, 26.1 to 34.2) months in the placebo arm (HR, 1.11; 95.87% CI, 0.88 to 1.39; $P = .3667$; Fig 2A). F2 OS was 78% (95% CI, 0.73 to 0.82) in the ipilimumab arm and 85% (95% CI, 0.79 to 0.89) in the placebo arm at 1 year; 56% (95% CI, 0.51 to 0.61) and 61% (95% CI, 0.54 to 0.68) at 2 years; and 41% (95% CI, 0.36 to 0.46) and 40% (95% CI, 0.32 to 0.47) at 3 years. Analysis of OS in predefined patient subgroups is shown in Figure 2B. Treatment effects were comparable across patient groups.

Treatment with ipilimumab was associated with a longer median PFS: 5.6 (95% CI, 5.3 to 6.3) months in the ipilimumab arm versus 3.8 (95% CI, 2.8 to 4.1) months in the placebo arm (HR, 0.67; 95.87% CI, 0.55 to 0.81), with an early separation of the PFS curves sustained over time (Fig 3). In addition, treatment with F3 ipilimumab resulted in a longer time to systemic nonhormonal cytotoxic therapy (HR, 0.65; 95.87% CI, 0.52 to 0.83; Fig 4A) and F4 to docetaxel therapy (HR, 0.70; 95% CI, 0.55 to 0.88) versus placebo (Fig 4B). Exploratory analysis of PSA response showed a higher PSA response rate with ipilimumab (23%; 95% CI, 19% to 27%) than with placebo (8%, 95% CI, 5% to 13%). The number of patients with a pain response was too small to evaluate potential treatment-related differences.

Safety

The safety analysis included 399 patients treated with ipilimumab and 199 patients treated with placebo. Three hundred eighty-one (96%) and 182 (92%) patients experienced an all-cause AE in the ipilimumab and placebo arms, respectively (Appendix Table A3, online only). Any-grade treatment-related AEs occurred in 325 (82%) and 98 (49%) patients who received ipilimumab and placebo, respectively.

The most common treatment-related AEs, observed in > 10% of ipilimumab-treated patients, were diarrhea (43%), rash (33%), pruritus (27%), fatigue (24%), nausea (19%), decreased appetite (16%), vomiting (11%), and asthenia (10%; Table 2). Grade 3 to 4 T2 treatment-related AEs were noted in 158 (40%) patients in the ipilimumab arm and 11 (6%) in the placebo arm. Serious grade 3 to 4 treatment-related AEs occurred in 107 (27%) and four (2%) patients, respectively (Appendix Table A3). Diarrhea (15%) was the only grade 3 to 4 treatment-related AE reported in ≥ 10% of ipilimumab-treated patients (Table 2). Nine (2%) patients died in the ipilimumab arm as a result of a treatment-related AE, including cardiac arrest (n = 2) and gastrointestinal perforation, renal failure, hepatitis, pneumonitis, multiorgan lymphatic infiltration that resulted in cardiac arrest, pneumonia, and hepatotoxicity (n = 1 each). The deaths as a result of pneumonia and hepatotoxicity were poststudy events that occurred > 70 days from the last treatment dose. No treatment-related deaths were reported in the placebo arm.

Any-grade immune-related AEs were reported in 309 (77%) patients in the ipilimumab arm and 57 (29%) patients in the

