Original Article

Geographic heterogeneity in the outcomes of patients receiving immune checkpoint inhibitors for advanced solid tumors: a meta-analysis

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Background: Little is known about the effect of geographic location on efficacy of immune checkpoint inhibitors (ICI). We performed a systematic review and meta-analysis to assess the heterogeneity of ICI efficacy between different geographic locations.

Methods: We searched PubMed, EMBASE, and the Cochrane Library through October 2019 for phase III randomized controlled trials (RCT) that provided sufficient data for hazard ratio (HR) and 95% confidence interval (CI) of overall survival (OS) or progression-free survival (PFS) according to designated geographic region. We calculated pooled HRs and 95% CIs for North American, European and Asian cancer patients, and assessed data heterogeneity using subgroup and sensitivity analysis. The INPLASY registration number was INPLASY202050062.

Results: Of 10151 publications identified in our research, 17 RCTs including 7462 patients met our selection criteria. The pooled HRs for OS of North American, European and Asian patients were 0.67 (95% CI: 0.57 to 0.78), 0.72 (95% CI: 0.64 to 0.81), and 0.74 (95% CI: 0.66 to 0.84) respectively; the pooled HRs for PFS of North American, European and Asian patients were 0.58 (95% CI: 0.49 to 0.69), 0.61 (95% CI: 0.41 to 0.90), and 0.87 (95% CI: 0.38 to 1.99) respectively. Both anti-PD-1 inhibitors and anti-PD-L1 inhibitors showed clinical benefit in North American and European arms while anti-PD-L1 inhibitors failed to show benefit in Asian arms.

Conclusions: Our meta-analysis indicates that the magnitude of benefit from ICI varies in North America, Europe, and Asia. Asian patients experience inferior outcomes compared to Western patients. Notably, anti-PD-L1 therapies do not result in survival improvements in Asian patients.

Keywords: Geographic location; immune checkpoint inhibitors (ICI); meta-analysis; programmed death-1 (PD-1) inhibitor; programmed death-ligand 1 (PD-L1) inhibitor

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Introduction

Immune checkpoint inhibitors (ICI) have radically changed the treatment modalities for a wide range of tumor types (1,2). Currently, seven ICI have been approved for cancer treatment. These agents can be divided into three main classes: the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor ipilimumab; the programmed death-1 (PD-1) inhibitors, nivolumab,

pembrolizumab and cemiplimab; the programmed death-ligand 1 (PD-L1) inhibitors, avelumab, durvalumab, and atezolizumab (3). Since the CTLA-4 inhibitor ipilimumab was approved on 28 March 2011 for the treatment of unresectable melanoma (4), the application of ICI has brought about dramatic clinical benefit to patients with melanoma or several other types of malignancies (5). It is noteworthy that since 2015 the combination of CTLA-4 inhibitor and PD-1/PD-L1 inhibitor have shown magnificent efficacy in patients with non-small cell lung cancer (NSCLC) (6,7), small cell lung cancer (SCLC) (8), renal cell cancer (RCC) (9), melanoma (10) and microsatellite instability (MSI)-high colorectal cancer (11) in comparison to ICI monotherapy. Despite unprecedented rates of long-lasting clinical responses of ICI, these novel drugs have been widely used in routine clinical practice in geographic locations where large-scale clinical trials have not been carried out to prove their efficacy and safety. Different populations display differential sensitivity and safety profiles to different treatments. Such discrepancies have been identified in chemotherapy and targeted therapy (12-14). Moreover, differences in exposure to carcinogens, lifestyle, and dietary habits all may exert an impact on the variation of immunotherapy efficacy (15). It has been reported that the PD-1 inhibitors were more efficacious in smoking NSCLC patients (16). Despite a series of promising biomarkers such as PD-L1 tumor expression, tumor-infiltrating lymphocyte (TIL) status, and tumor mutational burden (TMB) for predicting ICI response, it is difficult to predict the wide-ranging clinical benefits precisely without using a broad set of biomarkers due to the complexity of the antitumor immune response and the heterogeneity of the patients. Identifying regional disparities may provide new ideas for selecting patients precisely and establishing individualized treatments (17). Despite its novelty and widespread use in Asia, few studies have assessed regional differences in immunotherapy outcomes. In this study, we performed a meta-analysis based on phased III trials to assess whether there was a region-dependent influence on patients with solid tumors treated with ICI. Also, detailed subgroup analyses according to cancer type, setting line of treatment, class of ICI were performed to reveal the heterogeneity. We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-1800).

Methods

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (18) and the guidelines of the Cochrane Handbook (19). The protocol for this systematic review was registered on INPLASY (INPLASY202050062) and is available in full on the inplasy.com (https://doi.org/10.37766/inplasy2020.5.0062).

Search strategy

Articles that reported the association between geographic region and outcomes of cancer patients treated with ICI were independently searched by two reviewers (Manyu Li and Huiyun Zhang) in PubMed, EMBASE, and the Cochrane Library from their inception date to October 2019. The following keywords were used: "neoplasm", "malignant neoplasm", "carcinoma", "nivolumab", "pembrolizumab", "cemiplimab", "pidilizumab", "cetrelimab", "camrelizumab", "toripalimab", "sintilimab", "tislelizumab", "durvalumab", "atezolizumab", "avelumab", "bintrafusp alfa", "envafolimab", "ipilimumab", "randomized controlled trial." We expanded our search by reviewing abstracts and presentations from major conferences, including the American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) meeting, in order to make sure that all eligible articles were screened. Finally, references to the studies included in the final selection were also checked. There was no language limitation in the literature search, and the process is presented in Table S1.

Study selection

The inclusion criteria were as follows: (I) phase III randomized controlled trial (RCT); (II) in the experimental arm, ICI (anti-PD-1 inhibitors or anti-PD-L1 inhibitors or anti-CTLA-4 inhibitors) were applied alone or in combination with other drugs, either immunological drug or chemotherapy; (III) the control regimen cannot include ICI unless it is a standard therapy; (IV) studies provided efficacy data of patients from North America, Europe, and Asia, respectively, and the data was required to include hazard ratio (HR) and 95% confidence interval (CI) of overall survival (OS) or progression-free survival (PFS). Criteria for excluding studies were as follows: (I) nonrandomized studies; (II) phase I or phase II studies; (III) studies not published in English; (IV) hematologic malignancy studies; (V) reviews, meta-analyses, case reports, comments, editorials, letters, expert consensuses,

guidelines, or animal research; (VI) insufficient data about the OS and PFS of the designated geographic region. We only included the latest reports with sufficient efficacy data available and previous publications were discarded. Two independent reviewers (Manyu Li, Jiannan Yao) screened titles and abstracts of the literature search catalog to select potentially proper articles, then read over full texts to check the eligibility. Any discrepancy between two reviewers in the literature search and selection was solved through discussion or determined by a third reviewer (Yang Ge).

Data extraction

The following information was acquired from the selected studies: (I) study characteristics: publication year, first author, study design, setting line of treatment, type of cancer, and treatment regimens of each study arm. (II) Study population: median age, age range, and number of patients treated in each study arm. (III) Study outcomes: HR and 95% CI for OS and/or PFS in the overall population, HR and 95% CI for OS and/or PFS in patients from North America, Europe, and Asia. Two investigators (Manyu Li, Jiannan Yao) independently extracted data from the studies, and all disagreements were resolved via discussion or consultation with the third investigator (Guangyu An).

Quality assessment

The study quality was evaluated using the Cochrane Collaboration's "Risk of bias" tool (20). The criteria included randomized sequence generation, allocation concealment, blinding of patients, personnel and outcome assessors, incomplete outcome data, selective outcome reporting, and other bias. We designated the risk of each item as low, high, or unclear. Two authors independently assessed the risk of bias, and all discrepancies were resolved by discussion with the third author until achieving consensus among the three authors. The assessment of risk is summarized in Figures S1,S2.

Statistical analysis

The pooled HR and 95% CI of OS and PFS for patients from Asia, Europe, and North America were calculated, with HR<1.0 manifesting a better outcome in the experimental arm. We used the Q test and I^2 statistics to assess the heterogeneity among the RCTs. When the two primary indicators are in specific ranges (P>0.1 and I^2<50%), it was considered to show that no significant heterogeneity could be found between studies, and the fixed-effect model should be applied. If there was significant heterogeneity between the studies (P<0.1 or I^2>50%), we analyzed them through the random-effects model (19). To explore the source of heterogeneity, subgroup analysis was carried out according to the class of ICI, cancer type, and the setting line of treatment where possible. Publication bias was assessed by funnel plots. Furthermore, Begg's and Egger's tests were utilized to examine the publication bias across studies (21,22). Sensitivity analysis was utilized to examine whether the results could have been influenced by a single study by removing one study at a time. Our meta-analysis was performed using Review Manager 5.3 and STATA 14 software. For combined analysis, a P<0.05 was treated as statistically significant.

Results

Identification and selection

We identified 10,151 publications reporting on ICI applied in cancer treatment by searching relevant databases and other sources. After removing 1,106 duplicate studies, there were 9,045 articles left for preliminary screening of titles and abstracts, from which we selected 61 articles for full-text assessment. A total of 8,984 articles were excluded for following reasons: case reports, guidelines, expert consensuses, clinical experience; letters, reviews, editorials, comments, news, notes, meta-analyses; not phase III RCT, not English paper, hematologic malignancies or lymphoma studies, or repeat presentations of participants captured by another study. After full-text review, 40 articles were excluded due to missing data according to patients' region subgroup, while two articles were not phase III RCT. Despite containing designated region survival data, two trials were excluded for the following reasons: CheckMate 227 only included patients with a high TMB, and the intervention arm of JAVELIN Renal 101 is a combination of ICI with axitinib which is not the first-line therapy for advanced renal-cell carcinoma. Finally, 17 phase III RCTs (23-39) were included in the meta-analysis. The flow diagram of the search and selection steps are shown in *Figure 1*.

