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Platinum Priority – Prostate Cancer

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Final Analysis of the Ipilimumab Versus Placebo Following Radiotherapy Phase III Trial in Postdocetaxel Metastatic Castration-resistant Prostate Cancer Identifies an Excess of Long-term Survivors

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Abstract

Background: The phase 3 trial CA184-043 evaluated radiotherapy to bone metastases followed by Ipilimumab or placebo in men with metastatic castrate-resistant prostate cancer (mCRPC) who had received docetaxel previously. In a prior analysis, the trial's primary endpoint (overall survival [OS]) was not improved significantly.
Objective: To report the final analysis of OS.
Design, setting, and participants: A total of 799 patients were randomized to receive a single dose of radiotherapy to one or more bone metastases followed by either Ipilimumab ($n = 399$) or placebo ($n = 400$).
Outcome measurements and statistical analysis: OS was analyzed in the intention-to-treat population. Prespecified and exploratory subset analyses based on Kaplan-Meier/Cox methodology were performed.

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Results and limitations: During an additional follow-up of approximately 2.4 yr since the primary analysis, 721/799 patients have died. Survival analysis showed crossing of the curves at 7–8 mo, followed by persistent separation of the curves beyond that point, favoring the ipilimumab arm. Given the lack of proportional hazards, a piecewise hazard model showed that the hazard ratio (HR) changed over time: the HR was 1.49 (95% confidence interval 1.12, 1.99) for 0–5 mo, 0.66 (0.51, 0.86) for 5–12 mo, and 0.66 (0.52, 0.84) beyond 12 mo. OS rates were higher in the ipilimumab versus placebo arms at 2 yr (25.2% vs 16.6%), 3 yr (15.3% vs 7.9%), 4 yr (10.1% vs 3.3%), and 5 yr (7.9% vs. 2.7%). Disease progression was the most frequent cause of death in both arms. In seven patients (1.8%) in the ipilimumab arm and one (0.3%) in the placebo arm, the primary cause of death was reported as study drug toxicity. No long-term safety signals were identified.
Conclusions: In this preplanned long-term analysis, OS favored ipilimumab plus radiotherapy versus placebo plus radiotherapy for patients with postdocetaxel mCRPC. OS rates at 3, 4, and 5 yr were approximately two to three times higher in the ipilimumab arm.
Patient summary: After longer follow-up, survival favored the group of men who received ipilimumab, with overall survival rates being two to three times higher at 3 yr and beyond.

1. Introduction

Management of men with metastatic castration-resistant prostate cancer (mCRPC) has evolved dramatically since 2010, with taxanes (docetaxel and cabazitaxel), next-generation androgen receptor axis targeting agents (abiraterone and enzalutamide), and a bone-targeted radioisotope (radium-223) demonstrating improved overall survival (OS) in clinical trials [1–3]. In many other solid tumors, immunotherapy based on immune checkpoint blockade has emerged as an important treatment option [4,5]. Prostate cancer was one of the first malignancies in which cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibition was tested in preclinical models [6,7] and activity was subsequently confirmed in phase I-II development [8–10]. Recent data [11,12] also suggest that anti–PD-1 has activity in some patients with mCRPC, and a randomized phase III trial adding PD-L1 blockade to second-generation androgen receptor inhibitor treatment is currently underway (NCT03016312). Further, the autologous cell-based "vaccine" sipuleucel-T is approved by the US Food and Drug Administration for the treatment of mCRPC based on a survival benefit [13], although this treatment is not available outside of the USA.

