Medicine®

OPEN

The efficacy and safety of immune checkpoint inhibitors in metastatic castration-resistant prostate cancer
A systematic review and meta-analysis

Xing-Hui Wang, MD[a], Zhi-Qiang Wang, MD[b], Zhen-Yu Mu, MD[c], Li-Ping Zhu, MD[d], Chong-Fu Zhong, MD[e], Shanchun Guo, PhD[f],* ●

Abstract

Background: We aim to assess the efficacy and safety profiles of immune checkpoint inhibitors in patients with metastatic castration-resistant prostate cancer using a meta-analysis.

Methods: We extracted and examined data from phase I, II and III clinical trials from PubMed, Embase, Web of Science, and Cochrane Library, which included patients with metastatic castration-resistant prostate cancer who were treated with immune checkpoint inhibitors. We performed a meta-analysis to investigate several indexes of efficacy and safety, including the objective response rate, 1-year overall survival (OS) rate, prostate-specific antigen response rate, and adverse event rate of immune checkpoint inhibitors. The material data were calculated and pooled using The R Project for Statistical Computing and STATA 12.0 software.

Results: We identified 12 clinical trials in our study. We assessed the pooled frequencies of all-grade AEs and grade ≥ 3 AEs first and showed 0.82 (95% CI: 0.74–0.91, I^2 = 94%, P < .01) and 0.42 (95% CI: 0.33–0.54, I^2 = 96%, P < .01), respectively. The objective response rate was 0.10 (95% CI: 0.04–0.19, I^2 = 70%, P < .01), and the 1-year OS and prostate-specific antigen response rate were 0.55 (95% CI: 0.45–0.67, I^2 = 93%, P < .01) and 0.18 (95% CI: 0.16–0.20, I^2 = 43%, P = .03), respectively.

Conclusion: The immune checkpoint inhibitors therapy was well tolerated and showed potential to improve tumor responses in patients with metastatic castration-resistant prostate cancer.

Abbreviations: ADT = androgen deprivation therapy, AEs = adverse events, AR = androgen receptor, dMMR = deficient mismatch repair, ICIs = Immune checkpoint inhibitors, CTLA-4 = cytotoxic T lymphocyte antigen 4, PD-1 = programmed death-1, PD-L1 = PD-1 ligand, mCRPC = metastatic castration-resistant PC, RCT = randomized controlled trial, MSI = microsatellite instability, ORR = objective response rate.

Key Words: immune checkpoint inhibitor, immunotherapy, meta-analysis, metastatic castration-resistant prostate cancer, prostate cancer, oncology

1. Introduction

Prostate cancer (PC) is the second most frequent tumor and the fifth leading cause of tumor death in men worldwide.[1] Although most patients are diagnosed early and may be cured with surgery and/or radiation therapy, about one-third of men treated will fail therapy and develop advanced PC.[2,3] For decades,

the management of patients with advanced PC has been hormonal therapy, known as androgen deprivation therapy (ADT), which is intended to lower testosterone levels.[4] Despite initial responses, essentially all patients will develop metastatic castration-resistant PC (mCRPC).[5] Standard first-line treatment for mCRPC is docetaxel plus prednisone[6]; however, patients will usually develop inherent or acquired resistance during or

after docetaxel treatment. Patients with mCRPC are in critical need of innovative treatment strategies. From 2010, efforts to expand the treatment landscape for mCRPC resulted in the Food and Drug Administration (FDA) approval of 10 more agents that contributed to improved survival; new treatments included androgen receptor (AR)-targeted therapies (apalutamide, enzalutamide, abiraterone, darolutamide), a chemotherapy (cabazitaxel), a radioisotope (radium-223), a cancer vaccine (sipuleucel-T) and 3 DNA-damaging agents (olaparib, rucaparib, niraparib).[7] Despite the approval of a number of new agents for advanced diseases, each of these treatments has prolonged survival by only a few months. Thus, new therapies such as immunotherapy are greatly needed. For other tumor types, immunotherapy has demonstrated dramatic and durable treatment responses, leading many to believe that immunotherapies might be an ideal treatment approach for patients with advanced PC.[8]

Immune checkpoint inhibitors (ICIs) are novel biologic drugs to treat tumors by blocking the regulatory interactions that limit T-cell cytotoxicity to tumors.[9] Immune-checkpoint monotherapies or combination regimens targeting cytotoxic T lymphocyte antigen 4 (CTLA-4) and/or the programmed death-1 (PD-1)/PD-1 ligand (PD-L1) axis have become standard treatment for multiple tumors deemed immunologically "hot," including melanoma, nonsmall cell lung cancer (NSCLC), renal cell carcinoma (RCC), and bladder cancer, among others.[10–13] However, tumors that are immunologically "'cold'" due to a relatively low somatic mutation frequency and few tumor-infiltrating T cells, such as mCRPC, are considered relatively resistant to immune-checkpoint therapy.[14] Although the FDA granted accelerated approval to pembrolizumab for patients with microsatellite instability–high (MSI-H) or deficient mismatch repair (dMMR) solid tumors irrespective to tumor origins,[15] MSI-H/dMMR patients only account for 2% to 3% of mCRPC patients which limits the application of immunotherapy in PC.[16] Recently, ICIs have revolutionized the therapeutic landscape of clinical oncology by inducing durable T cell–mediated antitumor responses in patients with advanced malignancies.[17] Combinations of ICIs can convert tumors from "cold" to "hot," whereby tumor-infiltrating T cells are increased and compensatory inhibitory pathways are blocked, thereby generating antitumor responses.[18] The number of trials has rapidly increased due to the development of ICIs, used alone or in combination with other modalities. It is necessary to analyze previous studies to offer evidence-based guidelines for clinical practice. Thus, the current study aimed to systematically assess the clinical efficacy and safety of immune checkpoint inhibitors in mCRPC, and also performed subgroup analysis to determine the efficacy among patients with different ICIs.

2. Methods

2.1. Ethics statement

All analyses in this article were based on previously published studies, so ethical approval and patient consent are not applicable.

2.2. Search strategy

A literature search and review of major bibliographic databases was performed using the following search terms: "Prostate Cancer [Mesh]" OR "Ipilimumab [Mesh]" OR "Avelumab [Mesh]" OR "Pembrolizumab [Mesh]" OR "Atezolizumab [Mesh]" OR "Durvalumab [Mesh]" OR "Nivolumab [Mesh]" OR "Tremelimumab [Mesh]" OR "Anti-CTLA-4 Mab [Mesh]." We used this search strategy to search PubMed, Medline, Embase, and Cochrane Library from their inception to October 31, 2020. Articles published online ahead of print were included. Meeting

abstracts without published full-text original articles were not eligible for this study. Two reviewers (ZW and LZ) independently checked the articles for eligibility, and disagreements were further assessed and resolved by another reviewer (CZ).

2.3. Selection criteria

The selection criteria were defined according to the PICOS framework. The inclusion criteria were as follows: (1) population: participants with pathologically or cytologically confirmed prostate adenocarcinoma (detected prostate cancer cells via urine cytology), radiographic evidence of metastases (conventional imaging techniques, including computed tomography, magnetic resonance imaging, and positron emission tomography have been employed for metastatic tumor), prior disease progression despite ADT, and a castrate level of testosterone (<50 ng/dL); progression may present as either a continuous rise in serum prostate-specific antigen (PSA) levels (values identified at a minimum of 1 week intervals with a minimal value of 2.0 ng/mL, with estimations of PSADT with at least 3 values measured ≥ 4 weeks apart), the progression of pre-existing or new radiographic disease, and/or clinical progression with symptoms; (2) intervention: ICI alone, multiple ICIs, or ICI following radiotherapy; (3) comparison: ICI plus chemotherapy or ICI plus androgen receptor inhibitor; (4) outcomes: endpoints included at least one of the below targets: objective response rate (ORR), PSA response rate, 1-year OS rate, and rates of all grades of drug-related adverse events (AEs) and grade ≥ AEs; and (5) study design: randomized controlled trial (RCT) or nonrandomized controlled trial (non-RCT).

The exclusion criteria included: (1) nonhuman studies; (2) conference abstracts, letters, literature reviews, case reports; (3) insufficient data for extraction, and required clinical data were not available for analysis even after checking with the authors.

2.4. Data extraction

Two reviewers checked and screened reports and extracted data from the included studies and collected the following data: (1) study: the first author name, publication year, journal name, study cohort, and study phase; (2) cases: number of patients, age, and cancer type; (3) intervention: ICI alone, dual ICIs, doses, and usage; (4) outcomes: ORR, progression-free survival (PFS), OS, PSA response rate, and 1-year OS rate; and (5) toxicities: rates of any grade and grade 3 or higher AEs. Differences of opinion were discussed with a third reviewer.