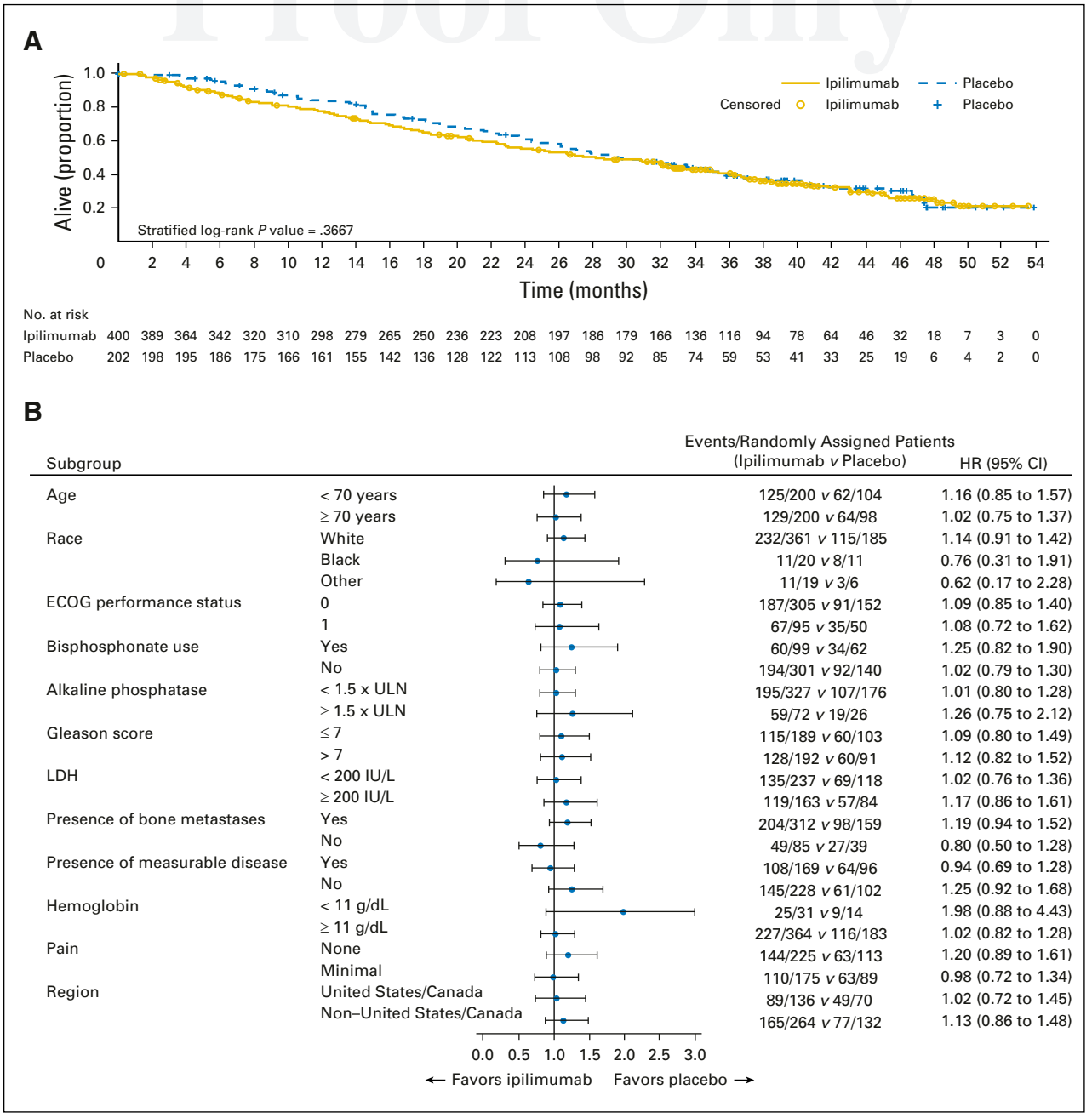

Fig 2. Overall survival in (A) intention-to-treat population and (B) patient subsets. ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IU, International Units; LDH, lactate dehydrogenase; ULN, upper limit of normal.

placebo arm. Grade 3 to 4 immune-related AEs occurred in 125 (31%) and three (2%) patients, respectively (Appendix Table A3).

Discontinuations due to treatment-related AEs occurred in 29% of patients in the ipilimumab arm and 3% in the placebo arm, mostly as a result of grade 3 to 4 AEs. The treatment-related AEs that led to ipilimumab discontinuation in ≥ 5% of patients was diarrhea (any grade, 10%; grade 3 to 4, 6%).

DISCUSSION

We report findings from a randomized, multicenter, double-blind, phase III study (CA184-095) that evaluated the potential benefit and safety of treatment with ipilimumab versus placebo in chemotherapy-naive patients with mCRPC without visceral metastases. Patient demographic and baseline disease characteristics were balanced between the treatment arms and comparable to prior phase III trials in similar populations of chemotherapy-naive patients with mCRPC.[3,5] The study results did not show an improvement in OS in patients treated with ipilimumab. Median OS

