International Immunopharmacology 74 (2019) 105709

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Effect of region on the Outcome of Patients Receiving PD-1/PD-L1 Inhibitors for Advanced Cancer

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ARTICLE INFO

Keywords:
Regional difference
PD-1/L1 inhibitors
North America
Europe
Overall survival

ABSTRACT

Background: Regional differences were associated with cancer incidence and mortality. However, the correlation between regional differences and cancer immunotherapy efficacy was still not evaluated. In this study, we performed a meta-analysis to investigate whether regional differences play a role in efficacy of PD-1/L1 inhibitors in cancer patients.

Methods: A meticulous review of relevant randomized controlled trials that were sourced from the PubMed, Embase and MEDLINE databases. Overall survival (OS) and progression-free survival (PFS) were the primary outcome and secondary outcome in our study, respectively. We also assessed difference on the hazard ratio (HR) between European and North American groups.

Results: A total of 14 randomized clinical trials including 9387 patients were finally eligible for meta-analysis in our study. With respect to the pooled HR in treatment with PD-1/L1 inhibitors, North American patients presented OS as 0.60 (95% CI 0.53 to 0.67), and PFS as 0.49 (95% CI 0.40 to 0.59), whereas European patients presented OS as 0.76 (95% CI 0.62 to 0.90), and PFS as 0.58 (95% CI 0.44 to 0.72), relative to their corresponding control groups. OS efficacy thus varied significantly ($P_{heterogeneity}$ = 0.028) between North American and European patients when treated with PD-1/L1 inhibitors.

Conclusions: Our findings were very surprising especially considering the higher prevalence of cancer in Europe. Although PD-1/L1 inhibitors improved OS and PFS in both North American and European patients compared with controls, the magnitude of benefit was region-dependent. North American patients can benefit more from PD-1/L1 inhibitors than European patients. More researches were urgently demanded to explore its potential molecular mechanisms.

1. Introduction

Over the past decades, the development of immunology and cancer biology has brought hope to decipher the mechanisms of tumor-induced immune tolerance [1–4]. The passive immunotherapy has shown significant clinical benefits against multiple solid and hematological malignancies, such as the transfer of tumor-targeted mono-antibodies and donor T cells. While active immunotherapy aim to improve anti-tumor effects through enhancing self-immunity [5–7]. Unfortunately, cancer cells always continuously exploit a variety of pathways to evade immune attack. Of these, cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein-1 (PD-1) receptor pathways were considered as the two most important immunosuppressive pathways, which are referred to as “immune checkpoints” [8,9]. Several immune checkpoint inhibitors (ICIs) have been developed to block these immunosuppressive pathways to enhance anti-tumor immune responses, and have demonstrated a significantly prolonged survival in cancer patients compared to traditional therapies. The discovery of PD-1/L1 and CTLA-4 inhibitors has been undoubtedly a definitive breakthrough in cancer immunotherapy [11–15]. It is estimated that nearly half of all cases and more than half of all cancer deaths will occur in Asia by 2018, partly because nearly 60% of the global population lives there. Although European population accounts for only 9% of the global population, the incidence of cancer accounts

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https://doi.org/10.1016/j.intimp.2019.105709
Received 26 March 2019; Received in revised form 1 May 2019; Accepted 17 June 2019
Available online 02 July 2019
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for 23.4% of all cancer cases and 20.3% of all cancer deaths. Furthermore, The Americas regions have 21% morbidity and 14.4% mortality among all cancers. Regional differences on cancer morbidity and mortality are mainly related to economic levels and lifestyles in different regions [16]. However, the correlation between regional differences and immunotherapy efficacy in cancer patients was still not evaluated. In this study, we performed a meta-analysis based on existed clinical data to systemically explore whether regional differences have potential effect on efficacy of PD-1/L1 inhibitors.

2. Methods

2.1. Search strategy and study selection

Our meta-analysis was based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement. We comprehensively searched for relevant clinical trials which compared immune checkpoint inhibitors with control group on PubMed, Medline, Embase, Google Scholar and Web of Science. September 2018 was the cut-off date. Key words included “nivolumab”, “pembrolizumab”, “atezolizumab”, “avelumab”, “durvalumab”, and “PD-1”. Two investigators, ZHW and SQR, independently reviewed the databases mentioned above, and only the clinical trials published in English are included here. We also personally assessed references from studies that were finally selected, and reviewed several other relevant studies, for a more expansive range of clinical data; using similar keywords, we additionally searched the European Society for Medical Oncology and American Society of Clinical Oncology databases.