Ipilimumab is a fully human monoclonal antibody that blocks the inhibitory signal mediated by CTLA-4, and as a consequence, enhances antitumor immunity and has immune-related side effects [14–16]. Two randomized phase III trials testing ipilimumab in men with mCRPC were designed and conducted, one in men who had not received chemotherapy previously (the "Ipi 095" trial, NCT01057810) and the other in men who had progressed after docetaxel (the "Ipi 043" trial, NCT00861614, where ipilimumab was used following radiotherapy (RT) directed to a bone lesion [17]). In both trials, progression-free survival (PFS; hazard ratio [HR]: 0.67; 95.87% confidence interval [CI], 0.55 to 0.81, and HR: 0.70, 95% CI 0.61–0.82, respectively), but not OS, was significantly improved [15,16]. In the 043 trial, which enrolled patients with more advanced disease, OS was improved nonsignificantly (HR: 0.85, 95% CI 0.72–1.00; $p = 0.053$), with Kaplan-Meier curves initially disfavoring the ipilimumab group and then crossing after approximately 6 mo [15]. In order to elucidate whether ipilimumab treatment is associated with improved long-term OS in men with prostate cancer, we continued to follow patients enrolled in the 043 trial; this manuscript reports mature results with an additional 2 yr of follow-up since the primary analysis.

2. Patients and methods

2.1. Patients

The randomized, double-blind, controlled phase 3 trial "CA184-043" was reported previously [15]. In brief, 043 was conducted in 191 centers from 26 countries; it enrolled male patients aged 18 yr or older with histologically or cytologically confirmed adenocarcinoma of the prostate, at least one bone metastases that could be irradiated or that warranted irradiation in the clinical judgment of the investigator, testosterone <0.50 ng/mL, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and progression ≤ 6 mo after receiving docetaxel. Exclusion criteria were more than two cytotoxic chemotherapy regimens for mCRPC, brain metastases, autoimmune disease, or known HIV, hepatitis B or C infection.

Review boards at all participating institutions approved the study, which was conducted according to the provisions of the Declaration of Helsinki and Good Clinical Practice Guidelines of the International Conference on Harmonization. All patients provided written informed consent to participate in the study.

2.2. Randomization and masking

Patients ($n = 799$) were randomized in a 1:1 ratio to receive bone-directed RT followed by either ipilimumab intravenously at 10 mg/kg or placebo every 3 wk for up to four doses. Nonprogressing patients could receive ipilimumab at 10 mg/kg or placebo as maintenance therapy every 3 mo.

Randomization was performed with an interactive voice response system, stratified by ECOG performance status (0 vs 1), alkaline phosphatase (<1.5 × upper limit of normal [ULN] vs ≥1.5 × ULN), hemoglobin (<11 vs ≥11 g/dl), and investigator site. An independent data monitoring committee had access to unblinded data.

2.3. Procedures

Patients first received a single dose of RT at 8 Gy to at least one and up to five bone fields based on investigator discretion. RT was delivered within 2 d prior to the initiation of either ipilimumab or placebo. Treatment was continued until confirmed disease progression, intolerable toxicity, clinical deterioration, death, patient withdrawal of consent, or loss to follow-up.

Tumor assessments by radiographic imaging and prostate-specific antigen (PSA) levels were performed every 12 and 6 wk, respectively. Safety characterization was based on events tabulated from the first dose of study drug to 70 d after the last dose of study drug (including maintenance therapy). This interval is considered the "on-study" period. We also evaluated the incidence of immune-related adverse events (irAEs), which were determined from a predefined list of MedDRA terms representing adverse events potentially associated with inflammation and considered to be causally related to drug exposure.

2.4. Statistical analysis

The purpose of the analysis was to quantify preplanned updated OS and safety results through the July 13, 2015 fin.l database lock for the extension phase of the trial.

The primary endpoint of the trial was OS, defined as time from randomization to death from any cause. For individuals who did not die, OS was censored at the date last known to be alive.

Yearly survival rates up to 5 yr were estimated for each treatment group using the Kaplan-Meier product limit method [18]. Two-sided 95% CIs for median survival were computed by treatment group using the Brookmeyer and Crowley [19] method. Descriptive statistics for safety were tabulated for all treated patients using National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 by treatment group. Safety analyses were performed using data obtained from the start of blinded study drug dosing up to 70 d after the last dose of study therapy. Demography, baseline characteristics, and safety were summarized descriptively.

Table 1 – Demographic and baseline characteristics.

