

Durvalumab and tremelimumab combination therapy versus durvalumab or tremelimumab monotherapy for patients with solid tumors

A systematic review and meta-analysis

Bi-Cheng Wang, MD^{a,*}, Peng-Cheng Li, MD^a, Ji-Quan Fan, MS^a, Guo-He Lin, MD^b, Quentin Liu, MD^c

Abstract

Background: The combination of durvalumab and tremelimumab results in clinical benefit, with a tolerable safety profile in patients with solid tumors.

Objective: To evaluate the efficacy and safety of durvalumab in combination with tremelimumab compared with either drug alone.

Methods: The online databases (PubMed, Web of Science, EMBASE, and Cochrane Library) were searched for potential clinical studies up to Nov 26, 2019. Eligible studies were prospective and registered clinical trials. Pooled odds ratios for objective response rate and disease control rate and pooled risk ratios for treatment-related adverse events were meta-analyzed. A random-effect model was used due to the synthesis of different cancer types.

Results: Overall, 5 studies were eligible for systematic review, 3 of which were further meta-analyzed. Durvalumab plus tremelimumab was superior to tremelimumab monotherapy in improving disease control rate in head and neck squamous cell carcinoma. However, there were no significant differences between dual immunotherapy and mono-immunotherapy in pancreatic ductal adenocarcinoma and gastric and gastroesophageal junction adenocarcinoma. Additionally, pooled analyses illustrated that no significant differences in treatment-related adverse events were displayed between the 2 groups.

Conclusion: Durvalumab and tremelimumab combination therapy had a good safety profile and resulted in clinical benefit in head and neck squamous cell carcinoma. Future explorations are needed to further confirm the application of durvalumab plus tremelimumab.

Abbreviations: 95% CI = 95% confidence interval, APC = antigen-presenting cell, CTLA-4 = cytotoxic T-lymphocyte antigen 4, DCR = disease control rate, GGA = gastric and gastroesophageal junction adenocarcinoma, HNSCC = head and neck squamous cell carcinoma, NSCLC = non-small cell lung cancer, OR = odds ratio, ORR = objective response rate, PD-1 = programmed cell death-1, PDA = pancreatic ductal adenocarcinoma, PD-L1 = programmed cell death ligand-1, PFS = progression-free survival = OS = overall survival, RR = risk ratio.

Keywords: durvalumab, immunotherapy, meta-analysis, solid tumor, tremelimumab

1. Introduction

Inhibitors of programmed cell death-1 (PD-1) and its ligand (PD-L1) have shown improved survival compared to chemotherapy on the treatment of advanced solid tumors.^[1,2] However, survival

outcomes still need to be improved in patients with recurrent or metastatic solid tumors.

During recent years, dual immune checkpoint inhibition has been a new treatment strategy for advanced patients.^[3,4] PD-1

Received: 13 March 2020 / Received in final form: 6 June 2020 / Accepted: 11 June 2020

http://dx.doi.org/10.1097/MD.000000000021273

Editor: Balaji Thas Moorthy.

This study was supported by the Independent Innovation Foundation of Wuhan Union Hospital (Grant number: 2019–109 to B-CW) and the Provincial Natural Science Research Project of Anhui Colleges (Grant number: KJ2017A200 to G-HL).

The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

^a Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, ^b Department of Oncology, the Second Affiliated Hospital of Anhui Medical University, Hefei, ^c State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Cancer Center, Sun Yat-sen University, Guangzhou, China.

^{*} Correspondence: Bi-Cheng Wang, Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1277 Jiefang Avenue, Wuhan 430022, China (e-mail: bcsnowell@163.com).

Copyright © 2020 the Author(s). Published by Wolters Kluwer Health, Inc.

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

How to cite this article: Wang B-C, Li P-C, Fan J-Q, Lin G-H, Liu Q. Durvalumab and tremelimumab combination therapy versus durvalumab or tremelimumab monotherapy for patients with solid tumors: a systematic review and meta-analysis. Medicine 2020;99:28(e21273).

inhibitors and cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitors are immune checkpoint antibodies with distinct but complementary mechanisms of action. Owing to the synergistic roles of the PD-1 or PD-L1 and CTLA-4 in T-cell activation, the combination of inhibitors targeting PD-1/PD-L1 and CTLA-4 signaling pathways warrants investigation.^[5] The combination of nivolumab, a fully human anti–PD-1 inhibitor, and ipilimumab, a fully human anti–CTLA-4 inhibitor, has shown encouraging clinical benefit characterized by antitumor effects and tolerable safety profiles.^[6–11]

Durvalumab plus tremelimumab is another combination regimen. Durvalumab is a highly selective human IgG1 monoclonal inhibitor that blocks interaction with PD-1 and CD80 to overcome blockage of primary human T-cell activation.^[12] Remarkable clinical activity and manageable safety of durvalumab were reported in various solid tumors, including melanoma, lung cancer, head and neck cancer, breast cancer, and urothelial carcinoma.^[13–19] Further, adding tremelimumab, a high affinity human IgG2 monoclonal antibody of CTLA-4,^[20] to durvalumab therapy has also been under detection in different cancers.^[21–26] Although combining durvalumab and tremelimumab results in clinical benefit, whether combination therapy is superior to durvalumab or tremelimumab monotherapy remains uncertain.

Accordingly, we conducted this systematic review and metaanalysis to assess the efficacy and safety of durvalumab plus tremelimumab combination therapy versus durvalumab or tremelimumab monotherapy in solid tumors.

2. Methods

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guideline.^[27] The data used in the analysis were not original raw data but were based on the published clinical studies with ethical approvals. Therefore, ethical approval was not necessary.

2.1. Search strategy

The electronic databases PubMed, Web of Science, EMBASE and Cochrane Library were systemically searched for all relevant records until Nov 26, 2019. Search terms were "tremelimumab", "durvalumab," and "trial or clinical trial or clinical study." Reference lists of relevant published studies and review articles were manually searched for more eligible trials.

2.2. Inclusion criteria and study selection

Eligible studies should meet all of the following criteria:

- (1) patients in the studies were diagnosed with solid tumors,
- (2) patients did not previously receive immunotherapy,
- (3) patients in 1 arm were treated with tremelimumab and durvalumab combination therapy,
- (4) studies were prospective and registered clinical trials,
- (5) the combination group did not include chemotherapy, target therapy, radiotherapy, or others,
- (6) efficacy and safety data were available.

We have no restrictions on language. Conference abstracts were excluded, due to the absence of raw data and the increase of heterogeneity. B-CW and P-CL independently conducted the selection process. Any discrepancies were resolved by discussion.

2.3. Data extraction

Detailed reviews of full-text articles regarding basic characteristics, outcomes and toxicities were performed by B-CW and P-CL independently. The first author, year of publication, register number, study design, county, cancer type, number of patients, mean age, lines of prior therapy, dosing schedule, objective response rate (ORR), disease control rate (DCR), overall survival (OS), progression-free survival (PFS), and treatment-related adverse events data reporting in the articles and supplementary materials were collected from each eligible study.

2.4. Statistical analysis

Data from randomized studies (ORR and DCR) was assessed by odds ratio (OR) and 95% confidence interval (CI). The treatment-related analyses were assessed by risk ratio (RR) and 95% CI. RevMan version 5.3 software (Cochrane Collaboration's Information Management System) was used to meta-analyzed the above-mentioned data. Heterogeneity among the studies was tested by I^2 statistic percentages and the Cochran Q Chi-squared test. A random-effects model was applied in the analyses owing to the small size of enrolled studies.

2.5. Risk of bias assessment

For pooled analyses of the ORR and DCR in randomized studies, the Cochrane Risk of Bias Tool was applied to evaluate the risk of bias.

3. Results

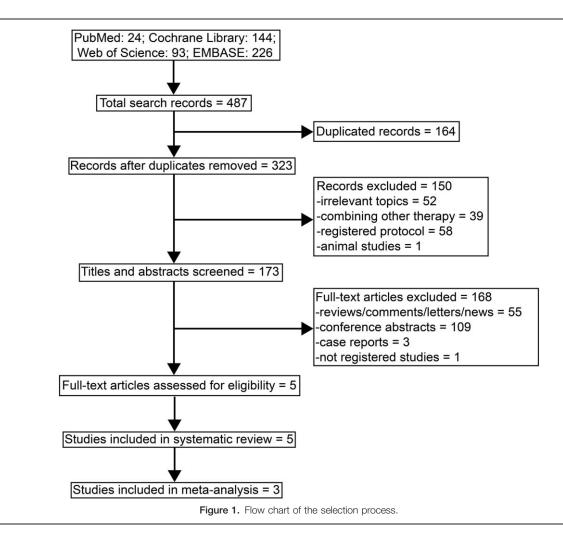
3.1. Search results

Figure 1 displays the selection process. Four hundred eightyseven potential records were included for the initial assessment. One hundred sixty-four duplicates were excluded. Further, 150 records were excluded after review of the titles and abstracts. One hundred seventy-three records underwent full-text assessment. We excluded 168 records because they were reviews/comments/ letters/ news (n=55), conference abstracts (n=109), case reports (n=3), or unregistered studies (n=1). Finally, 5 clinical studies were found to meet the inclusion criteria.^[28–32] All the selected studies were included in the systematic review, and 3 of 5 were included in the meta-analysis.^[28–30]

3.2. Characteristics

The basic characteristics of the 5 eligible studies are list in Table 1. One study was phase 1b clinical trial, 1 was phase 1b/2 clinical trial, and three were phase 2 clinical trials. There were 5 caner types including non-small cell lung cancer (NSCLC), mesothelioma, pancreatic ductal adenocarcinoma (PDA), head and neck squamous cell carcinoma (HNSCC), and gastric and gastroesophageal junction adenocarcinoma (GGA). All patients enrolled in the studies were diagnosed with advanced solid tumors. Most patients had received 1 line of prior systemic therapy. Three studies comprised durvalumab monotherapy and 2 studies contained tremelimumab monotherapy.

Table 2 showed the median PFS and OS in the studies. Mesothelioma patients treated with durvalumab plus tremelimumab had the longest median survival time (median PFS: 5.7 months, 95% confidence interval [CI] 1.7–9.7; median OS: 16.6



months, 95% CI 13.1–20.1). Although the median OS of patients with PDA, HNSCC, and GGA ranged from 3.1 to 10.6 months, the median PFS time was no more than 2 months.

3.3. Responses

The forest plots of odds ratios for ORR and DCR are shown in Figures 2 and 3. Pooled results showed that combining durvalumab and tremelimumab did not significantly improve the ORR compared with durvalumab (OR 1.12, 95% CI 0.43–2.90, P=.81) or tremelimumab (OR 2.40, 95% CI 0.47–12.32, P=.29) (Fig. 2). In addition, no statistically significant differences were observed in DCR when comparing combination therapy against monotherapy (durvalumab and tremelimumab versus durvalumab: OR 1.09, 95% CI 0.39–3.02, P=.87; durvalumab and tremelimumab versus tremelimumab: OR 2.76, 95% CI 0.28–27.24, P=.38) (Fig. 3).

In subgroup analyses, durvalumab plus tremelimumab was shown to have a higher rate of disease control in HNSCC compared to tremelimumab alone (OR 9.41, 95% CI 1.22–72.41, P=.03). In PDA and GGA, durvalumab plus tremelimumab was not superior to durvalumab or tremelimumab monotherapy.