We used the following inclusion criteria: (1) phase 2 or 3 randomized controlled trials; (2) trials assessed the efficacy of PD-1 and PD-L1 inhibitors, and/or their combined regimens; (3) trials comparing more effective ICIs (PD-1 inhibitors) with less effective ICIs (CTLA-4 inhibitors); (4) trails distinctly reported region-specific HR of OS or PFS in patients; and (5) presented subgroup effectiveness, with Asian, European and North American regions designated as cutoffs. We excluded trials that: (1) were single-arm trials; (2) did not present subgroup efficacy according to patients' regions, or not use North America, Europe and Asia as a cut-off region; (3) gauged PD-1/L1 inhibitors' efficacy in hematologic malignancies; (4) arranged patients to receive PD-1/L1 inhibitors in combination with non-immunological drugs. ZHW and SQR individually assessed every title and abstract from the literature search catalogue, strictly adopting an inclusion and exclusion criteria to select eligible studies. A consensus from all investigators involved resolved any conceivable discrepancies.

2.2. Data extraction and quality assessment

The data collated from the eligible studies included: (1) particulars of the study, such as first author, publication year, experimental and control groups' treatment regimens, clinical trial phases; (2) patient characteristics; (3) HR for OS in patients from these three regions; (4) HR for PFS in patients from these three regions.

The Cochrane risk of bias was used to assess each included study [31], as per the criteria listed here: (1) randomized Sequence Generation; (2) allocation concealment; (3) blinding of participants, personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective outcome reporting, and (7) other sources of bias. The risk of bias was designated low, high or unclear. Three investigators independently conducted data extraction and quality assessment, resolving any discrepancies via a consensus. Fig. 1 specifies the selection process, and Fig. S1 summarizes the risk of bias assessment, among the studies considered herein.

2.3. Statistical analysis

The pooled HR of OS and PFS in Asian, European and North American patients was calculated. The heterogeneity of individual studies was assessed via the Q test and I^2 statistics. I^2 values reflected low heterogeneity when $< 30\%$, moderate if 30% to 59%, substantial if 60% to 75%, and considerable when $> 75\%$. We deployed the fixed-effects model for meta-analysis with an I^2 value $< 50\%$, else used the random-effects model. When significant heterogeneity between the individual studies was observed, we implemented a sensitivity analysis via eliminating studies, one at a time, to examine the stability of combined results. Begg's and Egger's tests helped us assess the probability of any publication bias [32,33]. We also performed a subgroup analysis according to cancer types. The StataSE12.0 software (StataCorp, College Station, Texas) implemented all statistical analyses, whereas the Review Manager 5.3 software (Nordic Cochrane Center, Copenhagen, Denmark) generated the risk of bias graphs. A P value ≤ 0.05 was regarded statistically significant.

3. Results

3.1. Search results and patient characteristics

In total, 10,256 publications were selected via searching the above-mentioned database and reference lists, eventually identifying 56 potentially relevant studies. A full review of abstracts and articles, as per the selection criteria, further condensed this to a final of 14 studies for evaluation, which comprised twelve 3-phased, and two 2-phased trials. The number of studies, with the drug investigated, are respectively listed herewith: 4, nivolumab; 4, pembrolizumab; 2, atezolizumab; 1, durvalumab; 3, ipilimumab plus nivolumab. The tumor types were as follows: melanoma, 3 trials; lung cancer, 6 trials; renal cell carcinoma, 2 trials; gastric or gastroesophageal junction cancer, 2 trials; head and neck squamous-cell carcinoma, one trial. A total of 9384 patients were eligible for this meta-analysis, of whom 2319 (25.03%) had melanoma, 3951 (42.10%) had lung cancer, 1668 (17.78%) had renal cell carcinoma, 1085 (11.56%) had gastric tumors and 361 (3.85%) had head and neck squamous-cell carcinoma. The sample size in each study ranged between 272 and 2075. Of these, 1431 patients were enrolled in nivolumab trials, 811 in pembrolizumab trials, 1182 in atezolizumab trials, 315 in ipilimumab trials, 476 in durvalumab trials and 878 in nivolumab plus ipilimumab trials. Table 1 summarizes the characteristics of included studies.

