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Systematic Review and Meta-Analysis of PD-1 and CTLA-4 Bispecific Antibody in the Treatment of Gastric Cancer

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Abstract

Background: When treating esophageal or Gastric/Gastroesophageal Junction (G/GEJ) cancer, the PD-1/CTLA-4 dual blockade consistently showed a greater response rate compared to PD-1 monotherapy but increased toxicity.

Objective: The aim of this study is to evaluate the effectiveness and safety of PD-1/CTLA-4 therapy in patients with esophageal or G/GEJ cancer.

Method: An update of a Cochrane systematic review, and network meta-analysis comparing randomized trials evaluating Pembrolizumab, Ipilimumab and Nivolumab was performed. A database search from PubMed, Google Scholar, Medline, and Web of Science and Cochrane Library for randomized and non-randomized control trials involving treatment with PD-1 and CTLA-4 published from May 3rd, 2016 to March 23rd, 2022 was retrieved from original data. A total of 15 studies investigating outcomes such as Overall Survival (OS), Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), Objective Response Rate (ORR), Progression Free Survival (PFS), Disease Control Rate (DCR), Duration of Response (DOR) and Treatment Related Adverse Effect (TRAE) were analyzed. For PD-1 versus control, meta-analyses were performed using Rev-Man 5.3 on six studies.

Result: The final 15 studies with total number of 2,971 patients were included. Out of the 15 studies, 6 was included in the meta-analysis. The combination therapy of CTLA-4 and PD-1 resulted in improved OS (59%), CR (4%), PR (22%), SD (26%), ORR (36%), and PFS (47%). Results of the meta-analysis between PD-1 and control confirmed that the control group which is made up different chemotherapy regimens was more beneficial than PD-1 monotherapy in terms of OS (Heterogeneity: Tau^2=0.10; Chi^2=9.23, df=4 (P=0.06); I^2=57%), PFS (Heterogeneity: Chi^2=16.13, df=3 (P=0.001); I^2=81%) and DCR (Heterogeneity: Tau^2=0.03; Chi^2=22.00, df=1 (P<0.00001); I^2=95) The incidence of grade 3/4 TRAE increased with the combination therapy but there was no significant difference between chemotherapy and PD-1 monotherapy.

Conclusion: Combination therapy of CTLA-4 and PD-1 in this current study was superior to CTLA-4 or PD-1 monotherapy in terms of OS, CR, PR, SD, ORR and PFS, but the side effects of combination therapy were higher than monotherapy. Also, PD-1 monotherapy is not as effective when used compared to chemotherapy regimens. Considering the response variations to this combination therapy usage, more individualized treatments should be introduced in clinical practice.

Keywords: Gastric cancer; Gastro-esophageal junction cancer; PD-1/CTLA-4 inhibitors; Immunotherapy; Checkpoint inhibitors

Abbreviations

GEJ: Gastroesophageal Junction; GC: Gastric Cancer; CTLA-4: Cytotoxic T Lymphocyte-Associated Antigen; RCT: Randomized Control Trial; PD-1: Program Death-1; PD-L1: Program Death Ligand-1; OS: Overall Survival; CR: Complete Response; PR: Partial Response; SD: Stable

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Disease; PD: Progressive Disease; ORR: Objective Response Rate; PFS: Progression Free Survival; DCR: Disease Control Rate; DOR: Duration of Response; TRAE: Treatment related Adverse Effect; OR: Odd Ratio

Introduction

Gastric cancer is the third most frequent cancer worldwide and the fifth most common cancer overall, with an anticipated 1,000,000 new diagnoses and 783,000 patient deaths in 2018 [1]. Eastern Asia is considered to be a high-risk region and is where gastric cancer is most common. Lung cancer has been ranked second in terms of incidence and mortality [2].

The incidence of gastric cancer has decreased recently due to early detection and substantial local excision after surgery [3]. However, a lot of people continue to have advanced stages of disease. First-line chemotherapy, such as platinum and fluoropyrimidine, helps to increase overall survival by about 6.7 months [4].

Currently, using immunotherapy has significant clinical advantages, with both potential restrictions and encouraging results. Immune effector generations, their safety, and their application to numerous patients are typical obstacles. Regarding this, it's critical to understand how cancer cells behave and interact with the cells in their tumor microenvironment, including lymphocytes, parenchymal cells, and inflammatory cells. It's also important to understand the role these components play in tumor survival, growth, and metastasis [5,6]. In tumor microenvironment, cancer cells discharge cytokines that transform the microenvironment contexture, as non-cancer cells emit cytokines and growth factors that affect both tumor growth and behavior, such as invasion and metastasis [6]. In this dynamic microenvironment, cells interact, which leads to tumor progression.

Checkpoint inhibitors such as CTLA-4 and PD-1 are T-cell inhibitory receptors that play an important role in immune inhibition. CTLA-4 competes with CD28 on T-cells for receptors CD80 and CD86 on APCs interfering with T-cell activation down regulating the immune response due to its higher affinity [7-9]. PD-1 is expressed on activated T-cells, NK cells, and B-cells, while the transmembrane protein PD-L1 is expressed on several immune cells and tumor cells in the presence of inflammatory mediators. PD-1/PD-L1 axis is dynamically active in peripheral tissue to control inflammatory reactions [10], while, in malignancy, PD-1 on activated T-cells binds to PD-L1 on tumors which leads to tumor escape and following tumor progression [11,12]. PD-1/PD-L1 overexpression has been seen in numerous malignancies including GC, and restoration of antitumor T-cell activity by targeting checkpoint molecules has been revealed in several studies [13].

At present, immunotherapy has shown a certain effect in the treatment of gastric cancer. However, the number of large-scale clinical trials is currently small, and the toxic and side effects caused by immune checkpoint inhibitor by promoting T cell activation and autoimmune reactions are still debatable. We performed a meta-analysis to analyze the efficacy and safety of PD-1 *vs.* chemotherapy and to review CTLA-4 combined with PD-1 and monotherapy in patients with gastric cancer.