	Ipilimumab (*N* = 399)	Placebo (*N* = 400)
Age (yr),		
Median (Q1–Q3)	69.0 (63.0–74.0)	67.5 (62.0–72.5)
≥70, no. of patients (%)	184 (46)	166 (42)
Alkaline phosphatase, no. of patients (%)		
≥1.5 × ULN	163 (41)	151 (38)
Not reported	11 (2.8)	17 (4.3)
Gleason score, no. of patients (%)		
>7	192 (48)	187 (47)
Not reported	33 (8.3)	23 (5.8)
Hemoglobin (g/dl), no. of patients (%)		
<11	116 (29)	111 (28)
Not reported	16 (4.0)	20 (5.0)
ECOG PS, no. of patients (%)		
0	168 (42)	170 (43)
1	216 (54)	220 (55)
2	3 (0.8)	0
Not reported	12 (3.0)	10 (2.5)
Bone metastases, no. of patients (%)		
>5	103 (26)	111 (28)
Not reported	20 (5.0)	36 (9.0)
Visceral metastases, no. of patients (%)		
Yes	113 (28)	114 (29)
Not reported	6 (1.5)	11 (2.8)
Lactate dehydrogenase, no. of patients (%)		
>2 × ULN	58 (15)	53 (13)
Not reported	15 (3.8)	22 (5.5)
Prostate-specific antigen (ng/mL)		
No. of patients (%)	338 (85)	334 (84)
Median	138.5	176.5
(Q1–Q3)	(44.5–452.8)	(46.6–416.0)
Average daily worst pain intensity, no. of patients (%)		
≥4	197 (49)	186 (47)
Not reported	50 (13)	64 (16)

ECOG PS = Eastern Cooperative Oncology Group performance status; ULN = upper limit of normal.

3. Results

A total of 988 patients were enrolled and screened for study participation (Supplementary Fig. 1). Of these patients, 799 (399 in the ipilimumab arm and 400 in the placebo arm) were randomly assigned from May 2009 to February 2012 to blinded study treatment at a total of 153 sites [15] (Table 1). Approximately one-half (49%) of randomized patients were from sites in Europe, 27% were from sites in North America, 20% were from sites in South America, and 3.1% were from sites in Australia.

Overall, 387 and 392 patients received at least one dose of ipilimumab and placebo, respectively, and 198 (51%) and 267 (67%) received at least four treatment doses. After induction treatment, 95 (25%) and 62 (16%) patients entered the maintenance phase.

3.1. Overall survival

During an additional follow-up of approximately 2.4 yr since the primary analysis (final database lock: July 13, 2015; primary analysis database lock: February 6, 2013), 721/799 patients had died: 49/399 remained alive in the ipilimumab arm and 29/400 were alive in the placebo arm, with a median follow-up of 50 mo (40.7, 72.0) for the survivors. Kaplan-Meier analysis of OS showed crossing of the curves at 7–8 mo, with persistent separation favoring the ipilimumab arm beyond that point with longer follow-up (Fig. 1). Given the lack of proportional hazards, a piecewise hazard model showing a changing HR over time has been reported previously [15], and an update with the final database lock shows that the HR was 1.49 (95% CI 1.12–1.99) for 0–5 mo, 0.66 (0.51–0.86) for 5–12 mo, and 0.66 (0.52–0.84) beyond 12 mo.

Landmark OS rates for the ipilimumab and placebo groups are summarized in Table 2, which show that, in the ipilimumab arm, OS rates were significantly higher at 2 yr and beyond, and two to three times higher at 3, 4, and 5 yr.

Disease progression was the most frequent cause of death in both groups (270 patients, 69% and 298 patients, 75%, respectively). At the time of the final database lock, for seven men (1.8%) in the ipilimumab group and one man (0.25%) in the placebo group, the primary cause of death was reported as study drug toxicity. The seven deaths in the ipilimumab group were due to peritonitis, acute myeloid leukemia, diverticular perforation, pulmonary embolism, pneumonia, decreased performance status, and related cholangitis with a fatal outcome. Of note, only one of these deaths (acute myeloid leukemia) was reported after primary database lock. In the placebo group, one on-study death (0.25%) was reported due to multiorgan failure associated with study drug toxicity.