3.2. Primary outcome: overall survival

The analysis for OS comprised an aggregate 10 trials, with 7122 patients. The pooled HR of OS, at 0.60 (95% CI 0.53 to 0.67, Fig. 2), was recorded for North American patients; and individual studies in this analysis did not present significant heterogeneity ($I^2 = 0.0\%$, $p = 0.919$), hence the fixed-effects model was deployed. European patients' pooled HR for OS was 0.76 (95% CI 0.62 to 0.90, Fig. 3); and low heterogeneity ($I^2 = 55.2\%$, $p = 0.063$) was observed between individual studies, hence the random-effects model was deployed. Asian patients' pooled HR for OS was at 0.68 (95% CI 0.55–0.80, Table 3); and the fixed-effects model was again used, as no significant heterogeneity ($I^2 = 27.4\%$, $p = 0.240$) evidenced among individual studies. PD-1/L1 inhibitors significantly prolonged the OS in North American patients, European patients and Asian patients, relative to control groups. Notably, the OS benefit obtained from PD-1/L1 inhibitors in European patients compared to North American patients was smaller (HR: 0.76 vs 0.60). With reference to the pooled HR, a statistically significant difference in the OS efficacy of PD-1/L1 inhibitors between North American and European patients was observed ($P_{heterogeneity} = 0.028$, Table 1); thus manifesting a more significant overall survival benefit with PD-1/L1 inhibitors in North American patients, relative to European ones.

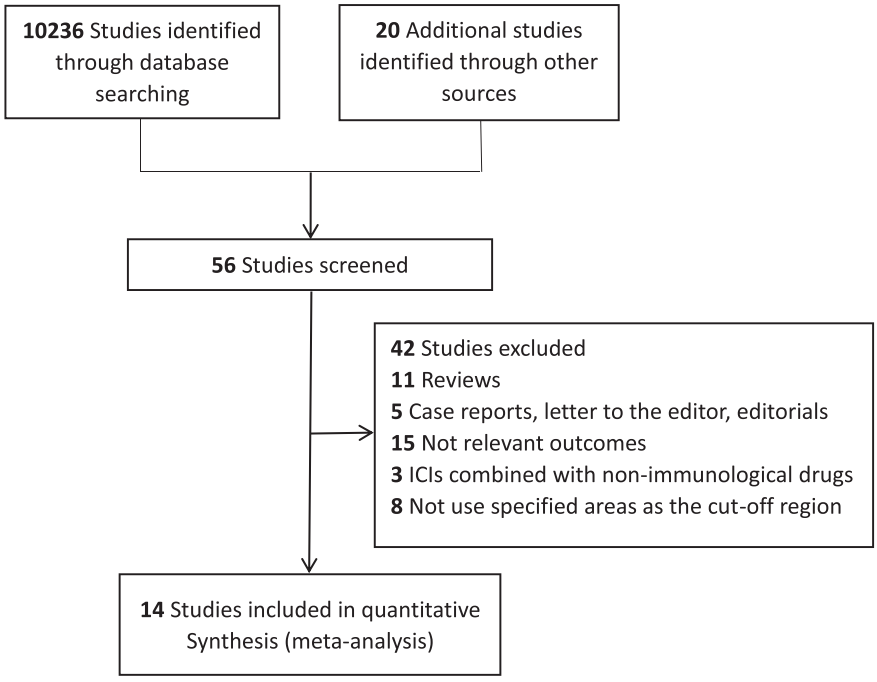

Fig. 1. Flow diagram of study selection process.

Table 1
Main characteristics of the studies included in the meta-analysis.