2.5. Quality assessment

The modified Jadad score was applied for methodological quality judgment of the RCTs depending on the following conditions: randomization (0 – 2 points), concealment of allocation (0 – 2 points), double blinding (0 – 2 points), and withdrawals and dropouts (0 – 1 point).[19] Included nonrandomized studies were assessed by methodological index for nonrandomized studies (MINORS).[20]

The work has been reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR (Assessing the Methodological Quality of Systematic Reviews) Guidelines.[21]

2.6. Data analyses

The data analyses were performed using STATA 12.0 software (Stata Corporation, College Station, TX) and The R Project for Statistical Computing. We used a fixed-effect model (Mantel-Haenszel test) a priori. If significant heterogeneity ($P < .1$ and $I^2 \geq 50\%$) was found, we assessed the results using a random-effect model (DerSimonian and Laird method). The efficacy of

Immune checkpoint inhibitors was evaluated by calculating the PSA response rates and 1-year OS rates with corresponding 95% CIs. The safety was determined by assessing the risk of any-grade AEs and grade ≥ 3 AEs. Heterogeneity was assessed using the chi-squared and I-squared statistics, and we performed subgroup analyses to evaluate heterogeneity. Publication bias was assessed using funnel plots or Egger funnel plots.

3. Results

3.1. Literature search results

The flowchart of the study search and selection is shown in Figure 1. After searching the database of PubMed, Embase, Web of Science, and Cochrone Library, we finally identified 2247 relevant references, of which 361 were duplicated. We screened the studies for eligibility, and disagreements were judicially assessed and resolved by a third reviewer. After removing duplicate articles, and further screening titles and abstracts,

1770 articles were excluded, including reviews, meta-analyses, conference abstracts, case reports, letters, guidelines, animal experiments, not meeting the requirements, and non-English literature. After the full-text review, a total of 12 studies with 1389 patients were identified that were eligible for inclusion in the meta-analysis.

3.2. Characteristics of included studies

Based on the inclusion and the exclusion criteria, we identified total 12 studies. The basic characteristics of the included 12 studies are listed in Table 1. The sample size of the included studies (2 RCTs and 10 non-RCTs) ranged from 6 to 400 patients and the average age across studies ranged from 57 to 75 years. We categorized the regimens by class as monotherapy with ipilimumab (10 cohorts; n = 924 patients), pembrolizumab (6 cohorts; n = 360 patients), and combination therapy with PD-1 inhibitors (nivolumab) plus CTLA-4 inhibitor (ipilimumab) (3 cohorts; n = 105 patients). There were 2 RCT
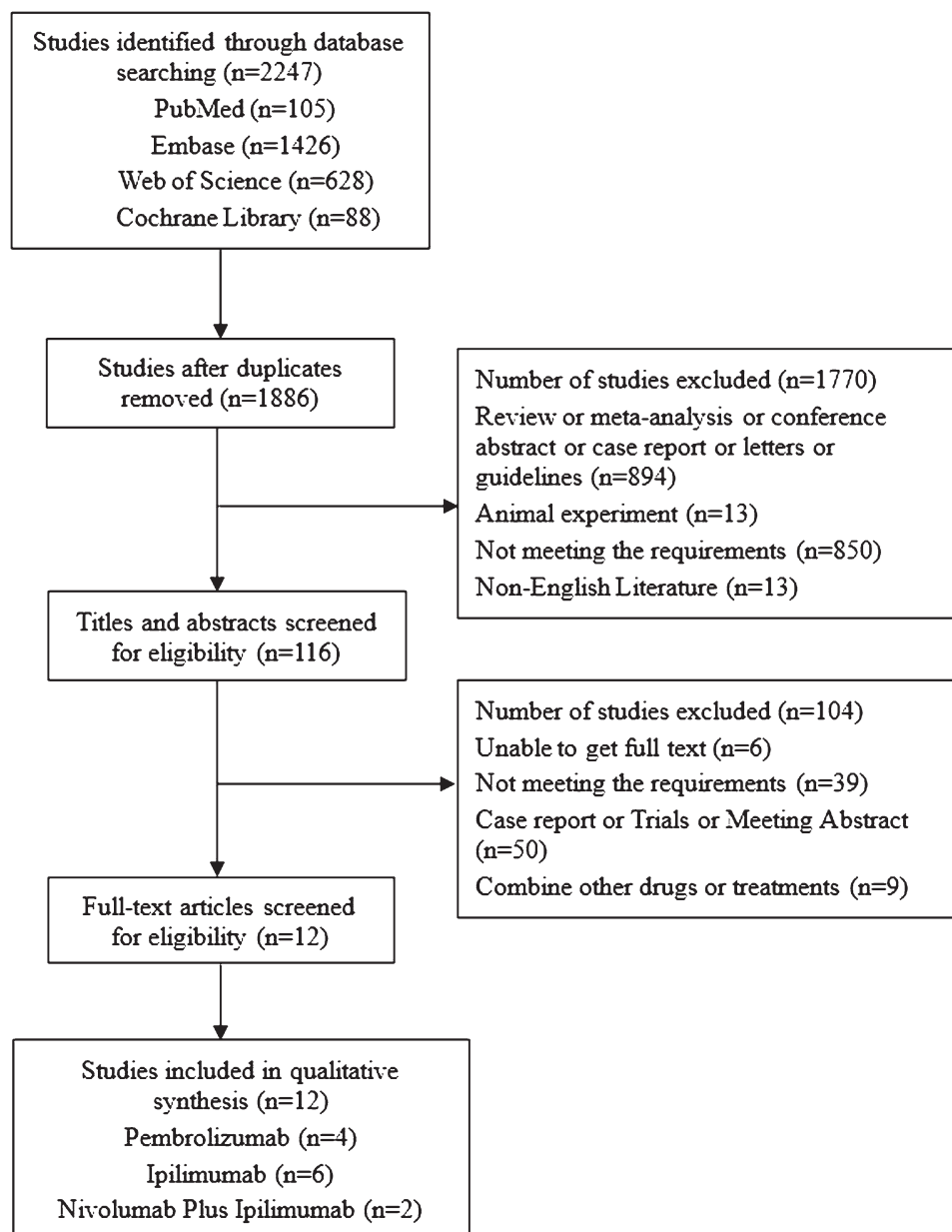
Figure 1. Flowchart of study selection procedure.

Table 1

Baseline characteristics and data of included studies using immune checkpoint inhibitors.

Author	Cohort	Year	Phase	Patient	Mean age (range)	Cancer type	Intervention	Dose	All AE rate (%)	3–4 AE rate	PSA (%)	1-year OS rate (%)	Quality
Fizazi et al[22]	1	2020	III	399	69 (63–74)	mCRPC	Ipilimumab	10mg/kg q3 weeks IV	98	76	13	47	5
Beer et al[23]	1	2016	III	400	70 (44–91)	mCRPC	Ipilimumab	10mg/kg q3 weeks IV	81	40	23	78	5
Subudhi et al[17]	1	2020	II	30	NR	mCRPC	Ipilimumab	3mg/kg q3 weeks IV	100	28		63	14
Graff et al[24]	1	2020	II	10	64.5 (59–69)	mPC	Ipilimumab	10mg/kg q3 weeks IV	60	NR	30	100	14
Small et al[25]	1	2007	NR	14	70.5 (56–79)	HRPC	Ipilimumab	3mg/kg single IV	NR	14	14	NR	14
Slovin et al[26]	1	2013	I/II	8	69 (55–78)	mCRPC	Ipilimumab	3mg/kg q3 weeks IV	100	25	25	NR	13
	2			7	68 (54–81)		Ipilimumab	3mg/kg q3 weeks IV	86	43	29		
	3			6	57 (51–68)		Ipilimumab	5mg/kg q3 weeks IV	83	50	17		
	4			16	65 (53–76)		Ipilimumab	10mg/kg q3 weeks IV	100	63	25		
	5			34	66 (50–83)		Ipilimumab	10mg/kg q3 weeks IV	85	38	12		
Antonarakis et al[27]	1	2019	II	133	68 (48–85)	mCRPC	Pembrolizumab	200mg q3 weeks IV	60	15	12	41	12
	2			66	68 (53–84)						8	35	
	3			59	71 (53–90)						2	62	
Hansen et al[28]	1	2018	NR	23	65 (46–83)	CRPC	Pembrolizumab	200mg q2 weeks IV	61	17	13	36.7	12
Tucker et al[29]	1	2019	NR	25	74 (51–87)	mCRPC	Pembrolizumab	200mg q3 weeks IV			12	44	12
Higa et al[30]	1	2019	NR	54	75 (61–83)	R/APC	Pembrolizumab	200mg q3 weeks IV	41	20	16	NR	12
Sharma et al[18]	1	2020	NR	45	69 (48–85)	mCRPC	Nivolumab plus Ipilimumab	1mg/kg + 3mg/kgq3 weeks IV	NR	93	17.6	67	12
	2			45	65 (46–84)		Nivolumab plus Ipilimumab	1mg/kg + 3mg/kgq3 weeks IV		96	10	58	
Boudadi et al[31]	1	2018	NR	15	NR	mPC	Nivolumab plus Ipilimumab	3mg/kg + 1mg/kgq3 weeks IV	NR	47	13	13	12

AE = adverse event, HRPC = Hormone-Refractory prostate cancer, IV = intravenous, mCRPC = metastatic castration-resistant prostate cancer, mPC = metastatic prostate cancer, NR = not related., OS = overall survival, PC = prostate cancer, PSA = prostate-specific antigen, R/APC = Recurrent or Advanced Prostate Cancer.