3.2. Safety

The safety profile for ipilimumab was similar to that reported previously, with irAEs most commonly occurring in the gastrointestinal tract and skin, and to a lesser extent in the liver and endocrine organs (Table 3). The majority of irAEs, including severe irAEs, occurred during the initial four doses of study drug. After year 1, irAEs were reported in nine patients in the ipilimumab arm.

4. Discussion

Long-term analyses of survival are rarely reported in mCRPC studies, although this is of even greater importance for immunotherapy trials, because a delayed effect on the

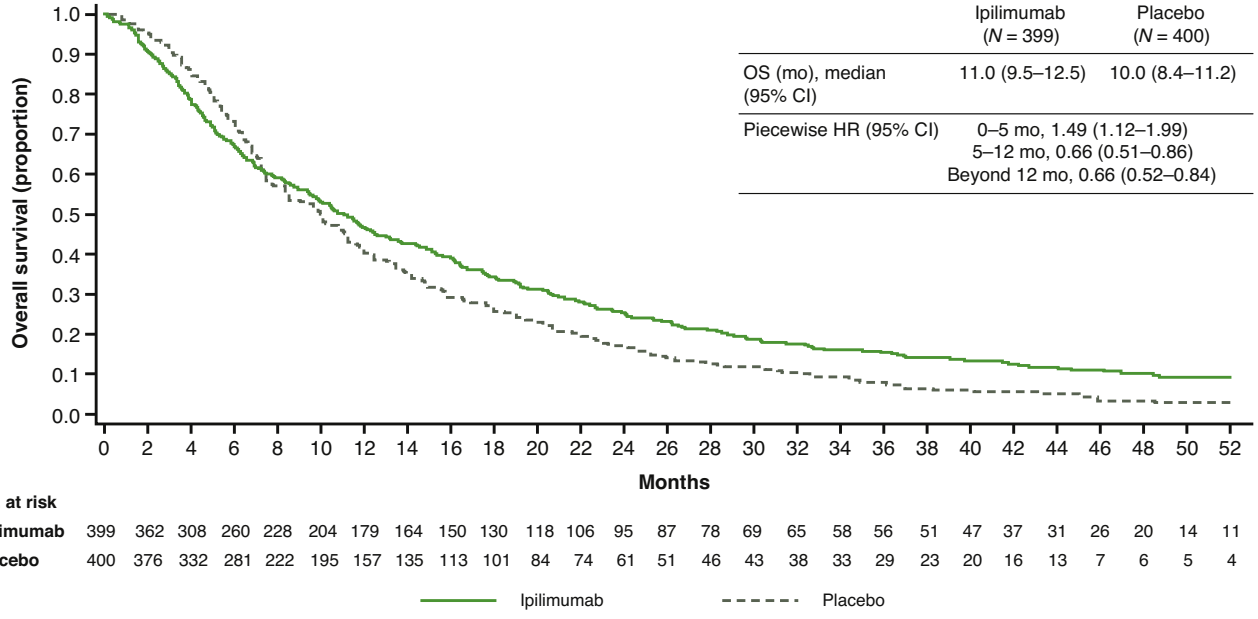

Fig. 1 – Overall survival. CI = confidence interval; HR = hazard ratio; OS = overall survival.

Table 2 – Overall survival.

	Ipilimumab + radiotherapy	Placebo + radiotherapy	Difference (95% CI[a])
1-yr OS rate	47%	41%	5.7% (−1.2, 13)
2-yr OS rate	25%	17%	8.6% (3.0, 14)
3-yr OS rate	15%	7.9%	7.4% (3.0, 12)
4-yr OS rate	10%	3.3%	6.8% (3.4, 10)
5-yr OS rate	7.9%	2.7%	5.2% (2.1, 8.3)

CI = confidence interval; OS = overall survival.
[a] 95% CIs were computed for binary rate differences.