CTLA-4/PD-1 pathway inhibition

CTLA-4 inhibition allows activation and proliferation of more T-cell clones, and lessens T-reg-mediated immunosuppression. T-cell activation is a complicated process that needs >1 stimulatory signal. Toll Cell Receptor (TCR) attachment to main histocompatibility complex offers specificity to T-cell activation; nonetheless more co-stimulatory signals are necessary.

PD-1 pathway inhibition reinstates the activity of antitumor T cells that have become quiescent. PD-1 is an associate of the B7/CD28 family of co-stimulatory receptors. It regulates T-cell activation through binding to its ligands, programmed death ligand 1 and programmed death ligand 2. Comparable to CTLA-4 signaling, PD-1 binding inhibits T-cell proliferation, and interferon-γ, tumor necrosis factor-α, and IL-2 production, and diminishes T-cell survival [14]. If a T cell experiences coincident TCR and PD-1 binding, PD-1-generated signals stop phosphorylation of key TCR signaling intermediates, which ceases early TCR signaling and lowers activation of T cells. PD-1 expression is a hallmark of "exhausted" T cells that have experienced high levels of stimulation or reduced CD4+ T-cell help [15,16]. This state of exhaustion, which happens during chronic infections and cancer, is characterized by T-cell dysfunction, resulting in suboptimal control of infections and tumors [17] (Figure 1 and Table 1).

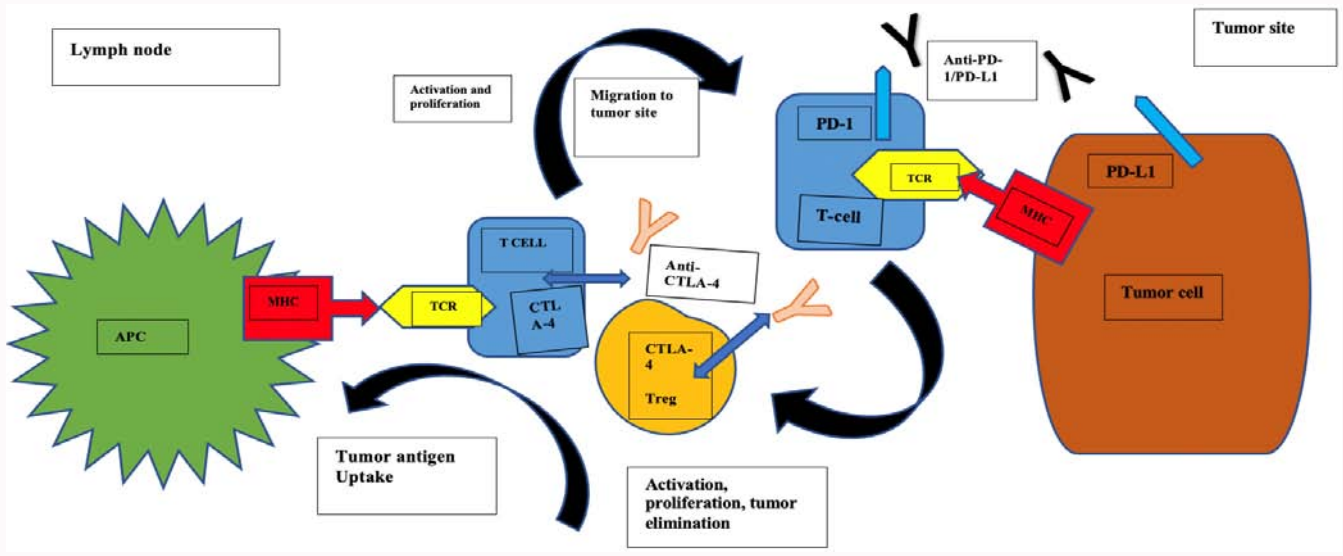

Figure 1: Schematic presentation of CTLA-4 and PD-1 pathway inhibition.

Table 1: Similarities and difference between CTLA-4 and PD-1.

Similarities	Difference
Both reduce cell proliferation, glucose metabolism, cytokine production, and survival.	CTLA-4 affect Treg functioning but the role of PD-1 on Tregs is unclear.
They both associated with B7 receptor family member.	CTLA-4 limits T-cells response early in an immune response, primarily in lymphoid tissues; PD-1 limits T-cell response later in an immune response, primarily peripheral tissues.
The level of expression is affected by the strength and duration of TCR signaling.	PD-1 engagement interferes with more T-cell signaling pathways than does CTLA-4 engagement.
They regulate an overlapping set of intracellular T-cell signaling proteins.	CTLA-4 ligands expressed by professional antigen-presenting cells. However, PD-1 ligands expressed by antigen-presenting cells and other immune cells.
Both are expressed by activated T-cells.	CTLA-4 expressed by T-cells while PD-1 is expressed by T-cells and other immune cells.

Materials and Method

Literature search strategy

The work has been described in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Guidelines. According to the PRISMA statement, a protocol includes objectives of the study, literature searching strategies, inclusion and exclusion criteria, outcomes measurements, and methods of statistical analysis. A systematic literature search was conducted using PubMed, Google scholar, Cochrane Library, EMBASE, Web of Science database. A data range for the search was set from May 3rd, 2016 to March 23rd, 2022. Searches were performed using a combination of MeSH (Medical Subject Headings) terms and key terms; Gastric cancer", gastro-esophageal junction cancer", Pembrolizumab, ipilimumab and Nivolumab", Immunotherapy" and Checkpoint Inhibitors". All articles collected by the initial search were screened by title and abstract to determine their relevance to the study questions. The bibliographies of relevant articles were cross referenced with the list of journals from the initial search and appropriate articles were subsequently added.

Data extraction

Data were extracted from the selected literature. Initially, information about the first author, publication year, type of trial, clinical trial number, tumor type study design clinical trial phase and interventions was obtained as shown is Table 2. Outcomes such OS, CR, PR, SD, PD, ORR, PFS, DCR, DOR and TRAE were subsequently collected. The quality of the RCTs was evaluated using a bias risk assessment tool developed by the Cochrane Collaboration [18].