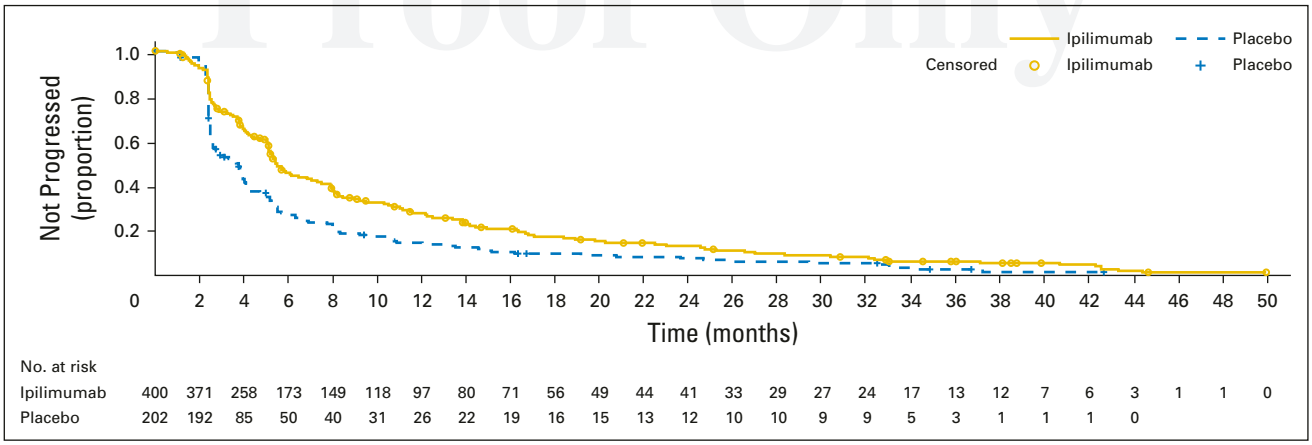

Fig 3. Progression-free survival in intention-to-treat population.

observed in patients in the placebo arm was longer than expected at study design (21.7 months). This outcome likely reflects improvements in the standard of care and a survival benefit provided by subsequent therapies, which 79% of patients in the placebo arm received after study discontinuation.

We observed a modestly longer median PFS after treatment with ipilimumab (5.6 months) versus placebo (3.8 months) as well as a higher PSA response rate (23% *v* 8% in an exploratory analysis), which suggests antitumor activity of ipilimumab in some chemotherapy-naive patients with mCRPC without visceral metastases. These results are consistent with findings of the prior CA184-043 trial, which evaluated ipilimumab after a single dose of bone-directed radiation therapy in patients with mCRPC who had received prior docetaxel therapy.[28] The CA184-095 study findings do not support the hypothesis generated in the exploratory analyses of the CA184-043 trial, which suggests a potential greater