3.4. Treatment-related adverse events

The forest plots of risk ratios for any grade and grade ≥ 3 treatment-related adverse events are shown in Figures 4 and 5. Durvalumab plus tremelimumab showed similar risks of any grade treatment-related adverse events with durvalumab monotherapy (RR 1.01, 95% CI 0.69–1.49, P=.95) and tremelimumab monotherapy (RR 1.02, 95% CI 0.79–1.32, P=.87) (Fig. 4). In subgroup analysis, P value did not indicate statistical significance. However, compared with durvalumab, combination therapy exhibited higher risks of any grade treatment-related adverse events in PDA (RR 1.10) and GGA (RR 4.06). However, a lower risk of any grade treatment-related adverse events was seen in HNSCC (RR 0.92). While compared with tremelimumab monotherapy, combination therapy showed a higher risk of any grade treatment-related adverse events in HNSCC (RR 1.05) but a lower risk in GGA (RR 0.68).

In comparison with patients in monotherapy groups, patients in the durvalumab and tremelimumab combination therapy group showed no significant increases in grade ≥ 3 treatmentrelated adverse events (durvalumab and tremelimumab versus durvalumab: RR 1.64, 95% CI 0.86–3.13, P=.14; durvalumab and tremelimumab versus tremelimumab: RR 0.87, 95% CI 0.46–1.65, P=.67) (Fig. 5). Although we failed to find the Table 1

Basic characteristics of the selected prospective and registered clinical trials.

Study	Year	Register number	Design	Country	Cancer type	No. patients	Mean age (yr)	Lines of prior therapy	Dosage
Scott Antonia	2016	NCT02000947	A multicenter, non- randomized, open-label, phase 1b trial	The United States	Non-small cell lung cancer	102	67.0	≥ 0	Durvalumab (3 mg/kg, 10 mg/ kg, 15 mg/kg, or 20 mg/kg every 4 wk, or 10 mg/kg) every 2 wk plus tremelimumab (1 mg/kg, 3 mg/kg, or 10 mg/kg) every 4 wk for 6 doses then every 12 wk for 3 doses.
Luana Calabrò	2018	NCT02588131	A non-randomized, open- label, single-center, phase 2 trial	Italy	Mesothelioma	40	64.0	≤ 1	Tremelinnumab (1 mg/kg) plus durvalumab (20 mg/kg) every 4 wk for 4 doses, followed by maintenance durvalumab at the same dose and schedule for 9 doses.
Eileen M. O'Reilly	2019	NCT02558894	A multicenter, randomized, open-label, phase 2 trial	Canada, Germany, the Netherlands, South Korea, Spain, and the United States	Pancreatic ductal adenocarcinoma	65	61.0	1	Durvalumab (1500 mg every 4 wk) plus tremelimumab (75 mg every 4 wk) for 4 cycles followed by durvalumab therapy (1500 mg every 4 wk); OR durvalumab monotherapy (1500 mg every 4 wk) for up to 12 mo or until the onset of progressive disease or unacceptable toxic effects.
Lillian L. Siu	2019	NCT02319044	A randomized, open-label, multicenter, global phase 2 study	15 countries in North America, Europe, and Asia Pacific	Head and neck squamous cell carcinoma	267	61.0	1	Durvalumab (20 mg/kg every 4 wk) plus tremelimumab (1 mg/kg every 4 wk) for 4 cycles, followed by durvalumab (10 mg/kg every 2 wk); 0R durvalumab (10 mg/kg every 2 wk) monotherapy; OR tremelimumab (10 mg/ kg every 4 wk for 7 doses then every 12 wk for 2 doses) monotherapy.
Ronan J. Kelly	2019	NCT02340975	A randomized, multicenter, open-label, phase 1b/2 study	Canada, Japan, Korea, Singapore, Taiwan/ China, and the United States	Gastric and gastroesophageal junction adenocarcinoma	113	54.0-64.0	≤ 2	Durvalumab 20 mg/kg plus tremelimumab 1 mg/kg every 4 wk for 4 cycles, followed by durvalumab 10 mg/kg every 2 wk for up to 12 mo; OR durvalumab monotherapy (10 mg/kg) every 2 wk; OR tremelimumab monotherapy (10 mg/kg) every 4 wk for 7 doses and then every 12 wk for 2 doses (for a total of up to 9 doses)

* ClinicalTrials.gov identifier.

Table 2

	and the second sec	A share the second s	a. A. P. A. Martin, and A. P. A. A.
Median progression-fre	e survival and ov	erali survival in th	e elininie stilnies
mealan progression ne	c our mur und of	cruit our treur int un	c cligible studies.

Study	Groups	mPFS	mOS
Scott Antonia 2016	D+T	NR	NR
Luana Calabrò 2018	D+T	5.7 mo (95% Cl 1.7-9.7)	16.6 mo (95% Cl 13.1-20.1)
Eileen M. O'Reilly 2019	D + T; D	1.5 mo (95% Cl 1.2-1.5) 1.3-1.5	3.1 mo (95%Cl 2.2-6.1) 3.6 mo
		mo	(95% Cl 2.7-6.1)
Lillian L. Siu 2019	D+T; D; T	2.0 mo (95% Cl 1.9-2.1) 1.9 mo	7.6 mo (95% Cl 4.9–10.6) 6.0 mo
		(95% Cl 1.8–2.8) 1.9 mo (95%	(95% Cl 4.0-11.3) 5.5 mo (95%
		Cl 1.8–2.0)	CI 3.9–7.0)
Ronan J. Kelly 2019	D+T; D; T	1.8 mo 1.6 mo (95% Cl 1.0-1.8)	7.0-10.6 mo 3.4 mo (95% Cl 1.7-
		1.7 mo (95% Cl 0.8-5.3)	4.4) 7.7 mo (95% Cl 2.1-13.7)

Cl=confidence interval, D=durvalumab, mOS=median overall survival, mPFS=median progression-free survival, NR=not reported, T=tremelimumab.

	D+		D			Odds Ratio	Odds Ratio
Study or Subgroup			Events	Iotal	weight	M-H. Random. 95% C	I M-H. Random. 95% Cl
1.1.1 Pancreatic ductal ad			100				
Eileen M. O' Reilly 2019 Subtotal (95% CI)	1	1 32 32		33 33		3.19 [0.13, 81.25] 3.19 [0.13, 81.25]	
Total events	1	1	0				
Heterogeneity: Not applica Test for overall effect: Z = 0		0.48)					
1.1.2 Head and neck squa	amous ce	ell carci	noma				
Lillian L. Siu 2019	10	129	6	65	80.7%	0.83 [0.29, 2.38]	
Subtotal (95% CI)		129		65	80.7%	0.83 [0.29, 2.38]	-
Total events	10)	6			127	
Heterogeneity: Not applica	ble		1.71				
Test for overall effect: Z = 0		0.72)					
1.1.3 Gastric and gastroe	sophage	al junct	ion aden	ocarci	noma		
Ronan J. Kelly 2019	6	5 71	0	24	10.7%	4.86 [0.26, 89.59]	-
Subtotal (95% CI)		71		24	10.7%	4.86 [0.26, 89.59]	
Total events	6	5	0				
Heterogeneity: Not applica	ble						
Test for overall effect: Z =	1.06 (P =	0.29)					
Total (95% CI)		232		122	100.0%	1.12 [0.43, 2.90]	+
Total events	17	1	6				NC 17
Heterogeneity: Tau ² = 0.00); $Chi^2 = 1$.77, df =	= 2 (P = 0.	41); l ²	= 0%		0.01 0.1 1 10 1
Test for overall effect: Z = 0	0.24 (P =	0.81)					Favours [D] Favours [D+T]
Test for subaroup difference	ces: Chi ² =	= 1.69. d	f = 2 (P =	0.43).	$ ^2 = 0\%$		
	D+T		т			Odds Ratio	Odda Datia
	_		1				Odds Ratio
01 J							
				otal V	vergint	M-H. Random. 95% CI	M-H. Random. 95% Cl
Study or Subgroup E 1.1.1 Head and neck squ	uamous o	cell card	cinoma				м-н. Random. 95% Ст
1.1.1 Head and neck squ Lillian L. Siu 2019	uamous o 10	cell card 129		63	52.7%	5.21 [0.65, 41.64]	M-H. Random, 95% CI
1.1.1 Head and neck squ Lillian L. Siu 2019 Subtotal (95% CI)	uamous o 10	cell card	cinoma 1	63			M-H. Random, 95% CI
1.1.1 Head and neck squ Lillian L. Siu 2019 Subtotal (95% CI) Total events	uamous o 10 10	cell card 129	cinoma	63	52.7%	5.21 [0.65, 41.64]	M-H. Random, 95% CI
1.1.1 Head and neck squ Lillian L. Siu 2019 Subtotal (95% CI)	uamous o 10 10 able	cell card 129 129	cinoma 1	63	52.7%	5.21 [0.65, 41.64]	M-H. Random, 95% CI
1.1.1 Head and neck squ Lillian L. Siu 2019 Subtotal (95% CI) Total events Heterogeneity: Not applica	10 10 10 able 1.56 (P =	cell card 129 129 = 0.12)	cinoma 1 1	63 63	52.7% 52.7%	5.21 [0.65, 41.64]	M-H. Random, 95% CI
1.1.1 Head and neck squ Lillian L. Siu 2019 Subtotal (95% CI) Total events Heterogeneity: Not applic: Test for overall effect: Z =	10 10 10 able 1.56 (P =	cell card 129 129 = 0.12)	cinoma 1 1	63 63	52.7% 52.7%	5.21 [0.65, 41.64]	M-H. Random, 95% CI
1.1.1 Head and neck squ Lillian L. Siu 2019 Subtotal (95% CI) Total events Heterogeneity: Not applica Test for overall effect: Z = 1.1.2 Gastric and gastro	10 10 able 1.56 (P =	cell card 129 129 = 0.12) geal jund	cinoma 1 1 ction ade	63 63 mocar 12	52.7% 52.7%	5.21 [0.65, 41.64] 5.21 [0.65, 41.64]	M-H. Random, 95% CI
1.1.1 Head and neck squ Lillian L. Siu 2019 Subtotal (95% CI) Total events Heterogeneity: Not applic: Test for overall effect: Z = 1.1.2 Gastric and gastro Ronan J. Kelly 2019	10 10 able 1.56 (P =	cell card 129 129 = 0.12) geal jund 71	cinoma 1 1 ction ade	63 63 mocar 12	52.7% 52.7% cinoma 47.3%	5.21 [0.65, 41.64] 5.21 [0.65, 41.64] 1.02 [0.11, 9.27]	M-H. Random, 95% CI
1.1.1 Head and neck squ Lillian L. Siu 2019 Subtotal (95% CI) Total events Heterogeneity: Not applic: Test for overall effect: Z = 1.1.2 Gastric and gastro Ronan J. Kelly 2019 Subtotal (95% CI) Total events	10 10 able 1.56 (P = esophag 6 6	cell card 129 129 = 0.12) geal jund 71	cinoma 1 1 ction ade 1	63 63 mocar 12	52.7% 52.7% cinoma 47.3%	5.21 [0.65, 41.64] 5.21 [0.65, 41.64] 1.02 [0.11, 9.27]	M-H. Random, 95% CI
1.1.1 Head and neck squ Lillian L. Siu 2019 Subtotal (95% CI) Total events Heterogeneity: Not applic: Test for overall effect: Z = 1.1.2 Gastric and gastro Ronan J. Kelly 2019 Subtotal (95% CI)	10 10 able 1.56 (P = 6 6 able	cell card 129 129 = 0.12) geal jund 71 71	cinoma 1 1 ction ade 1	63 63 mocar 12	52.7% 52.7% cinoma 47.3%	5.21 [0.65, 41.64] 5.21 [0.65, 41.64] 1.02 [0.11, 9.27]	M-H. Random, 95% Cl
1.1.1 Head and neck squ Lillian L. Siu 2019 Subtotal (95% CI) Total events Heterogeneity: Not applica Test for overall effect: Z = 1.1.2 Gastric and gastro Ronan J. Kelly 2019 Subtotal (95% CI) Total events Heterogeneity: Not applica Test for overall effect: Z =	10 10 able 1.56 (P = 6 6 able 0.01 (P =	cell card 129 129 = 0.12) geal jund 71 71	cinoma 1 1 ction ade 1	63 63 nocar 12 12	52.7% 52.7% cinoma 47.3%	5.21 [0.65, 41.64] 5.21 [0.65, 41.64] 1.02 [0.11, 9.27]	M-H. Random, 95% Cl
1.1.1 Head and neck squ Lillian L. Siu 2019 Subtotal (95% CI) Total events Heterogeneity: Not applica Test for overall effect: Z = 1.1.2 Gastric and gastro Ronan J. Kelly 2019 Subtotal (95% CI) Total events Heterogeneity: Not applica Test for overall effect: Z = Total (95% CI)	10 10 able 1.56 (P = 6 6 able 0.01 (P =	cell card 129 129 = 0.12) geal jund 71 71 = 0.99)	cinoma 1 1 ction ade 1	63 63 nocar 12 12	52.7% 52.7% ccinoma 47.3% 47.3%	5.21 [0.65, 41.64] 5.21 [0.65, 41.64] 1.02 [0.11, 9.27] 1.02 [0.11, 9.27]	M-H. Random, 95% Cl
1.1.1 Head and neck squ Lillian L. Siu 2019 Subtotal (95% CI) Total events Heterogeneity: Not applica Test for overall effect: Z = 1.1.2 Gastric and gastro Ronan J. Kelly 2019 Subtotal (95% CI) Total events Heterogeneity: Not applica Test for overall effect: Z =	uamous o 10 10 able 1.56 (P = 6 6 able 0.01 (P = 16	cell card 129 129 = 0.12) geal jund 71 71 = 0.99) 200	ction ade 1 ction ade 1 1	63 63 nocar 12 12 75 1	52.7% 52.7% cinoma 47.3% 47.3%	5.21 [0.65, 41.64] 5.21 [0.65, 41.64] 1.02 [0.11, 9.27] 1.02 [0.11, 9.27] 2.40 [0.47, 12.32]	