Characteristics of included studies

A total of 1,200 studies were retrieved through a database search. 250 articles were excluded as duplicates. The 950 remaining were screened after reading the titles and abstracts. After excluding articles that did not meet the requirements, the full text articles of the remaining 155 articles were then reviewed, and finally 15 studies were included. Of the 15 included studies, 6 were included in the meta-analysis as shown in Figure 2. The approximate number of patients recorded was 2,971 due to the fact that two studies didn't record the number of patients. Of these 15 studies, five were phase III, three were phase II, 1 is phase II/III and the rest were unrecordable. Among the selected studies, seven studies were randomized control trials and eight non-randomized control trials as shown is Table 2. Studies reported outcomes such as OS, CR, PR, SD, PD, ORR, PFS, DCR, DOR and TRAE (Table 3).

Statistical analysis

Statistical analysis was accomplished using the Review Manager (RevMan) software, version 5.4 presented by the Cochrane collaboration. Dichotomous variables were pooled using the Odds Ratio (OR) with a 95% CI. Random effect and fixed effect models were computed under statistical methods of Mantel-Haenszel (for OR or RR). Heterogeneity among studies was evaluated using the inconsistency statistic (I). If I was <50%, the eligible studies were considered to be homogenous; hence, the fixed effect model was used. In contrast, if I was >50%, the pooled results were said to be significant, heterogeneous, and the random effect model was used instead.

Inclusion criteria:

1. Treatment with PD-1/CTLA-4 and control (chemotherapy regimens and any best supportive care)
2. The control group was selected whose definition was an SOC treatment recommended by the National Comprehensive Cancer Network (NCCN) guidelines [34] or a placebo.
3. Only Published English articles
4. Histologically confirmed gastric or esophagogastric junction adenocarcinoma.
5. Randomized control trials papers were used.
6. Unresectable advanced, recurrent, or metastatic disease.
7. No prior systemic anticancer treatment given as primary therapy
8. Phase I, II and III trials reporting at least one of the following clinical outcomes.
9. ECOG performance status of 0-1.
10. At least one measurable lesion by computed tomography or magnetic resonance imaging per RECIST 1.1 criteria.

Exclusion criteria:

1. RCTs that were based on overlapping patients;
2. RCTs with ambiguous clinical outcomes.
3. Case Report
4. Single-arm trials
5. Observational studies
6. Animal studies

Definition of outcomes

The primary endpoint was overall survival. Secondary efficacy endpoints were progression-free survival, defined as the time from enrolment to the first documented disease progression or death from any cause, whichever occurred first objective response (proportion of patients with confirmed complete response or partial response), disease control (proportion of patients with confirmed complete response, partial response, or stable disease), duration of response,

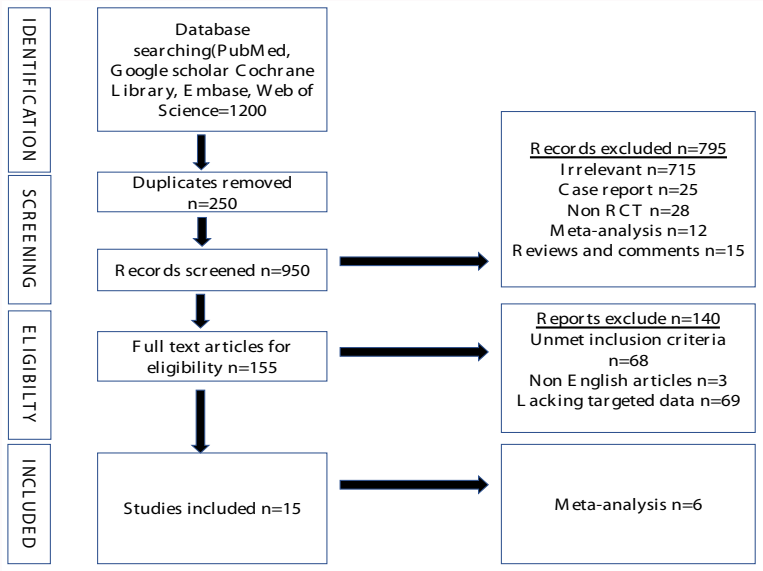

Figure 2: Flow diagram.

Table 2: Patient characteristics.

Authors name	Publication year	Type of Trial	Clinical Trials Number	Tumor Type	Study design	Phase	PD-1+CTLA-4	PD-1/Placebo	CTLA-4/ Placebo	CTLA-4 Only	PD-1 only
Kang et al. [19]	2017	Attraction-2	NCT02267343	G/GEJ	RCT	III	-	NIVO3 mg/kg / placebo n=268/131	-	-	-
Rotte et al. [20]	2019	KEYNOTE-012	NCT01928394	G/GEJ	nRCT	I/II	Nivo1 mg/kg +IPI3 mg/kg	-	-	IPI3mg/kg	Nivo1 mg/kg
Muro et al. [21]	2016	KEYNOTE-012	NCT01848834	G/GEJ	nRCT	IB	-	-	-	-	Pemb10 mg/kg n=20
Kim et al. [22]	2017	KEYNOTE-012	NCT02589496	GEJ	nRCT	II	-	-	-	-	Pemb mg/kg n=61
Bang et al. [23]	2017	-	NCT01585987	G/GEJ	RCT	II	-	-	IP10 mg/kg /placebo n=57/57	-	-
Janjigian et al. [24]	2018	CheckMate-032	NCT02743494	G/GEJ	nRCT	I/II	NIVO1 mg/kg +IP13 mg/kg n=49	-	-	-	NIVO3 mg/kg n=59
Shitara et al. [25]	2022	Checkmate 649	-	G/GEJ	nRCT	III	NIVO1 mg/kg +IPI3 mg/kg n=196	-	-	-	-
Kawakami et al. [26]	2021	KEYNOTE-062	JapicCTI-205400	G/GEJ	RCT	II/III	NIVO240 mg/kg +IPI1 mg/kg n=28	PEMB mg/kg / PLACEBO n=14/19	-	-	-
Fuchs et al. [27]	2018	KEYNOTE-059	NCT02335411	G/GEJ	nRCT	II	-	-	-	-	PEMB200mg n=259
Fuchs et al. [28]	2021	KEYNOTE-061	NCT02370498	G/GEJ	RCT	III	-	PEMB mg/kg / placebo n=196/199	-	-	-
Wainberg et al. [29]	2021	KEYNOTE-061	NCT02370498	G/GEJ	RCT	-	-	PEMB/ mg/kg placebo n=53/55	-	-	-
Fashoyin-Aje et al. [30]	2018	KEYNOTE-059	NCT02335411	G/GEJ	nRCT	-	-	-	-	-	PEMB mg/kg n=259
Chao et al. [31]	2021	KEYNOTE-061	NCT02370498	G/GEJ	RCT	-	-	PEMB mg/kg / Placebo n=296/296	-	-	PEMB n=259
Yee et al. [32]	2018	CheckMate 032	NCT01928394	G/GEJ	nRCT	I/II	NIVO1 mg/kg +IPI3 mg/kg	-	-	-	NIVO3 mg/kg
Chen et al. [33]	2019	ATTRACTION-2	NCT02267343	G/GEJ	RCT	III	-	NIVO3mg/kg/ Placebo n=268/131	-	-	-