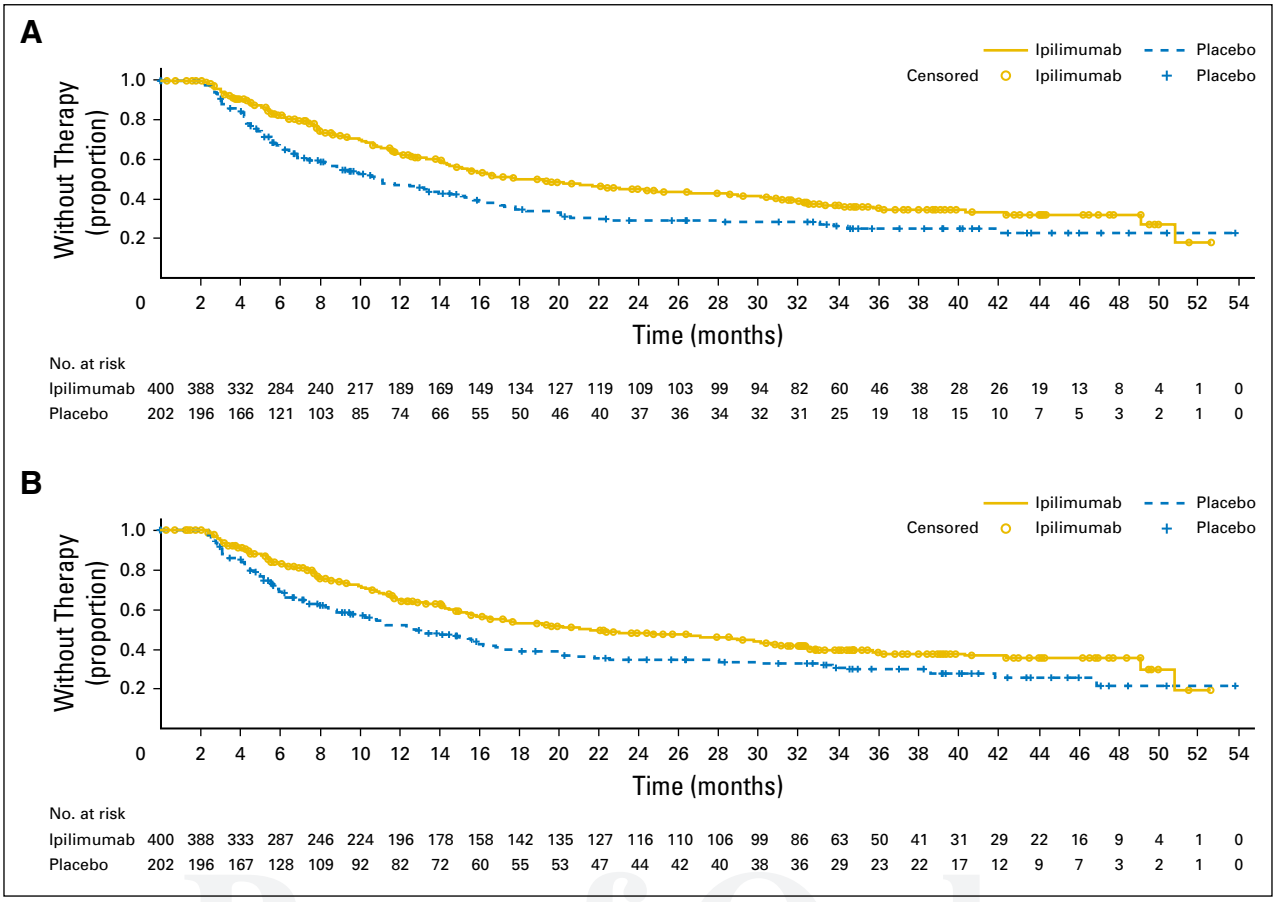

Fig 4. Time to (A) nonhormonal systemic therapy or (B) docetaxel therapy.

Table 2. Treatment-Related Adverse Events in > 10% of Treated Patients

Adverse Event	Ipilimumab (n = 399), No. (%)		Placebo (n = 199), No. (%)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Diarrhea	171 (43)	59 (15)	27 (14)	0
Rash	132 (33)	10 (3)	15 (8)	0
Pruritus	109 (27)	1 (< 1)	14 (7)	1 (< 1)
Fatigue	97 (24)	10 (3)	28 (14)	2 (1)
Nausea	75 (19)	7 (2)	15 (8)	0
Decreased appetite	64 (16)	5 (1)	9 (5)	0
Vomiting	43 (11)	4 (1)	5 (3)	0

benefit of ipilimumab in patients with mCRPC without visceral metastases.[28,30]

Multiple and not easily quantifiable factors may have contributed to the discordant observation of an improvement in median PFS without a significant difference in median OS between study arms. These include an insufficient level of antitumor activity in an unselected patient population; an unfavorable effect of AEs or comorbidities in an older patient population; type, dose, time of initiation, and duration of subsequent therapies; or other unknown factors.

The toxicity observed in this study was clinically relevant, but largely manageable and comparable with that reported in patients treated with ipilimumab in the postchemotherapy setting.[28] Treatment-related AEs noted in > 10% of patients were diarrhea, rash, pruritus, fatigue, nausea, decreased appetite, and vomiting. Nine treatment-related deaths were reported in the ipilimumab arm and none in the placebo arm. The duration of treatment was longer in the chemotherapy-naive patient population enrolled in this study than in the chemotherapy-pretreated patients included in the CA184-043 trial (mean number of cycles, 4.3 *v* 3.6),[28] as expected. The dose of ipilimumab (10 mg/kg) evaluated in this study was higher than the dose approved for the treatment of patients with unresectable or metastatic melanoma (3 mg/kg). The incidence of treatment-related grade 3 to 4 AEs in this study (40%) appears numerically higher than previously reported in patients with advanced melanoma (23%); the incidence of treatment-related grade 5 AEs was comparable (2%). However, no definitive conclusions can be drawn on a potential effect of dose-related toxicity on treatment efficacy in patients with mCRPC because patients received only one dose level of ipilimumab per trial design.