Figure 2. Forest plots of odds ratios for objective response in advanced solid tumors. (A) Durvalumab plus tremelimumab (D+T) versus durvalumab (D); (B) Durvalumab plus tremelimumab (D+T) versus tremelimumab (T).

statistical differences, subgroup analyses showed that combination therapy exerted higher risks of grade \geq 3 treatment-related adverse events in 3 cancer types (PDA: RR 3.5; HNSCC: RR 1.28; GGA: RR 1.74) against durvalumab monotherapy. Nevertheless, durvalumab plus tremelimumab displayed lower risks of grade \geq 3 treatment-related adverse events against tremelimumab monotherapy (HNSCC: RR 0.93; GGA: RR 0.34).

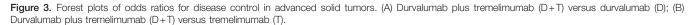
3.5. Bias assessment

All studies were open-label clinical trials, with 2 non-randomized and 3 randomized trials. The randomized clinical studies had reported all their pre-defined results. Accordingly, the metaanalyses of ORR and DCR were at moderate risk of reporting bias (Fig. 6).

4. Discussion

In this study, the combination therapeutic regimen showed no significant increase in treatment-related adverse events. However, higher effects were not observed in the combination therapy group. In the eligible studies, for advanced gastric and gastroesophageal junction adenocarcinoma, the combining durvalumab and tremelimumab displayed a numerically higher ORR than durvalumab monotherapy.^[30] Nevertheless, durvalumab plus tremelimumab showed similar efficacy to durvalumab monotherapy in recurrent or metastatic head and neck