time to response, best overall response, and the maximum percentage change from baseline in the sum of diameters of target lesions. Safety endpoints included treatment-related adverse events (Table 3).

Results

PD-1+CTLA-4 and CTLA-4/Control

Combination therapy with Nivolumab plus ipilimumab was reported in five studies with total number of 273 patient [20,24-26,32], unfortunately two studies were not able to provide the number of patients involved. Overall survival was confirmed in 59% of the population (complete response) was achieved in 4%, 22% of patients achieved confirmed Partial Response (PR), and 26% of had stable disease, resulting in an ORR of 36%, PFS of 47% and a Disease Control Rate (DCR) of 41%. Duration of response was seen in 11%, 47% in PD and 35% experienced at least one grade 3/4 TRAE. However only one studies with population of 114 patients reported the use of CTLA-4

Table 3: Tumor response results.

Author	Intervention	OS	CR	PR	SD	PD	ORR	PFS	DCR	DOR	TRAE
Kang et al. [19]	Nivo3 /Placebo 268/131	123 (46.1%)/45 (34.7%)	0/0	30 (11%)/0	78 (29%)/33 (25%)	124 (46%)/79 (60%)	30 (11.2%)/0	20 (7.6%)/1 (1.5%)	108 (48%)/33 (25%)	-	141 (33%)/43 (27%)
Rotte et al. [20]	Nivo1+IPI3	35%	Nil	Nil	Nil	Nil	24%	Nil	Nil	Nil	Nil
	Nivo1 IPI3	39%					12%	17% 8%			
Muro et al. [21]	Pemb10	11.4 (3.1%)	0	7 (37%)	2 (11%)	10 (30%)	7 (37%)	Nil	Nil	40 (30%)	26 (67%)
Kim et al. [22]	Pemb 61	Nil	3 (4.9%)	12 (19.7%)	20 (32.8%)	Nil	24.60%	Nil	57.40%	Nil	Nil
Bang et al. [23]	IP10/placebo 57/57	Nil	0/0	1 (1.8%)/4 (7.0%)	18 (31.6%)/23 (40.4%)	23 (40.4%)/11 (19.3%)	1 (1.8%)/4 (7.0%)	18.3%/38.5%	Nil	1 (1.8%)/4 (7.0%)	14 (71.9%/13 (22.8%)
Janjigian et al. [24]	Nivo1+IP13(49)	35%	1 (2%)	11 (22%)	8 (16)	23 (47%)	12(24%)	17%	20 (41%)	7.90%	47%
	NIVO3(59)	39%	1 (2%)	6 (10%)	12 (20)	34 (58%)	7(12%)	8%	19 (32%)	7.10%	17%
Shitara et al. [25]	Nivo1+IPI3 196	47%	10 (5%)	42 (21%)	52 (27%)	63 (32%)	52 (27%)	Nil	Nil	13.20%	175 (22%)
Kawakami et al. [26]	NIVO240+IPI1	83%	Nil	Nil	Nil	Nil	69%	77%	Nil	Nil	Nil
	Pemb/PLACEBO 14/19	11 (79%)/8 (47%)					57.1%/36.8%	6 (43%)/5 (28%)			
Fuchs et al. [27]	Pemb 259	23.40%	6 (2.3%)	24 (9.3%)	42 (16.2%)	145 (56.0%)	30 (11.6%)	14.10%	Nil	Nil	46 (17.8%)
Fuchs et al. [28]	Pemb/placebo 196/199	39 (19.9%)/16 (8.5%)	9 (4.6%)/5 (2.5%)	23 (11.7%)/22 (11.1%)	44 (22.4%)/90 (45.2%)	95 (48.5%)/42 (23.1%)	32 (16.3%)/27 (13.6%)	Nil	Nil	37 (19.1%)/10 (5.2%)	44 (15%) of 294/97 (35.1%) of 276
Wainberg et al. [29]	Pemb/placebo 53/55	Nil	5 (9%) /1(2%)	8 (15%)/4 (7%)	12 (23%)/28 (51%)	23 (43%)/11 (20%)	13 (25%)/5 (9%)	Nil	Nil	Nil	Nil
Fashoyin-Aje et al. [30]	Pemb 259	Nil	3(2.0%)	20 (13.5%)	Nil	Nil	30 (11.6%)	Nil	Nil	14 (61%)	Nil
Chao et al. [31]	Pemb/Placebo 296/296	100 (34%)/82 (28%)	2.4%/2.4%	8.8%/10.1%	22.6%/46.3%	51.7%/22.3%	11.1%/12.5%	4 (1.5%)/12 (4.1%)	Nil	47 (16.1%)/16 (5.5%)	Nil
	Pemb 259	25%	3.50%	8.10%	16.20%	56.00%	11.60%	2.00%			
Yee et al. [32]	Nivo1+IPI3	6.90%	Nil	Nil	Nil	Nil	24%	Nil	Nil	Nil	Nil
	NIVO3	6.20%					12%				
Chen et al. [33]	Nivo/placebo 268/131	73 (27.3%)/15 (11.6%)	3 (1.1%)/0	29 (10.8%)/0	76 (28.4%)/33 (25.2%)	124 (46.3%)/79 (60.3%)	32 (11.9%)/0	24 (9.3%)/1 (1.5%)	108 (40.3%)/33 (25.2%)	Nil	142 (43.0%)/43 (26.7%)

vs. control [23]. PR, SD, ORR, PFS, DOR and TRAE were collected as outcomes with 1.81%/7.0%, 31.6%/40.4%, 1.8%/7.0%, 18.3%/38.5%, 1.8%/7.0% and 71.9%/22.8% respectively.