Figure 2. (A) Forest plot for pooled OS for patients receiving immune checkpoint inhibitors. (B) Forest plot for pooled PFS. (C) Forest plot for pooled PSA. (D) Forest plot for any grade AEs. AEs = adverse events, PSA = prostate specific antigen, PFS = progression-free survival.

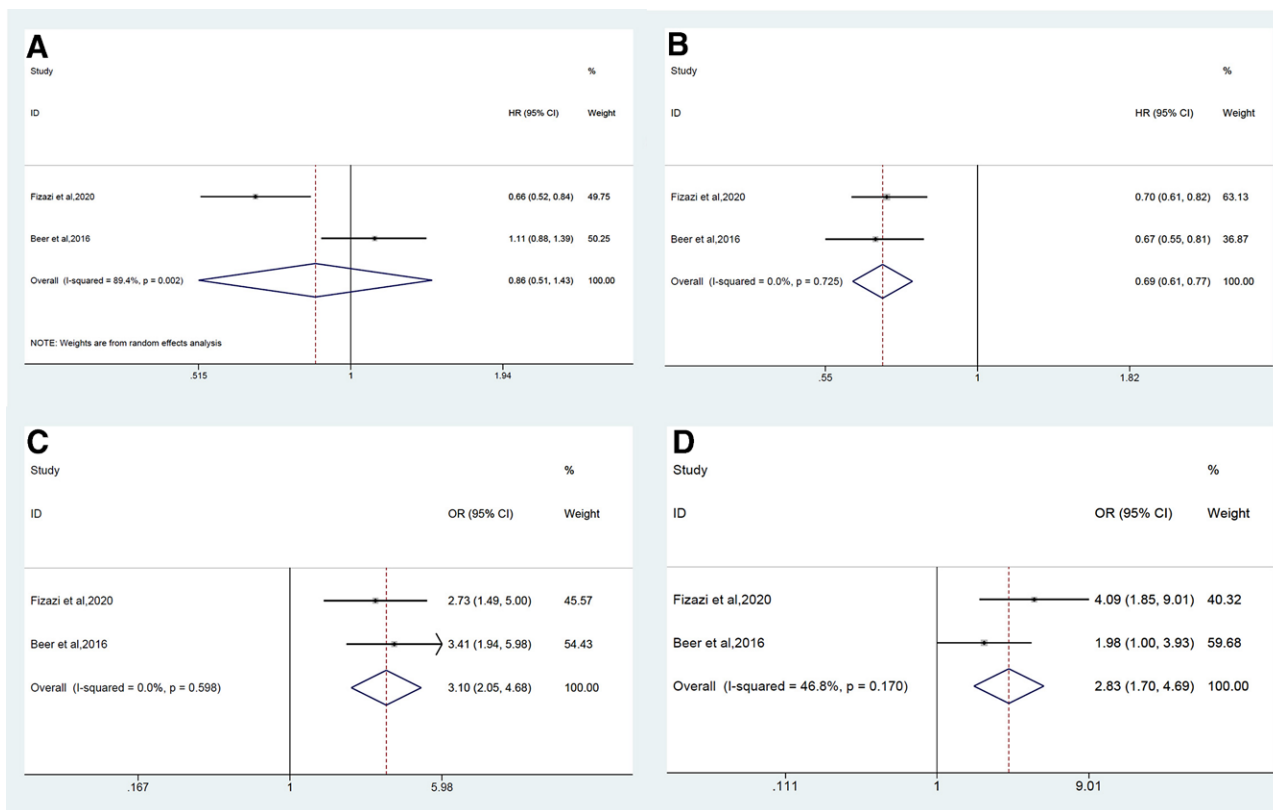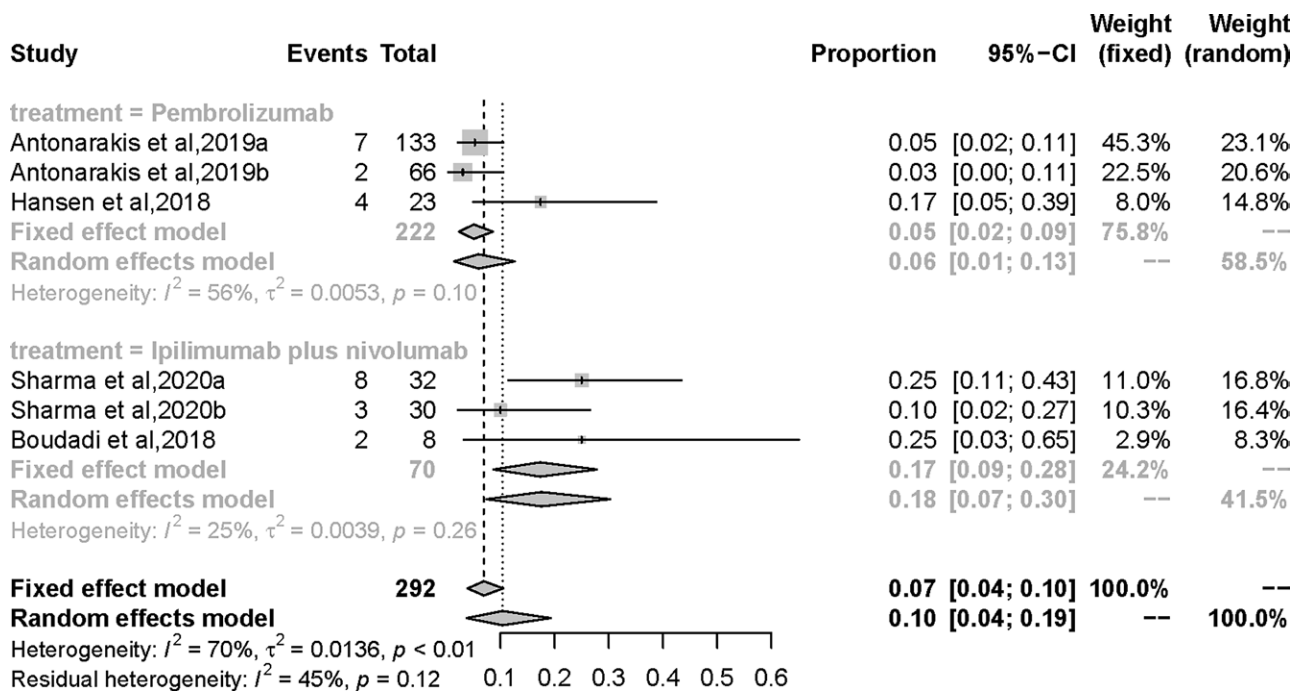| Study	Events	Total		Proportion	95%−CI	Weight (fixed)	Weight (random)
treatment = Pembrolizumab							
Antonarakis et al,2019a	7	133		0.05	[0.02; 0.11]	45.3%	23.1%
Antonarakis et al,2019b	2	66		0.03	[0.00; 0.11]	22.5%	20.6%
Hansen et al,2018	4	23		0.17	[0.05; 0.39]	8.0%	14.8%
Fixed effect model		222		0.05	[0.02; 0.09]	75.8%	−−
Random effects model				0.06	[0.01; 0.13]	−−	58.5%
Heterogeneity: $I^2 = 56\%$, $\tau^2 = 0.0053$, $p = 0.10$							
treatment = Ipilimumab plus nivolumab							
Sharma et al,2020a	8	32		0.25	[0.11; 0.43]	11.0%	16.8%
Sharma et al,2020b	3	30		0.10	[0.02; 0.27]	10.3%	16.4%
Boudadi et al,2018	2	8		0.25	[0.03; 0.65]	2.9%	8.3%
Fixed effect model		70		0.17	[0.09; 0.28]	24.2%	−−
Random effects model				0.18	[0.07; 0.30]	−−	41.5%
Heterogeneity: $I^2 = 25\%$, $\tau^2 = 0.0039$, $p = 0.26$							
Fixed effect model		**292**		**0.07**	**[0.04; 0.10]**	**100.0%**	**−−**
Random effects model				**0.10**	**[0.04; 0.19]**	**−−**	**100.0%**
Heterogeneity: $I^2 = 70\%$, $\tau^2 = 0.0136$, $p < 0.01$							
Residual heterogeneity: $I^2 = 45\%$, $p = 0.12$			0.1 0.2 0.3 0.4 0.5 0.6				

Figure 3. Forest plot for pooled ORR for patients receiving immune checkpoint inhibitors. ORR = objective response rate.