	D+	-	D			Odds Ratio	Odds Ratio
Study or Subgroup			Events	Total	Weight	M-H. Random, 95% C	M-H. Random. 95% CI
1.1.1 Pancreatic ductal	l adenocard	inoma					
Eileen M. O' Reilly 2019 Subtotal (95% CI)	9 3	32	2	33 33	20.7%	1.60 [0.25, 10.29] 1.60 [0.25, 10.29]	
Total events	3		2				
Heterogeneity: Not appli	icable						
Test for overall effect: Z	= 0.50 (P =	0.62)					
1.1.2 Head and neck so	quamous co	ell carci	noma				~~
Lillian L. Siu 2019	17	129	14	65	47.9%	0.55 [0.25, 1.21]	
Subtotal (95% CI)		129	20	65	47.9%	0.55 [0.25, 1.21]	
Total events	17		14				
Heterogeneity: Not appli	icable						
Test for overall effect: Z		0.14)					
1.1.3 Gastric and gastr	oesophage	al junct	ion aden	ocarci	noma		
Ronan J. Kelly 2019	18		3	24		2.38 [0.63, 8.92]	
Subtotal (95% CI)	10	71	5	24		2.38 [0.63, 8.92]	
Total events	18		3				
Heterogeneity: Not appli	The second se						
Test for overall effect: Z		0.20)					
Total (95% CI)		232		122	100.0%	1.09 [0.39, 3.02]	
Total events	38		19		100.070	1.00 [0.00, 0.02]	
				14). 12	= 50%		1 1 1 I
Heterogeneity: Tau ² = 0.	.41; Chi ² = 3	.96, df =		14); l²	= 50%		
Heterogeneity: Tau ² = 0. Test for overall effect: Z	.41; Chi ² = 3 = 0.17 (P =	.96, df = 0.87)	= 2 (P = 0.	2201.014		6	0.01 0.1 1 10 1 Favours [D] Favours [D+T]
Heterogeneity: Tau ² = 0.	.41; Chi ² = 3 = 0.17 (P =	.96, df = 0.87)	= 2 (P = 0.	2201.014		6	
Heterogeneity: Tau ² = 0. Test for overall effect: Z	.41; Chi ² = 3 = 0.17 (P =	.96, df = 0.87)	= 2 (P = 0.	2201.014		6 Odds Ratio	
Heterogeneity: Tau ² = 0. Test for overall effect: Z	.41; Chi ² = 3 = 0.17 (P = ences: Chi ² : D+T	96, df = 0.87) = 3.93. d	= 2 (P = 0. If = 2 (P = T	0.14).	l² = 49.1%	Odds Ratio	Favours [D] Favours [D+T]
Heterogeneity: Tau ² = 0. Test for overall effect: Z Test for subaroup differe	.41; Chi ² = 3 = 0.17 (P = ences: Chi ² : D+T <u>Events T</u>	96, df = 0.87) 3.93. d	= 2 (P = 0. If = 2 (P = T vents To	0.14).	l² = 49.1%	Odds Ratio	Favours [D] Favours [D+T] Odds Ratio
Heterogeneity: Tau ² = 0. Test for overall effect: Z Test for subaroup differe Study or Subgroup	.41; Chi ² = 3 = 0.17 (P = ences: Chi ² : D+T <u>Events T</u>	96, df = 0.87) 3.93. d	= 2 (P = 0. If = 2 (P = T vents To	0.14), otal V	l² = 49.1%	Odds Ratio M-H. Random. 95% Cl	Favours [D] Favours [D+T] Odds Ratio
Heterogeneity: Tau ² = 0. Test for overall effect: Z Test for subaroup differe Study or Subgroup 1.1.1 Head and neck s	.41; Chi ² = 3 = 0.17 (P = ences: Chi ² : D+T Events T squamous of 17	.96, df = 0.87) = 3.93. d otal <u>E</u> cell care	= 2 (P = 0. If = 2 (P = T <u>vents Te</u> cinoma	0.14), otal V 63	² = 49.1% Veight	Odds Ratio	Favours [D] Favours [D+T] Odds Ratio
Heterogeneity: Tau ² = 0. Test for overall effect: Z Test for subaroup differe Study or Subgroup 1.1.1 Head and neck s Lillian L. Siu 2019 Subtotal (95% CI)	.41; Chi ² = 3 = 0.17 (P = ences: Chi ² = D+T <u>Events T</u> squamous o 17	.96, df = 0.87) = 3.93. d otal <u>E</u> cell care 129	= 2 (P = 0. If = 2 (P = T <u>vents Tr</u> cinoma 1	0.14), otal V 63	l ² = 49.19 <u>Veight</u> 44.9%	Odds Ratio M-H. Random. 95% Cl 9.41 [1.22, 72.41]	Favours [D] Favours [D+T] Odds Ratio
Heterogeneity: Tau ² = 0. Test for overall effect: Z Test for subaroup differe Study or Subaroup 1.1.1 Head and neck s Lillian L. Siu 2019 Subtotal (95% CI) Total events	.41; Chi ² = 3 = 0.17 (P = ences: Chi ² = D+T <u>Events T</u> squamous o 17 17	.96, df = 0.87) = 3.93. d otal <u>E</u> cell care 129	= 2 (P = 0. If = 2 (P = T <u>vents Te</u> cinoma	0.14), otal V 63	l ² = 49.19 <u>Veight</u> 44.9%	Odds Ratio M-H. Random. 95% Cl 9.41 [1.22, 72.41]	Favours [D] Favours [D+T] Odds Ratio
Heterogeneity: Tau ² = 0. Test for overall effect: Z Test for subaroup differe Study or Subgroup 1.1.1 Head and neck s Lillian L. Siu 2019 Subtotal (95% CI)	.41; Chi ² = 3 = 0.17 (P = ences: Chi ² : D+T <u>Events T</u> squamous o 17 17 slicable	.96, df = 0.87) = 3.93. d otal <u>E</u> cell card 129 129	= 2 (P = 0. If = 2 (P = T <u>vents Tr</u> cinoma 1	0.14), otal V 63	l ² = 49.19 <u>Veight</u> 44.9%	Odds Ratio M-H. Random. 95% Cl 9.41 [1.22, 72.41]	Favours [D] Favours [D+T] Odds Ratio
Heterogeneity: Tau ² = 0. Test for overall effect: Z Test for subaroup differe <u>Study or Subaroup</u> 1.1.1 Head and neck s Lillian L. Siu 2019 Subtotal (95% CI) Total events Heterogeneity: Not app Test for overall effect: Z	.41; Chi ² = 3 = 0.17 (P = ences: Chi ² = D+T Events T squamous o 17 17 Jicable Z = 2.15 (P =	8.96, df = 0.87) = 3.93. d otal E: cell card 129 129 = 0.03)	= 2 (P = 0. If = 2 (P = T <u>vents Tr</u> cinoma 1 1	0.14). otal V 63 63	l ² = 49.19 <u>Veight</u> 44.9% 44.9%	Odds Ratio M-H. Random. 95% Cl 9.41 [1.22, 72.41]	Favours [D] Favours [D+T] Odds Ratio
Heterogeneity: Tau ² = 0. Test for overall effect: Z Test for subaroup differe Study or Subgroup 1.1.1 Head and neck s Lillian L. Siu 2019 Subtotal (95% CI) Total events Heterogeneity: Not app Test for overall effect: Z 1.1.2 Gastric and gast	.41; Chi ² = 3 = 0.17 (P = ences: Chi ² = D+T Events T squamous o 17 17 Jicable Z = 2.15 (P = troesophag	9.96, df = 0.87) = 3.93. d otal E: cell card 129 129 = 0.03) eal jund	2 (P = 0. If = 2 (P = T vents Tr cinoma 1 1 1	0.14). <u>otal V</u> 63 63 63	l ² = 49.19 <u>Veight</u> 44.9% 44.9% cinoma	Odds Ratio M-H. Random. 95% Cl 9.41 [1.22, 72.41] 9.41 [1.22, 72.41]	Favours [D] Favours [D+T] Odds Ratio
Heterogeneity: Tau ² = 0. Test for overall effect: Z Test for subaroup differe <u>Study or Subaroup</u> 1.1.1 Head and neck s Lillian L. Siu 2019 Subtotal (95% CI) Total events Heterogeneity: Not app Test for overall effect: Z	.41; Chi ² = 3 = 0.17 (P = ences: Chi ² = D+T Events T squamous o 17 17 Jicable Z = 2.15 (P =	8.96, df = 0.87) = 3.93. d otal E: cell card 129 129 = 0.03)	= 2 (P = 0. If = 2 (P = T <u>vents Tr</u> cinoma 1 1	0.14), otal V 63 63 63	l ² = 49.19 <u>Veight</u> 44.9% 44.9%	Odds Ratio M-H. Random. 95% Cl 9.41 [1.22, 72.41]	Favours [D] Favours [D+T] Odds Ratio
Heterogeneity: Tau ² = 0. Test for overall effect: Z Test for suboroup differe <u>Study or Subgroup</u> 1.1.1 Head and neck s Lillian L. Siu 2019 Subtotal (95% CI) Total events Heterogeneity: Not appi Test for overall effect: Z 1.1.2 Gastric and gast Ronan J. Kelly 2019	.41; Chi ² = 3 = 0.17 (P = ences: Chi ² = D+T Events T squamous o 17 17 Jicable Z = 2.15 (P = troesophag	e.96, df = 0.87) = 3.93. d otal E: cell card 129 129 = 0.03) real june 71	2 (P = 0. If = 2 (P = T vents Tr cinoma 1 1 1	0.14), otal V 63 63 63	I ² = 49.19 <u>Veight</u> 44.9% 44.9% cinoma 55.1%	Odds Ratio M-H. Random. 95% CI 9.41 [1.22, 72.41] 9.41 [1.22, 72.41] 1.02 [0.25, 4.18]	Favours [D] Favours [D+T] Odds Ratio
Heterogeneity: Tau ² = 0. Test for overall effect: Z Test for suboroup differe <u>Study or Subgroup</u> 1.1.1 Head and neck s Lillian L. Siu 2019 Subtotal (95% CI) Total events Heterogeneity: Not appi Test for overall effect: Z 1.1.2 Gastric and gast Ronan J. Kelly 2019 Subtotal (95% CI)	.41; Chi ² = 3 = 0.17 (P = ences: Chi ² : D+T Events T squamous of 17 17 licable Z = 2.15 (P : troesophag 18 18	e.96, df = 0.87) = 3.93. d otal E: cell card 129 129 = 0.03) real june 71	2 (P = 0. If = 2 (P = T vents Tri- cinoma 1 1 ction ade 3	0.14), otal V 63 63 63	I ² = 49.19 <u>Veight</u> 44.9% 44.9% cinoma 55.1%	Odds Ratio M-H. Random. 95% CI 9.41 [1.22, 72.41] 9.41 [1.22, 72.41] 1.02 [0.25, 4.18]	Favours [D] Favours [D+T] Odds Ratio
Heterogeneity: Tau ² = 0. Test for overall effect: Z Test for subaroup differe Study or Subgroup 1.1.1 Head and neck s Lillian L. Siu 2019 Subtotal (95% CI) Total events Heterogeneity: Not appi Test for overall effect: Z 1.1.2 Gastric and gast Ronan J. Kelly 2019 Subtotal (95% CI) Total events	.41; Chi ² = 3 = 0.17 (P = ences: Chi ² : D+T Events T squamous of 17 17 licable Z = 2.15 (P = 18 18 18 18	8.96, df = 0.87) = 3.93. d otal E: cell card 129 129 = 0.03) real jund 71 71	2 (P = 0. If = 2 (P = T vents Tri- cinoma 1 1 ction ade 3	0.14), otal V 63 63 63	I ² = 49.19 <u>Veight</u> 44.9% 44.9% cinoma 55.1%	Odds Ratio M-H. Random. 95% CI 9.41 [1.22, 72.41] 9.41 [1.22, 72.41] 1.02 [0.25, 4.18]	Favours [D] Favours [D+T] Odds Ratio
Heterogeneity: Tau ² = 0. Test for overall effect: Z Test for suboroup differe <u>Study or Suboroup</u> 1.1.1 Head and neck s Lillian L. Siu 2019 Subtotal (95% CI) Total events Heterogeneity: Not app Test for overall effect: Z 1.1.2 Gastric and gast Ronan J. Kelly 2019 Subtotal (95% CI) Total events Heterogeneity: Not app Test for overall effect: Z	41; Chi ² = 3 = 0.17 (P = ences: Chi ² : D+T Events T squamous of 17 17 0icable Z = 2.15 (P = 18 18 18 0icable Z = 0.03 (P =	8.96, df = 0.87) = 3.93. d otal E: cell card 129 129 = 0.03) real jund 71 71	2 (P = 0. If = 2 (P = T vents Tri- cinoma 1 1 ction ade 3	0.14). otal V 63 63 63 enocar 12 12	² = 49.19 <u>Veight</u> 44.9% 44.9% cinoma 55.1% 55.1%	Odds Ratio M-H. Random. 95% Cl 9.41 [1.22, 72.41] 9.41 [1.22, 72.41] 1.02 [0.25, 4.18] 1.02 [0.25, 4.18]	Favours [D] Favours [D+T] Odds Ratio
Heterogeneity: Tau ² = 0. Test for overall effect: Z Test for suboroup differe Study or Suboroup differe 1.1.1 Head and neck s Lillian L. Siu 2019 Subtotal (95% CI) Total events Heterogeneity: Not appl Test for overall effect: Z 1.1.2 Gastric and gast Ronan J. Kelly 2019 Subtotal (95% CI) Total events Heterogeneity: Not appl Test for overall effect: Z Total (95% CI)	41; Chi ² = 3 = 0.17 (P = ences: Chi ² : D+T Events T squamous of 17 17 0icable Z = 2.15 (P = 18 18 18 0icable Z = 0.03 (P =	e.96, df = 0.87) = 3.93. d otal E: cell card 129 129 = 0.03) real jund 71 71 = 0.98)	2 (P = 0. If = 2 (P = T vents Tr cinoma 1 1 ction ade 3 3	0.14). otal V 63 63 63 enocar 12 12	I ² = 49.19 <u>Veight</u> 44.9% 44.9% cinoma 55.1%	Odds Ratio M-H. Random. 95% CI 9.41 [1.22, 72.41] 9.41 [1.22, 72.41] 1.02 [0.25, 4.18]	Favours [D] Favours [D+T] Odds Ratio
Heterogeneity: Tau ² = 0. Test for overall effect: Z Test for suboroup differe Study or Suboroup 1.1.1 Head and neck s Lillian L. Siu 2019 Subtotal (95% CI) Total events Heterogeneity: Not appl Test for overall effect: Z 1.1.2 Gastric and gast Ronan J. Kelly 2019 Subtotal (95% CI) Total events Heterogeneity: Not appl Test for overall effect: Z Total (95% CI) Total events	41; Chi ² = 3 = 0.17 (P = ences: Chi ² : D+T Events T squamous of 17 17 Nicable Z = 2.15 (P = 18 18 18 18 Nicable Z = 0.03 (P = 35	e.96, df = 0.87) = 3.93. d otal E: cell card 129 129 = 0.03) real jund 71 71 = 0.98) 200	2 (P = 0. If = 2 (P = T vents Tr cinoma 1 1 1 ction ade 3 3 4	0.14). otal V 63 63 enocar 12 12 12 75 1	I ² = 49.19 Veight 44.9% 44.9% 55.1% 55.1% 00.0%	Odds Ratio M-H. Random. 95% Cl 9.41 [1.22, 72.41] 9.41 [1.22, 72.41] 1.02 [0.25, 4.18] 1.02 [0.25, 4.18] 2.76 [0.28, 27.24]	Favours [D] Favours [D+T]
Heterogeneity: Tau ² = 0. Test for overall effect: Z Test for suboroup differe Study or Suboroup 1.1.1 Head and neck s Lillian L. Siu 2019 Subtotal (95% CI) Total events Heterogeneity: Not appl Test for overall effect: Z 1.1.2 Gastric and gast Ronan J. Kelly 2019 Subtotal (95% CI) Total events Heterogeneity: Not appl Test for overall effect: Z Total (95% CI)	.41; Chi ² = 3 = 0.17 (P = ences: Chi ² : D+T Events T squamous of 17 17 olicable Z = 2.15 (P = 18 18 licable Z = 0.03 (P = 35 1.95; Chi ² =	e.96, df = 0.87) = 3.93. d otal E: cell card 129 = 0.03) real jund 71 71 = 0.98) 200 3.44, df	2 (P = 0. If = 2 (P = T vents Tr cinoma 1 1 1 ction ade 3 3 4	0.14). otal V 63 63 enocar 12 12 12 75 1	I ² = 49.19 Veight 44.9% 44.9% 55.1% 55.1% 00.0%	Odds Ratio M-H. Random. 95% Cl 9.41 [1.22, 72.41] 9.41 [1.22, 72.41] 1.02 [0.25, 4.18] 1.02 [0.25, 4.18] 2.76 [0.28, 27.24]	Favours [D] Favours [D+T] Odds Ratio



squamous cell carcinoma and pancreatic ductal adenocarcinoma.^[28,29] It is important to assess what factors might have contributed to the failure of combinatorial therapy.

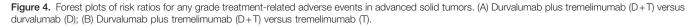
Tumor cells elude recognition and destruction by the immune system via activating the immune checkpoint signaling pathway.^[33–35] Nowadays, immune checkpoint inhibitors have revolutionized the treatment of patients with solid tumors.^[36,37] Both CTLA-4 and PD-1 are able to regulate the activation of T-cell, however, the mechanisms of action were distinct.

The action mechanism of CTLA-4 remains less clear. To our minds, CTLA-4 was used by regulatory T (Treg) cells to elicit suppression; however, CTLA-4 also operates to trigger inhibitory signals in conventional T cells. T cell motility is increased by

CTLA-4 via limiting contact time between T cells and antigenpresenting cells (APCs). In this condition, CTLA-4 ligation transmits "arrest" signals between T cells and APC.^[38] Another study has demonstrated that anti-CTLA-4 treatment increases the action of Treg and CD4 T cells but decreases the action of CD8 T cells.^[39] Accordingly, blockage of CTLA-4 might overcome immune resistance in the host peripheral immune system.