PD-1 and CTLA-4 monotherapy

Eight studies were retrieved for PD-1 treatment which were either nivolumab or pembrolizumab [20-22,24,27,30-32]. There were 917 patients involve in the treatment, although 2 studies could not provide the number of patients. The results after the treatment collected were OS, CR, PR, SD, PD, ORR, PFS, DCR, DOR and TRAE presenting with 22%, 3%, 16.3%, 19%, 50%, 17%, 10.3%, 45%, 33% and 34% respectively. Only one study was recorded for CTLA-4 (ipilimumab) with OS (39%) and PFS (8%) as outcome after treatment [20].

Meta-analysis results of PD-1 *vs.* Control (Efficacy and safety outcome)

Meta-analysis Results (CR, PR, SD, PD, DOR and TRAE)

No statistically significant difference could be identified from analyzing four studies with total of 813 patient in the intervention group [28,29,31,33] and 681 patients in the control for complete response. Heterogeneity: Chi^2=2.39, df=3 (P=0.50); I^2=0%, Test for overall effect: Z=1.62 (P=0.11) (Figure 3A).

Partial response was recorded in five studies with 1081 patients in the intervention group and 812 patients in the control group [19,28,29,31,33]. There was no statistical difference between the two therapies. Heterogeneity: Chi^2=17.46, df=4 (P=0.002); I^2=77%, Test for overall effect: Z=3.36 (P=0.0008) (Figure 3B).

Five studies collected for stable disease with 1081patients in the intervention group and 812 patients in the control [19,28,29,31,33]. Results demonstrated less stable disease in the control as compared to the PD-1 Group. Heterogeneity: Chi^2=81.55, df=4 (P<0.00001); I^2=95%, Test for overall effect: Z=8.84 (P<0.00001) (Figure 3C).

Five studies retrieved for progressive disease also observed a significant difference [19,28,29,31,33], favoring the control group with 812 patients than the intervention group with 1,081 patients when used alone. Heterogeneity: Chi^2=83.49, df=4 (P<0.00001); I^2=95%, Test for overall effect: Z=5.21 (P<0.00001) (Figure 3D).

Duration of response included 492 patients in the intervention group and 495 patients in the control group. There was a significant difference where duration of response was less in the control than the PD-1 among the two studies [28,31]. Heterogeneity: Chi^2=0.36, df=1 (P=0.55); I^2=0%, Test for overall effect: Z=5.60 (P<0.00001) (Figure 3E).

Both the control and intervention group saw no difference in treatment related adverse effect. Heterogeneity: Tau^2=1.29; Chi^2=56.60, df=2 (P<0.00001); I^2=96%, Test for overall effect: Z=0.26 (P=0.79). Some of the common adverse events recorded in the three studies with total population of 1,368 patients were pruritus, diarrhea, rash, fatigue, decreased appetite, nausea, malaise, hypothyroidism, pyrexia, colitis, Anemia etc [19,28,33] (Figure 3F).