Characteristics of included studies and patients

Among the 17 studies, five involved nivolumab

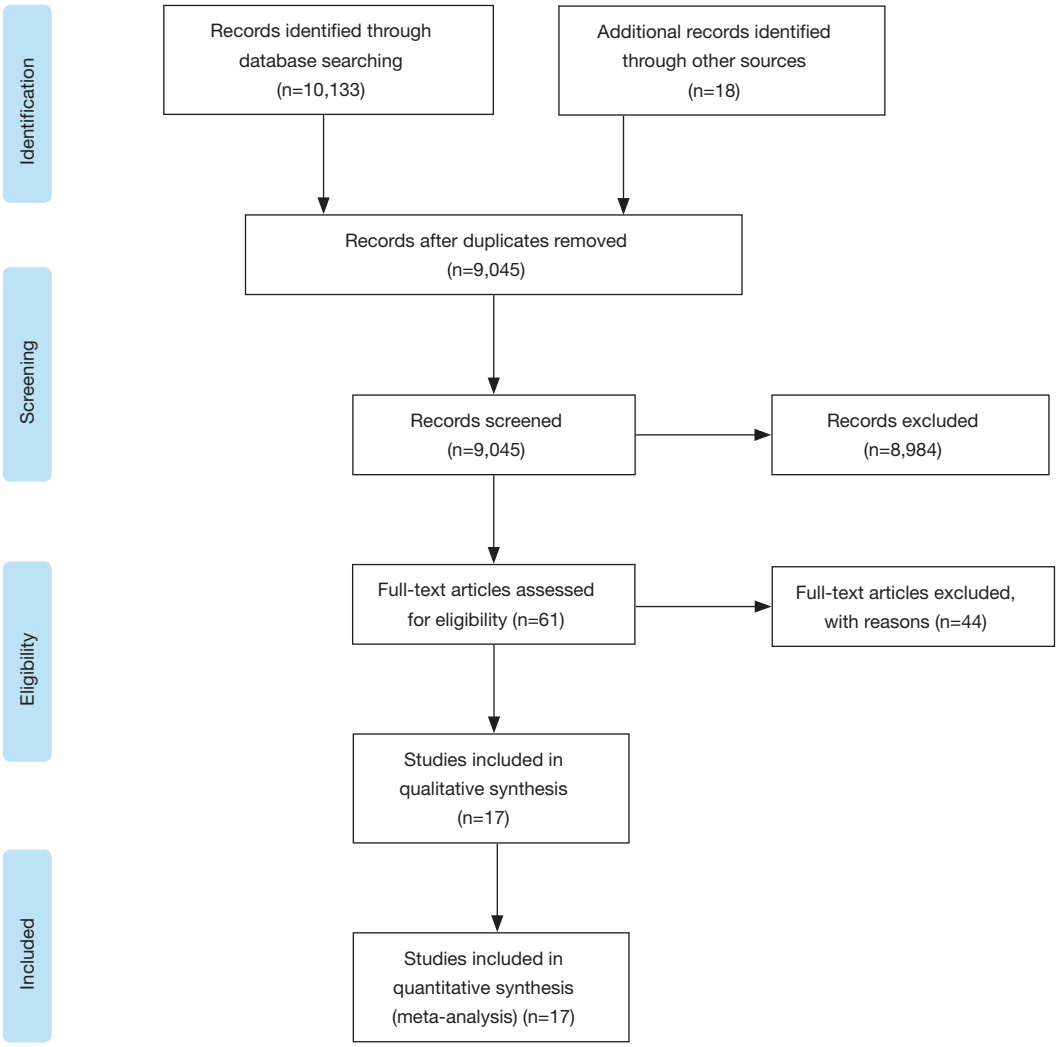

Figure 1 Flow diagram of study eligibility and selection process.

(23-27), five involved pembrolizumab (28,32,36-38), two involved durvalumab (34,39), one each involved atezolizumab (35), avelumab (29), and ipilimumab (33), one compared combined treatment of nivolumab and ipilimumab with ICI alone (nivolumab or ipilimumab) (31), and one compared pembrolizumab with ipilimumab (30). The cancer types were respectively: lung cancer, eight trials (23,24,34-39); melanoma, two trials (30,31); gastric or gastro-oesophageal junction cancer, three trials (27-29); head and neck cancer, two trials (26,32); RCC, one trial (25); and prostate cancer, one trial (33). The sample size in each study ranged from 272 to 2,075. Overall, 7,462 patients were enrolled in our meta-analysis, 2,073 patients from North America, 3,457 patients from Europe, and 1,932 patients from Asia. The main characteristics and results in each trial are presented in *Table 1*.

Primary outcome: overall survival

OS data stratified by regions were available in 17 studies. North American patients' pooled HR for OS using the random-effects model was 0.67 (95% CI: 0.57 to 0.78, I^2=47%, P=0.03; *Figure 2A*). The pooled HR from OS for European patients using the random-effects model was 0.72 (95% CI: 0.64 to 0.81, I^2=48%, P=0.04; *Figure 2B*). Since low heterogeneity (I^2=33%, P=0.15) was observed between individual studies, we deployed the fixed-effects model to calculate the pooled HR of OS from Asian patients, and

Table 1 Baseline characteristics of studies included in this meta-analysis.

Author	Year	Cancer type	Line	Blinding	Treatment regimen	No. of patients	Age	Overall survival, HR (95% CI)			
								Total	North America	Europe	Asia
Antonia (34)	2018	NSCLC	1	Double-blind	Durvalumab	476	64 [31–84]	0.68 (0.54–0.86)	NA	0.86 (0.61–1.21)	0.67 (0.41–1.11)
					Placebo	237	64 [23–90]				
Fehrenbacher (35)	2018	NSCLC	>1	None	ITT850: Atezolizumab	425	NA	0.75 (0.64–0.89)	0.61 (0.45–0.81)	0.82 (0.66–1.03)	0.75 (0.51–1.11)
					Docetaxel	425	NA				
					ITT1225: Atezolizumab	613	63 [25–84]	0.80 (0.70–0.92)	0.72 (0.56–0.93)	0.79 (0.66–0.95)	0.87 (0.62–1.20)
					Docetaxel	612	64 [34–85]				
Reck (36)	2019	NSCLC	1	None	Pembrolizumab	154	64.5 [33–90]	0.63 (0.47–0.86)	NA	NA	0.35 (0.12–1.01)
					Chemotherapy	151	66 [38–85]				
Mok (37)	2019	NSCLC	1	None	Pembrolizumab	637	63.0 [57.0–69.0]	0.81 (0.71–0.93)	NA	NA	0.79 (0.59–1.05)
					Chemotherapy	637	63.0 [57.0–69.0]				
Brahmer (23)	2015	Squamous cell NSCLC	>1	None	Nivolumab	135	62 [39–85]	0.59 (0.44–0.79)	0.59 (0.36–0.98)	0.50 (0.34–0.72)	NA
					Docetaxel	137	64 [42–84]				
Paz-Ares (38)	2018	Squamous cell NSCLC	1	Double-blind	Pembrolizumab + chemotherapy	278	65 [29–87]	0.64 (0.49–0.85)	NA	NA	0.44 (0.22–0.89)
					Chemotherapy	281	65 [36–88]				
Borghaei (24)	2015	Non-squamous cell NSCLC	>1	None	Nivolumab	292	61 [37–84]	0.73 (0.59–0.89)	0.52 (0.37–0.72)	0.81 (0.61–1.07)	NA
					Docetaxel	290	64 [21–85]				
Paz-Ares (39)	2019	SCLC	1	None	Durvalumab + platinum-etoposide	268	62 [58–68]	0.73 (0.59–0.91)	NA	0.72 (0.56–0.92)	0.82 (0.43–1.54)
					Platinum-etoposide	269	63 [57–68]				

Table 1 (*continued*)

Table 1 (*continued*)

Author	Year	Cancer type	Line	Blinding	Treatment regimen	No. of patients	Age	Overall survival, HR (95% CI)			
								Total	North America	Europe	Asia
Kang (27)	2017	Gastro-oesophageal junction cancer	>1	Double-blind	Nivolumab	330	62 [54–69]	0.63 (0.51–0.78)	NA	NA	0.63 (0.51–0.78)
					Placebo	163	61 [53–68]				
Shitara (28)	2018	Gastric or gastro-oesophageal junction cancer	>1	None	Pembrolizumab	296	62.5 [54–70]	0.82 (0.66–1.03)	NA	NA	0.90 (0.59–1.38)
					Paclitaxel	296	60.0 [53–68]				
Bang (29)	2019	Gastric or gastro-oesophageal junction cancer	>1	None	Avelumab	185	59 [29–86]	1.1 (0.9–1.4)	NA	NA	1.26 (0.79–2.00)
					Chemotherapy	186	61 [18–82]				
Robert (30)	2015	Melanoma	>1	None	Pembrolizumab Q2W	279	61 [18–89]	0.63 (0.47–0.83)	0.49 (0.19–1.26)	NA	NA
					Pembrolizumab Q3W	277	62 [18–88]	0.69 (0.52–0.90)	0.55 (0.22–1.39)	NA	NA
					Ipilimumab	278	62 [51–69]				
Larkin (31)	2019	Melanoma	1	Double-blind	Nivolumab	316	58.7 [25–90]	0.63 (0.52–0.77)	0.72 (0.47–1.12)	0.59 (0.46–0.77)	NA
					Nivolumab + ipilimumab	314	59.3 [18–88]	0.52 (0.42–0.64)	0.43 (0.27–0.71)	0.51 (0.39–0.67)	NA
					Ipilimumab	315	60.8 [18–89]				
Ferris (26)	2016	Head and neck cancer	>1	None	Nivolumab	240	59 [29–83]	0.69 (0.53–0.91)	0.55 (0.36–0.85)	0.91 (0.62–1.33)	NA
					Standard therapy	121	61 [28–78]				

Table 1 (*continued*)

Table 1 (*continued*)

Author	Year	Cancer type	Line	Blinding	Treatment regimen	No. of patients	Age	Overall survival, HR (95% CI)			
								Total	North America	Europe	Asia
Cohen (32)	2019	Head and neck cancer	>1	None	Pembrolizumab	247	60 [55–66]	0.8 (0.65–0.98)	1.27 (0.82–1.97)	0.68 (0.52–0.88)	NA
					Standard-of-care	248	60 [54–66]				
Kwon (33)	2014	Prostate cancer	>1	Double-blind	Ipilimumab	399	69 [47–86]	0.85 (0.72–1.00)	0.99 (0.69–1.42)	NA	NA
					Placebo	400	69 [47–86]				
Motzer (25)	2015	Clear-cell renal carcinoma	>1	None	Nivolumab	410	62 [23–88]	0.76 (0.62–0.92)	0.66 (0.48–0.91)	0.86 (0.63–1.16)	NA
					Everolimus	411	62 [18–86]				

HR, hazard ratio; CI, confidence interval; NA, not applicable; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

the result was 0.74 (95% CI: 0.66 to 0.84; *Figure 2C*).In summary, patients from North America, Europe, and Asia all showed a significantly reduced risk of death when treated with ICI compared to control. Despite no substantial differences in heterogeneity ($P_{heterogeneity}$≥0.05; *Table 2*), when we collated the OS data of these three designated regions with each other, North American patients derived the best clinical benefit, European patients ranked second, and Asian patients derived the least clinical benefit.

Secondary outcomes: progression-free survival

Seven RCTs provided data on PFS according to geographic region. Based on the included trials, there was no heterogeneity within-study in the North American arm (I^2=0%, P=0.62), suggesting that the pooled estimate should be deployed based on the fixed-effects model. However, there was high heterogeneity within-study in the European arm (I^2=88%, P<0.0001) and Asian arm (I^2=93%, P<0.0001), suggesting that the pooled estimate should be calculated based on the random-effects model. In summary, a significant improvement in PFS emerged exclusively in patients from North America (HR 0.58, 95% CI: 0.49 to 0.69; *Figure 3A*) and Europe (HR 0.61, 95% CI: 0.41 to 0.90; *Figure 3B*), but not in patients from Asia (HR 0.87, 95% CI: 0.38 to 1.99; *Figure 3C*). When we compared the PFS data of these three designated regions with each other, the differences did not achieve statistical significance. ($P_{heterogeneity}$≥0.05; *Table 2*)

Subgroup analyses

In order to further explore the source of heterogeneity, subgroup analyses were conducted according to class of ICI applied in the intervention arm, cancer type and setting line of treatment. The detailed outcomes are shown in *Table 3*, and Figures S3-S5.