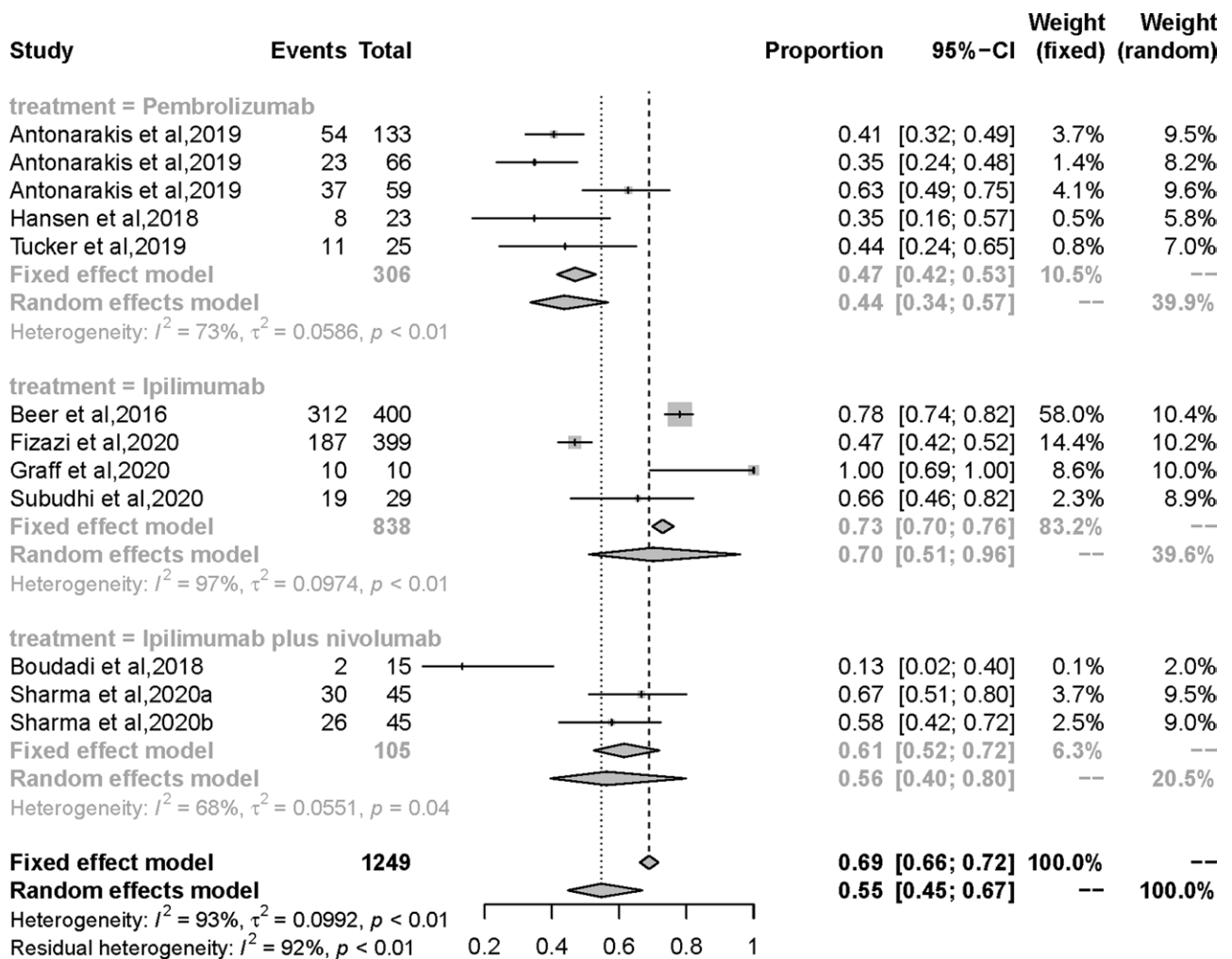| Study	Events	Total		Proportion	95%−CI	Weight (fixed)	Weight (random)
treatment = Pembrolizumab							
Antonarakis et al,2019	54	133		0.41	[0.32; 0.49]	3.7%	9.5%
Antonarakis et al,2019	23	66		0.35	[0.24; 0.48]	1.4%	8.2%
Antonarakis et al,2019	37	59		0.63	[0.49; 0.75]	4.1%	9.6%
Hansen et al,2018	8	23		0.35	[0.16; 0.57]	0.5%	5.8%
Tucker et al,2019	11	25		0.44	[0.24; 0.65]	0.8%	7.0%
Fixed effect model		306		0.47	[0.42; 0.53]	10.5%	−−
Random effects model				0.44	[0.34; 0.57]	−−	39.9%
Heterogeneity: $I^2 = 73\%$, $\tau^2 = 0.0586$, $p < 0.01$							
treatment = Ipilimumab							
Beer et al,2016	312	400		0.78	[0.74; 0.82]	58.0%	10.4%
Fizazi et al,2020	187	399		0.47	[0.42; 0.52]	14.4%	10.2%
Graff et al,2020	10	10		1.00	[0.69; 1.00]	8.6%	10.0%
Subudhi et al,2020	19	29		0.66	[0.46; 0.82]	2.3%	8.9%
Fixed effect model		838		0.73	[0.70; 0.76]	83.2%	−−
Random effects model				0.70	[0.51; 0.96]	−−	39.6%
Heterogeneity: $I^2 = 97\%$, $\tau^2 = 0.0974$, $p < 0.01$							
treatment = Ipilimumab plus nivolumab							
Boudadi et al,2018	2	15		0.13	[0.02; 0.40]	0.1%	2.0%
Sharma et al,2020a	30	45		0.67	[0.51; 0.80]	3.7%	9.5%
Sharma et al,2020b	26	45		0.58	[0.42; 0.72]	2.5%	9.0%
Fixed effect model		105		0.61	[0.52; 0.72]	6.3%	−−
Random effects model				0.56	[0.40; 0.80]	−−	20.5%
Heterogeneity: $I^2 = 68\%$, $\tau^2 = 0.0551$, $p = 0.04$							
Fixed effect model		**1249**		**0.69**	**[0.66; 0.72]**	**100.0%**	**−−**
Random effects model				**0.55**	**[0.45; 0.67]**	**−−**	**100.0%**
Heterogeneity: $I^2 = 93\%$, $\tau^2 = 0.0992$, $p < 0.01$							
Residual heterogeneity: $I^2 = 92\%$, $p < 0.01$			0.2 0.4 0.6 0.8 1				

Figure 4. Forest plot for pooled 1-year OS rate. OS = overall survival.

reporting on the comparison of ipilimumab versus placebo; therefore, this meta-analysis was based on the comparison of non-RCTs.

3.3. Quality assessment of included studies

The included 2 RCT studies were of high-quality, which scored 5 points through modifies Jadad scale.[22,23] Ten non-RCT studies assessed using the MINORS index scored from 12 to 14 points,[17,18,24–31] which were acceptable for the present meta-analysis (Table 1).

3.4. Efficacy assessment of RCT studies

For mCRPC, 2 RCTs were selected in which chemotherapy-naive (n = 602) and docetaxel-pretreated patients (n = 799) were randomized to ipilimumab or placebo. In both studies, ipilimumab failed to show overall survival benefit over placebo (HR = 0.86, 95% CI: 0.51–1.43, P = .553). Random effect model was used to analyze the effect size since obvious heterogeneity was observed (I^2 = 89.4%, P = .002). However, there were

significantly improved PFS and PSA with treatment of ipilimumab compared with placebo (HR = 0.69, 95% CI: 0.61–0.77) and (HR = 3.10, 95% CI: 2.05–4.68), respectively (P < .001). Heterogeneity was not detected between studies. Additionally, the incidences of any grade AEs from ipilimumab therapy were higher (HR = 2.83, 95% CI: 1.70–4.69, P < .001) (Fig. 2), which could not be neglected.