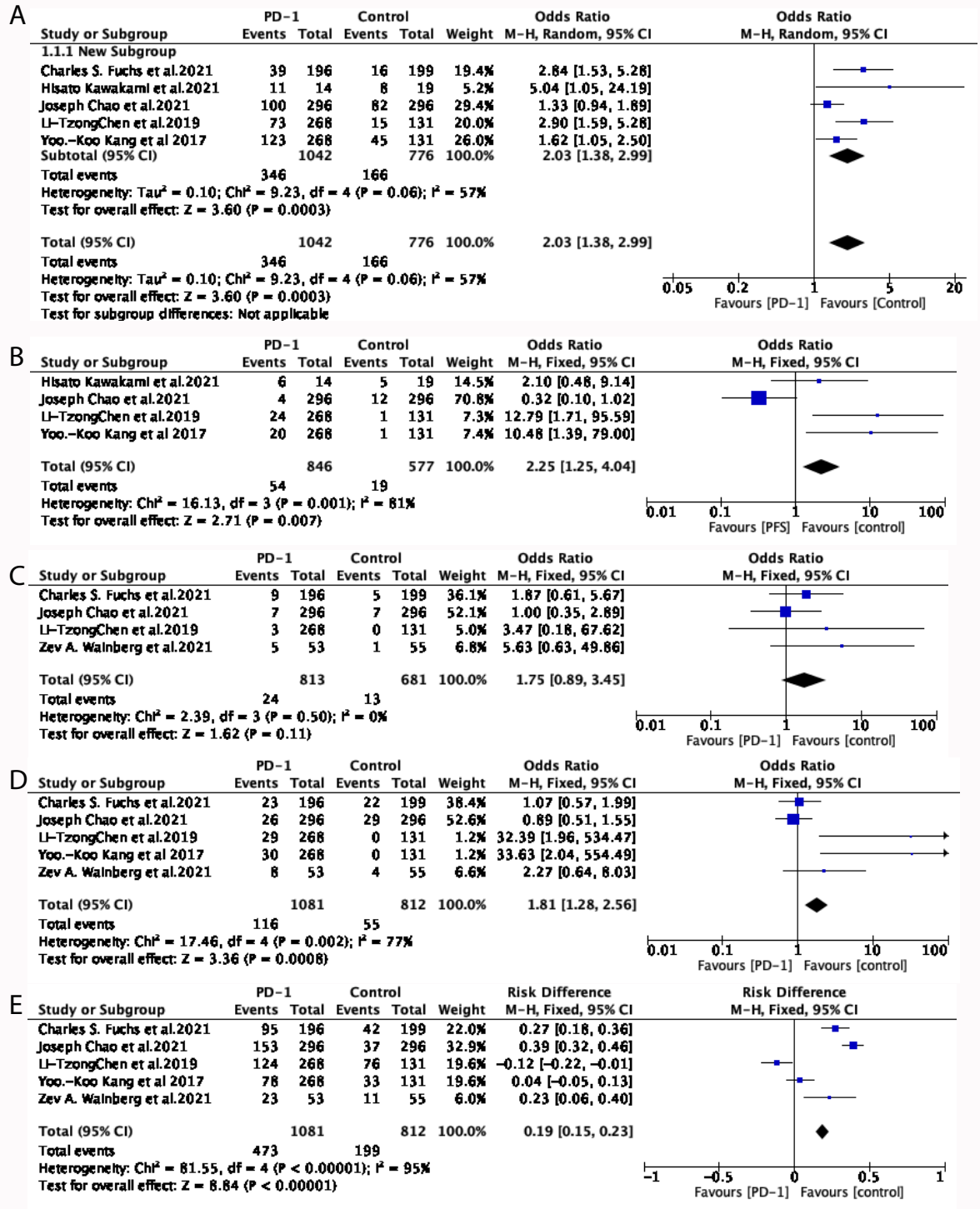

Figure 3: Forest plot of PD-1and Control therapy in esophageal or G/GEJ cancer patients;
(A) CR: Complete Response, (B) PR: Partial Response, (C) SD: Stable disease, (D) PD: Progressive disease, (G) ORR: Objective response rate, (H) DCR: Disease control rate, (E) DOR: Duration of response and (F) TRAE: Treatment related adverse event, (I) OS: Overall survival, (J) PFS: Progression free survival.

Overall Response Rate (ORR) and Disease Control Rate (DCR)

For overall response rate outcome, six studies with 1,095 patients in the intervention group and 831 in the control were included in the analysis for evaluation [19,26,28,29,31,33]. In ORR, there was no significant difference between the two-treatment groups. Heterogeneity: Tau^2=0.71; Chi^2=20.40, df=5 (P=0.001); I^2=75%. Test for overall effect: Z=1.96 (P=0.05). However, two studies collected for disease control rate observed a significant difference [19,33]. The control group saw a decrease DCR with 536 patients than the PD-1 with 262 patients. Heterogeneity: Tau^2=0.03; Chi^2=22.00, df=1 (P < 0.00001); I^2=95%, Test for overall effect: Z=2.05 (P=0.04) (Figure 3G, 3H).

Overall Survival (OS) and Progression-Free Survival (PFS)

The primary endpoint OS which is recorded by five studies [19,26,28,31,33], and they involved a total 1,818 patients (1,042

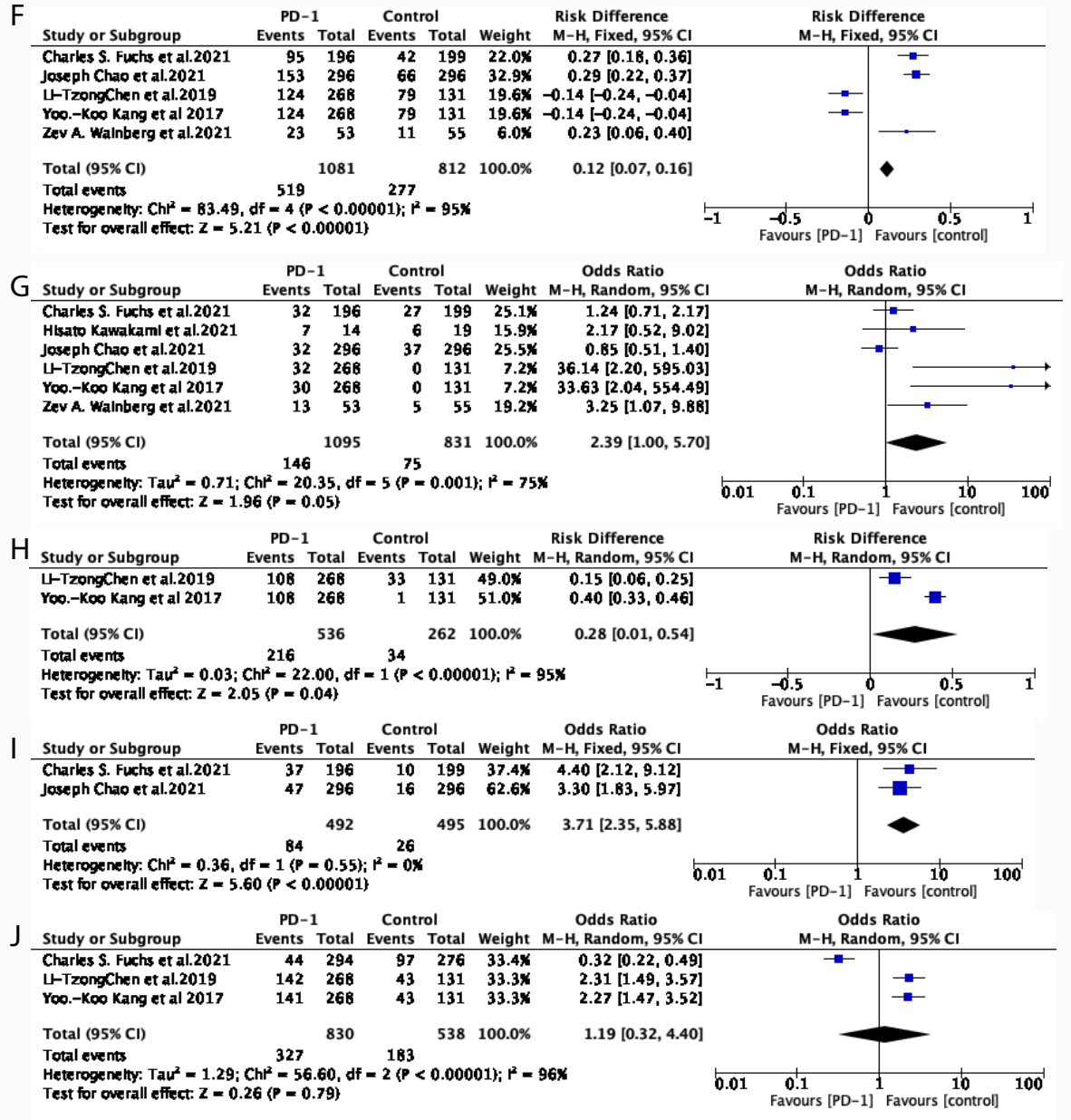

Figure 3: Forest plot of PD-1and Control therapy in esophageal or G/GEJ cancer patients;
(A) CR: Complete Response, (B) PR: Partial Response, (C) SD: Stable disease, (D) PD: Progressive disease, (G) ORR: Objective response rate, (H) DCR: Disease control rate, (E) DOR: Duration of response and (F) TRAE: Treatment related adverse event, (I) OS: Overall survival, (J) PFS: Progression free survival.