Previous clinical trials of sipuleucel-T, a cell-mediated immunotherapy requiring leukapheresis, ex vivo activation, and reinfusion of autologous peripheral blood mononuclear cells, showed efficacy in patients with mCRPC. Although treatment with sipuleucel-T extended OS in a proportion of patients with mCRPC (32% survival at 3 years with sipuleucel-T *v* 23% with placebo), it did not induce tumor regression or an improvement in PFS.[15]

In conclusion, analysis of the CA184-095 final study results indicates that this randomized, double-blind, phase III trial in asymptomatic or minimally symptomatic patients with mCRPC did not meet its primary end point for OS but did demonstrate modest improvements in PFS and PSA response after treatment with ipilimumab versus placebo. Two large randomized trials have now conclusively demonstrated that treatment with ipilimumab does not extend OS in unselected populations of patients with mCRPC but does result in measurable antitumor activity. Future work should be directed at determining how to harness such antitumor activity, potentially through identification of biomarkers that may enable prediction of benefit from treatment with ipilimumab. Based on current evidence, a potential role for newer immune checkpoint inhibitors, such as nivolumab and pembrolizumab, and other immunostimulatory strategies, either as single agents or in combination therapy, remains to be defined in patients with mCRPC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Q:6

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Randomized, Double-Blind, Phase III Trial of Ipilimumab Versus Placebo in Asymptomatic or Minimally Symptomatic Patients With Metastatic Chemotherapy-Naive Castration-Resistant Prostate Cancer

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Table A1. Study Drug Doses Received by Patients

Study Drug Dose	Ipilimumab 10 mg/kg, No. (%)	Placebo, No. (%)
No. of patients	399	199
One dose	29 (7)	4 (2)
Two doses	47 (12)	4 (2)
Three doses	72 (18)	16 (8)
Four doses	129 (32)	117 (59)
Five or more doses	122 (31)	58 (29)
Median no. of doses (range)	4.0 (1-17)	4.0 (1-16)

Table A2. Frequency of Subsequent Treatments

Therapy	Ipilimumab 10 mg/kg, No. (%)	Placebo, No. (%)
No. of patients	399	199
Patients who received subsequent therapy	268 (67)	158 (79)
Immunotherapy only	1 (< 1)	0
Sipuleucel-T	1 (< 1)	0
Nonhormonal systemic therapy only	67 (17)	34 (17)
Cabazitaxel	10 (3)	10 (5)
Carboplatin	2 (< 1)	1 (< 1)
Carboplatin, docetaxel	1 (< 1)	0
Carboplatin, paclitaxel	1 (< 1)	0
Cisplatin	1 (< 1)	0
Cyclophosphamide	1 (< 1)	2 (1)
Docetaxel	62 (16)	29 (15)
Estramustine	1 (0.3)	0
Mitoxantrone	5 (1)	2 (1)
Paclitaxel	3 (< 1)	0
Taxane	1 (< 1)	1 (< 1)
Vinblastine	0	1 (< 1)
Vinorelbine	0	2 (1)
Hormonal therapy only	60 (15)	27 (14)
Abiraterone	38 (10)	13 (7)
Bicalutamide	10 (3)	7 (4)
Cyproterone	5 (1)	1 (< 1)
Diethylstilbestrol	3 (< 1)	3 (2)
Enzalutamide	12 (3)	7 (4)
Flutamide	2 (< 1)	2 (1)
Ketoconazole	7 (2.0)	3 (2)
Megestrol	1 (< 1)	1 (< 1)
Nilutamide	2 (< 1)	2 (1)
Immunotherapy and nonhormonal systemic therapy	0	0
Immunotherapy and hormonal therapy	1 (< 1)	2 (1)
Nonhormonal systemic therapy and hormonal therapy	127 (32)	85 (43)
Immunotherapy, nonhormonal systemic therapy, and hormonal therapy	6 (2)	8 (4)

Table A3. Safety Summary: Treated Patient Population

	Ipilimumab 10 mg/kg, No. (%)			Placebo, No. (%)		
	Patients	Any Grade	Grade 3-4	Patients	Any Grade	Grade 3-4
No. of patients	399			199		
Deaths	259 (65)			130 (65)		
Death within 30 days of last dose	13 (3)			2 (1)		
Death within 70 days of last dose	35 (9)			5 (3)		
Treatment-related death	9 (2)			0		
All AEs		381 (96)	223 (56)		182 (92)	59 (30)
Treatment-related AEs		325 (82)	158 (40)		98 (49)	11 (6)
All serious AEs		213 (53)	153 (38)		53 (27)	39 (20)
Treatment-related serious AEs		135 (34)	107 (27)		7 (4)	4 (2)
All AEs that led to treatment discontinuation		139 (35)	103 (26)		20 (10)	14 (7)
Immune-related AEs		309 (77)	125 (31)		57 (29)	3 (2)

Abbreviation: AE, adverse event.

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