We found a statistically significant advantage in favor of anti-PD-1 inhibitors and anti-PD-L1 inhibitors in both North American (anti-PD-1 inhibitors: HR: 0.63, 95% CI: 0.51 to 0.78; anti-PD-L1 inhibitors: HR: 0.67, 95% CI: 0.55 to 0.82; *Table 3*) and European arms (anti-PD-1 inhibitors: HR: 0.67, 95% CI: 0.57 to 0.80; anti-PD-L1 inhibitors: HR: 0.79, 95% CI: 0.71 to 0.89; *Table 3*), while only anti-PD-1 inhibitors had statistically significant differences in Asian arms (anti-PD-1 inhibitors: HR: 0.68, 95% CI: 0.55 to 0.85; anti-PD-L1 inhibitors: HR: 0.85, 95% CI: 0.70

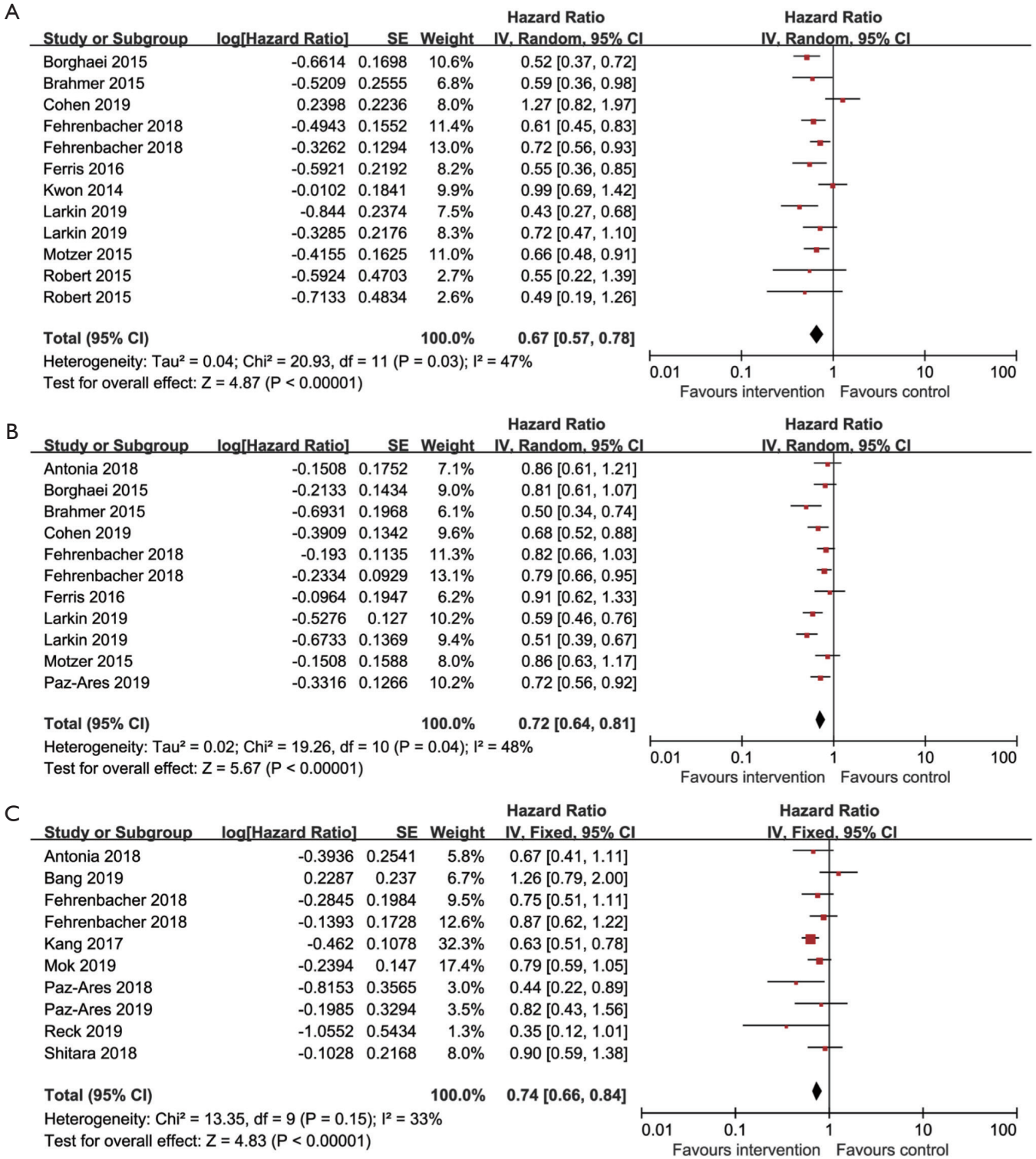

Figure 2 Forest plot of the hazard ratios and 95% CI for overall survival in North American (A), European (B), Asian (C) patients assigned to intervention arm, compared with those assigned to the control arm.

Table 2 Pooled hazard ratios for OS and PFS in North America, Europe, and Asia

Outcomes	Number of trials	Number of patients	Region	HR [95% CI]	I^2	$P_{heterogeneity}$
OS	9	7,184	North America	0.67 [0.57, 0.78]	47%	0.46
	9	6,801	Europe	0.72 [0.64, 0.81]	48%	
PFS	4	2,633	North America	0.58 [0.49, 0.69]	0%	0.83
	3	1,799	Europe	0.61 [0.41, 0.90]	88%	
OS	9	7,184	North America	0.67 [0.57, 0.78]	47%	0.27
	9	6,919	Asia	0.74 [0.66, 0.84]	33%	
PFS	4	2,633	North America	0.58 [0.49, 0.69]	0%	0.35
	3	1,423	Asia	0.87 [0.38, 1.99]	93%	
OS	9	6,801	Europe	0.72 [0.64, 0.81]	48%	0.59
	9	6,919	Asia	0.74 [0.66, 0.84]	33%	
PFS	3	1,799	Europe	0.61 [0.41, 0.90]	88%	0.45
	3	1,423	Asia	0.87 [0.38, 1.99]	93%	

OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.

to 1.04; *Table 3*). Furthermore, there was a tendency for anti-PD-1 inhibitors to be more efficient compared with anti-PD-L1 inhibitors in all three designated geographic regions, despite no statistical significance.

Additionally, there was an evident region-independent trend in several types of cancer, such as lung cancer and melanoma which had significantly prolonged OS while other types of cancer such as head and neck cancer, prostate cancer and gastric or gastro-oesophageal junction cancer failed to acquire benefit from the administration of ICI. The detailed outcomes are shown in *Table 3*.

Regardless of geographic regions, ICI applied in first-line treatment (North American: HR: 0.56, 95% CI: 0.34 to 0.93; European: HR: 0.65, 95% CI: 0.53 to 0.80; Asian: HR: 0.58, 95% CI: 0.42 to 0.79; *Table 3*) always brought more clinical benefit compared to those applied in subsequent lines (North American: HR: 0.69, 95% CI: 0.58 to 0.82; European: HR: 0.77, 95% CI: 0.69 to 0.86; Asian: HR: 0.82, 95% CI: 0.65 to 1.03 *Table 3*).

Publication bias

Slight asymmetry can be detected in funnel plots of the overall survival from North American arm, European arm, Asian arm, and their combination (*Figure 4*), which suggests the potential for publication bias. We performed Egger's test and Begg's test via STATA 14.0 software. The results are summarized in *Table 4*. All the p values were >0.05 after both tests, suggesting there was no significant publication bias in this meta-analysis.

Sensitivity analysis

In order to assess the potential for significant heterogeneity between different studies, we performed a sensitivity analysis (Figure S6). There was no significant difference after removing any single study, which supports the stability of the combined results and the rationality of the meta-analysis.

Discussion

Based on previous research, the interaction of genetic background and environment may lead to discrepancy in ICI efficiency in different regions (40). Given few clinical trials that assessed geographic regions as a potential factor affecting the efficacy of ICI, we performed a systematic review and meta-analysis of phase III RCTs to explore the clinical efficacy of ICI between North America, Europe, and Asia.

In a previous meta-analysis by Wang *et al.* (40), 14 phase II/III trials with ICI applied in advanced cancer patients were included. Compared with the aforementioned study, all the studies we included are phase III RCTs which are sufficiently powered to detect differences. Additionally, phase III trials ensure longer follow-up. In order to evaluate

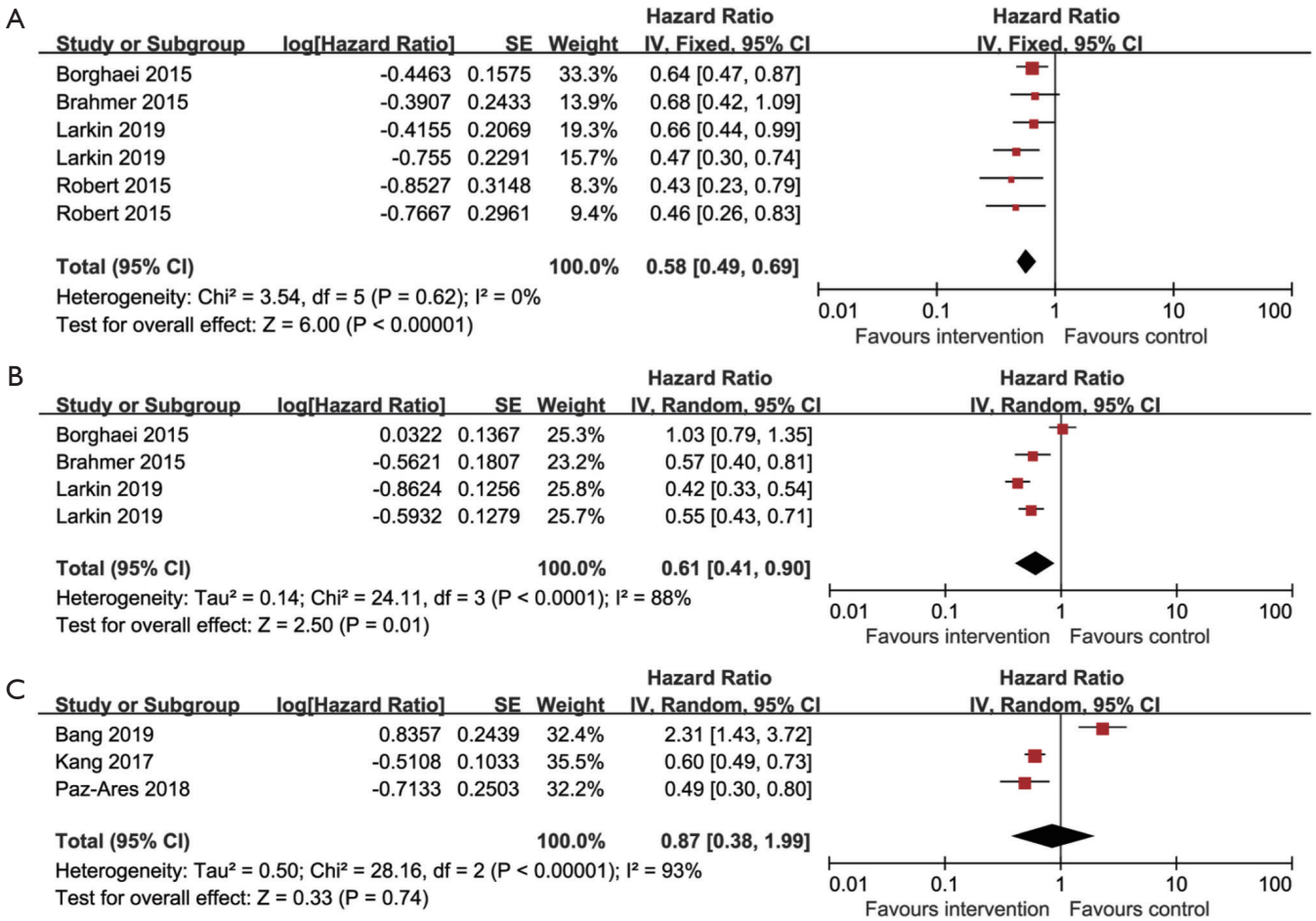

Figure 3 Forest plot of the hazard ratios and 95% CI for progression-free survival in North American (A), European (B), Asian (C) patients assigned to intervention arm, compared with those assigned to the control arm.

the heterogeneity of efficacy of ICI more comprehensively, our meta-analysis not only included trials for anti-PD-1/anti-PD-L1 inhibitors but also anti-CTLA-4 inhibitors. Importantly, we found that with the addition of extensive new Phase III trial data, the significant difference in OS between North American and European ICI-treated patients disappeared. This could be explained by the inclusion of more high-quality RCTs and longer follow-up. In our expanded analysis, Asian patients gained the least OS advantage among all three designated geographic locations. Moreover, a benefit in PFS was observed in all three regions in the Wang *et al.* study, while a benefit in PFS was observed only in North America and Europe in our study. In conclusion, our data indicated that ICI were less effective in Asia compared to North America and Europe.