patients in the intervention group and 776 patients in the control group). The meta-analysis of the pooled data showed that the overall survival was not reached lower in the intervention group than in the group treated with control (Heterogeneity: Tau^2=0.10; Chi^2=9.23, df=4 (P=0.06); I^2=57%, Test for overall effect: Z=3.60 (P=0.0003).

Secondary endpoint PFS collected by four studies involving 846 patients in the intervention group [19,26,31,33] and 577 in the control group also showed a significant difference, favoring the control group. Heterogeneity: Chi^2=16.13, df=3 (P=0.001); I^2=81%. Test for overall effect: Z=2.71 (P=0.007) (Figure 3I, 3J).

Publication bias

The funnel plot on Overall survival and complete response between PD-1 and control is shown in Figure 4. Because all studies laid inside the 95% CI limits, no evidence of publication bias was noted. Egger test was performed to provide statistical evidence regarding funnel plot symmetry. Result still did not reveal any evidence of publication bias (Heterogeneity: Tau^2=0.10; Chi^2=9.08, df=4 (P=0.06); I^2=56% and Heterogeneity: Tau^2=0.10; Chi^2=9.08, df=4 (P=0.06); I^2=56% (Figure 5a, 5b).

Discussion

Nearly two-thirds of the patients diagnosed with GC are not able to receive the tumor resection treatment. Even with screening programs, more than 80% GC patients also reoccurred locally or distally following surgery [35]. Presently, understanding the pathophysiology of GC from biological and genomic perspective has led to the development of target-oriented treatment [35,36]. Immunotherapy has been confirmed to play a vital role in target-oriented therapy [6,37-39]. Both CTLA-4 and PD-1 antibodies are

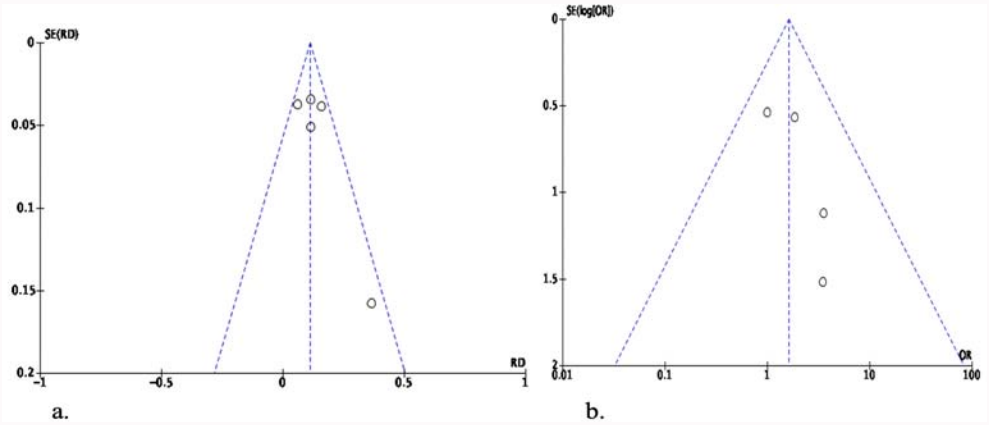

Figure 4: Funnel plot of (a) OS and (b) CR.