Table 3 – Adverse events.

On-study adverse events	Ipilimumab (*N* = 393)			Placebo (*N* = 396)		
	Any grade	Grade 3 or 4	Grade 5	Any grade	Grade 3 or 4	Grade 5
Any event	385 (98)	231 (59)	67 (17)	365 (92)	162 (41)	45 (11)
Immune-related events	250 (64)	102 (26)	1 (0.3)	86 (22)	11 (2.8)	1 (0.3)
Gastrointestinal	160 (41)	72 (18)	1 (0.3)	56 (14)	3 (0.8)	0
Diarrhea	154 (39)	59 (15)	0	55 (14)	3 (0.8)	0
Colitis	28 (7.1)	18 (4.6)	0	3 (0.8)	0	0
Diverticular perforation	1 (0.3)	0	1 (0.3)	0	0	0
Skin	139 (35)	5 (1.3)	0	29 (7.3)	0	0
Pruritus	80 (20)	1 (0.3)	0	15 (3.8)	0	0
Rash	70 (18)	3 (0.8)	0	16 (4.0)	0	0
Hepatic	34 (8.7)	16 (4.1)	0	18 (4.5)	7 (1.8)	0
Increased aspartate aminotransferase	22 (5.6)	9 (2.3)	0	13 (3.3)	4 (1.0)	0
Alanine aminotransferase	20 (5.1)	6 (1.5)	0	8 (2.0)	3 (0.8)	0
Endocrine	19 (4.8)	7 (1.8)	0	6 (1.5)	2 (0.5)	0
Hypothyroidism	9 (2.3)	2 (0.5)	0	1 (0.3)	0	0
Neurological	9 (2.3)	2 (0.5)	0	1 (0.3)	0	0

Data are *n* (%). Patients may have had more than one event.

immune system is expected. This global study was the first phase 3 trial testing ipilimumab in men with mCRPC that included long-term follow-up, and the primary endpoint of OS was not improved at the initial analysis [15]; this intent-to-treat analysis with longer follow-up shows that beyond the crossing of the curves at 7–8 mo, there is persistent separation of the curves favoring the ipilimumab plus RT arm. This favorable impact of ipilimumab plus RT on OS was associated with an increased number of patients alive at 2 yr and beyond, some of whom had complete responses to treatment [20,21]. The primary analysis of this trial showed improved PFS over placebo (HR: 0.70, 95% CI 0.61–0.82; $p < 0.0001$) and a higher proportion of patients with a confirmed ≥50% PSA decline at any time (13% [95% CI 9.5–18] for ipilimumab and 5.3% [95% CI 3.0–8.4] for placebo) [15]. PFS, but not OS, was also improved significantly (HR: 0.67; 95.87% CI, 0.55–0.81) in a second trial testing ipilimumab monotherapy in men with docetaxel-naïve mCRPC [16]. Of note, the PFS improvement observed across these two CRPC ipilimumab trials is unique among all immunotherapeutic approaches in clinical development for prostate cancer [4,5]. In this long-term analysis, prespecified OS rates were significantly greater at 2, 3, 4, and 5 yr in the ipilimumab versus placebo arms, respectively.

It is likely that the failure of the primary analysis [15] of this trial to originally demonstrate significantly improved OS (HR: 0.85, 0.72–1.00; $p = 0.053$) with ipilimumab plus RT is due to the apparently initial worse outcome for patients in this arm during the first 7 mo. Crossover of the Kaplan-Meier survival curves was observed, after which time the ipilimumab arm appears to continuously show better OS than the placebo arm. Since this trial was first reported, this phenomenon of crossing curves has been described repetitively in phase 3 trials testing CTLA-4 or PD-1/PD-L1 inhibitors in various cancers, including lung [22] and bladder cancer [23]. Of note, hyperprogression of cancer has been described with these immunotherapies, and they may explain this phenomenon, at least in part [24]. An excess in side effects was observed in the ipilimumab arm during the initial weeks of the trial: this may also have favored directly or indirectly an excess of early death events in this arm. Finally, it is plausible that men with more indolent cancers and those with a lower burden of cancer may also be more sensitive to immunotherapy, which may account for the delayed effect on survival.