Study	Year	Phase	Cancer type	Treatment regimen	Number of patients	Age	Overall survival HR (95% CI)
Antonia [17]	2017	3	Non–small-cell lung cancer	Durvalumab	476	64 (31–84)	NA
				Placebo	237	64 (23–90)	
Brahmer [18]	2015	3	Non–small-cell lung cancer	Nivolumab	135	62 (39–85)	0.59 (0.44–0.78)
				Docetaxel	137	64 (42–84)	
Fehrenbacher [19]	2016	2	Non–small-cell lung cancer	Atezolizumab	144	62 (42–82)	0.68 (0.51, 0.89)
				Docetaxel	143	62 (36–84)	
Fehrenbacher [20]	2018	3	Non–small-cell lung cancer	ITT850: Atezolizumab	425	NA	0.75 (0.64–0.89)
				Docetaxel	425	NA	
				ITT1225: Atezolizumab	613	63 (25–84)	0.80 (0.70–0.92)
				Docetaxel	612	64 (34–85)	
Reck [21]	2016	3	Non–small-cell lung cancer	Pembrolizumab	154	64.5 (33–90)	0.50 (0.37–0.68)
				Chemotherapy	151	66.0 (38–85)	
Ribas [22]	2015	2	Melanoma	Pembrolizumab 2 mg/kg	180	62 (15–87)	0.57 (0.45–0.73) PFS
				Pembrolizumab 10 mg/kg	181	60 (27–89)	0.50 (0.39–0.64) PFS
				Chemotherapy control	179	63 (27–87)	
Robert [23]	2015	3	Melanoma	Pembrolizumab every 2 weeks	279	61 (18–89)	0.63 (0.47–0.83)
					277	63 (22–89)	0.69 (0.52–0.90)
				Pembrolizumab every 3 weeks	278	62 (18–88)	
				Ipilimumab			
Wolchok [24]	2017	3	Melanoma	Nivolumab plus ipilimumab	314	NA	NA
				Nivolumab	316		
				Ipilimumab	315		
Kang [25]	2017	3	Gastric or gastroesophageal junction cancer	Nivolumab	330	62 (54–69)	0.65 (0.53–0.80)
				Placebo	163	61 (53–68)	
Shitara [26]	2018	3	Gastric or gastroesophageal junction cancer	Pembrolizumab	296	62.5 (54–70)	0.82 (0.66–1.03)
				Paclitaxel	296	60.0 (53–68)	
Motzer [27]	2015	3	Renal cell carcinoma	Nivolumab	410	62 (23–88)	0.76 (0.62–0.92)
				Everolimus	411	62 (18–86)	
Motzer [28]	2018	3	Renal cell carcinoma	Nivolumab plus Ipilimumab	425	42 (37–47)	0.66 (0.53–0.82)
				Sunitinib	422	27 (22 – 31)	
Hellmann [29]	2018	3	Lung cancer	Nivolumab plus Ipilimumab	139	64 (41–87)	0.58 (0.43–0.77)
				Chemotherapy	160	64 (29–80)	
Ferris [30]	2016	3	Head and neck squamous-cell carcinoma	Nivolumab	240	59 (29–83)	0.69 (0.53–0.91)
				Standard therapy	121	61 (28–78)	

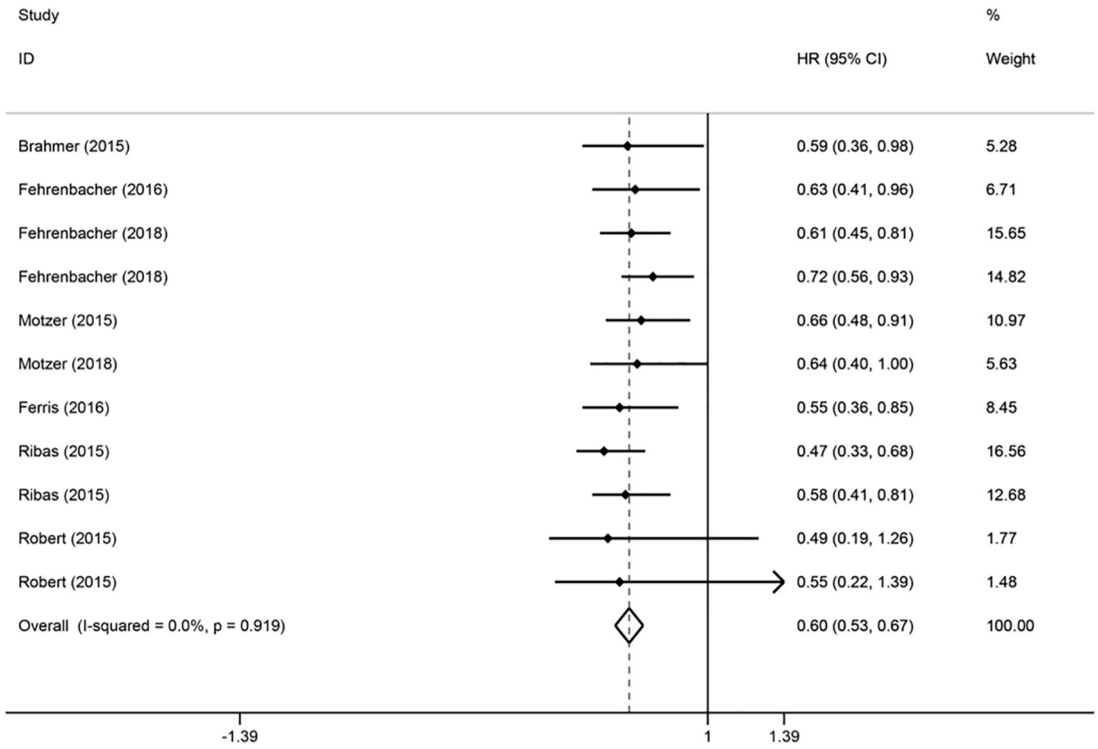

Fig. 2. Forest plot of hazard ratios for overall survival in North American patients.