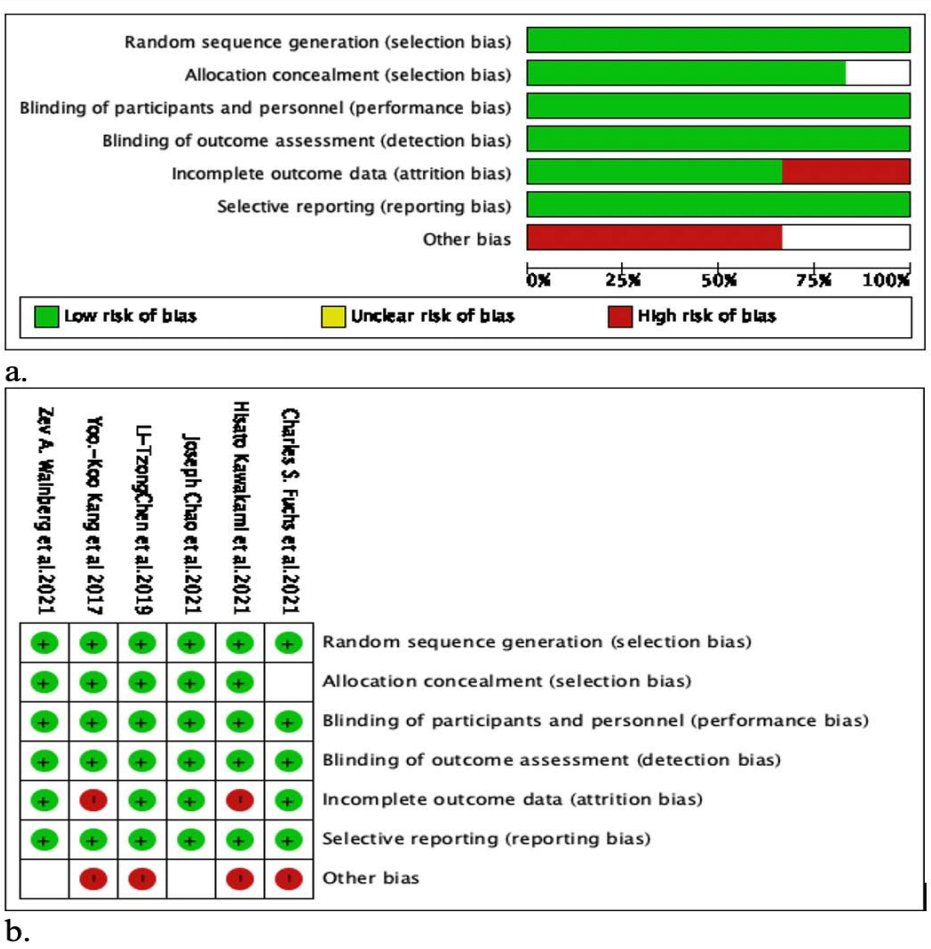

Figure 5: (a) Risk of bias graph: Review authors' judgments about each risk of bias item presented as percentages across all included studies. (b) Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

broadly applied in immunotherapy in recent years.

Several studies have previously investigated the role of anti-CTLA-4 and anti-PD-1 antibodies in the treatment of various cancers, including GC [39,40]. In the present study, we have explored the combined role of anti-CTLA-4 and anti-PD-1 antibodies in GC cells. These studies showed that combination of anti-CTLA-4 and anti-PD-1 antibodies showed a better overall survival and progression free survival (59% and 47%) than PD-1 monotherapy with 22% and 10.3% in the treatment of patient. This drug combination has consistently shown higher efficacy than nivolumab monotherapy, although a higher incidence of immune-related adverse events including colitis and hepatitis has been a major concern [26]. Others studies also established the results of long-term follow-up of ATTRACTION-2 showed that compared, nivolumab significantly prolonged the OS (5.26 *vs.* 4.14 months), with numerically higher OS (10.6% *vs.* 3.2%) and PFS rates (3.8% *vs.* 0%) at 2 years in patients

with unresectable advanced or recurrent G/GEJ cancer after two or more prior chemotherapy regimens [19]. For CTLA-4 *vs.* control, this report presents the first investigation of ipilimumab 10 mg/kg in patients with gastric or GEJ cancer and the first randomized clinical trial of an immune checkpoint inhibitor in this patient population. The TRAE grade 3/4 was 71.9% (ipilimumab) compared to 22.8% control (BSC) which was satisfactory and no other event such as gastrointestinal perforations or hepatotoxicity was noted. Ipilimumab did not improve PFS as compared to the control (18.3%/38.5%). One possible explanation for this observation is that the first-line active chemotherapy was controlling the disease in some patients in both groups at study entry, and removal of the active chemotherapy may have permitted disease progression to recommence [23]. In these studies, the side effects in the combination therapy CTLA-4 and PD-1 were higher (35%) than those in the PD-1 monotherapy group (34%), in which pruritus, diarrhea, rash, fatigue, decreased appetite, nausea, malaise, hypothyroidism, pyrexia, colitis, Anemia etc. were significantly increased. Most side effects are easier to control, and no grade 5 toxicity has been observed.

This meta-analysis included 6 randomized controlled trial studies. The results showed that the OS, PFS, PR, SD, PD, DCR and DOR of the control group were significantly better than PD-1 monotherapy. PD-1 monotherapy such as nivolumab or pembrolizumab are not as effective compared to chemotherapy. Although previous meta-analyses constantly revealed improvements in the OS rather than the PFS in esophageal or G/GEJ cancer treatment with PD-1/PD-L1 inhibitor [41,42]. Furthermore, a previous study included only two studies in the analysis demonstrating improvement of the OS and PFS in the control group, rather than the anti-PD-1 or anti-PD-L1 groups, to treat esophageal or G/GEJ cancer patients [43]. Some clinical trials have been published in recent years. The CheckMate 227 trial included 793 untreated stage IV or relapsed non-small cell lung cancer patients. The results showed that the ORR (45.3%) of nivolumab combined with ipilimumab in first-line treatment of NSCLC was higher than that of chemotherapy alone (26.9%), and the mPFS of nivolumab combined with ipilimumab and chemotherapy alone was 7.2 months versus 5.5 months ($p<0.001$), mOS was 17.1 months versus 14.9 months ($p=0.007$), and was independent of the expression level of PD-L1 [44].

Furthermore, in the non-contrast MAPS-II trial, patients with melanoma or non-small cell lung cancer was randomly divided into nivolumab monotherapy group and nivolumab combined with ipilimumab treatment group. The results showed that both groups had clinical benefits, with DCR of 40% and 52%, and ORR of 19% and 28%, respectively, and the mPFS of nivolumab combined with ipilimumab treatment group was better than that of nivolumab monotherapy group (5.6 months *vs.* 4.0 months) [45]. However there was no significant difference between the PD-1 and control for CR and TRAE.

This current study had several boundaries. Firstly, 6 RCTs were included, but the sample size varied between studies, resulting in a smaller sample size among different subgroups, which may be the main source of affecting both the quantitative and qualitative studies. Secondly, to compare efficacy, the OS, and the PFS, more studies need to be performed with each subgroup. Thirdly, the control groups of the included studies received different types of chemotherapies. Finally, ethnic variations were not evaluated in the current study. Although such differences play a role in the development of gastric cancer [46], in general, the efficacy and toxicities of inhibitors do not vary drastically across geographic regions or races [47]. Hence, more studies evaluating these differences in the use of CTLA-4/PD-1 inhibitors are necessary.

Conclusion

In conclusions, our study suggested that combination of CTLA-4/PD-1 exhibited better survival outcomes than PD-1 or CTLA-4 monotherapy in terms of OS, CR, PR, SD, ORR and PFS, but the side effects of combination therapy were higher than the monotherapy and most of the side effects were easier to control because the treatment related adverse events was recorded at grade ¾. Nevertheless, the meta-analysis confirmed that chemotherapy regimens provided better OS, PFS, PR, SD, PD, DCR and DOR outcome than PD-1 monotherapy. Additionally, clinical trials are required to verify the effect of dose reduction on effectiveness and adverse reactions in order to advance clinical efficacy and patient prognosis.

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