A potentially T-cell–mediated antitumor effect of ipilimumab, as quantified by a PSA decline of >50%, was observed in 13–23% of men enrolled in the two phase 3 trials [15,16]. Although an effect on PSA might not fully explain treatment effects in men with CRPC [25], these data suggest that only a minority of men with mCRPC derive a benefit from the single agent ipilimumab. This finding further emphasizes the need for identifying biomarkers predicting for ipilimumab activity. Clinically applicable biomarkers remain elusive. For example, neoepitope signature and mutational load [26,27], mismatch repair deficiency [28], lactate dehydrogenase or C-reactive protein levels [29], early rise in eosinophils and lymphocytes [30], and, recently, inactivation of CDK12 [31] have been reported to predict the efficacy of immune checkpoint inhibitors. More specifically, in men with mCRPC treated with ipilimumab, the UCSF group recently reported that low pretreatment baseline levels of PD-1(+) CD4 Teff cells correlate with longer survival [32]. They also showed that responses to ipilimumab were also associated with increased T-cell diversity [33]. Although fairly apparent in melanoma, the role of the gut microbiome in predicting checkpoint inhibitor efficacy [34] is unknown in men with prostate cancer. Unfortunately, tissue and stool samples were not collected systematically in the present trial, and therefore aiming at identifying biomarkers for efficacy and toxicity is not possible.

The safety profile of ipilimumab in this study was generally consistent with the experience in other studies using 10 mg/kg ipilimumab, and no new safety signals were identified in this long-term analysis. Common toxicities of ipilimumab (eg, inflammatory events reflecting ipilimumab's immune-based mechanism of action) affected the gastrointestinal tract and skin most frequently. There were seven deaths (1.8%) attributed to study drug toxicity in the ipilimumab group, and the frequency of gastrointestinal perforations was consistent with prior ipilimumab experience in advanced melanoma, where its incidence was approximately 1.0% [35]. Identifying biomarkers predicting for severe toxicity of immunotherapy is also a priority, and ipilimumab was previously shown to induce greater diversification in the T-cell repertoire in patients who develop irAEs than others [33]. Of note, the dose of ipilimumab (10 mg/kg) evaluated in this trial was higher than that approved for the treatment of patients with advanced melanoma (3 mg/kg), and this likely explains the observed degree of toxicity.

In terms of trial design, this study was based, to some degree, on preclinical data showing that the combination of anti-CTLA-4 and RT could induce potent off-target (abscopal) effects [36] and that such off-target effects are immunologically mediated [37]. Since bone-directed RT was administered in both study arms, its role in the efficacy outcomes is unclear. Of note, a second ipilimumab phase 3 trial in men with mCRPC (CA184-095) [16] was performed using ipilimumab monotherapy.

As in all randomized trials, there are limitations in the ascertainment of information about the effectiveness of subsequent treatments on patients in the long term. At the primary analysis cutoff, the use of subsequent cancer therapy was 41% versus 47% in the ipilimumab versus placebo arms [15]. This suggests that treatments used beyond progression in the experimental arm are unlikely to explain the observed long-term OS difference between arms. Subsequent anticancer therapies were not collected for the final database lock (July 13, 2015), so we cannot provide any update. Of note, patients were accrued in the trial from May 2009 to February 2012, a period of time when postdocetaxel life-prolonging therapies were either unavailable or scarcely available in most of the participating countries.

5. Conclusions

In summary, this long-term analysis shows that OS is improved with ipilimumab plus RT versus placebo plus RT in patients with postdocetaxel mCRPC, and treatment was associated with a fraction of patients with long-term survival. As these data were analyzed after the primary OS analysis [15], they must be considered hypothesis generating rather than definitive. As such, ipilimumab is not registered in the mCRPC indication.