PD-1 is frequently expressed on tumor-infiltrating lymphocytes (especially CD4+ T cells).^[40–42] In the peripheral tissues, PD-1 limits the activation of T-cell through suppressing the induction of cytokines and the expression of anti-apoptotic proteins. PD-1 is also over-expressed on intra-tumoral Treg cells and might enhance the immunosuppressive capability.^[43–46] PD-L1 is

	D+	т	D			Risk Ratio	Risk Ratio
Study or Subgroup			Events	Total	Weight	M-H. Random, 95% C	M-H. Random. 95% Cl
1.1.1 Pancreatic ductal	adenocard	cinoma					
Eileen M. O' Reilly 2019) 11		10	32		1.10 [0.54, 2.22]	
Subtotal (95% CI)		32		32	23.5%	1.10 [0.54, 2.22]	
Total events	11	1	10				
Heterogeneity: Not applic							
Test for overall effect: Z =	= 0.27 (P =	0.79)					
1.1.2 Head and neck sq	uamous co	ell carci	noma				
Lillian L. Siu 2019	77	7 133	41	65	72.8%	0.92 [0.73, 1.16]	
Subtotal (95% CI)		133		65	72.8%	0.92 [0.73, 1.16]	•
Total events	77	7	41				
Heterogeneity: Not applic	cable						
Test for overall effect: Z =	= 0.71 (P =	0.48)					
1.1.3 Gastric and gastro	pesophage	al junct	ion aden	ocarci	noma		
Ronan J. Kelly 2019	12	-	1	24	3.7%	4.06 [0.56, 29.58]	
Subtotal (95% CI)	12	71		24	3.7%	4.06 [0.56, 29.58]	
Total events	12		1				production of the second se
Heterogeneity: Not applic		-					
Test for overall effect: Z =		0.17)					
		,					
Total (95% CI)	100	236		121	100.0%	1.01 [0.69, 1.49]	•
Total events	100	5	52				
	A 01.12 C	100 10	0 /0 0				
Heterogeneity: Tau ² = 0.0			2 (P = 0.	27); l²	= 24%		0.01 0.1 1 10 1
Test for overall effect: Z =	= 0.06 (P =	0.95)	•			,	0.01 0.1 1 10 1 Favours [D+T] Favours [D]
	= 0.06 (P =	0.95)	•			6	
Test for overall effect: Z =	= 0.06 (P =	0.95)	•			6 Risk Ratio	
Test for overall effect: Z =	= 0.06 (P = nces: Chi ² : D+T	0.95) = 2.30. d	f = 2 (P = T	0.32).	l² = 13.0%	Risk Ratio	Favours [D+T] Favours [D]
Test for overall effect: Z = Test for suboroup different	= 0.06 (P = nces: Chi ² : D+T <u>Events T</u>	0.95) = 2.30. d	f = 2 (P = T ents To	0.32).	l² = 13.0%	Risk Ratio	Favours [D+T] Favours [D] Risk Ratio
Test for overall effect: Z = Test for subaroup different Study or Subgroup	= 0.06 (P = nces: Chi ² D+T <u>Events Tr</u> quamous c	0.95) = 2.30. d	f = 2 (P = T <u>ents To</u> inoma	0.32). tal W	l² = 13.0%	Risk Ratio I-H. Random. 95% Cl	Favours [D+T] Favours [D] Risk Ratio
Test for overall effect: Z = Test for subaroup different Study or Subaroup 1.1.1 Head and neck so	= 0.06 (P = nces: Chi ² D+T Events Tr quamous c 77	0.95) = 2.30. d otal Ev	f = 2 (P = T <u>ents To</u> inoma 36	0.32). tal W	l² = 13.0% eight N	Risk Ratio	Favours [D+T] Favours [D] Risk Ratio
Test for overall effect: Z = Test for subaroup different Study or Subaroup 1.1.1 Head and neck so Lillian L. Siu 2019	= 0.06 (P = nces: Chi ² D+T Events Tr quamous c 77	0.95) = 2.30. d otal Ev cell carc 133	f = 2 (P = T <u>ents To</u> inoma 36	0.32). tal W	l² = 13.09 eight N 14.7%	Risk Ratio I-H. Random. 95% CI 1.05 [0.80, 1.36]	Favours [D+T] Favours [D] Risk Ratio
Test for overall effect: Z = Test for subaroup different Study or Subgroup 1.1.1 Head and neck so Lillian L. Siu 2019 Subtotal (95% CI) Total events	= 0.06 (P = nces: Chi ² : D+T <u>Events Tr</u> uamous c 77 77	0.95) = 2.30. d otal Ev cell carc 133	f = 2 (P = T <u>ents To</u> inoma 36	0.32). tal W	l² = 13.09 eight N 14.7%	Risk Ratio I-H. Random. 95% CI 1.05 [0.80, 1.36]	Favours [D+T] Favours [D] Risk Ratio
Test for overall effect: Z = Test for subaroup different Study or Subaroup 1.1.1 Head and neck so Lillian L. Siu 2019 Subtotal (95% CI)	= 0.06 (P = nces: Chi ² : D+T <u>Events Tr</u> uamous c 77 77 cable	0.95) = 2.30. d otal Ev cell carc 133 133	f = 2 (P = T <u>ents To</u> inoma 36	0.32). tal W	l² = 13.09 eight N 14.7%	Risk Ratio I-H. Random. 95% CI 1.05 [0.80, 1.36]	Favours [D+T] Favours [D] Risk Ratio
Test for overall effect: Z = Test for subaroup different Study or Subaroup 1.1.1 Head and neck so Lillian L. Siu 2019 Subtotal (95% CI) Total events Heterogeneity: Not applit Test for overall effect: Z	= 0.06 (P = nces: Chi ² D+T Events Tr juamous o 77 77 cable = 0.33 (P =	0.95) = 2.30. d otal Ev cell carc 133 133 = 0.74)	f = 2 (P = T <u>reents To</u> inoma 36 36	0.32). tal W 65 9 65 9	l ² = 13.09 eight N 14.7% 44.7%	Risk Ratio I-H. Random. 95% CI 1.05 [0.80, 1.36]	Favours [D+T] Favours [D] Risk Ratio
Test for overall effect: Z = Test for subgroup different Study or Subgroup 1.1.1 Head and neck so Lillian L. Siu 2019 Subtotal (95% CI) Total events Heterogeneity: Not appli Test for overall effect: Z 1.1.2 Gastric and gastr	= 0.06 (P = nces: Chi ² : D+T <u>Events Tr</u> uamous o 77 77 cable = 0.33 (P = oesophag	0.95) = 2.30. d otal Ev cell carc 133 133 = 0.74) eal junc	f = 2 (P = T <u>reents To</u> inoma 36 36 36	0.32). tal W 65 9 65 9	l ² = 13.09 eight N 14.7% 04.7%	Risk Ratio 1-H. Random. 95% Cl 1.05 [0.80, 1.36] 1.05 [0.80, 1.36]	Favours [D+T] Favours [D] Risk Ratio
Test for overall effect: Z = Test for subgroup different Study or Subgroup 1.1.1 Head and neck so Lillian L. Siu 2019 Subtotal (95% CI) Total events Heterogeneity: Not appli Test for overall effect: Z 1.1.2 Gastric and gastr Ronan J. Kelly 2019	= 0.06 (P = nces: Chi ² D+T Events Tr juamous o 77 77 cable = 0.33 (P =	0.95) = 2.30. d otal Ev cell carc 133 133 = 0.74) real junc 71	f = 2 (P = T <u>reents Too</u> inoma 36 36 36 tion adee 3	0.32). tal W 65 9 65 9	l ² = 13.09 eight N 4.7% 94.7% 5.3%	Risk Ratio <u>I-H. Random. 95% CI</u> 1.05 [0.80, 1.36] 1.05 [0.80, 1.36] 0.68 [0.22, 2.05]	Favours [D+T] Favours [D] Risk Ratio
Test for overall effect: Z = Test for subgroup different Study or Subgroup 1.1.1 Head and neck so Lillian L. Siu 2019 Subtotal (95% CI) Total events Heterogeneity: Not appli Test for overall effect: Z 1.1.2 Gastric and gastr Ronan J. Kelly 2019 Subtotal (95% CI)	= 0.06 (P = nces: Chi ² = D+T <u>Events Tr</u> nuamous of 77 77 cable = 0.33 (P = 0esophag 12	0.95) = 2.30. d otal Ev cell carc 133 133 = 0.74) eal junc	f = 2 (P = T ents To inoma 36 36 36 tion ade 3	0.32). tal W 65 9 65 9	l ² = 13.09 eight N 14.7% 04.7%	Risk Ratio 1-H. Random. 95% Cl 1.05 [0.80, 1.36] 1.05 [0.80, 1.36]	Favours [D+T] Favours [D] Risk Ratio
Test for overall effect: Z = Test for subgroup different Study or Subgroup 1.1.1 Head and neck so Lillian L. Siu 2019 Subtotal (95% CI) Total events Heterogeneity: Not appli Test for overall effect: Z 1.1.2 Gastric and gastr Ronan J. Kelly 2019 Subtotal (95% CI) Total events	= 0.06 (P = nces: Chi ² : D+T <u>Events Tr</u> juamous o 77 77 cable = 0.33 (P = 0esophag 12 12	0.95) = 2.30. d otal Ev cell carc 133 133 = 0.74) real junc 71	f = 2 (P = T <u>reents Too</u> inoma 36 36 36 tion adee 3	0.32). tal W 65 9 65 9	l ² = 13.09 eight N 4.7% 94.7% 5.3%	Risk Ratio <u>I-H. Random. 95% CI</u> 1.05 [0.80, 1.36] 1.05 [0.80, 1.36] 0.68 [0.22, 2.05]	Favours [D+T] Favours [D] Risk Ratio
Test for overall effect: Z = Test for subgroup different Study or Subgroup 1.1.1 Head and neck so Lillian L. Siu 2019 Subtotal (95% CI) Total events Heterogeneity: Not appli Test for overall effect: Z 1.1.2 Gastric and gastr Ronan J. Kelly 2019 Subtotal (95% CI)	= 0.06 (P = nces: Chi ² = D+T <u>Events Tr</u> quamous of 77 77 cable = 0.33 (P = 0esophag 12 12 cable	0.95) = 2.30. d otal Ev cell carc 133 133 = 0.74) eal junc 71 71	f = 2 (P = T ents To inoma 36 36 36 tion ade 3	0.32). tal W 65 9 65 9	l ² = 13.09 eight N 4.7% 94.7% 5.3%	Risk Ratio <u>I-H. Random. 95% CI</u> 1.05 [0.80, 1.36] 1.05 [0.80, 1.36] 0.68 [0.22, 2.05]	Favours [D+T] Favours [D] Risk Ratio
Test for overall effect: Z = Test for subgroup different Study or Subgroup 1.1.1 Head and neck so Lillian L. Siu 2019 Subtotal (95% CI) Total events Heterogeneity: Not appli Test for overall effect: Z 1.1.2 Gastric and gastr Ronan J. Kelly 2019 Subtotal (95% CI) Total events Heterogeneity: Not appli Test for overall effect: Z	= 0.06 (P = nces: Chi ² = D+T Events Tr quamous of 77 cable = 0.33 (P = 0esophag 12 12 cable = 0.69 (P =	0.95) = 2.30. d otal Ev cell carc 133 133 = 0.74) eal junc 71 71 = 0.49)	f = 2 (P = T ents To inoma 36 36 tion ade 3 3	0.32). tal W 665 9 65 9 65 9 10 10 12	l ² = 13.09 eight N 44.7% 44.7% 5.3% 5.3%	Risk Ratio 1-H. Random. 95% Cl 1.05 [0.80, 1.36] 1.05 [0.80, 1.36] 0.68 [0.22, 2.05] 0.68 [0.22, 2.05]	Favours [D+T] Favours [D] Risk Ratio
Test for overall effect: Z = Test for suboroup different Study or Suboroup different 1.1.1 Head and neck so Lillian L. Siu 2019 Subtotal (95% CI) Total events Heterogeneity: Not appli Test for overall effect: Z 1.1.2 Gastric and gastr Ronan J. Kelly 2019 Subtotal (95% CI) Total events Heterogeneity: Not appli Test for overall effect: Z Total (95% CI)	= 0.06 (P = nces: Chi ² = D+T Events Tr quamous of 77 77 cable = 0.33 (P = 0esophag 12 12 cable = 0.69 (P =	0.95) = 2.30. d otal Ev cell carc 133 133 = 0.74) eal junc 71 71	f = 2 (P = T ents To inoma 36 36 tion ade 3 3	0.32). tal W 65 9 65 9	l ² = 13.09 eight N 44.7% 44.7% 5.3% 5.3%	Risk Ratio <u>I-H. Random. 95% CI</u> 1.05 [0.80, 1.36] 1.05 [0.80, 1.36] 0.68 [0.22, 2.05]	Favours [D+T] Favours [D] Risk Ratio
Test for overall effect: Z = Test for suboroup different 1.1.1 Head and neck so Lillian L. Siu 2019 Subtotal (95% CI) Total events Heterogeneity: Not appli Test for overall effect: Z 1.1.2 Gastric and gastr Ronan J. Kelly 2019 Subtotal (95% CI) Total events Heterogeneity: Not appli Test for overall effect: Z Total (95% CI) Total events	= 0.06 (P = nces: Chi ² : D+T Events Tr Juamous of 77 cable = 0.33 (P = 0esophag 12 12 cable = 0.69 (P =	0.95) = 2.30. d cell carc 133 133 = 0.74) eal junc 71 71 = 0.49) 204	f = 2 (P = T ents To inoma 36 36 tion ader 3 3 3	0.32). tal W 65 9 665 9 10 12 12 12	² = 13.09 eight N (4.7% 04.7% 5.3% 5.3% 00.0%	Risk Ratio 1-H. Random. 95% Cl 1.05 [0.80, 1.36] 1.05 [0.80, 1.36] 0.68 [0.22, 2.05] 0.68 [0.22, 2.05]	Favours [D+T] Favours [D] Risk Ratio
Test for overall effect: Z = Test for suboroup different Study or Suboroup different 1.1.1 Head and neck so Lillian L. Siu 2019 Subtotal (95% CI) Total events Heterogeneity: Not appli Test for overall effect: Z 1.1.2 Gastric and gastr Ronan J. Kelly 2019 Subtotal (95% CI) Total events Heterogeneity: Not appli Test for overall effect: Z Total (95% CI)	= 0.06 (P = nces: Chi ² : D+T Events Tr juamous of 77 cable = 0.33 (P = 0esophag 12 12 cable = 0.69 (P =	0.95) = 2.30. d otal Ev cell carc 133 133 = 0.74) ral junc 71 71 = 0.49) 204 0.57, df	f = 2 (P = T ents To inoma 36 36 tion ader 3 3 3	0.32). tal W 65 9 665 9 10 12 12 12	² = 13.09 eight N (4.7% 04.7% 5.3% 5.3% 00.0%	Risk Ratio <u>I-H. Random. 95% CI</u> 1.05 [0.80, 1.36] 1.05 [0.80, 1.36] 0.68 [0.22, 2.05] 0.68 [0.22, 2.05] 1.02 [0.79, 1.32]	Favours [D+T] Favours [D] Risk Ratio



