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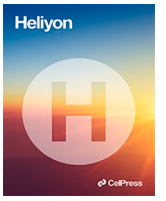

Review article

Efficacy and safety of PD-1 Monoclonal antibodies in the treatment of esophageal squamous cell carcinoma: Systematic review and meta Regression

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ABSTRACT

Background: Esophageal Squamous Cell Carcinoma (ESCC) contributes to the global burden of disease. Conventional treatments such as surgical resection and chemotherapy offer limited long-term survival rates. Recently, immunotherapies targeting PD-1 have shown promise in other cancers, but their efficacy in ESCC remains unclear.

Methods: The 31 studies eligible for this study included a total of 10,681 patients who were subjected to immunotherapy, either alone or in combination with traditional chemotherapy. A comprehensive search was conducted on September 1, 2023, across databases including CENTRAL, PubMed, MEDLINE, Web of Science, Embase, and Scopus.

Results: For OSR, results indicate a significantly improved survival at different time points (6, 12, and 24 months), with an odds ratio of 0.636 (95 % CI 0.595–0.680; $Z = -13.292$; $p < 0.00001$). In terms of PFS, PD-1 inhibitors demonstrated improvements at different time points; pooled odds ratio was 0.568 (95 % CI 0.511–0.633; $Z = -10.357$; $p < 0.00001$). Regarding ORR, the pooled analysis showed an overall odds ratio of 1.724 (95 % CI 1.554–1.913; $Z = 10.289$; $p < 0.00001$), indicating improved treatment response. DCR did not suggest a significant advantage for PD-1 inhibitors over chemotherapy, with an odds ratio of 0.904 (95 % CI 0.784–1.043; $Z = -1.381$; $p = 0.167$).

Conclusions: There is compelling evidence reinforcing the efficacy and safety of PD-1 inhibitors, as monotherapy or in combination with chemotherapy, for the treatment of ESCC. PD-1 inhibitors demonstrate a significant advantage in terms of OSR, PFS, and ORR.

1. Introduction

Esophageal Squamous Cell Carcinoma (ESCC) contributes to the global burden of disease, particularly in developing countries where prevalence is higher [1]. Current treatment modalities for ESCC include surgical resection, esophagectomy, chemotherapy and radiation therapy [2]. While these are conventional approaches, five-year survival rates for ESCC are still disappointingly low at approximately 15 % [3,4]. The dawn of immunotherapy, specifically immune checkpoint inhibitors designed to inhibit Programmed

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Glossary

ESCC	esophageal squamous cell carcinoma
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PD-L2	programmed death ligand 2
PD-1 inhibitors	immune checkpoint inhibitors that block PD-1
OSR	overall survival rate
PFS	progression-free survival
ORR	objective response rate; synonymous with overall response rate
DCR	disease control rate
OR	odds ratio
CI	confidence interval

Cell Death Protein 1 (PD-1), have emerged as a promising treatment approach [5]. Novel agents which target PD-1, possess the ability to adjust the immune system so as to efficiently identify and target cancer cells [6] (see Figs. 4–6).

PD-1 is an immune checkpoint receptor primarily expressed on T cells, B cells, and interestingly, an increased expression on natural killer (NK) cells in gastrointestinal cancers such as ESCC [7]. PD-1 regulates the immune response by binding to programmed death ligand 1 (PD-L1) and programmed death ligand 2 (PD-L2), which are often overexpressed on tumor cells [8]. This results in restricted T-cell activity which is protective in autoimmune diseases but problematic in cancer treatment. Immune checkpoint inhibitors target PD-1 in order to liberate the immune system to create a heightened anti-tumor response [9].

The use of PD-1 inhibitors in cancers of the skin and lung has been demonstrated previously [10,11]. However, their function in ESCC remains uncertain. Initial studies show potential in improving Overall Survival (OS) and Progression-Free Survival (PFS), but the number of studies is limited and decisive evidence regarding long-term efficacy and safety in ESCC is deficient [12]. Comparative research against standard therapies or other immunotherapeutic agents is also limited.