Evidence was recently provided that PD-1/PD-L1 blockade is active in a subset of men with CRPC [11,12]. Based on the reported efficacy in other cancers, a combination trial of ipilimumab and nivolumab is undergoing in men with mCRPC (NCT02985957), with preliminary data supporting activity [38], as well as in a set of patients with the ARV7 mutation [39].

CRediT :

Author contributions: Karim Fizazi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Fizazi, Drake, Beer, Kwon, Scher, Gerritsen, Bossi, Logothetis.
Acquisition of data: Fizazi, Drake, Beer, Kwon, Scher, Gerritsen, Bossi, Logothetis.
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Drafting of the manuscript: Fizazi.
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Appendix A. Supplementary data

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References

[1] Gillessen S, Attard G, Beer TM, et al. Management of patients with advanced prostate cancer: the report of the Advanced Prostate Cancer consensus Conference APCCC 2017. Eur Urol 2018;73:178–211.

[2] Horwich A, Hugosson J, de Reijke T, et al. Prostate cancer: ESMO consensus conference guidelines 2012. Ann Oncol 2013;24:1141–62.

[3] Fitzpatrick JM, Bellmunt J, Fizazi K, et al. Optimal management of metastatic castration-resistant prostate cancer: highlights from a European expert consensus panel. Eur J Cancer 2014;50:1617–27.

[4] LaFleur MW, Muroyama Y, Drake CG, Sharpe AH. Inhibitors of the PD-1 pathway in tumor therapy. J Immunol 2018;200:375–83.

[5] Quinn DI, Shore ND, Egawa S, Gerritsen WR, Fizazi K. Immunotherapy for castration-resistant prostate cancer: progress and new paradigms. Urol Oncol 2015;33:245–60.

[6] Kwon ED, Hurwitz AA, Foster BA, et al. Manipulation of T cell costimulatory and inhibitory signals for immunotherapy of prostate cancer. Proc Natl Acad Sci USA 1997;94:8099–103.

[7] Kwon ED, Foster BA, Hurwitz AA, et al. Elimination of residual metastatic prostate cancer after surgery and adjunctive cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) blockade immunotherapy. Proc Natl Acad Sci USA 1999;96:15074–9.

[8] Madan RA, Mohebtash M, Arlen PM, et al. Ipilimumab and a poxviral vaccine targeting prostate-specific antigen in metastatic castration-resistant prostate cancer: a phase 1 dose-escalation trial. Lancet Oncol 2012;13:501–8.

[9] van den Eertwegh AJ, Versluis J, van den Berg HP, et al. Combined immunotherapy with granulocyte-macrophage colony-stimulating factor-transduced allogeneic prostate cancer cells and ipilimumab in patients with metastatic castration-resistant prostate cancer: a phase 1 dose-escalation trial. Lancet Oncol 2012;13:509–17.

[10] Slovin S, Higano CS, Hamid O, et al. Ipilimumab alone or in combination with radiotherapy in metastatic castration-resistant prostate cancer: results from an open-label, multicenter phase I/II study. Ann Oncol 2013;24:1813–21.

[11] Graff JN, Alumkal JJ, Drake CG, et al. Early evidence of anti-PD-1 activity in enzalutamide-resistant prostate cancer. Oncotarget 2016;7:52810–7.

[12] Hansen A, Massard C, Ott PA, et al. Pembrolizumab for patients with advanced prostate adenocarcinoma: preliminary results from the KEYNOTE-028 study. Ann Oncol 2016;27(Suppl 6):725PD.

[13] Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411–22.

[14] Fong L, Small EJ. Anti-cytotoxic T-lymphocyte antigen-4 antibody: the first in an emerging class of immunomodulatory antibodies for cancer treatment. J Clin Oncol 2008;26:5275–83.

[15] Kwon ED, Drake CG, Scher HI, et al. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol 2014;15:700–12.