3.3. Secondary outcomes: progression-free survival

The analysis of PFS was based on Five trials comprising 2691 patients. The pooled HR of PFS in North American patients was 0.49 (95% CI 0.40–0.59, Table 2). The fixed-effects model was used because there was no significant heterogeneity between the individual studies in this analysis (I^2 = 0.0%, p = 0.958). The pooled HR of PFS in European patients was 0.58 (95% CI 0.44–0.72, Table 2). The random-effects model was used due to the low heterogeneity among the included studies (I^2 = 0.0%, p = 0.539). The pooled HR of PFS in Asian patients was 0.43 (95% CI 0.28–0.59, Table 3). The fixed-effects model was used because there was no significant heterogeneity between the individual studies in this analysis (I^2 = 0.0%, p = 0.595). The above results indicated a longer PFS for Asian, European and North American patients treated with PD-1/L1 inhibitors, relative to control groups. Although a lower pooled HR in North American patients compared with European

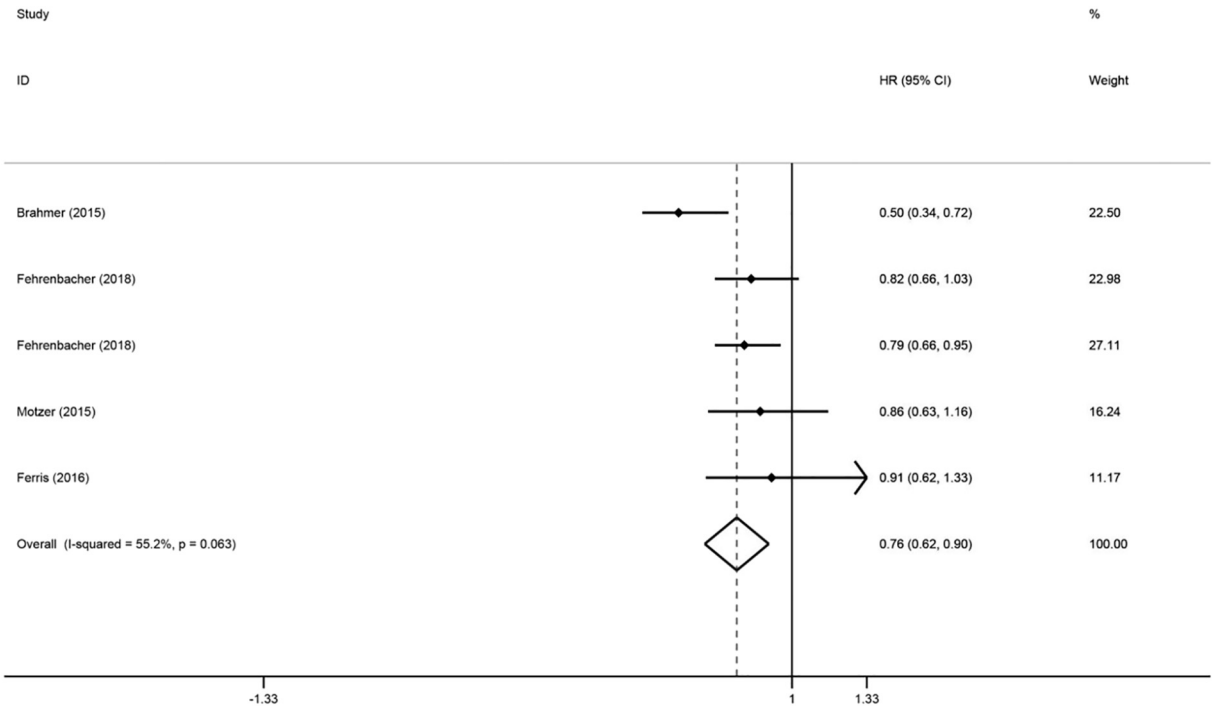

Fig. 3. Forest plot of hazard ratios for overall survival in European patients.

Table 2
Pooled hazard ratios for OS and PFS according to North America and Europe.