Previous reviews on immunotherapy in esophageal cancer combine ESCC with adenocarcinoma and evaluate several checkpoint inhibitors, not explicitly focusing on PD-1 inhibitors [13]. The lack of specificity may hinder clinical decision-making in ESCC management. Additionally, the rapid developments in immunotherapy, including new data from clinical trials and long-term safety will outdate past reviews. Therefore, a targeted systematic review on the efficacy and safety of PD-1 inhibitors in ESCC is necessary so as to lead both clinical practice and future research.

The objective of this systematic review is to evaluate the efficacy and safety of PD-1 inhibitors in the treatment of ESCC.

2. Methods

2.1. Search strategy

Our comprehensive search was conducted last time on September 1, 2023, in major databases.

- Cochrane Central Register of Controlled Trials (CENTRAL),
- PubMed
- MEDLINE (including MEDLINE InProcess) (OvidSP)
- Web of Science
- Embase (OvidSP)
- Scopus databases

Full search strategy in Supplement.

2.2. Inclusion and exclusion criteria

The only studies allowed were those that were conducted in English. Randomized control trials and observational cohort studies that evaluate the impact of PD-1 on patients with esophageal squamous cell carcinoma at any stage or grade and over the course of follow-up in comparison to conventional chemotherapy, either the drug alone or compounded with other chemotherapy that matches our aim outcome in this analysis, met the inclusion criteria. We disregarded records with a single arm, irrelevant to our PICO, that compared chemotherapy to radiotherapy and other treatments, records with insufficient data, abstracts, and animal and vivo studies.

2.3. Data extraction and measured outcomes

The outcomes for this paper were 6-, 12-, and 24-month Overall Survival Rate (OSR), 6-, 12-, and 24-month Progression-Free Survival (PFS), Objective Response Rate (ORR), Disease Control Rate (DCR), and Adverse Effects and Safety Profile. Where

available, these outcomes, as well as data regarding demographics, were extracted from each study. This was done by two independent investigators, with any discrepancies resolved by the senior author. For each outcome, statistical comparisons were made within these subgroups in addition to the entire cohort.

2.4. Statistical analysis

The retrieved data was subjected to a meta-analysis using the Comprehensive Meta-Analysis 4.0 software. The heterogeneity test was aided by the chi-square test, and a quantification value of 22 was found. If $P > 0.1$ and $I^2 < 50$ % showed that studies were homogeneous, a fixed-effects model was applied; if $P < 0.1$ and $I^2 > 50$ % showed that there was significant heterogeneity between studies, a random-effects model was applied. For continuous variables, the mean difference (MD) was computed; for binary variables, the odds ratio (OR) was computed; and for each effect size, the point estimate and 95 percent confidence interval (CI) were provided. The test level was set at 0.05.

3. Results

3.1. Included studies

Through the initial search a total of 1574 articles were obtained. After title and abstract screening, 1509 articles were excluded based on aforementioned exclusion criteria. Further full text screening was completed on the remaining articles, resulting in 16 studies to be included in the meta-analysis.

3.1.1. Study characteristics

The characteristics of the included studies are described in Table 1.

4. Assessment of publication bias

Funnel plots of outcomes resulted in symmetrical shapes, indicating minimal publication bias. There was no evidence that statistically insignificant results were excluded from these studies (see Fig. 1).

4.1. Assessment of risk of bias

We assessed risk of bias in each randomized controlled trial using a modified version of Cochrane's tool for assessing risk of bias as outlined in the Cochrane Handbook for Systematic Reviews of Interventions. Six of the domains assessed were sequence generation, allocation concealment, blinding, incomplete outcome data, and within-study selective outcome reporting. Two review authors independently assessed the risk of bias for each study based on these domains with judgments of 'low risk of bias', 'high risk of bias', and 'unclear risk'. We resolved discrepancies by discussion and consensus. The summary of quality assessment domains of included studies is shown in Fig. 2

5. Outcomes

5.1. Overall Survival Rate

In a comprehensive analysis of pooled data from studies examining 6-month, 12-month, and 24-month OSR, the overall odds ratio was 0.636 (95 % CI 0.595–0.680; $Z = -13.292$; $p < 0.00001$) (see Fig. 3). The data also displayed minimal heterogeneity ($Q = 41.069$; $df = 45$; $p = 0.639$; $I^2 = 0.000$; $Tau^2 = 0.000$). These results provide compelling evidence for the impact of PD-1 inhibitors, as monotherapy or in combination with chemotherapy, in improving the overall survival rates across different time intervals for patients with ESCC.