The heterogeneity across included RCTs mainly resulted from class of ICI applied in the intervention arm, cancer type, and line of treatment. Therefore, we performed subgroup analyses and sensitivity analyses to determine sources of heterogeneity. To elaborate the benefit regarding the class of ICI applied, subgroup analyses of anti-PD-1 inhibitors or anti-PD-L1 inhibitors were performed in the three designated geographic regions. Anti-PD-1 inhibitors led to outcomes with statistical significance in North America, Europe, and Asia, while anti-PD-L1 inhibitors only had a statistically significant difference in North America and Europe. This evidence for the inferiority of efficacy of anti-PD-L1 inhibitors in Asia invites critical interpretation. The different mechanisms of action of anti-PD-L1 inhibitors and anti-PD-1 inhibitors may help provide a biologic rationale for this finding (41). Theoretically, the PD-1 antibody can bind to PD-1 protein

Table 3 Pooled hazard ratios and 95% CI of overall survival according to class of ICI, cancer type, and the setting line of ICI treatment

Analysis	Region	N	Random-effects model		Heterogeneity	
			HR [95% CI]	P	I^2	P
PD-1	All	12	0.66 [0.59, 0.73]	<0.00001	44%	0.02
	North America	7	0.63 [0.51, 0.78]	<0.0001	46%	0.06
	Europe	6	0.67 [0.57, 0.80]	<0.00001	57%	0.03
	Asia	5	0.68 [0.55, 0.85]	0.0007	35%	0.18
PD-L1	All	4	0.78 [0.71, 0.85]	<0.00001	0%	0.56
	North America	1	0.67 [0.55, 0.82]	<0.0001	0%	0.41
	Europe	3	0.79 [0.71, 0.89]	<0.0001	0%	0.83
	Asia	4	0.85 [0.70, 1.04]	0.11	2%	0.40
Lung cancer	All	8	0.72 [0.67, 0.79]	<0.00001	12%	0.31
	North America	3	0.63 [0.54, 0.74]	<0.00001	0%	0.49
	Europe	5	0.76 [0.68, 0.86]	<0.00001	17%	0.31
	Asia	6	0.75 [0.63, 0.88]	0.0006	0%	0.50
Melanoma	All	2	0.55 [0.48, 0.65]	<0.00001	0%	0.66
	North America	2	0.56 [0.42, 0.74]	<0.0001	0%	0.45
	Europe	1	0.55 [0.46, 0.66]	<0.00001	0%	0.44
Head and neck cancer	All	2	0.80 [0.58, 1.10]	0.17	67%	0.03
	North America	2	0.83 [0.37, 1.89]	0.66	86%	0.007
	Europe	2	0.76 [0.58, 1.00]	0.05	33%	0.22
Others	All	2	0.82 [0.65, 1.03]	0.08	31%	0.23
	North America	2	0.80 [0.54, 1.19]	0.27	63%	0.10
	Europe	1	0.86 [0.63, 1.17]	0.34	NA	NA
First-line	All	6	0.62 [0.53, 0.71]	<0.00001	28%	0.18
	North America	1	0.56 [0.34, 0.93]	0.02	61%	0.11
	Europe	3	0.65 [0.53, 0.80]	<0.0001	56%	0.08
	Asia	5	0.58 [0.42, 0.79]	0.0006	0%	0.44
Subsequent line	All	11	0.74 [0.68, 0.82]	<0.00001	41%	0.03
	North America	8	0.69 [0.58, 0.82]	<0.0001	47%	0.05
	Europe	6	0.77 [0.69, 0.86]	<0.00001	19%	0.29
	Asia	4	0.82 [0.65, 1.03]	0.09	54%	0.07

HR, hazard ratio; CI, confidence interval; ICI, immune checkpoint inhibitors; HR, hazard ratio.

on T cells, which means that it blocks the binding of PD-1 to PD-L1 and PD-L2 at the same time. However, the PD-L1 antibody can only block the binding of PD-1 to PD-L1, which means the intact interaction of PD-1 and PD-L2 may inhibit the activation of T cells. Therefore, treatment with anti-PD-L1 may provide an opportunity for tumors escaping from the antitumor immune response through the PD-1/PD-L2 axis. Indeed, PD-L2 expression status predicts the clinical benefit of ICI treatment independent of PD-L1 expression status (42,43). Since all RCTs

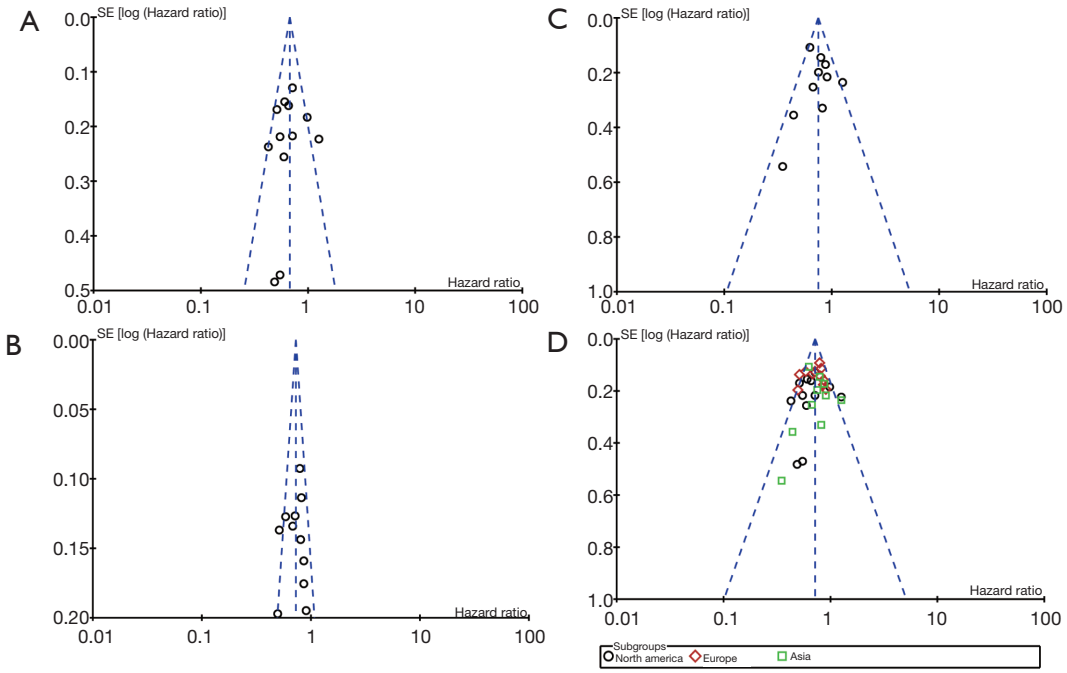

Figure 4 Funnel plots for overall survival data from North American (A), European (B), Asian (C) and combined arms (D) in included RCTs for the visual detection of systematic publication bias and small study effect. RCT, randomized controlled trial.

Table 4 Evaluation of publication bias in overall survival with Begg's test and Egger's test

Outcomes	Trials	No. of patients	Region	HR (95% CI)	Begg's test		Egger's test	
					Z	P	*T*	P
OS	9	7,184	North America	0.67 [0.57, 0.78]	0.34	0.732	–0.50	0.625
OS	9	6,801	Europe	0.72 [0.64, 0.81]	0.00	1.000	–0.43	0.679
OS	9	6,919	Asia	0.74 [0.66, 0.84]	0.54	0.592	–0.06	0.954
OS	17	12,028	Total	0.71 [0.66, 0.77]	0.70	0.486	–0.70	0.491

HR, hazard ratio; CI, confidence interval; OS, overall survival.

except one included in the Asian subgroup were studies of NSCLC and GC, moderate to high PD-L2 expression was found in NSCLC and GC patients, which strengthens our observation of the poor performance of anti-PD-L1 compared with anti–PD-1 in the Asian subgroup. However, due to the absence of head-to-head clinical trial data, these suggestive findings should be interpreted with caution.

To further interpret the disparate results for anti-PD-L1 inhibitor efficacy in Asia compared to Western regions, we reviewed each relevant RCT individually. RCTs with North American subgroups displayed improved OS in all involved patients, not just in North American regions. A similar finding was observed in studies with European subgroups with a single exception (34). However, the most striking result emerged with the Asian subgroup. With one exception demonstrating a failure to improve OS in both overall participants and Asian subgroup (29), the other RCTs demonstrated improved OS in all participants but not in the Asian subgroup. This finding is notable because it indicates that global OS data may hide disparities in ICI efficacy between Asian and Western countries.

In general, clinical trials for western medicine are firstly carried out in western countries. The assessment of efficacy and toxicity in other regions are usually conducted

subsequently. However, the discrepancies in efficacy and safety profiles vary widely between various regions. As reported, approximately 20% of new agents approved between 2010–2015 displayed variations in response and/or exposure among ethnic/racial groups, leading to region-specific recommendations for prescribing in some cases (44). Additionally, it has been demonstrated that ethnic differences in clinical efficacy exist in cancer patients receiving targeted therapy or chemotherapy (45,46), it is also highly likely that the efficiency of patients undergoing immunotherapy varies among different geographic location.

Several factors that are closely correlated with geographic location and ethnicity may impact the efficacy of ICI therapy (47). Firstly, the patterns of oncogene-driven mutations vary substantially between Asian and non-Asian countries. It is widely acknowledged that EGFR mutations are much more common in Asians, while KRAS mutations are more common in Western populations (47). About 47.9% of Asians carry EGFR mutation, while the incidence was about 15% in the Caucasian population. Conversely, the rate of KRAS mutation was higher in the Caucasian population (30% *vs.* 7%) (46). The gene mutations mentioned above are proven to be involved in the immunologic response (48). Many studies have demonstrated that clinical benefit of ICI could be observed in EGFR wild-type patients but not in EGFR mutation-positive NSCLC patients in comparison to docetaxel (35,49-51). Furthermore, EGFR mutations might bring about a potentially higher hazard of hyper progression after the immunotherapy (52).