Outcomes	Number of trials	Number of patients	Region	HR (95% CI)	I^2	$P_{heterogeneity}$*
OS	8	6037	North America	0.60(0.53, 0.67)	0.0%	0.028
	4	3530	Europe	0.76(0.62, 0.90)	55.2%	
PFS	4	2337	North America	0.49(0.40, 0.59)	0.0%	0.30
	2	1012	Europe	0.58(0.44, 0.72)	0.0%	

* P value for difference on HR between North American and European patients.

Table 3
Pooled hazard ratios for OS and PFS in Asian patients.

Outcomes	Number of trials	Region	HR (95% CI)	I^2	P
OS	4	Asia	0.68 (0.55–0.80)	27.4%	0.240
PFS	3	Asia	0.43 (0.28–0.59)	0.0%	0.595

ones was observed, the difference there was not statistically significant ($P_{heterogeneity}$ = 0.30, Table 2), manifesting similar PFS efficacy in both European and North American patients treated with PD-1/L1 inhibitors.

3.4. Subgroup analyses

In order to explore whether this particular relationship was related to tumor types, we conducted a subgroup analysis. Considering that the PFS data were much less unequivocal than the OS data, we only performed a subgroup analysis for patients' OS. Regardless of the types of tumor, North American patients treated with PD-1/L1 inhibitor always experienced a tendency of significantly prolonged survival compared to European patients (Table 4).

4. Discussion

Although immune checkpoint inhibitors targeting CTLA-4 and PD-1 have demonstrated higher efficacy compared to standard of care chemotherapeutic approaches in several solid and hematologic malignancies, not all patients benefit from this promising therapy, with objective response rate lower than 30% [34–35]. Recent studies revealed that the efficacy of immune checkpoint inhibitors could correlate with special patient population, such as older patients and smoking patients [36–37]. However, little is known whether cancer immunotherapy efficacy is associated with regional difference. In this study, we performed a meta-analysis to systematically explore the correlation between regional difference and efficacy of PD-1/L1 inhibitors based on 9384 patients. Our meta-analysis showed that by using North America, Europe and Asia as the cut-off region, PD-1/L1 inhibitors can significantly improve overall survival among patients from different regions in comparison with controls. The heterogeneity test suggested that there was significant difference on survival benefits between North American and European patients. North American patients treated with PD-1/L1 inhibitors had a larger treatment effect than European patients. Therefore, we focused on the difference in efficacy between North American and European patients.

To the best of our knowledge, this is the first study to explore the potential effect of regional difference on cancer immunotherapy efficacy. The present study clearly show significant difference on the efficacy of PD-1/L1 inhibitors between North American and European patients and we demonstrated for the first time that the efficacy of PD-1/L1 inhibitors in North American patients was better than that in European patients.

Our findings were surprising especially considering the higher prevalence of cancer in Europe. This meant that cancer patients in high-risk European regions benefited less from immunotherapy than those in North America. Considering the few researches on regional differences in cancer immunotherapy efficacy, the potential molecular mechanism remains little known. A recent study by Kugel et al. demonstrated that older cancer patients benefited more from immunotherapy and had a longer survival than younger patients. Intratumoral CD8þ:Treg ratios were significantly amplified in older melanoma patients that were treated with PD-1 inhibitors, relative to younger patients, and similar phenomenon were found in old mice as well. As compared with non-smoker patients, smoker patients receiving anti-PD-L1/PD-1 therapy exhibited improved objective response, durable clinical benefits, and progression-free survival. Wang et al. reported that tobacco smoke and related carcinogens induced PD-L1 expression in normal and cancerous lung epithelial cells in vitro and in TTF1 positive lung epithelial cells in mice, thus leading to the enhanced response to anti-PD-1 antibodies [37–39]. These findings will provide some directive significance for revealing the potential molecular mechanisms of regional differences in efficacy of PD-1/L1 inhibitors.

This meta-analysis presents significant research and clinical values. We found the efficacy of PD-1/L1 inhibitors was region-dependent. North American patients benefited more from PD-1/L1 inhibitors, relative to European ones. Future research on new immunotherapeutic methodologies should consider regional factors as well. Although we have demonstrated that North American patients can benefit better from ICIs, we could not establish a comparison of tolerance and toxicity of ICIs between North American patients and European patients. Despite the above limitations, as far as we know, this is by far the first and most comprehensive study that incorporates results from 14 clinical trials involving 9384 patients.