As subgroups: at 6 months, 16 studies were analyzed and the pooled odds ratio was 0.693 (95 % CI 0.623–0.771; $Z = -6.728$; $p < 0.00001$). At 12 months, 16 studies were analyzed and the pooled odds ratio was 0.604 (95 % CI 0.548–0.665; $Z = -10.250$; $p < 0.00001$). At 24 months, 14 studies were analyzed and the pooled odds ratio was 0.596 (95 % CI 0.496–0.716; $Z = -5.514$; $p < 0.00001$).

5.2. Progression-Free Survival

In the analysis of PFS, significant improvements in PFS were observed at multiple time points. There was also minimal to moderate heterogeneity suggesting sustained effectiveness and stability in studies over a longer time frame.

At 6 months, analysis included 16 studies. The pooled odds ratio was 0.568 (95 % CI 0.511–0.633; $Z = -10.357$; $p < 0.00001$). There was moderate heterogeneity ($Q = 38.906$; $df = 15$; $p = 0.001$; $I^2 = 0.614$; $Tau^2 = 0.078$).

At 12 months, analysis included 16 studies. The pooled odds ratio was 0.390 (95 % CI 0.329–0.463; $Z = -10.819$; $p < 0.00001$). There was moderate heterogeneity ($Q = 30.587$; $df = 15$; $p = 0.001$; $I^2 = 0.510$; $Tau^2 = 0.130$).

At 24 months, analysis included 12 studies. The pooled odds ratio was 0.332 (95 % CI 0.213–0.517; $Z = -4.884$; $p < 0.00001$).

Table 1
Study characteristics.

Study	Design	Year	Age	Sample size	Drug	Dose	Compound	Follow up duration	Comparison
Ahn et al. [14]	retrospective design	2022	patients aged 18 years and above	first-line therapy cohort was 948 patients second-line therapy cohort, was 60 patients	Pembrolizumab Nivolumab		combination carboplatin, paclitaxel, pembrolizumab; combination fluorouracil, cisplatin, pembrolizumab; combination pembrolizumab and carboplatin; and monotherapy pembrolizumab or nivolumab.	NA	Non-immunotherapy includes monotherapy use and combination use of carboplatin, paclitaxel, protein-bound paclitaxel, fluorouracil, docetaxel, oxaliplatin, cisplatin,
Cao et al. [15]	RCTs	2022	*Asian subgroup* **Pembrolizumab** 66.0 (45–80) **Chemotherapy** 64.0 (33–84) *China cohort* **Pembrolizumab** 61.5 (45–74) **Chemotherapy** 59.0 (41–77)	*Asian subgroup* **Pembrolizumab** n = 110 **Chemotherapy** n = 111 *China cohort* **Pembrolizumab** n = 60 **Chemotherapy** n = 59	Pembrolizumab	200 mg	paclitaxel, docetaxel, or irinotecan	NA	Pembrolizumab **VERSUS** Chemotherapy
Doki et al. [16]	RCTs	2022	**Nivolumab + Chemotherapy** 64 (40–90) **Nivolumab + Ipilimumab** 63 (28–81) **Chemotherapy** 64 (26–81)	**Nivolumab + Chemotherapy** (n = 321) **Nivolumab + Ipilimumab** (n = 325) **Chemotherapy** (N = 324)	Nivolumab	240 mg	Ipilimumab 1 mg/kg fluorouracil and cisplatin	13-month minimum follow-up	Nivolumab + Chemotherapy **VERSUS** Nivolumab + Ipilimumab **VERSUS** Chemotherapy
Huang et al. [17]	RCTs	2020	**Camrelizumab group** 60 (54–65) **Chemotherapy group** 60 (54–65)	**Camrelizumab group** (n = 228) **Chemotherapy group** (n = 220)	Camrelizumab	200 mg		median follow-up duration was 8·3 months (IQR 4·1–12·8) in the camrelizumab group and 6·2 months (3·6–10·1) in the chemotherapy group.	or chemotherapy with docetaxel or irinotecan
Kao et al. [18]	Retrospective Study	2023	**Nivolumab + chemo** (53 ± 7.544) **Nivolumab + Ipilimumab** (56 ± 5.090) **Chemotherapy** (59 ± 10.886)	**Nivolumab + chemo** (n = 25) **Nivolumab + Ipilimumab** (n = 7) **Chemotherapy** (n = 27)	Nivolumab	240 mg	platinum (cisplatin, carboplatin, and oxaliplatin), 5-fluorouracil (5FU), and taxanes (paclitaxel and docetaxel)	NA	nivolumab + chemotherapy **VERSUS** nivolumab + ipilimumab **VERSUS** chemotherapy
Kato et al. [19]	RCTs	2019	**Nivolumab group** 64 (57–69) **Chemotherapy group** 67 (57–72)	**Nivolumab group** (n = 210) **Chemotherapy group** (n = 209)	Nivolumab	240 mg		minimum follow-up time (ie, time from random assignment of the last patient to data cutoff) of 17.6 months	Paclitaxel and docetaxel