Aside from the wide divergence in genetic backgrounds, many factors may exert effects on the therapeutic benefit to patients from diverse geographic regions such as dietary habits, environmental pollution, tobacco and alcohol consumption, socioeconomic status, and others (53). Taking tobacco use for example, the amount of former/current smokers was higher in non-Asian population compared with Asian (54). It has been reported that ICI were more efficient in smoking NSCLC patients (16). Furthermore, certain viral infections have evident regional characteristics, such as the hepatitis B virus (HBV). Research showed that Asia comprised approximately 62% of worldwide HBV burden (55). Moreover, the number of Chinese patients with HBV exceeded 93 million, which is significantly higher than those in Europe and the United States (56). Whether HBV infection plays a key role in the efficacy of ICI is still unknown since those certain patients are usually excluded by most of the RCTs. More studies are warranted to explain this issue. More recently, works of literature have emerged that offer contradictory findings of the impact of antibiotic treatment on ICI therapy in different regions. According to Pinato *et al.* (57), exposure to broad-spectrum antibiotic therapy prior to ICI therapy is associated with worse treatment response and OS in patients of multicenter ICI therapy studies. This could potentially explain the disadvantage in outcomes among Asian subgroups who are more likely to be overprescribed antibiotics as well as access them illicitly and over-the-counter (58). However, there is a contrary outcome reported by Metges *et al.*, who found survival advantages for French patients receiving antibiotics prior to the ICI therapy (59). More features regarding the molecular mechanism of regional differences and evaluation of the influence of antibiotics should be taken into account in future clinical trial design.

Several types of cancer, such as lung cancer and melanoma displayed a region-independent benefit from the ICI treatment, whereas other types of cancer such as head and neck cancer, prostate cancer and gastric or gastro-oesophageal junction cancer showed little benefit or even failed to improve the survival data from the administration of ICI agents. These results reflect those of Teufel *et al.* (2019) (60), who also observed that patients with pancreatic cancer or hepatocellular carcinoma or head and neck squamous cell displayed resistance against ICI and could not benefit from ICI treatment. Distinguishing cancer cells as foreign is the necessary prerequisite to the induction of adaptive immune responses for tumors. High TMB and elevated neoantigen expression are foundational to antitumor immunity according to several reports (17,61,62). This analysis adds to the body of findings indicating that tumor types characterized as poorly immunogenic are inherently less sensitive to immunotherapy.

When we assessed whether the setting line of ICI treatment impacted the risk of death among different geographic locations, the results of three were in line with each other. Reduced risk of death was identified when ICI agents were applied in first-line treatment compared with subsequent-line treatment regardless of region. The primary mechanism of ICI treatment is harnessing the immune system to fight malignancy (17,63). Therefore, a functional immune system is essential for ICI to produce a marked effect, so ICI added to first-line treatment regimen is more likely to produce a better clinical outcome.

To our knowledge, this is the first assessment of regional differences in ICI treatment efficacy exclusive to Phase III trial data. However, this meta-analysis also has

several shortcomings. Firstly, our meta-analysis is based on published data so no clinicopathological characteristics of individual patients are examined. This precludes the possibility of exploring potential associations between variables. Secondly, it is noteworthy that some subgroup analyses included few trials, which might reduce their statistical power. In addition, some RCTs of anti-PD-L1 inhibitors were not included due to the lack of survival data of designated region, which makes us unable to evaluate the regional differences of survival data. Consequently, our analysis should be interpreted cautiously considering the above concern. Furthermore, despite using the random-effects model and conducting subgroup analyses, the heterogeneity among the included studies is still an issue that cannot be ignored. The origin of heterogeneity lies in the diversity of patient baseline characteristics, such as cancer type, PD-L1 expression level, ECOG, and other factors. In addition, ICI dosage could also account for the heterogeneity. Finally, the impact of regional variation should be assessed in terms of safety as well as clinical benefit. Accordingly, further meta-analysis from updated information will be required.

Conclusions

In conclusion, our meta-analysis indicates that ICI could significantly prolong patients' OS compared to control treatment in a region-independent fashion. However, the magnitude of benefit varies by geographic location. Asian patients experience inferior outcomes compared to Western patients. Notably, anti-PD-L1 therapies do not result in survival improvements in Asian patients. We recommend that more region-related characteristics should be taken into consideration in the design of clinical trials with ICI, such as exposure to antibiotic therapy, tobacco and alcohol consumption, socioeconomic status, and other factors. More detailed high-quality clinical studies are warranted to clarify the impact of geographic region on efficacy of ICI and explore the potential subgroups susceptible to specific ICI.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr-20-1800). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Table S1 Strategy used for PubMed, EMBASE and the Cochrane Library searches