3.5. Efficacy assessment of the trials

The pooled ORR, 1-year OS rate and PSA response rate were used to measure the efficacy of immune checkpoint inhibitors in mCRPC.

In total, 4 trials were used to analyze the ORR, 11 trials were used to assess the PSA response rate, and 9 trials were assessed for the 1-year OS rate. The pooled ORR, 1-year OS rate, and PSA response rate were 0.10 (95% CI: 0.04–0.19, I^2 = 70%, P < .01), 0.55 (95% CI: 0.45–0.67, I^2 = 93%, P < .01) and 0.18 (95% CI: 0.16–0.20, I^2 = 43%, P = .03), respectively (Figures 3, 4 and 5). We performed asymmetry tests using Egger funnel plots to assess publication bias for the PSA response rate.
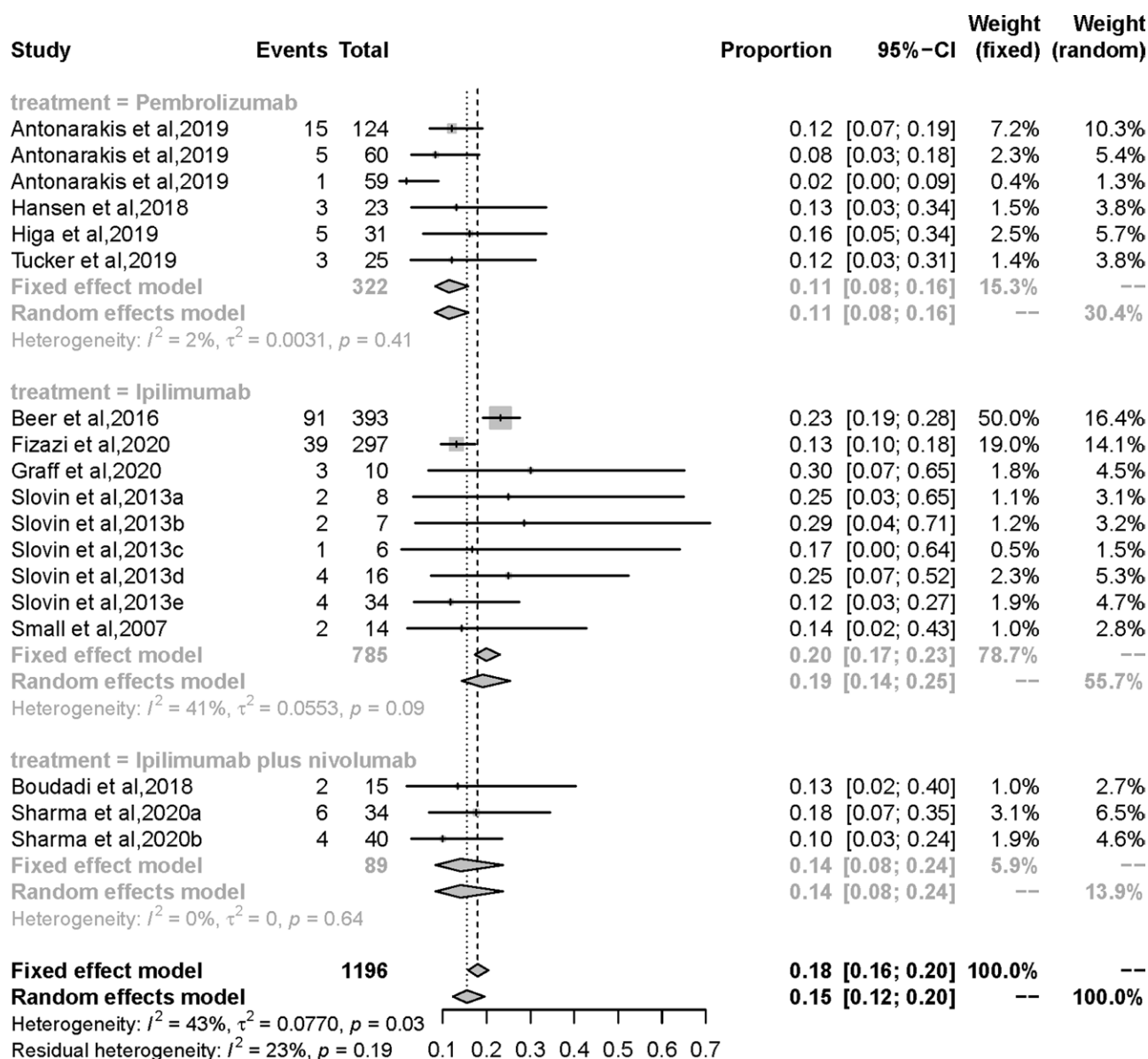

Figure 5. Forest plot for pooled PSA response rate. PSA = prostate specific antigen.
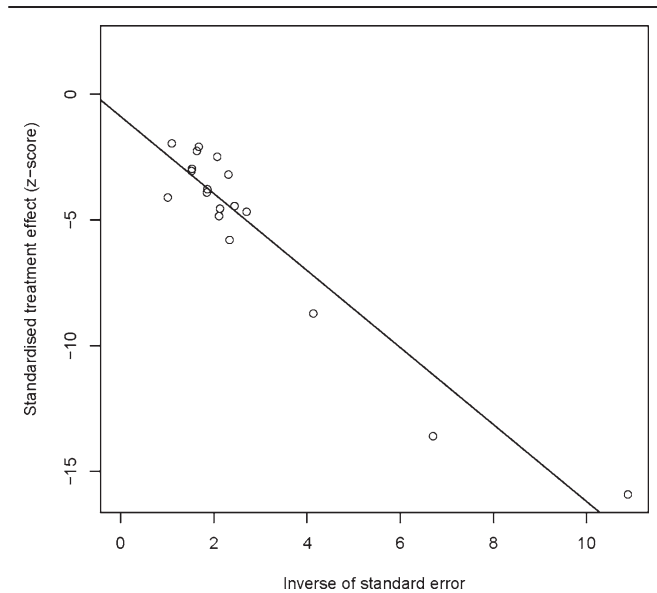
Figure 6. Asymmetry test using egger funnel plots to investigate publication bias for PSA response rate. PSA = prostate specific antigen.

Egger funnel plots examination did not show evidence of publication bias (Fig. 6).

3.6. Subgroup analysis of heterogeneity

To determine any potential heterogeneity, we further do subgroup analyses based on drug type. We analyzed subgroups according to drug type, and the main analysis data were listed

in Figure 5. We observed significant heterogeneity in the ipilimumab group (I^2 = 41%, P = .09). No significant heterogeneity was found in the pembrolizumab (I^2 = 2%, P = .41) and nivolumab plus ipilimumab (I^2 = 0%, P = .54) subgroups. The above data indicate that drug type may serve as potential sources of heterogeneity.

3.7. Safety assessment of included studies

The overall risks of all-grade AEs and grade ≥ 3 AEs were determined to assess the safety of immune checkpoint inhibitors as treatments for mCRPC. In total, 8 studies were selected to calculate the pooled rate of all-grade AEs, and 10 studies were used to calculate grade ≥ 3 AE rates. We selected a random-effects model to assess the summarized rate of AEs. The pooled rates of any grade AEs and grade ≥ 3 AEs were 0.82 (95% CI: 0.74–0.91, I^2 = 94%, P < .01) and 0.42 (95% CI: 0.33–0.54, I^2 = 96%, P < .01), respectively (Figures 7 and 8).