mainly upregulated on the surface of cancer cells. In addition, PD-L1 is expressed in tumor-infiltrating immune cells. These basic characteristics suggest that anti-PD-1/PD-L1 therapeutics could reverse immune resistance in the tumor microenvironment.^[47]

Consequently, dual inhibition of CTLA-4 and PD-1/PD-L1 might be a reasonable and potentially synergistic therapeutic modality advanced cancer patient. In a randomized, doubleblind, phase II study, the response rates of melanoma patients were significantly higher in nivolumab plus ipilimumab group (61%) than in ipilimumab group (11%) (P < .001).^[48] A phase III clinical study, Checkmate-067, showed a median PFS of 11.5 months in patients treated with nivolumab and ipilimumab combination therapy, compared with 2.9 and 6.9 months in patients treated with ipilimumab or nivolumab monotherapy, respectively.^[13] Another open-label, phase III trial displayed that nivolumab plus ipilimumab prolong median OS compared to chemotherapy in advanced NSCLC patients regardless of the status of PD-L1 (17.1 versus 13.9 months), and suggested combining nivolumab and ipilimumab as a first-line treatment for advanced NSCLC.^[6]

The blockage of CTLA-4 and PD-1 exerts critical anti-tumor effects.^[49] However, such benefits were not observed when solid tumor patients were treated with durvalumab and tremelimumab in our study.

Even nivolumab and durvalumab are working to block the PD-1/PD-L1 signaling pathway, the combining sites are different. Nivolumab is a PD-1 inhibitor, whereas durvalumab is a PD-L1 inhibitor. There are now lacking the head-to-head clinical studies