4.1. Publication bias and sensitivity analysis

There was no evidence of significant publication bias in primary and secondary outcomes based on Begg's and Egger's tests. The sensitivity analysis indicated the combined results were quite stable and removing any single study did not significantly alter our results (data not presented).

5. Conclusions

In conclusion, our meta-analysis showed that PD-1/L1 inhibitors can significantly prolong patients' OS and PFS compared to controls, but the magnitude of benefit was region-dependent. North American patients benefited more from PD-1/L1 inhibitors than European patients. More studies were urgently demanded to explore its potential molecular mechanisms.

Table 4
Pooled hazard ratios for overall survival according to tumor types.

Type of tumors	Region	HR	95% CI
Non–small-cell lung cancer	North America	0.65	0.54–0.76
	Europe	0.71	0.52–0.90
Renal cell carcinoma	North America	0.64	0.60–1.00
	Europe	0.86	0.63–1.16
Head and neck squamous-cell carcinoma	North America	0.55	0.34–0.85
	Europe	0.91	0.62–1.33

Funding

Scientific Research Projects of Wuxi Health Planning Commission (Z201703Z201703), Wuxi, Jiangsu, China; The National Undergraduate Training Programs for Innovation (Nantong university, 201910304030Z; 201910304028Z), China; Training Program of Innovation and Entrepreneurship for College Students in Jiangsu (NO. 201913993001Y and 201913993021H), Jiangsu, China.

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2019.105709.