4. Discussion

mCRPC is not considered curable, thus the current treatment goal is generally prolonging survival as long as possible and increasing patients' quality of lives.[32] Although the treatment scenario of mCRPC has been recently revolutionized by the approval of several agents able to increase survival,[33–35] none of these drugs is curative and yields only around 36 months for the median survival.[36,37] Therefore, there is an urgent need for more effective agents, more capable of shrinking visceral and bone lesions, prolonging PFS, and having less adverse effects, in contrast to the conventional chemotherapies. We performed a systematic review and meta-analysis of the published literature presented in major databases. In our study, we pooled 2 RCTs
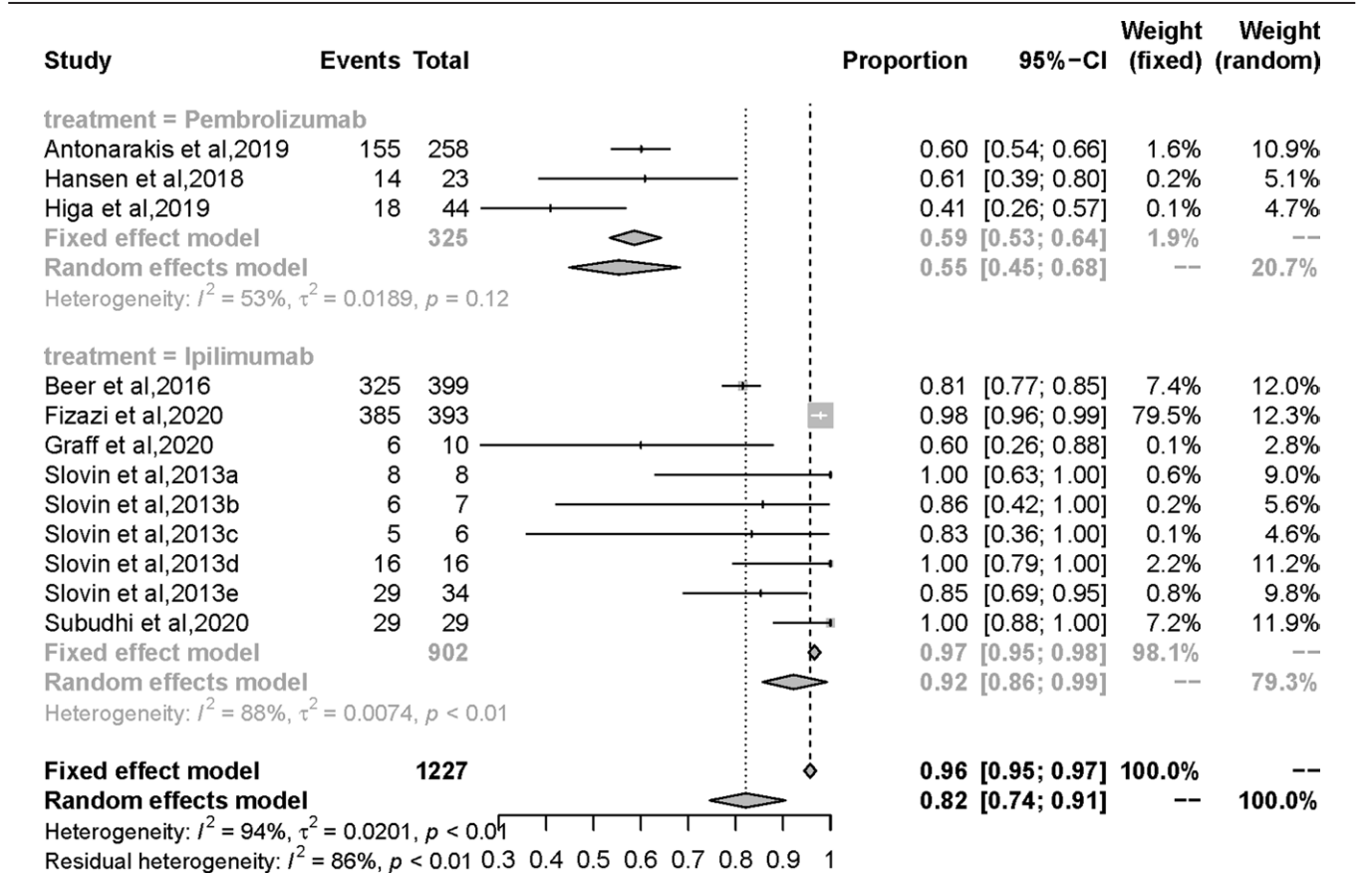

Figure 7. Forest plot for the pooled rates of any grade AEs. AEs = adverse events.

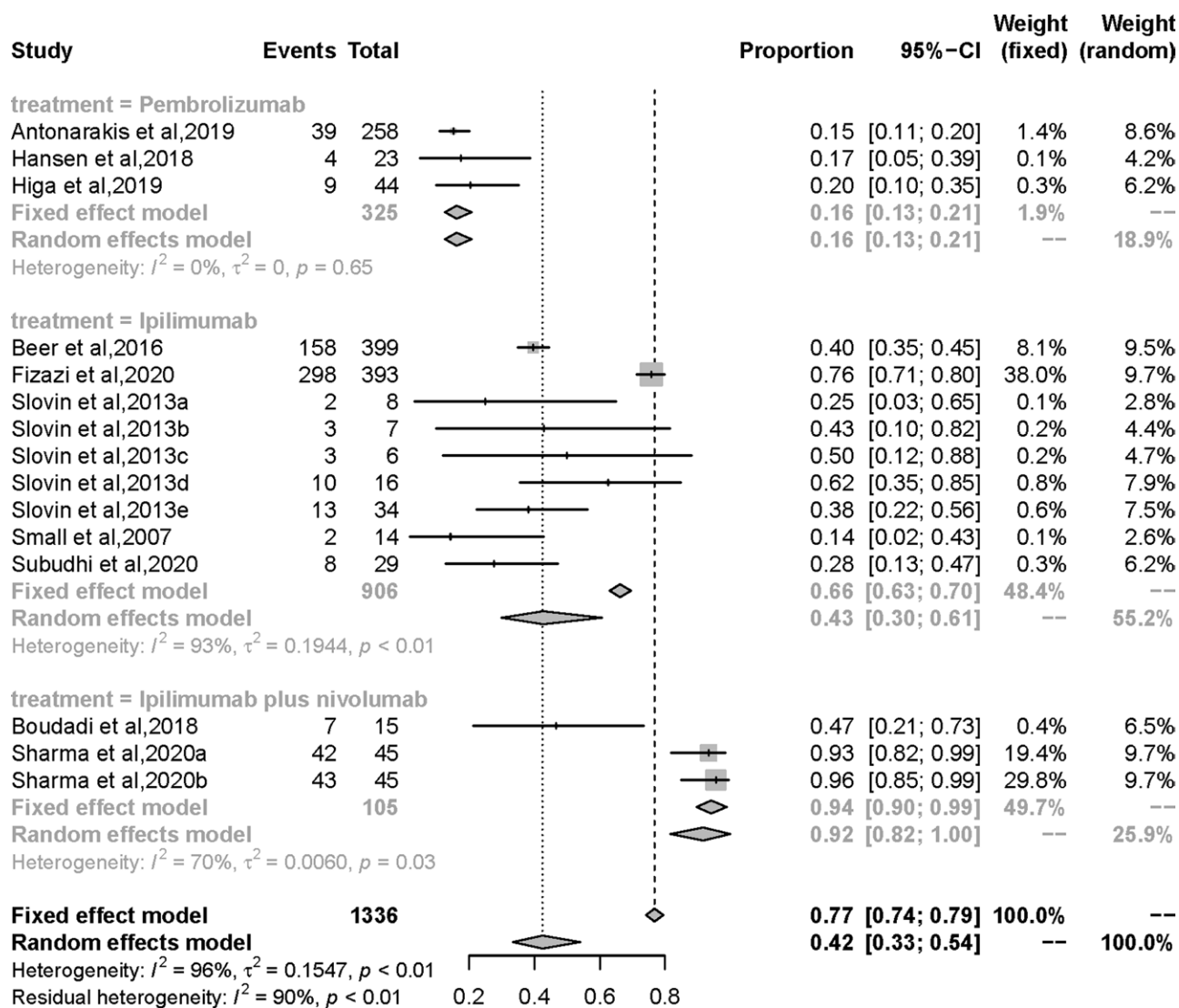| Study	Events	Total		Proportion	95%−CI	Weight (fixed)	Weight (random)
treatment = Pembrolizumab							
Antonarakis et al,2019	39	258		0.15	[0.11; 0.20]	1.4%	8.6%
Hansen et al,2018	4	23		0.17	[0.05; 0.39]	0.1%	4.2%
Higa et al,2019	9	44		0.20	[0.10; 0.35]	0.3%	6.2%
Fixed effect model		325		0.16	[0.13; 0.21]	1.9%	--
Random effects model				0.16	[0.13; 0.21]	--	18.9%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.65$							
treatment = Ipilimumab							
Beer et al,2016	158	399		0.40	[0.35; 0.45]	8.1%	9.5%
Fizazi et al,2020	298	393		0.76	[0.71; 0.80]	38.0%	9.7%
Slovin et al,2013a	2	8		0.25	[0.03; 0.65]	0.1%	2.8%
Slovin et al,2013b	3	7		0.43	[0.10; 0.82]	0.2%	4.4%
Slovin et al,2013c	3	6		0.50	[0.12; 0.88]	0.2%	4.7%
Slovin et al,2013d	10	16		0.62	[0.35; 0.85]	0.8%	7.9%
Slovin et al,2013e	13	34		0.38	[0.22; 0.56]	0.6%	7.5%
Small et al,2007	2	14		0.14	[0.02; 0.43]	0.1%	2.6%
Subudhi et al,2020	8	29		0.28	[0.13; 0.47]	0.3%	6.2%
Fixed effect model		906		0.66	[0.63; 0.70]	48.4%	--
Random effects model				0.43	[0.30; 0.61]	--	55.2%
Heterogeneity: $I^2 = 93\%$, $\tau^2 = 0.1944$, $p < 0.01$							
treatment = Ipilimumab plus nivolumab							
Boudadi et al,2018	7	15		0.47	[0.21; 0.73]	0.4%	6.5%
Sharma et al,2020a	42	45		0.93	[0.82; 0.99]	19.4%	9.7%
Sharma et al,2020b	43	45		0.96	[0.85; 0.99]	29.8%	9.7%
Fixed effect model		105		0.94	[0.90; 0.99]	49.7%	--
Random effects model				0.92	[0.82; 1.00]	--	25.9%
Heterogeneity: $I^2 = 70\%$, $\tau^2 = 0.0060$, $p = 0.03$							
Fixed effect model		**1336**		**0.77**	**[0.74; 0.79]**	**100.0%**	--
Random effects model				**0.42**	**[0.33; 0.54]**	--	**100.0%**
Heterogeneity: $I^2 = 96\%$, $\tau^2 = 0.1547$, $p < 0.01$							
Residual heterogeneity: $I^2 = 90\%$, $p < 0.01$		0.2 0.4 0.6 0.8					