or 1 o 1	D+1	1	D			Risk Ratio	Risk Ratio
Study or Subgroup			Events	lotal	Weight	M-H. Random, 95% C	I M-H. Random. 95% Cl
1.1.1 Pancreatic ductal ad							
Eileen M. O' Reilly 2019 Subtotal (95% CI)	7	32	2	32	19.5% 19.5%	3.50 [0.79, 15.58] 3.50 [0.79, 15.58]	
Total events	7		2		10.070	0.00 [0.10, 10.00]	
Heterogeneity: Not applica	1.00		-				
Test for overall effect: Z =		0.10)					
1.1.2 Head and neck squa	amous ce	Il carci	noma				
Lillian L. Siu 2019	21	133	8	65	75.7%	1.28 [0.60, 2.74]	
Subtotal (95% CI)		133		65	75.7%	1.28 [0.60, 2.74]	
Total events	21		8				
Heterogeneity: Not applica	ble						
Test for overall effect: Z = 0		0.52)					
1.1.3 Gastric and gastroe	sophage	al junct	ion aden	ocarci	noma		
Ronan J. Kelly 2019	2	71	0	24	4.8%	1.74 [0.09, 34.94]	
Subtotal (95% CI)		71		24	4.8%	1.74 [0.09, 34.94]	
Total events	2		0				
Heterogeneity: Not applica	ble						
Test for overall effect: Z = 0	0.36 (P = 0	0.72)					
Total (95% CI)		236		121	100.0%	1.58 [0.82, 3.06]	•
Total events	30		10				
Total events Heterogeneity: Tau ² = 0.00				50); l²	= 0%		
	; Chi ² = 1.	39, df =		50); l²	= 0%		0.01 0.1 1 10 10 Eavours [D+T] Eavours [D]
Heterogeneity: Tau ² = 0.00); Chi ² = 1. 1.37 (P = 0	.39, df = 0.17)	= 2 (P = 0.				0.01 0.1 1 10 10 Favours [D+T] Favours [D]
Heterogeneity: $Tau^2 = 0.00$ Test for overall effect: Z = T); Chi² = 1. 1.37 (P = (ces: Chi² =	.39, df = 0.17)	= 2 (P = 0. If = 2 (P =			Pick Potio	Favours [D+T] Favours [D]
Heterogeneity: Tau ² = 0.00 Test for overall effect: Z = Test for subaroup difference); Chi ² = 1. 1.37 (P = 0 ces: Chi ² = D+T	39, df = 0.17) 1.38. d	= 2 (P = 0. If = 2 (P = T	0.50).	l² = 0%	Risk Ratio	Favours [D+T] Favours [D] Risk Ratio
Heterogeneity: Tau ² = 0.00 Test for overall effect: Z = Test for subaroup difference Study or Subgroup E); Chi ² = 1. 1.37 (P = 0 ces: Chi ² = D+T cvents To	39, df = 0.17) 1.38. d	= 2 (P = 0. If = 2 (P = T <u>vents To</u>	0.50).	l² = 0%		Favours [D+T] Favours [D]
Heterogeneity: Tau ² = 0.00 Test for overall effect: Z = Test for suboroup difference Study or Subgroup E 1.1.1 Head and neck squ); Chi ² = 1. 1.37 (P = (ces: Chi ² = D+T <u>vents Te</u> jamous c	39, df = 0.17) 1.38. d otal Events	= 2 (P = 0. If = 2 (P = T <u>vents To</u> cinoma	0.50). otal V	l² = 0% /eight	I-H. Random. 95% Cl	Favours [D+T] Favours [D] Risk Ratio
Heterogeneity: Tau ² = 0.00 Test for overall effect: Z = Test for suboroup difference Study or Subgroup E 1.1.1 Head and neck squ Lillian L. Siu 2019); Chi ² = 1. 1.37 (P = 0 ces: Chi ² = D+T vents To Jamous c 21	39, df = 0.17) 1.38. d otal Ev ell card	= 2 (P = 0. If = 2 (P = T <u>vents To</u>	0.50). otal V 65	l² = 0% /eight	0.93 [0.48, 1.82]	Favours [D+T] Favours [D] Risk Ratio
Heterogeneity: Tau ² = 0.00 Test for overall effect: Z = 1 Test for suboroup difference Study or Subgroup E 1.1.1 Head and neck squ Lillian L. Siu 2019 Subtotal (95% CI)); Chi ² = 1. 1.37 (P = 0 ces: Chi ² = D+T vents To jamous c 21	39, df = 0.17) 1.38. d otal Events	= 2 (P = 0. If = 2 (P = T <u>vents To</u> cinoma 11	0.50). otal V 65	l² = 0% /eight	I-H. Random. 95% Cl	Favours [D+T] Favours [D] Risk Ratio
Heterogeneity: Tau ² = 0.00 Test for overall effect: Z = 1 Test for suboroup difference Study or Subgroup E 1.1.1 Head and neck squ Lillian L. Siu 2019 Subtotal (95% CI) Total events); Chi ² = 1. 1.37 (P = (ces: Chi ² = D+T Jamous c 21 21	39, df = 0.17) 1.38. d otal Ev ell card	= 2 (P = 0. If = 2 (P = T <u>vents To</u> cinoma	0.50). otal V 65	l² = 0% /eight	0.93 [0.48, 1.82]	Favours [D+T] Favours [D] Risk Ratio
Heterogeneity: Tau ² = 0.00 Test for overall effect: Z = 1 Test for suboroup difference Study or Subgroup E 1.1.1 Head and neck squ Lillian L. Siu 2019 Subtotal (95% CI) Total events Heterogeneity: Not applica); Chi ² = 1. 1.37 (P = (39, df = 0.17) 1.38. d otal Ev ell card 133 133	= 2 (P = 0. If = 2 (P = T <u>vents To</u> cinoma 11	0.50). otal V 65	l² = 0% /eight	0.93 [0.48, 1.82]	Favours [D+T] Favours [D] Risk Ratio
Heterogeneity: Tau ² = 0.00 Test for overall effect: Z = 1 Test for suboroup difference Study or Subgroup E 1.1.1 Head and neck squ Lillian L. Siu 2019 Subtotal (95% CI) Total events); Chi ² = 1. 1.37 (P = (39, df = 0.17) 1.38. d otal Ev ell card 133 133	= 2 (P = 0. If = 2 (P = T <u>vents To</u> cinoma 11	0.50). otal V 65	l² = 0% /eight	0.93 [0.48, 1.82]	Favours [D+T] Favours [D] Risk Ratio
Heterogeneity: Tau ² = 0.00 Test for overall effect: Z = 1 Test for suboroup difference Study or Subgroup E 1.1.1 Head and neck squ Lillian L. Siu 2019 Subtotal (95% CI) Total events Heterogeneity: Not applica Test for overall effect: Z = 1.1.2 Gastric and gastro); Chi ² = 1. 1.37 (P = (bes: Chi ² = D+T tramous c 21 21 able 0.20 (P = esophage	39, df = 0.17) 1.38. d 0tal Ev ell caro 133 133 0.84) eal junc	2 (P = 0. If = 2 (P = T <u>vents Tr</u> cinoma 11 11 11	0.50). otal W 65 65	1² = 0% /eight 1 92.4% 92.4% cinoma	M-H. Random. 95% Cl 0.93 [0.48, 1.82] 0.93 [0.48, 1.82]	Favours [D+T] Favours [D] Risk Ratio
Heterogeneity: Tau ² = 0.00 Test for overall effect: Z = 1 Test for suboroup difference Study or Subgroup E 1.1.1 Head and neck squ Lillian L. Siu 2019 Subtotal (95% Cl) Total events Heterogeneity: Not applica Test for overall effect: Z = 1.1.2 Gastric and gastro Ronan J. Kelly 2019); Chi ² = 1. 1.37 (P = (bes: Chi ² = D+T Jamous c 21 21 able 0.20 (P =	39, df = 0.17) 1.38. d 0tal Evell card 133 133 0.84) eal june 71	2 (P = 0. If = 2 (P = T <u>vents Tr</u> cinoma 11 11	0.50). otal V 65 65 nocar 12	I ² = 0% /eight I 92.4% 92.4% cinoma 7.6%	M-H. Random. 95% Cl 0.93 [0.48, 1.82] 0.93 [0.48, 1.82] 0.34 [0.03, 3.44]	Favours [D+T] Favours [D] Risk Ratio
Heterogeneity: Tau ² = 0.00 Test for overall effect: Z = 1 Test for suboroup difference Study or Subgroup E 1.1.1 Head and neck squ Lillian L. Siu 2019 Subtotal (95% Cl) Total events Heterogeneity: Not applica Test for overall effect: Z = 1.1.2 Gastric and gastro Ronan J. Kelly 2019 Subtotal (95% Cl)); Chi ² = 1. 1.37 (P = (bes: Chi ² = D+T vents T(iamous c 21 21 able 0.20 (P = esophagi 2	39, df = 0.17) 1.38. d 0tal Ev ell caro 133 133 0.84) eal junc	2 (P = 0. If = 2 (P = T vents To cinoma 11 11 11 ction ade 1	0.50). otal W 65 65	1² = 0% /eight 1 92.4% 92.4% cinoma	M-H. Random. 95% Cl 0.93 [0.48, 1.82] 0.93 [0.48, 1.82]	Favours [D+T] Favours [D] Risk Ratio
Heterogeneity: Tau ² = 0.00 Test for overall effect: Z = - Test for suboroup difference Study or Subgroup E 1.1.1 Head and neck squ Lillian L. Siu 2019 Subtotal (95% Cl) Total events Heterogeneity: Not applica Test for overall effect: Z = 1.1.2 Gastric and gastro Ronan J. Kelly 2019 Subtotal (95% Cl) Total events); Chi ² = 1. 1.37 (P = (bes: Chi ² = D+T vents T(iamous c 21 21 able 0.20 (P = esophage 2 2	39, df = 0.17) 1.38. d 0tal Evell card 133 133 0.84) eal june 71	2 (P = 0. If = 2 (P = T <u>vents Tr</u> cinoma 11 11 11	0.50). otal V 65 65 nocar 12	I ² = 0% /eight I 92.4% 92.4% cinoma 7.6%	M-H. Random. 95% Cl 0.93 [0.48, 1.82] 0.93 [0.48, 1.82] 0.34 [0.03, 3.44]	Favours [D+T] Favours [D] Risk Ratio
Heterogeneity: Tau ² = 0.00 Test for overall effect: Z = 1 Test for suboroup difference Study or Subgroup E 1.1.1 Head and neck squ Lillian L. Siu 2019 Subtotal (95% Cl) Total events Heterogeneity: Not applica Test for overall effect: Z = 1.1.2 Gastric and gastro Ronan J. Kelly 2019 Subtotal (95% Cl) Total events Heterogeneity: Not applica); Chi ² = 1. 1.37 (P = (2.21) 21 21 21 21 21 22 22 22 22 22	39, df = 0.17) 1.38. d 0tal En ell card 133 133 133 0.84) eal jund 71 71	2 (P = 0. If = 2 (P = T vents To cinoma 11 11 11 ction ade 1	0.50). otal V 65 65 nocar 12	I ² = 0% /eight I 92.4% 92.4% cinoma 7.6%	M-H. Random. 95% Cl 0.93 [0.48, 1.82] 0.93 [0.48, 1.82] 0.34 [0.03, 3.44]	Favours [D+T] Favours [D] Risk Ratio
Heterogeneity: Tau ² = 0.00 Test for overall effect: Z = - Test for suboroup difference Study or Subgroup E 1.1.1 Head and neck squ Lillian L. Siu 2019 Subtotal (95% Cl) Total events Heterogeneity: Not applica Test for overall effect: Z = 1.1.2 Gastric and gastro Ronan J. Kelly 2019 Subtotal (95% Cl) Total events); Chi ² = 1. 1.37 (P = (2.21) 21 21 21 21 21 22 22 22 22 22	39, df = 0.17) 1.38. d 0tal En ell card 133 133 133 0.84) eal jund 71 71	2 (P = 0. If = 2 (P = T vents To cinoma 11 11 11 ction ade 1	0.50). otal V 65 65 nocar 12	I ² = 0% /eight I 92.4% 92.4% cinoma 7.6%	M-H. Random. 95% Cl 0.93 [0.48, 1.82] 0.93 [0.48, 1.82] 0.34 [0.03, 3.44]	Favours [D+T] Favours [D] Risk Ratio
Heterogeneity: Tau ² = 0.00 Test for overall effect: Z = 1 Test for suboroup difference Study or Subgroup E 1.1.1 Head and neck squ Lillian L. Siu 2019 Subtotal (95% Cl) Total events Heterogeneity: Not applica Test for overall effect: Z = 1.1.2 Gastric and gastro Ronan J. Kelly 2019 Subtotal (95% Cl) Total events Heterogeneity: Not applica); Chi ² = 1. 1.37 (P = (bes: Chi ² = D+T vents T(jamous c 21 21 able 0.20 (P = esophage 2 able 0.92 (P =	39, df = 0.17) 1.38. d 0tal En ell card 133 133 133 0.84) eal jund 71 71	2 (P = 0. If = 2 (P = T vents To cinoma 11 11 11 ction ade 1	0.50). <u>otal W</u> 65 65 nocar 12 12	I ² = 0% /eight I 92.4% 92.4% cinoma 7.6%	M-H. Random. 95% Cl 0.93 [0.48, 1.82] 0.93 [0.48, 1.82] 0.34 [0.03, 3.44]	Favours [D+T] Favours [D] Risk Ratio
Heterogeneity: Tau ² = 0.00 Test for overall effect: Z = 1 Test for suboroup difference Study or Suboroup difference 1.1.1 Head and neck squ Lillian L. Siu 2019 Subtotal (95% CI) Total events Heterogeneity: Not applica Test for overall effect: Z = 1.1.2 Gastric and gastro Ronan J. Kelly 2019 Subtotal (95% CI) Total events Heterogeneity: Not applica Test for overall effect: Z =); Chi ² = 1. 1.37 (P = (bes: Chi ² = D+T vents T(jamous c 21 21 able 0.20 (P = esophage 2 able 0.92 (P =	39, df = 0.17) 1.38. d 0tal Ev ell card 133 133 133 133 133 133 133 133 133 13	2 (P = 0. If = 2 (P = T vents To cinoma 11 11 11 ction ade 1	0.50). <u>otal W</u> 65 65 nocar 12 12	I ² = 0% <u>leight</u> 92.4% 92.4% cinoma 7.6% 7.6%	M-H. Random. 95% Cl 0.93 [0.48, 1.82] 0.93 [0.48, 1.82] 0.34 [0.03, 3.44] 0.34 [0.03, 3.44]	Favours [D+T] Favours [D] Risk Ratio
Heterogeneity: Tau ² = 0.00 Test for overall effect: Z = 1 Test for suboroup difference Study or Subgroup E 1.1.1 Head and neck squ Lillian L. Siu 2019 Subtotal (95% CI) Total events Heterogeneity: Not applic: Test for overall effect: Z = 1.1.2 Gastric and gastro Ronan J. Kelly 2019 Subtotal (95% CI) Total events Heterogeneity: Not applic: Test for overall effect: Z = Total (95% CI)); Chi ² = 1. 1.37 (P = (bes: Chi ² = D+T vents To amous c 21 21 able 0.20 (P = esophage 2 able 0.92 (P = 2 23	39, df = 0.17) 1.38. d 0tal Excell card 133 133 133 133 133 133 133 133 133 13	2 (P = 0. If = 2 (P = T vents To cinoma 11 11 11 11 11 11 11 11 12	0.50). <u>otal W</u> 65 65 nocar 12 12 77 1	I ² = 0% <u>/eight 1</u> 02.4% 92.4% cinoma 7.6% 7.6% 7.6% 00.0%	M-H. Random. 95% Cl 0.93 [0.48, 1.82] 0.93 [0.48, 1.82] 0.34 [0.03, 3.44] 0.34 [0.03, 3.44] 0.86 [0.46, 1.64]	Favours [D+T] Favours [D] Risk Ratio

Figure 5. Forest plots of risk ratios for grade \geq 3 treatment-related adverse events in advanced solid tumors. (A) Durvalumab plus tremelimumab (D+T) versus durvalumab (D); (B) Durvalumab plus tremelimumab (D+T) versus tremelimumab (T).

comparing the efficacy between anti-PD-1 therapy and anti-PD-L1 therapy. According to previously published studies, PD-1 antibodies and PD-L1 antibodies showed unequal treatment effects.^[50–52]

The lack of efficacy of adding tremelimumab to durvalumab may be attributed to the mechanism of action, as tremelimumab is an IgG2 monoclonal antibody that does not cause lysis of regulatory T cells through the way of antibody-dependent cell-mediated cytotoxicity, which is observed with ipilimumab.^[53]

For patients treated previously systematic chemotherapeutics in the eligible studies, the immune microenvironment might have been changed. Tumor-infiltrating lymphocytes are associated with the response to immunotherapy.^[54–56] However, T cell exhaustion could drive a decline in the ability of T cells to kill tumor cells. A recent study indicated that T cells were stored in dense antigen-presenting-cell niches within the tumor microenvironment, but tumors that failed to form these immune niches were not extensively infiltrated by T cells. Patients with advanced or recurrent disease lack these niches, suggesting that niche breakdown in tumor tissues may be a key factor of immune resistance or escape.^[57]

Several limitations exist in this analysis. All enrolled studies are phase I or II clinical trials, whereas data from randomized controlled phase III studies are lacking. In addition, open-label studies might increase publication bias even the trials were conducted in various centers. The analysis of ORR and DCR

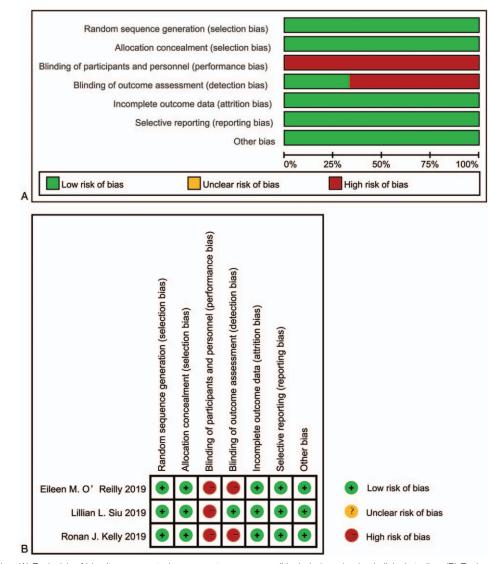


Figure 6. Risk of bias. (A) Each risk of bias item presented as percentages across all included randomized clinical studies; (B) Each risk of bias item for each included randomized clinical study. 'green+': low risk, 'red -': high risk, 'yellow?': unclear risk of bias.

comprised 3 types of cancers that might not fully represent the efficacy of combination therapy in solid tumors. The type of tumors was complex and different cancer types had different inflamed and tumor mutation burden backgrounds, which could directly diminish the interpretability of the meta-analysis.

5. Conclusion

Durvalumab and tremelimumab combination therapy appeared active for the treatment of HNSCC. However, future studies are also needed to identify the patients that most possibly benefit from dual immune checkpoint inhibitors.

Acknowledgment

We thank the members of the BCSNOWELL STUDIO for providing statistical supports and helping to improve the grammar and spelling.