No.	Search strategy	Items found
PubMed		
#1	Neoplasms[MeSH Terms]	3228191
#2	((((((((Neoplasia*[Title/Abstract]) OR Neoplasm*[Title/Abstract]) OR Tumor*[Title/Abstract]) OR Cancer*[Title/Abstract]) OR Malignan*[Title/Abstract]) OR Malignant Neoplasm*[Title/Abstract]) OR Neoplasm*, Malignant[Title/Abstract]) OR Benign Neoplasm*[Title/Abstract]) OR Neoplasm*, Benign[Title/Abstract])	132344
#3	Carcinoma[MeSH Terms]	624097
#4	((((((((((((((Carcinoma*[Title/Abstract]) OR Epithelial Neoplasm*, Malignant[Title/Abstract]) OR Malignant Epithelial Neoplasm*[Title/Abstract]) OR Neoplasm*, Malignant Epithelial[Title/Abstract]) OR Epithelial Tumor*, Malignant[Title/Abstract]) OR Malignant Epithelial Tumor*[Title/Abstract]) OR Tumor*, Malignant Epithelial[Title/Abstract]) OR Epithelioma*[Title/Abstract]) OR Carcinoma*, Undifferentiated[Title/Abstract]) OR Undifferentiated Carcinoma*[Title/Abstract]) OR Carcinoma*, Anaplastic[Title/Abstract]) OR Anaplastic Carcinoma*[Title/Abstract]) OR Carcinoma, Spindle-Cell[Title/Abstract]) OR Carcinoma, Spindle Cell[Title/Abstract]) OR Spindle-Cell Carcinoma*[Title/Abstract]) OR Carcinomatos*[Title/Abstract])	14141
#5	(#1 OR #2 OR #3 OR #4)	3247133
#6	Nivolumab[MeSH Terms]	1817
#7	((((((((((Opdivo[Title/Abstract]) OR ONO-4538[Title/Abstract]) OR ONO 4538[Title/Abstract]) OR ONO4538[Title/Abstract]) OR MDX-1106[Title/Abstract]) OR MDX 1106[Title/Abstract]) OR MDX1106[Title/Abstract]) OR BMS-936558[Title/Abstract]) OR BMS 936558[Title/Abstract]) OR BMS936558[Title/Abstract])	93
#8	(((((pembrolizumab[Title/Abstract]) OR lambrolizumab[Title/Abstract]) OR Keytruda[Title/Abstract]) OR MK-3475[Title/Abstract]) OR SCH-900475[Title/Abstract])	2680
#9	((((Libtayo[Title/Abstract]) OR cemiplimab-rwlc[Title/Abstract]) OR REGN2810[Title/Abstract]) OR cemiplimab[Title/Abstract])	30
#10	(((((((Pidilizumab[Title/Abstract]) OR CT-011[Title/Abstract]) OR CT 011[Title/Abstract]) OR AMP-514[Title/Abstract]) OR MEDI0680[Title/Abstract]) OR PDR-001[Title/Abstract]) OR BCD-100[Title/Abstract])	34
#11	(((((((((camrelizumab[Title/Abstract]) OR SHR-1210[Title/Abstract]) OR toripalimab[Title/Abstract]) OR JS001[Title/Abstract]) OR sintilimab[Title/Abstract]) OR IBI308[Title/Abstract]) OR BGB-A317[Title/Abstract]) OR Tislelizumab[Title/Abstract]) OR GB226[Title/Abstract])	45
#12	((((Durvalumab[Title/Abstract]) OR MEDI4736[Title/Abstract]) OR MEDI-4736[Title/Abstract]) OR Imfinzi[Title/Abstract])	330
#13	(((((((atezolizumab[Title/Abstract]) OR anti-PDL1[Title/Abstract]) OR immunoglobulin G1, anti-(human CD antigen CD274) (human monoclonal MDPL3280a heavy chain), disulfide with human monoclonal MDPL3280a kappa-chain, dimer[Title/Abstract]) OR MPDL3280A[Title/Abstract]) OR tecentriq[Title/Abstract]) OR RG7446[Title/Abstract]) OR RG-7446[Title/Abstract])	57
#14	(((avelumab[Title/Abstract]) OR MSB0010718C[Title/Abstract]) OR Bavencio[Title/Abstract])	303
#15	((((((BMS-936559) OR MDX1105) OR M7824) OR KN035) OR CS1001) OR ZKAB001)	33
#16	((((((((((tremelimumab[Title/Abstract]) OR ticilimumab[Title/Abstract]) OR CP 675[Title/Abstract]) OR CP675 cpd[Title/Abstract]) OR CP-675[Title/Abstract]) OR CP-675,206[Title/Abstract]) OR CP-675206[Title/Abstract]) OR CP675206[Title/Abstract]) OR CP 675206[Title/Abstract])	5295
#17	Ipilimumab[MeSH Terms]	1642
#18	(Anti-CTLA-4 MAb Ipilimumab[Title/Abstract]) OR Anti CTLA 4 MAb Ipilimumab[Title/Abstract]) OR Ipilimumab, Anti-CTLA-4 MAb[Title/Abstract]) OR Yervoy[Title/Abstract]) OR MDX 010[Title/Abstract]) OR MDX010[Title/Abstract]) OR MDX-010[Title/Abstract]) OR MDX-CTLA-4[Title/Abstract]) OR MDX CTLA 4[Title/Abstract])	93
#19	(CTLA-4 [Title/Abstract] OR cytotoxic T-lymphocyte-associated protein 4 [Title/Abstract] OR PD-1 [Title/Abstract] OR programmed death receptor 1 [Title/Abstract] OR programmed death ligand1 [Title/Abstract] OR PD-L1 [Title/Abstract] OR immune checkpoint inhibitor [Title/Abstract] OR Programmed Cell Death 1 Receptor antagonist [Title/Abstract] OR Programmed Cell Death 1 Receptor inhibitor [Title/Abstract] OR CTLA-4 Antigen antagonists [Title/Abstract] OR CTLA-4 Antigen inhibitors [Title/Abstract])	21112
#20	(#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19)	28917
#21	(randomized controlled trial[Publication Type] OR controlled clinical trial[Publication Type] OR clinical trial[Publication Type])	839547
#22	(clinical Trials as Topic[MeSH Terms] OR Randomized Controlled Trials as Topic[MeSH Terms] OR Controlled Clinical Trials as Topic[MeSH Terms] OR Double-Blind Method[MeSH Terms] OR single-blind method[MeSH Terms] OR Control Groups[MeSH Terms] OR Random Allocation[MeSH Terms] OR cross-over studies[MeSH Terms] OR drug therapy[MeSH Subheading])	2501963
#23	(#21 OR #22)	2922112
#24	("Animals"[Mesh] NOT ("Humans"[Mesh] AND "Animals"[Mesh]))	4630286
#25	(#5 AND #20 AND #23)	5164
#26	(#25 NOT #24)	Final search 5018
EMBASE		
#1	'neoplasm'/exp	4758577
#2	'acral tumor' OR 'acral tumour' OR 'neoplasia' OR 'neoplasms' OR 'neoplasms by histologic type' OR 'neoplasms, cystic, mucinous, and serous' OR 'neoplasms, embryonal and mixed' OR 'neoplasms, germ cell and embryonal' OR 'neoplasms, glandular and epithelial' OR 'neoplasms, hormone-dependent' OR 'neoplasms, post-traumatic' OR 'neoplastic disease' OR 'tumor' OR 'tumour'	3160381
#3	'malignant neoplasm'/exp	3559360
#4	'cancer' OR 'cancers' OR 'malignant neoplasia' OR 'malignant neoplastic disease' OR 'malignant tumor' OR 'malignant tumour' OR 'neoplasia, malignant' OR 'tumor, malignant' OR 'tumour, malignant'	4066523
#5	'carcinoma'/exp	1202176
#6	'carcinoma 63' OR 'carcinoma, brown-pearce' OR 'carcinoma, krebs 2' OR 'carcinoma, neuroendocrine' OR 'carcinoma, scirrhous' OR 'epithelial carcinoma' OR 'epithelial malignant tumor' OR 'epithelial malignant tumour' OR 'internal carcinoma' OR 'malignant epithelial tumor' OR 'malignant epithelial tumour' OR 'microcarcinoma' OR 'neoplasm,malignant epithelial' OR 'neoplasms, ductal, lobular, medullary' OR 'primary carcinoma'	8323
#7	'nivolumab'/exp	13544
#8	'bms 936558' OR 'bms936558' OR 'cmab 819' OR 'cmab819' OR 'mdx 1106' OR 'mdx1106' OR 'ono 4538' OR 'ono4538' OR 'opdivo'	1199
#9	'pembrolizumab'/exp	11478
#10	'keytruda' OR 'lambrolizumab' OR 'mk 3475' OR 'mk3475' OR 'sch 900475' OR 'sch900475'	1290
#11	'cemiplimab'/exp	143
#12	'cemiplimab rwlc' OR 'cemiplimab-rwlc' OR 'libtayo' OR 'regn 2810' OR 'regn2810' OR 'sar 439684' OR 'sar439684'	87
#13	'pidilizumab'/exp	443
#14	'ct 011' OR 'ct011'	224
#15	'cetrelimab'/exp	7
#16	'jnj 63723283' OR 'jnj63723283'	11
#17	'camrelizumab'/exp	29
#18	'shr-1210'	64
#19	'toripalimab'/exp	32
#20	'js 001' OR 'js001' OR 'tab 001' OR 'tab001'	43
#21	'sintilimab'/exp	29
#22	'ibi 308' OR 'ibi308' OR 'tyvyt'	18
#23	'tislelizumab'/exp	59
#24	'bgb a317' OR 'bgba317'	49
#25	'gb226'	3
#26	'amp-514' OR 'medi0680' OR 'pdr-001' OR 'bcd-100'	99
#27	'durvalumab'/exp	2723
#28	'imfinzi' OR 'medi 4736' OR 'medi4736'	653
#29	'atezolizumab'/exp	3954
#30	'monoclonal antibody mpdl 3280a' OR 'monoclonal antibody mpdl3280a' OR 'mpdl 3280a' OR 'mpdl3280a' OR 'rg 7446' OR 'rg7446' OR 'tecentriq' OR 'tecntriq'	736
#31	'avelumab'/exp	1654
#32	'bavencio' OR 'msb 0010682' OR 'msb 0010718c' OR 'msb 10682' OR 'msb 10718c' OR 'msb0010682' OR 'msb0010718c' OR 'msb10682' OR 'msb10718c' OR 'pf 06834635' OR 'pf 6834635' OR 'pf06834635' OR 'pf6834635'	264
#33	'bms 936559'/exp	372
#34	'bms936559' OR 'mdx 1105' OR 'mdx1105'	84
#35	'bintrafusp alfa'/exp	39
#36	'bintrafusp alpha' OR 'm 7824' OR 'm7824' OR 'msb 0011359c' OR 'msb0011359c'	59
#37	'envafolimab'/exp	9
#38	'asc 22' OR 'asc22' OR 'kn 035' OR 'kn035'	30
#39	'cs1001' OR 'zkab001'	5
#40	'envafolimab'/exp	9
#41	'cp 675 206' OR 'cp 675, 206' OR 'cp 675206' OR 'cp675 206' OR 'cp675, 206' OR 'cp675206' OR 'tremelimumab'	729
#42	'ipilimumab'/exp	12066
#43	'bms 734016' OR 'bms734016' OR 'mdx 010' OR 'mdx 101' OR 'mdx010' OR 'mdx101' OR 'strentarga' OR 'yervoy'	1090
#44	randomized AND controlled AND ('trial'/exp OR trial) OR (controlled AND trial, AND randomized;) OR 'randomized controlled trial'/exp OR 'randomized controlled trial' OR (pragmatic AND ('clinical'/exp OR clinical) AND trials) OR (randomised AND controlled AND ('study'/exp OR study)) OR (randomised AND controlled AND ('trial'/exp OR trial)) OR (randomized AND controlled AND study;) OR (trial, AND randomized AND controlled)	908562
#45	#1 OR #2 OR #3 OR #4 OR #5 OR #6	6144263
#46	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43	27206
#47	'ctla-4' OR 'cytotoxic t-lymphocyte-associated protein 4' OR 'pd-1' OR 'programmed death receptor 1' OR 'programmed death ligand1' OR 'pd-l1' OR 'immune checkpoint inhibitor' OR 'programmed cell death 1 receptor antagonist' OR 'programmed cell death 1 receptor inhibitor' OR 'ctla-4 antigen antagonist' OR 'ctla-4 antigen inhibitor'	43159
#48	#46 OR #47	58020
#49	#44 AND #45 AND #48	Final search 4177
The Cochrane Library		
#1	MeSH descriptor: [Neoplasms] explode all trees	71851
#2	Neoplasia*:ti,ab,kw OR Neoplasm*:ti,ab,kw OR Tumor*:ti,ab,kw OR Cancer*:ti,ab,kw OR Malignan*:ti,ab,kw OR Malignant Neoplasm*:ti,ab,kw OR Neoplasm*, Malignant:ti,ab,kw OR Benign Neoplasm*:ti,ab,kw OR Neoplasm*, Benign:ti,ab,kw	196131
#3	MeSH descriptor: [Carcinoma] explode all trees	12426
#4	Carcinoma*:ti,ab,kw OR Epithelial Neoplasm*, Malignant:ti,ab,kw OR Malignant Epithelial Neoplasm*:ti,ab,kw OR Neoplasm*, Malignant Epithelial:ti,ab,kw OR Epithelial Tumor*, Malignant:ti,ab,kw OR Malignant Epithelial Tumor*:ti,ab,kw OR Tumor*, Malignant Epithelial:ti,ab,kw OR Epithelioma*:ti,ab,kw OR Carcinoma*, Undifferentiated:ti,ab,kw OR Undifferentiated Carcinoma*:ti,ab,kw OR Carcinoma*, Anaplastic:ti,ab,kw OR Anaplastic Carcinoma*:ti,ab,kw OR Carcinoma, Spindle-Cell:ti,ab,kw OR Carcinoma, Spindle Cell:ti,ab,kw OR Spindle-Cell Carcinoma*:ti,ab,kw OR Carcinomatos*:ti,ab,kw	39759
#5	#1 OR #2 OR #3 OR #4	210985
#6	MeSH descriptor: [Nivolumab] explode all trees	306
#7	Opdivo:ti,ab,kw OR ONO-4538:ti,ab,kw OR ONO 4538:ti,ab,kw OR ONO4538:ti,ab,kw OR MDX-1106:ti,ab,kw OR MDX 1106:ti,ab,kw OR MDX1106:ti,ab,kw OR BMS-936558:ti,ab,kw OR BMS 936558:ti,ab,kw OR BMS936558:ti,ab,kw	153
#8	pembrolizumab:ti,ab,kw OR lambrolizumab:ti,ab,kw OR Keytruda:ti,ab,kw OR MK-3475:ti,ab,kw OR SCH-900475:ti,ab,kw	1106
#9	Libtayo:ti,ab,kw OR cemiplimab-rwlc:ti,ab,kw OR REGN2810:ti,ab,kw OR cemiplimab:ti,ab,kw	37
#10	Pidilizumab:ti,ab,kw OR CT-011:ti,ab,kw OR CT 011:ti,ab,kw OR AMP-514:ti,ab,kw OR MEDI0680:ti,ab,kw OR PDR-001:ti,ab,kw OR BCD-100:ti,ab,kw OR JNJ-63723283:ti,ab,kw	1270
#11	camrelizumab:ti,ab,kw OR SHR-1210:ti,ab,kw OR toripalimab:ti,ab,kw OR JS001:ti,ab,kw OR sintilimab:ti,ab,kw OR IBI308:ti,ab,kw OR BGB-A317:ti,ab,kw OR Tislelizumab:ti,ab,kw OR GB226:ti,ab,kw	96
#12	Durvalumab:ti,ab,kw OR MEDI4736:ti,ab,kw OR MEDI-4736:ti,ab,kw OR Imfinzi:ti,ab,kw	385
#13	atezolizumab:ti,ab,kw OR anti-PDL1:ti,ab,kw OR immunoglobulin G1, anti-(human CD antigen CD274) (human monoclonal MDPL3280a heavy chain), disulfide with human monoclonal MDPL3280a kappa-chain, dimer:ti,ab,kw OR MPDL3280A:ti,ab,kw OR tecentriq:ti,ab,kw OR RG7446:ti,ab,kw OR RG-7446:ti,ab,kw	778
#14	avelumab:ti,ab,kw OR MSB0010718C:ti,ab,kw OR Bavencio:ti,ab,kw	153
#15	BMS-936559:ti,ab,kw OR MDX1105:ti,ab,kw OR M7824:ti,ab,kw OR KN035:ti,ab,kw OR CS1001:ti,ab,kw OR ZKAB001:ti,ab,kw	23
#16	tremelimumab:ti,ab,kw OR ticilimumab:ti,ab,kw OR CP 675:ti,ab,kw OR CP675 cpd:ti,ab,kw OR CP-675:ti,ab,kw OR CP-675,206:ti,ab,kw OR CP-675206:ti,ab,kw OR CP675206:ti,ab,kw OR CP 675206:ti,ab,kw	223
#17	MeSH descriptor: [Ipilimumab] explode all trees	108
#18	Anti-CTLA-4 MAb Ipilimumab:ti,ab,kw OR Anti CTLA 4 MAb Ipilimumab:ti,ab,kw OR Ipilimumab, Anti-CTLA-4 MAb:ti,ab,kw OR Yervoy:ti,ab,kw OR MDX 010:ti,ab,kw OR MDX010:ti,ab,kw OR MDX-010:ti,ab,kw OR MDX-CTLA-4:ti,ab,kw OR MDX CTLA 4:ti,ab,kw	106
#19	CTLA-4:ti,ab,kw OR cytotoxic T-lymphocyte-associated protein 4:ti,ab,kw OR PD-1:ti,ab,kw OR programmed death receptor 1:ti,ab,kw OR programmed death ligand1:ti,ab,kw	1874
#20	PD-L1:ti,ab,kw OR immune checkpoint inhibitor:ti,ab,kw OR Programmed Cell Death 1 Receptor antagonist:ti,ab,kw OR Programmed Cell Death 1 Receptor inhibitor:ti,ab,kw OR CTLA-4 Antigen antagonists:ti,ab,kw OR CTLA-4 Antigen inhibitors:ti,ab,kw	1871
#21	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20	5485
#22	#5 AND #21	Final search 4015