Figure 8. Forest plot for the pooled rates of grade ≥ 3 AEs. AEs = adverse events.

of ipilimumab to verify that it performs better for extended PFS over placebo (HR = 0.69, 95% CI: 0.61–0.77) in patients with mCRPC and a higher proportion of patients with a confirmed ≥50% PSA decline (HR = 3.10, 95% CI: 2.05–4.68). Although targeting the immune checkpoint molecule CTLA-4 with ipilimumab in patients with mCRPC failed to demonstrate a survival benefit in 2 phase 3 clinical trials, there was a subset of men who derived significant durable clinical responses after treatment with ipilimumab. Of note, the PFS improvement observed across these 2 mCRPC ipilimumab trials is unique among all immunotherapeutic approaches in clinical development for PC.[22,23]

This study demonstrated that the ORR, 1-year OS rate, and PSA response rate for mCRPC patients treated with the ICIs were 0.10 (95% CI: 0.04–0.19, $I^2 = 70\%$, $P < .01$), 0.55 (95% CI: 0.45–0.67, $I^2 = 93\%$, $P < .01$) and 0.18 (95% CI: 0.16–0.20, $I^2 = 43\%$, $P = .03$), respectively, indicating an antitumor activity. So far, none of the clinical trials that has explored ICIs monotherapy in PCa have shown a significant survival benefit.[38] The absence of validated predictive biomarkers impedes clinicians in selecting patients expected to respond to immunotherapy.[39] Initial data in other solid tumors suggested that PD-L1 levels expressed on tumor cells could be a biomarker of response. Further research, however, showed that PD-L1 negative cancers also could respond to ICIs, making the overall data

inconsistent.[40] The KEYNOTE-028 trial included 23 patients with mCRPC and initially suggested that PD-L1 expression (≥1% modified proportion score or interface pattern) could predict response to ICIs (ORR = 17.4%, 95% CI: 5–38.8).[28] These results were not replicated in a larger cohort study in the larger KEYNOTE-199 trial evaluating pembrolizumab in patients with mCRPC and with prior exposure to docetaxel (258 patients); this trial stratified patients according to the level of PD-L1 expression and the presence of measurable disease. The ORRs were 5% (95% CI: 2–11) and 3% (95% CI: 1–11) in those presenting with measurable disease in the PD-L1 + and PD-L1− cohorts, respectively.[27] The sensitivity to PD-1/PD-L1 blockers did not seem to be related to PD-L1 expression on cancer or immune cells. Further studies are exploring the combination of ICIs. In the CheckMate 650 trial, 63 patients were evaluable for determining tumoral PD-L1 expression status. In patients with PD-L1 ≥ 1% versus PD-L1 < 1%, the ORR (95% CI) was 36.4% (10.9–69.2) versus 12.1% (3.4–28.2), respectively.[18]

It is well known that the tumor mutation burden (TMB) has been considered as a biomarker of response to ICIs.[41] This is because of a common feature among tumors with a higher probability of response to these drugs, which is the higher prevalence of somatic mutations in their genomes.[42] However, PC are both cold tumors with low TMB and are consequently not responsive to ICIs—a situation that creates a challenge for the

successful application of immunotherapy in these cancers.[43–45] Treatment with ipilimumab and nivolumab resulted in an ORR of 56.3% in patients with a TMB above the median (74.5 mutations/patient) in the CheckMate 650 trial as well as longer radiographic progression-free survival when compared with those who had a TMB below the median (7.4 months [95% CI: 6.5 months to not estimated] vs 2.4 months [95% CI: 1.8–3.9 months], $P < .0001$).[18]

High ORRs to ICIs in tumors with microsatellite instability or mismatch repair (MMR) deficiency is a prime example of high TMB tumors responding to immunotherapy with ICIs. MMR deficiency induces frameshift mutations in tumors that can increase the likelihood of neoantigen formation in tumors.[46] Due to the accumulation of neoantigens and presence of more tumor-reactive T-cells in tumor tissues, MMR-deficient tumors are most likely to be associated with high ORR to ICIs.[42] Pembrolizumab is approved for patients with metastatic, microsatellite instability (MSI)-high or mismatch repair-deficient (dMMR) solid tumors.[15] However, very few men with PC were included in these initial studies.[16] Only 1 (6%) of the 18 mCRPC patients were found to be MSI-high also had high TMB.[29] Alterations in DDR genes can lead to genomic instability, which can also yield increased neoantigen formation and greater immunogenicity. DDR alterations can be found in 22.7% of PC patients with BRCA2 and ATM being the most frequently affected genes.[46,47] With this in mind, an exploratory analysis of the KEYNOTE-199 trial indicated a potential correlation between alterations in DDR genes captured by whole-exome DNA sequencing and response to an anti-PD-1 antibody, but the ORR was still low (11%).[27] In the CheckMate 650 trial, treatment with ipilimumab plus nivolumab was associated with an ORR of 40% among the 10 patients with DDR gene alterations presenting with measurable disease.[18]

It is well known that ICIs inhibit immune checkpoints and promote T-cell function. ICIs are already widely used in clinical setting to against tumor cells. Unfortunately, ICIs also have a series of immune-related AEs as a side effect. In this study, we performed a meta-analysis to assess AEs and the safety of ICIs. The overall rate of any-grade AEs was 82%, while in all included patients the risk of grade ≥ 3 AEs only reached 42%. Our analysis data indicated that ICIs have a wide range of AEs that should not be ignored in patients with mCRPC. Our data also indicated ICIs have a latent treatment potential for mCRPC patients with an acceptable risk tolerance.

In this study, we found severe heterogeneity in the selected 12 articles. We speculate potential sources of this heterogeneity might come from the use of different doses of ICIs. Thus, for the objectivity of the results, we used random-effect models for the analysis. We also generated Egger funnel plots to further assess publication bias and determined that publication bias was not a factor contributing to heterogeneity.

4.1. Limitations

A few of limitations may exist in our analysis. First, due to a larger number of RCTs of ICIs has not been conducted in mCRPC patients, most of the included studies were completed phase I, II, and III randomized single-arm trials, and potential treatment bias might exist in these studies. Second, the trials in our meta-analysis lacked data showing comparisons of the ICIs with chemotherapy drugs, due to the scarcity of control studies on mCRPC patients. In one study, we found that 17% (8/48) had a ≥ 50% confirmed PSA decline with pembrolizumab, and 8% (4/48) had a ≥ 90% PSA decline with durations of response ranging from 3.1 to 16.3 months. Despite prior progression on enzalutamide, 48% (23/48) of men were treated with concurrent enzalutamide. The median PSA progression-free-survival was 1.8 months (range 0.4–13.7 months), with 31% of patients

remaining on pembrolizumab therapy and 54% of men remain alive with a median follow-up of 7.1 months. In our analysis, included data of RCTs indicate that our analysis results are relatively consistent with the results of the currently finished RCTs of ICIs to mCRPC, although lacks no direct comparison with chemotherapy or other treatments. We also performed a single-rate meta-analysis to determine the pooled precise indicators of efficacy and safety of ICIs and provide statistical references for clinicians. To enhance T-cell activities in mCRPC, several combination strategies are currently under development, including ICIs combined with anticancer vaccination, PARP inhibition, radium-223, chemotherapy, or enzalutamide.