References

[1] L.M. Francisco, P.T. Sage, A.H. Sharpe, The PD-1 pathway in tolerance and autoimmunity, Immunol. Rev. 236 (2010) 219–242.
[2] M.A. Postow, M.K. Callahan, J.D. Wolchok, Immune checkpoint blockade in cancer therapy, J. Clin. Oncol. 33 (2015) 1974–1982.
[3] P. Sharma, J.P. Allison, The future of immune checkpoint therapy, Science 348 (2015) 56–61.
[4] D.M. Pardoll, The blockade of immune checkpoints in cancer immunotherapy, Nat. Rev. Cancer 12 (2012) 252–264.
[5] I. Mellman, G. Coukos, G. Dranoff, Cancer immunotherapy comes of age, Nature 480 (2011) 480–489.
[6] M.K. Callahan, M.A. Postow, J.D. Wolchok, Targeting T cell co-receptors for cancer therapy, Immunity 44 (2016) 1069–1078.
[7] J.M. Michot, C. Bigenwald, S. Champiat, et al., Immune-related adverse events with immune checkpoint blockade: a comprehensive review, Eur. J. Cancer 54 (2016) 139–148.
[8] M. Saresella, V. Rainone, N.M. Al-Daghri, et al., The PD-1/PD-L1 pathway in human pathology, Curr. Mol. Med. 12 (2012) 259–267.
[9] I. Melero, S. Hervas-Stubbs, M. Glennie, et al., Immunostimulatory monoclonal antibodies for cancer therapy, Nat. Rev. Cancer 7 (2007) 95–106.
[11] R.S. Herbst, P. Baas, D.W. Kim, et al., Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial, Lancet 387 (2016) 1540–1550.
[12] J. Hamanishi, M. Mandai, T. Ikeda, et al., Safety and antitumor activity of anti-PD-1 antibody, nivolumab, in patients with platinum-resistant ovarian cancer, J. Clin. Oncol. 33 (2015) 4015–4022.
[13] J. Weber, J.A. Thompson, O. Hamid, et al., A randomized, double-blind, placebo-controlled, phase II study comparing the tolerability and efficacy of ipilimumab administered with or without prophylactic budesonide in patients with unresectable stage III or IV melanoma, Clin. Cancer Res. 15 (2009) 5591–5598.
[14] B. Zhang, Q. Wu, Y.L. Zhou, et al., Immune-related adverse events from combination immunotherapy in cancer patients: a comprehensive meta-analysis of randomized controlled trials, Int. Immunopharmacol. 63 (2018) 292–298.
[15] J.D. Wolchok, B. Neyns, G. Linette, et al., Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study, Lancet Oncol. 11 (2010) 155–164.
[16] Global Cancer Statistics, GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries, (2018), https://doi.org/10.3322/caac.21492 Epub 2018 Sep 12.
[17] S.J. Antonia, A. Villegas, D. Daniel, et al., Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer, N. Engl. J. Med. 377 (20) (2017) 1919–1929.
[18] J. Brahmer, K.L. Reckamp, P. Baas, et al., Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer, N. Engl. J. Med. 373 (2) (2015) 123–135.
[19] L. Fehrenbacher, A. Spira, M. Ballinger, et al., Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial, Lancet (London, England) 387 (10030) (2016) 1837–1846.
[20] L. Fehrenbacher, J. von Pawel, K. Park, et al., Updated efficacy analysis including secondary population results for OAK: a randomized phase III study of atezolizumab versus docetaxel in patients with previously treated advanced non-small cell lung cancer, J. Thorac. Oncol. 13 (8) (2018) 1156–1170.
[21] M. Reck, D. Rodriguez-Abreu, A.G. Robinson, et al., Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer, N. Engl. J. Med. 375 (19) (2016) 1823–1833.
[22] A. Ribas, I. Puzanov, R. Dummer, et al., Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial, Lancet Oncol. 16 (8) (2015) 908–918.
[23] C. Robert, J. Schachter, G.V. Long, et al., Pembrolizumab versus ipilimumab in advanced melanoma, N. Engl. J. Med. 372 (26) (2015) 2521–2532.
[24] J.D. Wolchok, V. Chiarion-Sileni, R. Gonzalez, et al., Overall survival with combined nivolumab and ipilimumab in advanced melanoma, N. Engl. J. Med. 377 (14) (2017) 1345–1356.
[25] Y.K. Kang, N. Boku, T. Satoh, et al., Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial, Lancet (London, England) 390 (10111) (2017) 2461–2471.
[26] K. Shitara, M. Ozguroglu, Y.J. Bang, et al., Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial, Lancet (London, England) 392 (10142) (2018) 123–133.
[27] R.J. Motzer, B. Escudier, D.F. McDermott, et al., Nivolumab versus everolimus in advanced renal-cell carcinoma, N. Engl. J. Med. 373 (19) (2015) 1803–1813.
[28] R.J. Motzer, N.M. Tannir, D.F. McDermott, et al., Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma, N. Engl. J. Med. 378 (14) (2018) 1277–1290.
[29] M.D. Hellmann, T.E. Ciuleanu, A. Pluzanski, et al., Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden, N. Engl. J. Med. 378 (22) (2018) 2093–2104.
[30] R.L. Ferris, G. Blumenschein Jr., J. Fayette, et al., Nivolumab for recurrent squamous-cell carcinoma of the head and neck, N. Engl. J. Med. 375 (19) (2016) 1856–1867.
[31] J.P. Higgins, D.G. Altman, P.C. Gøtzsche, et al., The Cochrane Collaboration's tool for assessing risk of bias in randomised trials, Bmj 343 (2011) d5928.
[32] C.B. Begg, M. Mazumdar, Operating characteristics of a rank correlation test for publication bias, Biometrics 50 (1994) 1088–1101.
[33] M. Egger, G. Davey Smith, M. Schneider, et al., Bias in meta-analysis detected by a simple, graphical test, Bmj 315 (1997) 629–634.
[34] C.J.D. Wallis, M. Butaney, R. Satkunasivam, et al., Association of patient sex with efficacy of immune checkpoint inhibitors and overall survival in advanced cancers: a systematic review and meta-analysis, JAMA Oncol. (2019).
[35] B. Zhang, Y.L. Zhou, X. Chen, et al., Efficacy and safety of CTLA-4 inhibitors combined with PD-1 inhibitors or chemotherapy in patients with advanced melanoma, Int. Immunopharmacol. 68 (2019) 131–136.
[36] Q. Wu, Q. Wang, X. Tang, et al., Correlation between patients' age and cancer immunotherapy efficacy, Oncoimmunology 8 (2019) e1568810.
[37] B. Li, X. Huang, L. Fu, Impact of smoking on efficacy of PD-1/PD-L1 inhibitors in non-small cell lung cancer patients: a meta-analysis, Onco. Targets Ther. 11 (2018) 3691–3696.
[38] C.H. Kugel 3rd, S.M. Douglass, et al., Age correlates with response to anti-PD1, reflecting age-related differences in intratumoral effector and regulatory T-cell populations, Clin. Cancer Res. (2018), https://doi.org/10.1158/1078-0432.CCR-18-1116.
[39] G.Z. Wang, L. Zhang, X.C. Zhao, et al., The aryl hydrocarbon receptor mediates tobacco-induced PD-L1 expression and is associated with response to immunotherapy, Nat. Commun. 10 (2019) 1125.