[16] Beer TM, Kwon ED, Drake CG, et al. Randomized, double-blind, phase III trial of ipilimumab versus placebo in asymptomatic or minimally symptomatic patients with metastatic chemotherapy-naive castration-resistant prostate cancer. J Clin Oncol 2017;35:40–7.

[17] Kaur P, Asea A. Radiation-induced effects and the immune system in cancer. Front Oncol 2012;2:191.

[18] Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.

[19] Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics 1982;38:29–41.

[20] Cabel L, Loir E, Gravis G, et al. Long-term complete remission with Ipilimumab in metastatic castrate-resistant prostate cancer: case report of two patients. J Immunother Cancer 2017;5:31.

[21] Graff Jn, Puri S, Bifulco Cb, Fox Ba, Beer Tm. Sustained complete response to CTLA-4 blockade in a patient with metastatic, castration-resistant prostate cancer. Cancer Immunol Res 2014;2:399–403.

[22] Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 2015;373:1627–39.

[23] Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med 2017;376:1015–26.

[24] Champiat S, Dercle L, Ammari S, et al. Hyperprogressive disease is a new pattern of progression in cancer patients treated by anti-PD-1/PD-L1. Clin Cancer Res 2017;23:1920–8.

[25] Morris MJ, Molina A, Small EJ, et al. Radiographic progression-free survival as a response biomarker in metastatic castration-resistant prostate cancer: COU-AA-302 results. J Clin Oncol 2015;33:1356–63.

[26] Snyder A, Makarov V, Merghoub T, et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. N Engl J Med 2014;371:2189–99.

[27] Alexandrov LB, Nik-Zainal S, Wedge DC, et al. Signatures of mutational processes in human cancer. Nature 2013;500:415–21.

[28] Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015;372:2509–20.

[29] Simeone E, Gentilcore G, Giannarelli D, et al. Immunological and biological changes during ipilimumab treatment and their potential correlation with clinical response and survival in patients with advanced melanoma. Cancer Immunol Immunother 2014;63:675–83.

[30] Delyon J, Mateus C, Lefeuvre D, et al. Experience in daily practice with ipilimumab for the treatment of patients with metastatic melanoma: an early increase in lymphocyte and eosinophil counts is associated with improved survival. Ann Oncol 2013;24:1697–703.

[31] Wu YM, Cieślik M, Lonigro RJ, et al. Inactivation of CDK12 delineates a distinct immunogenic class of advanced prostate Cancer. Cell 2018;173:1770–82.
[32] Kwek SS, Lewis J, Zhang L, et al. Preexisting levels of CD4 T cells expressing PD-1 are related to overall survival in prostate cancer patients treated with ipilimumab. Cancer Immunol Res 2015;3:1008–16.
[33] Oh DY, Cham J, Zhang L, et al. Immune toxicities elicited by CTLA-4 blockade in cancer patients are associated with early diversification of the T-cell repertoire. Cancer Res 2017;77:1322–30.
[34] Routy B, Le Chatelier E, Derosa L, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science 2018;359:91–7.
[35] US Yervoy (ipilimumab) [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2013.
[36] Dewan MZ, Galloway AE, Kawashima N, et al. Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody. Clin Cancer Res 2009;15:5379–88.
[37] Demaria S, Kawashima N, Yang AM, et al. Immune-mediated inhibition of metastases after treatment with local radiation and CTLA-4 blockade in a mouse model of breast cancer. Clin Cancer Res 2005;11:728–34.
[38] Sharma P, Pachynski R, Narayan V, et al. Initial results from a phase II study of nivolumab (NIVO) plus ipilimumab (IPI) for the treatment of metastatic castration-resistant prostate cancer (mCRPC; Checkmate 650). 2019 Genitourinary Cancer symposium. J Clin Oncol 2019;37(7_suppl):142.
[39] Boudadi K, Suzman DL, Anagnostou V, et al. Ipilimumab plus nivolumab and DNA-repair defects in AR-V7-expressing metastatic prostate cancer. Oncotarget 2018;9:28561–71.