Author contributions

XW, ZW, CZ, and SG contributed substantially to the study and design, data collection, and data analysis. XW, ZW, and CZ contributed substantially to the acquisition, analysis, interpretation of data and performed the statistical analysis. ZW, ZW, LZ, and CZ have been involved in the drafting and revision of the article. XW and CW have full access to all data and the final responsibility for the decision to submit the article for publication. All authors read and approved the final article.

References

[1] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424.

[2] Mohler JL, Kantoff PW, Armstrong AJ, et al. Prostate cancer, version 1.2014. J Natl Compr Cancer Netw. 2013;11:1471–9.

[3] Smith MR, Kabbinavar F, Saad F, et al. Natural history of rising serum prostate-specific antigen in men with castrate nonmetastatic prostate cancer. J Clin Oncol. 2005;23:2918–25.

[4] Barata PC, Sartor AO. Metastatic castration-sensitive prostate cancer: Abiraterone, docetaxel, or…. Cancer. 2019;125:1777–88.

[5] Tilki D, Evans CP. The changing landscape of advanced and castration resistant prostate cancer: latest science and revised definitions. Canadian J Urol. 2014;21(2 Supp 1):7–13.

[6] Basch EM, Somerfield MR, Beer TM, et al. American Society of Clinical Oncology endorsement of the Cancer Care Ontario Practice Guideline on nonhormonal therapy for men with metastatic hormone-refractory (castration-resistant) prostate cancer. J Clin Oncol. 2007;25:5313–8.

[7] Galletti G, Leach BI, Lam L, Tagawa ST. Mechanisms of resistance to systemic therapy in metastatic castration-resistant prostate cancer. Cancer Treat Rev. 2017;57:16–27.

[8] Rekoske BT, McNeel DG. Immunotherapy for prostate cancer: False promises or true hope? Cancer. 2016;122:3598–607.

[9] Weinmann SC, Pisetsky DS. Mechanisms of immune-related adverse events during the treatment of cancer with immune checkpoint inhibitors. Rheumatology (Oxford, England). 2019;58(Suppl 7):vii59–67.

[10] Coit DG, Andtbacka R, Anker CJ, et al. Melanoma, version 2.2013: featured updates to the NCCN guidelines. J Natl Compr Cancer Netw. 2013;11:395–407.

[11] Ettinger DS, Wood DE, Aggarwal C, et al. NCCN guidelines insights: non-small cell lung cancer, Version 1.2020. J Natl Compr Cancer Netw. 2019;17:1464–72.

[12] Motzer RJ, Jonasch E, Michaelson MD, et al. NCCN guidelines insights: kidney cancer, Version 2.2020. J Natl Compr Cancer Netw. 2019;17:1278–85.

[13] Flaig TW, Spiess PE, Agarwal N, et al. Bladder Cancer, Version 3.2020, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw. 2020;18:329–54.

[14] Elia AR, Caputo S, Bellone M. Immune checkpoint-mediated interactions between cancer and immune cells in prostate adenocarcinoma and melanoma. Front Immunol. 2018;9:1786.

[15] Prasad V, Kaestner V, Mailankody S. Cancer drugs approved based on biomarkers and not tumor type-FDA approval of pembrolizumab for mismatch repair-deficient solid cancers. JAMA Oncol. 2018;4:157–8.

[16] Abida W, Cheng ML, Armenia J, et al. Analysis of the prevalence of microsatellite instability in prostate cancer and response to immune checkpoint blockade. JAMA Oncol. 2019;5:471–8.

[17] Subudhi SK, Vence L, Zhao H, et al. Neoantigen responses, immune correlates, and favorable outcomes after ipilimumab treatment of patients with prostate cancer. Sci Transl Med. 2020;12:eaaz3577.

[18] Sharma P, Pachynski RK, Narayan V, et al. Nivolumab plus ipilimumab for metastatic castration-resistant prostate cancer: preliminary analysis of patients in the CheckMate 650 Trial. Cancer Cell. 2020;38:489–499.e3.

[19] Zeng X, Zhang Y, Kwong JS, et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. J Evidence-Based Med. 2015;8:2–10.

[20] Slim K, Nini E, Forestier D, et al. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg. 2003;73:712–6.

[21] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ (Clin Res ed). 2009;339:b2535.

[22] Fizazi K, Drake CG, Beer TM, et al. 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. Eur Urol. 2020;78:822–30.

[23] 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.

[24] Graff JN, Stein MN, Surana R, et al. Phase II study of ipilimumab in men with metastatic prostate cancer with an incomplete response to androgen deprivation therapy. Front Oncol. 2020;10:1381.

[25] Small EJ, Tchekmedyian NS, Rini BI, et al. A pilot trial of CTLA-4 blockade with human anti-CTLA-4 in patients with hormone-refractory prostate cancer. Clin Cancer Res. 2007;13:1810–5.

[26] Slovin SF, 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.

[27] Antonarakis ES, Piulats JM, Gross-Goupil M, et al. Pembrolizumab for treatment-refractory metastatic castration-resistant prostate cancer: multicohort, open-label Phase II KEYNOTE-199 study. J Clin Oncol. 2020;38:395–405.

[28] Hansen AR, Massard C, Ott PA, et al. Pembrolizumab for advanced prostate adenocarcinoma: findings of the KEYNOTE-028 study. Ann Oncol. 2018;29:1807–13.

[29] Tucker MD, Zhu J, Marin D, et al. Pembrolizumab in men with heavily treated metastatic castrate-resistant prostate cancer. Cancer Med. 2019;8:4644–55.

[30] Higa J, Wilenius K, Savino S, et al. Real world experience with pembrolizumab in recurrent or advanced prostate cancer. Clin Genitourin Cancer. 2020;18:e397–401.

[31] 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.

[32] Mohammadzadeh M, Shirmohammadi M, Ghojazadeh M, et al. Aghdas SAM: Dendritic cells pulsed with prostate-specific membrane antigen in metastatic castration-resistant prostate cancer patients: a systematic review and meta-analysis. Prostate Int. 2018;6:119–25.

[33] Roviello G, Sigala S, Sandhu S, et al. Generali D: Role of the novel generation of androgen receptor pathway targeted agents in the management of castration-resistant prostate cancer: a literature based meta-analysis of randomized trials. Eur J Cancer (Oxford, England: 1990). 2016;61:111–21.

[34] Francini E, Petrioli R, Roviello G. No clear evidence of a clinical benefit of a sequential therapy regimen with abiraterone acetate and enzalutamide. Expert Rev Anticancer Ther. 2014;14:1135–40.

[35] Petrioli R, Francini E, Roviello G. Is there still a place for docetaxel rechallenge in prostate cancer? World J Clin Oncol. 2015;6:99–103.

[36] Afshar M, Evison F, James ND, Patel P. Shifting paradigms in the estimation of survival for castration-resistant prostate cancer: a tertiary academic center experience. Urol Oncol. 2015;33:338.e331–337.

[37] Roviello G, Gatta Michelet MR, D'Angelo A, et al. Role of novel hormonal therapies in the management of non-metastatic castration-resistant prostate cancer: a literature-based meta-analysis of randomized trials. Clin Transl Oncol. 2020;22:1033–9.

[38] Claps M, Mennitto A, Guadalupi V, et al. Immune-checkpoint inhibitors and metastatic prostate cancer therapy: Learning by making mistakes. Cancer Treat Rev. 2020;88:102057.

[39] Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol Off J Am Soc Clin Oncol. 2010;28:3167–75.

[40] Weinstock M, McDermott D. Targeting PD-1/PD-L1 in the treatment of metastatic renal cell carcinoma. Ther Adv Urol. 2015;7:365–77.

[41] Goodman AM, Kato S, Bazhenova L, et al. Tumor mutational burden as an independent predictor of response to immunotherapy in diverse cancers. Mol Cancer Ther. 2017;16:2598–608.

[42] Maleki Vareki S. High and low mutational burden tumors versus immunologically hot and cold tumors and response to immune checkpoint inhibitors. J ImmunoTher Cancer. 2018;6:157.

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

[44] Strasner A, Karin M. Immune infiltration and prostate cancer. Front Oncol. 2015;5:128.

[45] Martinez-Bosch N, Vinaixa J, Navarro P. Immune evasion in pancreatic cancer: from mechanisms to therapy. Cancers. 2018;10:6–16.

[46] Germano G, Lamba S, Rospo G, et al. Inactivation of DNA repair triggers neoantigen generation and impairs tumour growth. Nature. 2017;552:116–20.

[47] Robinson D, Van Allen EM, Wu YM, et al. Integrative clinical genomics of advanced prostate cancer. Cell. 2015;161:1215–28.