Author contributions

Study design, data extraction, and data analysis: BW, GL, and PL; manuscript writing and edition: BW, JF and QL. Conceptualization: Bi-Cheng Wang, Peng-Cheng Li, Guo-He Lin. Data curation: Bi-Cheng Wang, Peng-Cheng Li, Guo-He Lin. Formal analysis: Bi-Cheng Wang. Funding acquisition: Bi-Cheng Wang, Guo-He Lin. Investigation: Bi-Cheng Wang. Methodology: Bi-Cheng Wang, Guo-He Lin. Project administration: Bi-Cheng Wang. Resources: Bi-Cheng Wang. Software: Bi-Cheng Wang, Peng-Cheng Li, Guo-He Lin. Supervision: Bi-Cheng Wang, Ji-Quan Fan, Quentin Liu. Validation: Bi-Cheng Wang. Visualization: Bi-Cheng Wang. Writing - original draft: Bi-Cheng Wang, Ji-Quan Fan, Quentin Liu.

Writing – review & editing: Bi-Cheng Wang, Ji-Quan Fan, Quentin Liu.

References

- Wang BC, Cao RB, Li PD, et al. The effects and safety of PD-1/PD-L1 inhibitors on head and neck cancer: a systematic review and metaanalysis. Cancer Med 2019;8:5969–78.
- [2] Wang BC, Zhang ZJ, Fu C, et al. Efficacy and safety of anti-PD-1/PD-L1 agents vs chemotherapy in patients with gastric or gastroesophageal junction cancer: a systematic review and meta-analysis. Medicine (Baltimore) 2019;98:e18054.
- [3] Nizam A, Aragon-Ching JB. Frontline immunotherapy treatment with nivolumab and ipilimumab in metastatic renal cell cancer: a new standard of care. Cancer Biol Ther 2019;20:6–7.
- [4] Reck M, Borghaei H, O'Byrne KJ. Nivolumab plus ipilimumab in nonsmall-cell lung cancer. Future Oncol 2019;15:2287–302.
- [5] Das R, Verma R, Sznol M, et al. Combination therapy with anti-CTLA-4 and anti-PD-1 leads to distinct immunologic changes in vivo. J Immunol 2015;194:950–9.
- [6] Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. N Engl J Med 2019;381:2020–31.
- [7] Ready N, Hellmann MD, Awad MM, et al. First-line nivolumab plus ipilimumab in advanced non-small-cell lung cancer (CheckMate 568): outcomes by programmed death ligand 1 and tumor mutational burden as biomarkers. J Clin Oncol 2019;37:992–1000.
- [8] Reck M, Schenker M, Lee KH, et al. Nivolumab plus ipilimumab versus chemotherapy as first-line treatment in advanced non-small-cell lung cancer with high tumour mutational burden: patient-reported outcomes results from the randomised, open-label, phase III CheckMate 227 trial. Eur J Cancer 2019;116:137–47.
- [9] Morse MA, Overman MJ, Hartman L, et al. Safety of nivolumab plus low-dose ipilimumab in previously treated microsatellite instability-high/ mismatch repair-deficient metastatic colorectal cancer. Oncologist 2019;24:1453–61.
- [10] Hellmann MD, Rizvi NA, Goldman JW, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. Lancet Oncol 2017;18:31–41.
- [11] Antonia SJ, Lopez-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. Lancet Oncol 2016;17:883–95.
- [12] Stewart R, Morrow M, Hammond SA, et al. Identification and characterization of MEDI4736, an antagonistic anti-PD-L1 monoclonal antibody. Cancer Immunol Res 2015;3:1052–62.
- [13] Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015;373:23–34.
- [14] Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. N Engl J Med 2018;379:2342–50.
- [15] Garassino MC, Cho BC, Kim JH, et al. Durvalumab as third-line or later treatment for advanced non-small-cell lung cancer (ATLANTIC): an open-label, single-arm, phase 2 study. Lancet Oncol 2018;19:521–36.
- [16] Segal NH, Ou SI, Balmanoukian A, et al. Safety and efficacy of durvalumab in patients with head and neck squamous cell carcinoma: results from a phase I/II expansion cohort. Eur J Cancer 2019;109:154– 61.
- [17] Loibl S, Untch M, Burchardi N, et al. A randomised phase II study investigating durvalumab in addition to an anthracycline taxane-based neoadjuvant therapy in early triple-negative breast cancer: clinical results and biomarker analysis of GeparNuevo study. Ann Oncol 2019;30:1279–88.
- [18] Powles T, O'Donnell PH, Massard C, et al. Efficacy and safety of durvalumab in locally advanced or metastatic urothelial carcinoma: updated results from a phase 1/2 open-label study. JAMA Oncol 2017;3: e172411.
- [19] Massard C, Gordon MS, Sharma S, et al. Safety and efficacy of durvalumab (MEDI4736), an anti-programmed cell death ligand-1 immune checkpoint inhibitor, in patients with advanced urothelial bladder cancer. J Clin Oncol 2016;34:3119–25.

- [20] Ribas A, Camacho LH, Lopez-Berestein G, et al. Antitumor activity in melanoma and anti-self responses in a phase I trial with the anti-cytotoxic T lymphocyte-associated antigen 4 monoclonal antibody CP-675,206. J Clin Oncol 2005;23:8968–77.
- [21] Venkatraman D, Anderson A, Digumarthy S, et al. Phase 2 study of tremelimumab plus durvalumab for previously-treated malignant pleural mesothelioma (MPM). J Clin Oncol 2019;37:
- [22] Senan S, Shire N, Mak G, et al. ADRIATIC: a phase III trial of durvalumab 6 tremelimumab after concurrent chemoradiation for patients with limited stage small cell lung cancer. Ann Oncol 2019;30:
- [23] Lee JJ, Yothers G, George TJ, et al. Phase II study of dual immune checkpoint blockade (ICB) with durvalumab (Durva) plus tremelimumab (T) following palliative hypofractionated radiotherapy (SBRT) in patients (pts) with microsatellite-stable (MSS) metastatic colorectal cancer (mCRC) progressing on chemotherapy: NSABP FC-9. Cancer Res 2019;79:
- [24] Grande E, Guerrero F, Puente J, et al. DUTRENEO Trial: A phase II randomized trial of DUrvalumab and TREmelimumab as NEOadjuvant approach in muscle-invasive urothelial bladder cancer (MIBC) patients prospectively selected by immune signature scores. J Clin Oncol 2019;37:
- [25] Sonpavde G, Peters S, Nordquist LT, et al. A phase 3b safety study of fixed-dose durvalumab + tremelimumab or durvalumab monotherapy in advanced solid malignancies (STRONG): urothelial and non-urothelial urinary tract carcinoma module A. J Clin Oncol 2018;36:
- [26] Necchi A, Mariani L, Raggi D, et al. APACHE: an open label, randomized, phase II study of Durvalumab (Durva), alone or in combination with Tremelimumab (Treme), in patients (pts) with advanced germ cell tumors (GCT): results at the end of first stage. Cancer Res 2018;78:
- [27] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Open Med 2009;3:e123–30.
- [28] Siu LL, Even C, Mesia R, et al. Safety and efficacy of durvalumab with or without tremelimumab in patients with PD-L1-low/negative recurrent or metastatic HNSCC: the phase 2 CONDOR randomized clinical trial. JAMA Oncol 2019;5:195–203.
- [29] O'Reilly EM, Oh DY, Dhani N, et al. Durvalumab with or without tremelimumab for patients with metastatic pancreatic ductal adenocarcinoma: a phase 2 randomized clinical trial. JAMA Oncol 2019;5:1431– 8.
- [30] Kelly RJ, Lee J, Bang YJ, et al. Safety and efficacy of durvalumab and tremelimumab alone or in combination in patients with advanced gastric and gastroesophageal junction adenocarcinoma. Clin Cancer Res 2019;26:846–54.
- [31] Calabro L, Morra A, Giannarelli D, et al. Tremelimumab combined with durvalumab in patients with mesothelioma (NIBIT-MESO-1): an openlabel, non-randomised, phase 2 study. Lancet Resp Med 2018;6:451–60.
- [32] Antonia S, Goldberg SB, Balmanoukian A, et al. Safety and antitumour activity of durvalumab plus tremelimumab in non-small cell lung cancer: a multicentre, phase 1b study. Lancet Oncol 2016;17:299–308.
- [33] Dunn GP, Bruce AT, Ikeda H, et al. Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol 2002;3:991–8.
- [34] Drake CG, Jaffee E, Pardoll DM. Mechanisms of immune evasion by tumors. Adv Immunol 2006;90:51–81.
- [35] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646–74.
- [36] Topalian SL, Weiner GJ, Pardoll DM. Cancer immunotherapy comes of age. J Clin Oncol 2011;29:4828–36.
- [37] Li Z, Chen L, Rubinstein MP. Cancer immunotherapy: are we there yet? Exp Hematol Oncol 2013;2:33.
- [38] Schneider H, Downey J, Smith A, et al. Reversal of the TCR stop signal by CTLA-4. Science 2006;313:1972–5.
- [39] Miska J, Abdulreda MH, Devarajan P, et al. Real-time immune cell interactions in target tissue during autoimmune-induced damage and graft tolerance. J Exp Med 2014;211:441–56.
- [40] Mora JR, von Andrian UH. T-cell homing specificity and plasticity: new concepts and future challenges. Trends Immunol 2006;27:235–43.
- [41] Ott PA, Hodi FS, Robert C. CTLA-4 and PD-1/PD-L1 blockade: new immunotherapeutic modalities with durable clinical benefit in melanoma patients. Clin Cancer Res 2013;19:5300–9.
- [42] Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 2008;26:677–704.
- [43] Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 2010;236:219–42.

- [44] Okazaki T, Chikuma S, Iwai Y, et al. A rheostat for immune responses: the unique properties of PD-1 and their advantages for clinical application. Nat Immunol 2013;14:1212–8.
- [45] Fife BT, Pauken KE, Eagar TN, et al. Interactions between PD-1 and PD-L1 promote tolerance by blocking the TCR-induced stop signal. Nat Immunol 2009;10:1185–92.
- [46] Freeman GJ, Long AJ, Iwai Y, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med 2000;192:1027–34.
- [47] Topalian SL, Drake CG, Pardoll DM. Targeting the PD-1/B7-H1(PD-L1) pathway to activate anti-tumor immunity. Curr Opin Immunol 2012;24:207–12.
- [48] Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med 2015;372: 2006–17.
- [49] Wei Y, Du Q, Jiang X, et al. Efficacy and safety of combination immunotherapy for malignant solid tumors: a systematic review and meta-analysis. Crit Rev Oncol Hematol 2019;138:178–89.
- [50] Cohen EEW, Soulieres D, Le Tourneau C, et al. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic headand-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study. Lancet 2019;393:156–67.

- [51] Ferris RL, Blumenschein GJr, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med 2016;375:1856–67.
- [52] Schmid P, Adams S, Rugo HS, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. N Engl J Med 2018;379: 2108–21.
- [53] Romano E, Kusio-Kobialka M, Foukas PG, et al. Ipilimumab-dependent cell-mediated cytotoxicity of regulatory T cells ex vivo by nonclassical monocytes in melanoma patients. Proc Natl Acad Sci U S A 2015; 112:6140–5.
- [54] Eroglu Z, Zaretsky JM, Hu-Lieskovan S, et al. High response rate to PD-1 blockade in desmoplastic melanomas. Nature 2018; 553:347–50.
- [55] Savas P, Virassamy B, Ye C, et al. Single-cell profiling of breast cancer T cells reveals a tissue-resident memory subset associated with improved prognosis. Nat Med 2018;24:986–93.
- [56] Peranzoni E, Lemoine J, Vimeux L, et al. Macrophages impede CD8 T cells from reaching tumor cells and limit the efficacy of anti-PD-1 treatment. Proc Natl Acad Sci U S A 2018;115:E4041–50.
- [57] Jansen CS, Prokhnevska N, Master VA, et al. An intra-tumoral niche maintains and differentiates stem-like CD8 T cells. Nature 2019; 576:465–70.