http://dx.doi.org/10.21037/tcr-20-1800

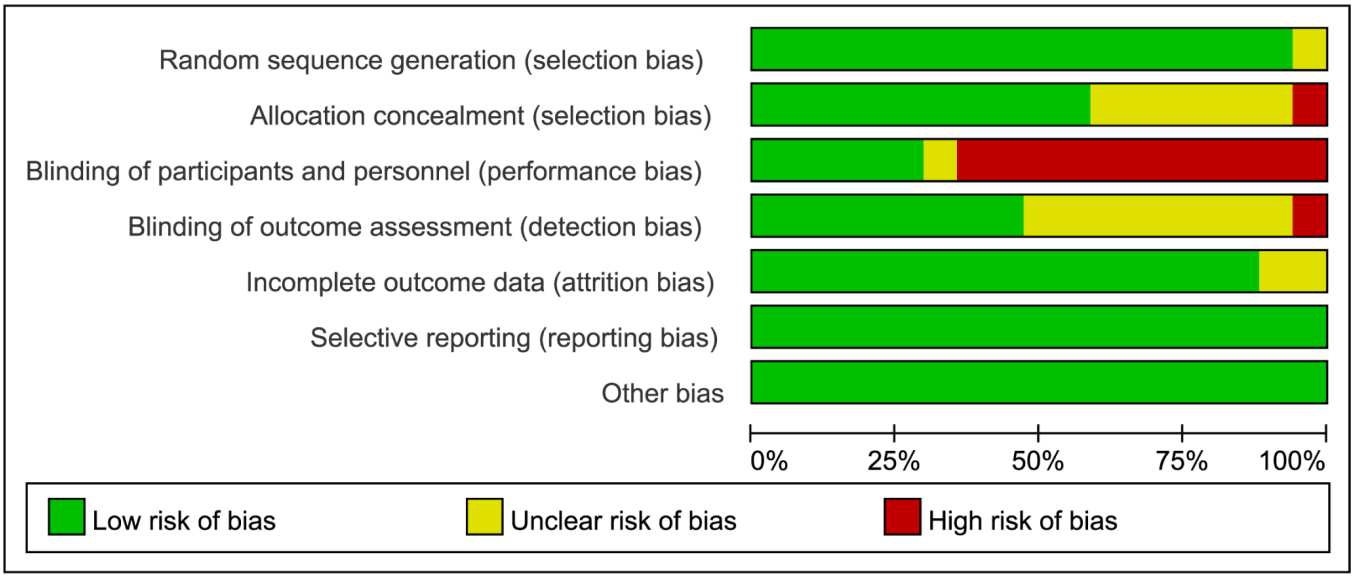

Figure S1 Risk of bias graph: Review authors' judgments about each risk of bias item presented as percentages across all included studies.

http://dx.doi.org/10.21037/tcr-20-1800

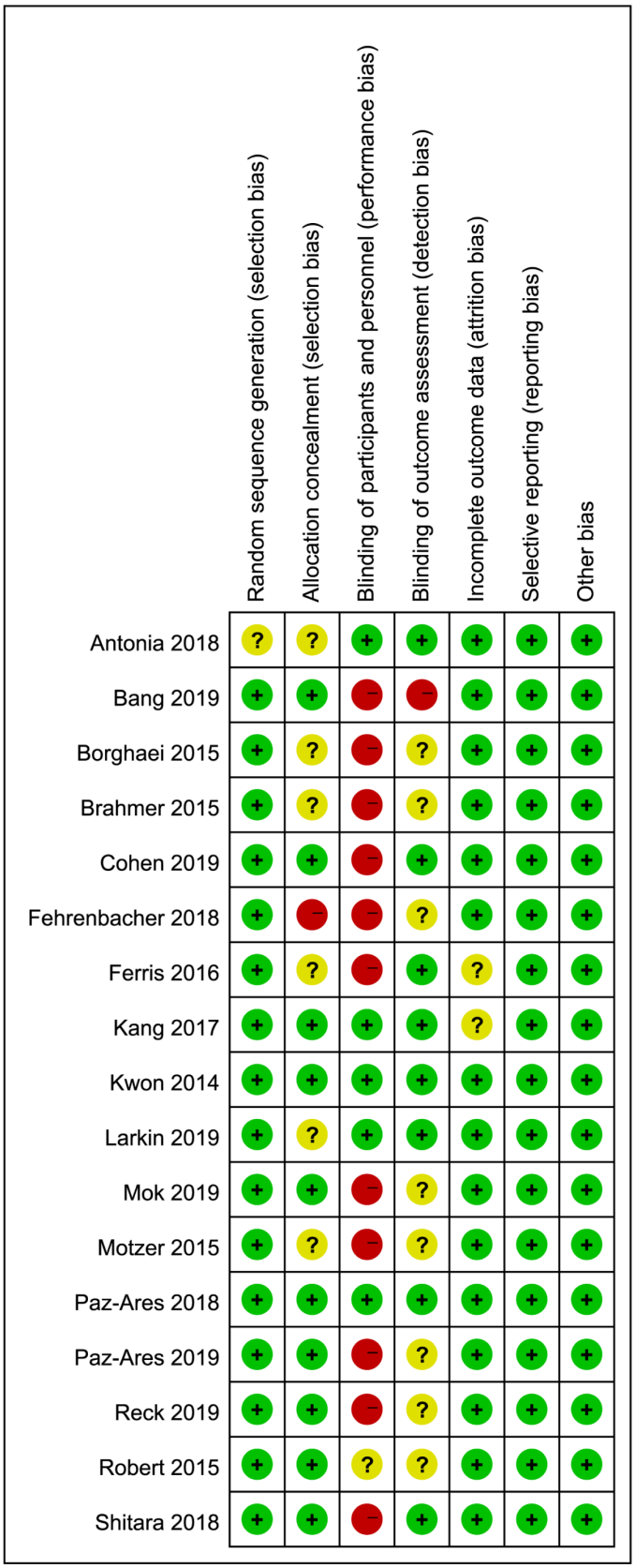

Figure S2 Risk of bias summary: Review authors' judgments about each risk of bias item for each included study.

http://dx.doi.org/10.21037/tcr-20-1800

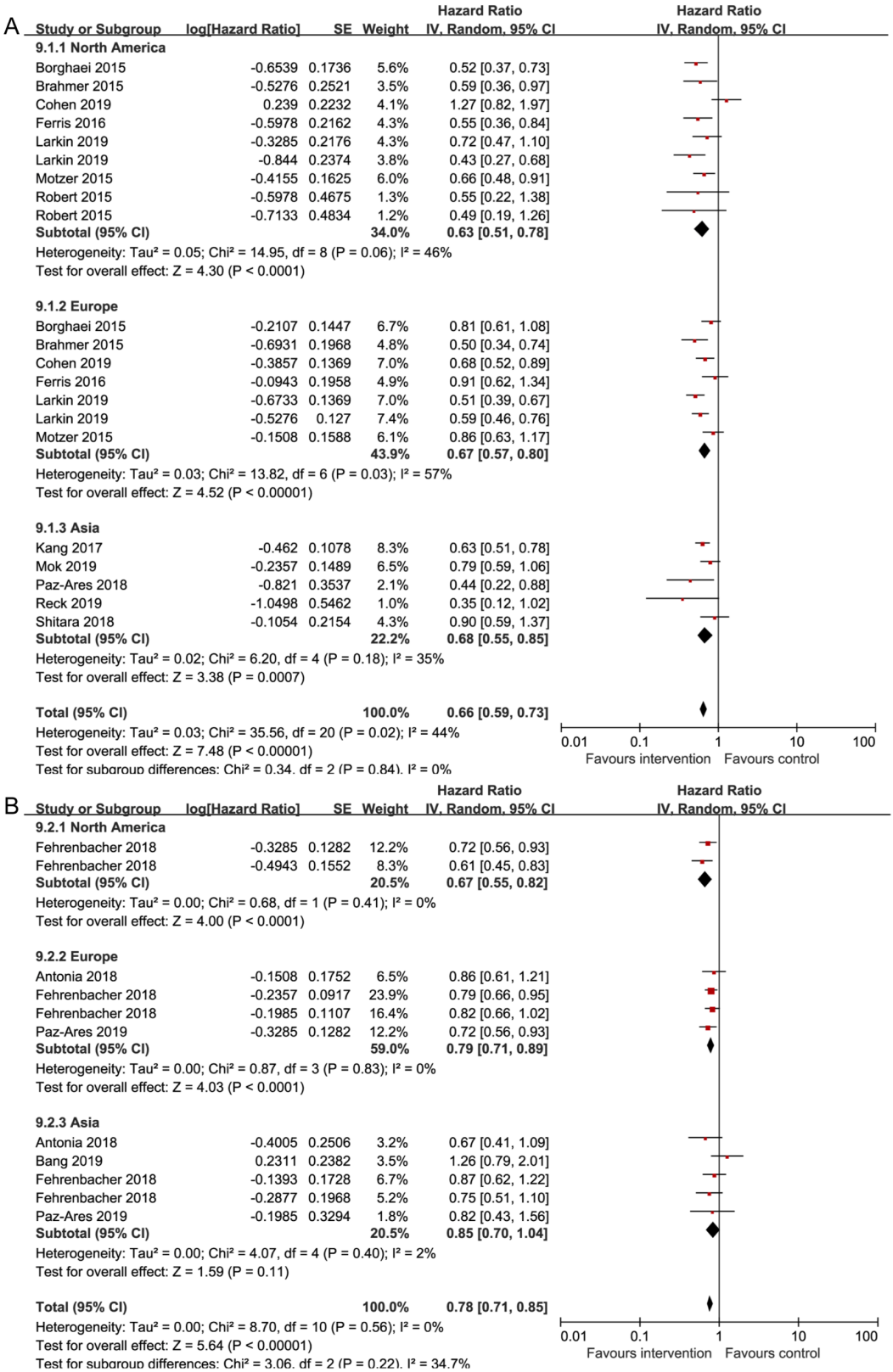

Figure S3 Pooled hazard ratios and 95% CI for overall survival in patients treated with anti-PD-1 inhibitors (A) or anti-PD-L1 inhibitors (B) according to class of ICI.

http://dx.doi.org/10.21037/tcr-20-1800

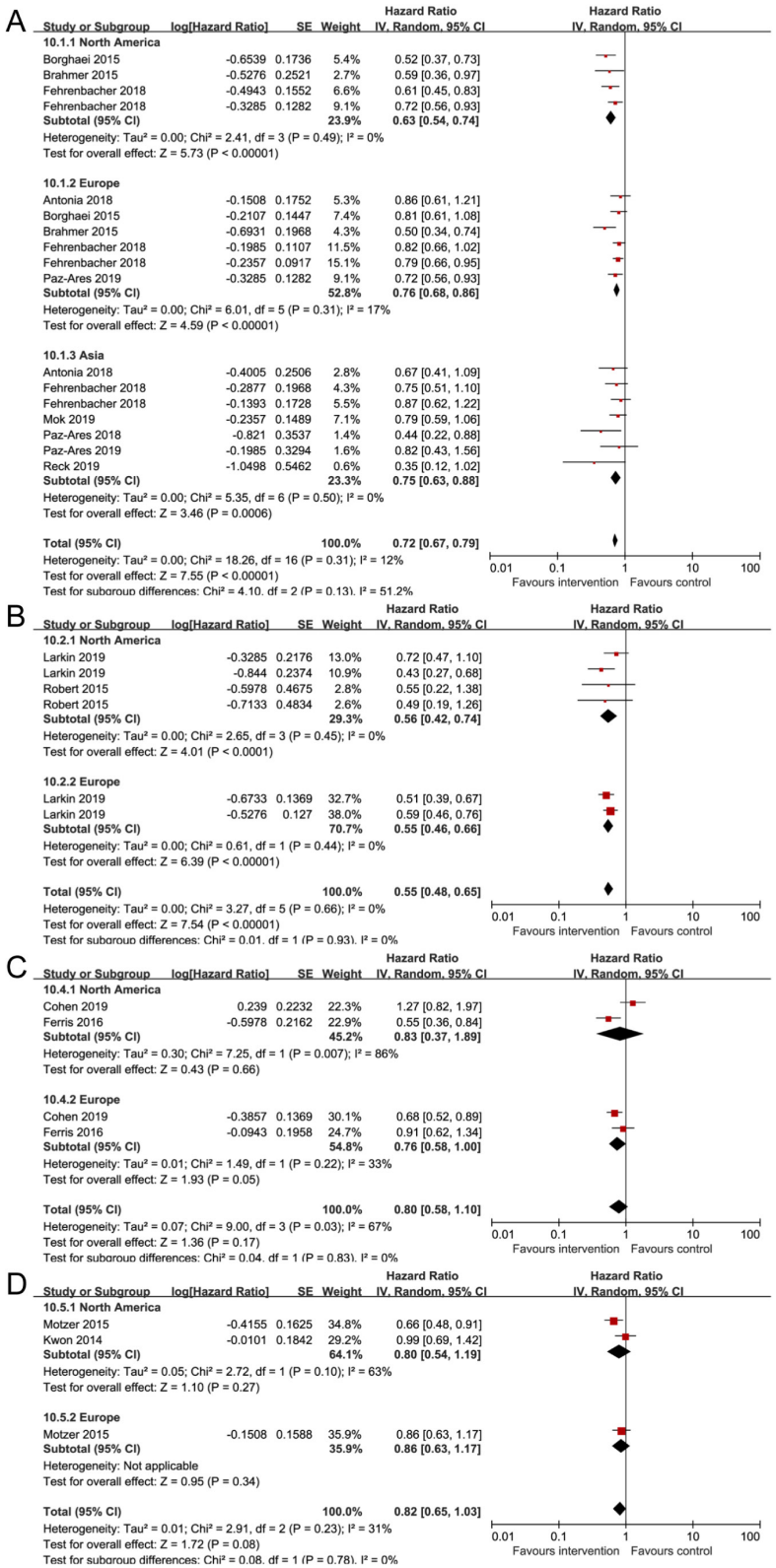

Figure S4 Pooled hazard ratios and 95% CI for overall survival in lung cancer (A), melanoma (B), head and neck cancer (C), and other cancers (D) according to cancer type.

http://dx.doi.org/10.21037/tcr-20-1800

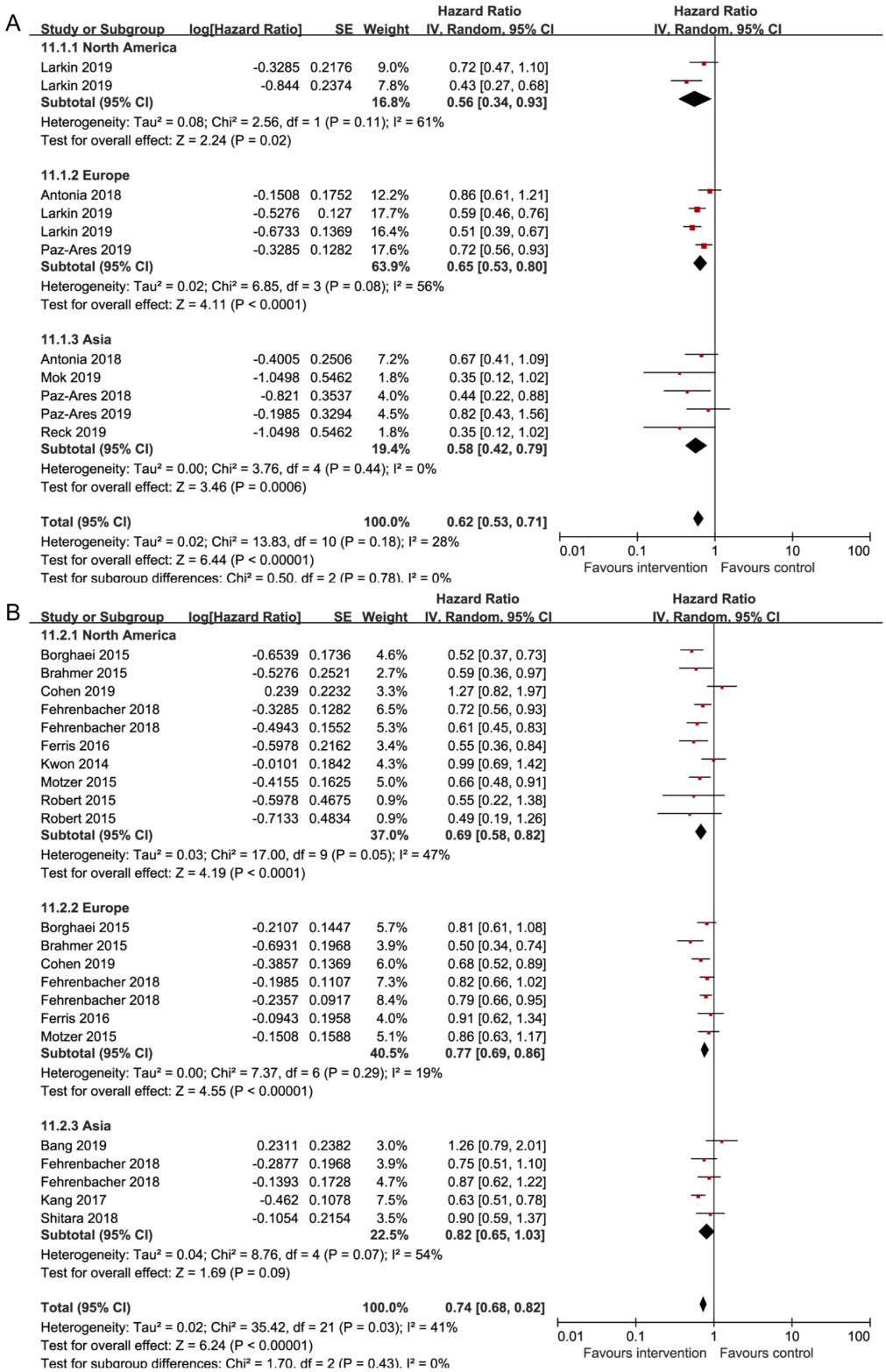

Figure S5 Pooled hazard ratios and 95% CI for overall survival in first-line (A) or subsequent line (B) according to the setting line of ICI treatment.

http://dx.doi.org/10.21037/tcr-20-1800

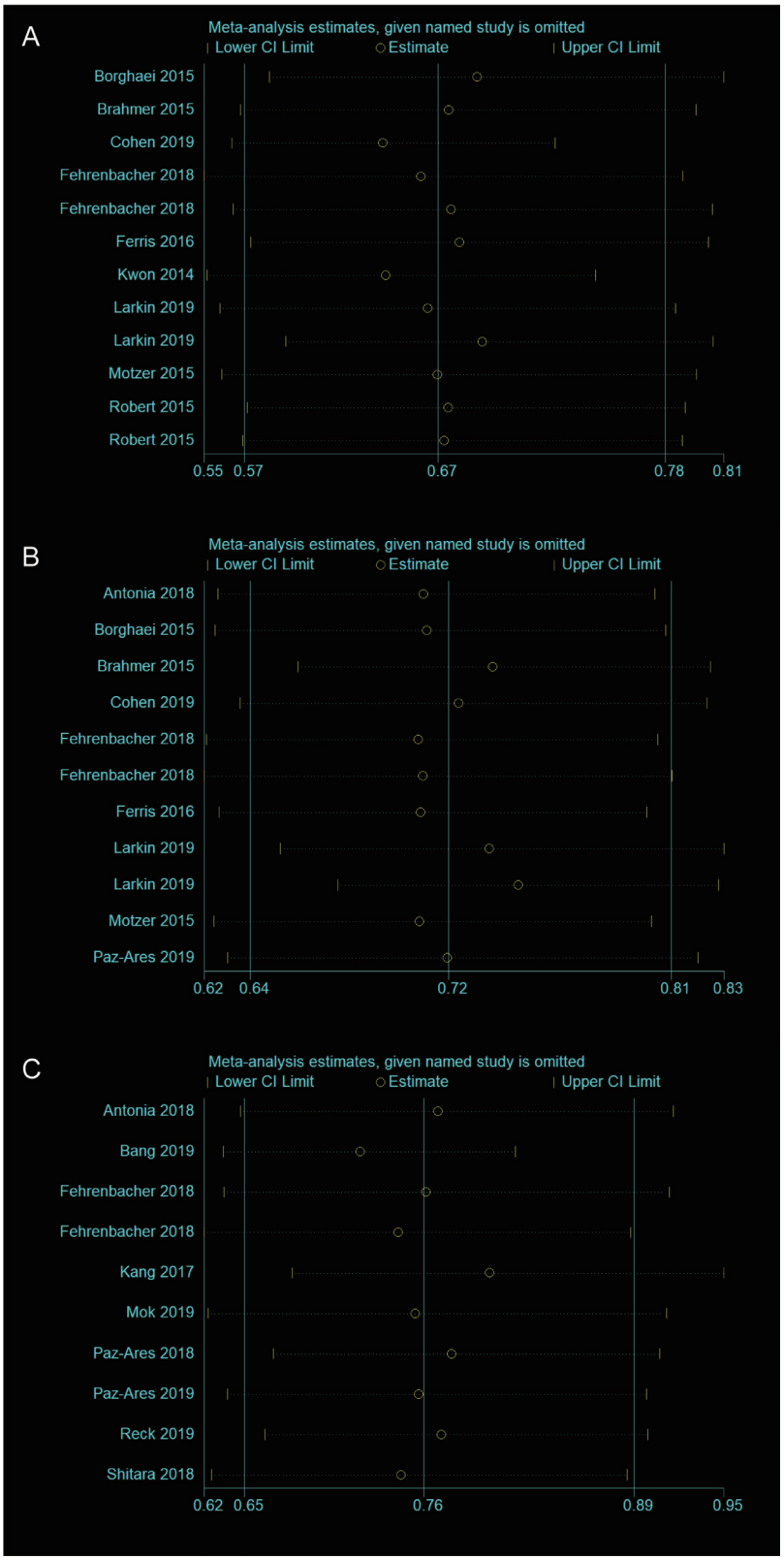

Figure S6 Sensitivity analysis from North American, European, and Asian arms: Sensitivity analysis of overall survival from North American (A), European(B), and Asian (C) arms in included RCTs to determine the robustness of findings in regards to different aspects of trial methodology.

http://dx.doi.org/10.21037/tcr-20-1800