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Table 1 (*continued*)

Study	Design	Year	Age	Sample size	Drug	Dose	Compound	Follow up duration	Comparison
Lee et al. [20]	RCT	2023	**Total** 65.0 (37–77) **Part A** [56.0 (44–77)] **Part B** [65.5 (37–68)]	**Part A** n = 6 **Part B** n = 10	Durvalumab	1500 mg	Tremelimumab 75 mg Cisplatin 80 mg/m2 + 5FU 800 mg/m2/day	16 patients. Follow-up range 5–100 weeks median of 4.0 treatment cycles	Durvalumab + Tremelimumab + Chemotherapy
Lin et al. [21]	Retrospective, single-center, three-arm study	2022	**Group A** 57 [50–72] **Group B** 70 [42–80] **Group C** 69 [56–80]	**Group A** (n = 22) **Group B** (n = 9) **Group C** (n = 8)	Pembrolizumab	200 mg	aclitaxel and nedaplatin	median follow-up time was 14 months (3–34 months)	**pembrolizumab + chemo as induction therapy.** After 4 cycles: radical surgery **(group A)** radical radiotherapy **(group B)** or neither **(group C)**
Lu et al.[22]	Retrospective Study	2023	**Anti-PD-1 + chemotherapy** 67 (48–78) **Chemotherapy alone** 65 (46–76)	**Anti-PD-1 + chemotherapy** n = 25 **Chemotherapy alone** n = 25	Tislelizumab Camrelizumab, Pembrolizumab	200 mg	The chemotherapy drugs were paclitaxel (175 mg/m2) and cisplatin (75 mg/m2), which were given on the first day	median duration of follow-up was 16.2 months (range, 4.8–23.9 months)	tislelizumab, camrelizumab, pembrolizumab **VERSUS** Chemotherapy
Lu et al.[23]	RCT	2022	**Sintilimab and chemotherapy** 63 (IQR; 57–67) **Placebo and chemotherapy** 63 (IQR; 56–67)	**Sintilimab and chemotherapy** (n = 327) **Placebo and chemotherapy** (n = 332)	Sintilimab	3 mg/kg for <60 kg or 200 mg for ≥60 kg	cisplatin plus paclitaxel or cisplatin plus 5-fluorouracil	Median follow-up for overall survival was 16.0 months	Sintilimab and chemotherapy **VERSUS** Placebo and chemotherapy
Luo et al. [24]	RCTs	2021	**Camrelizumab + chemotherapy** 62 (56–66) **Placebo + chemotherapy** 62 (56–67)	**Camrelizumab + chemotherapy** (n = 298) **Placebo + chemotherapy** (n = 298)	Camrelizumab	200 mg	6 cycles of paclitaxel and cisplatin	median follow-up was 10.8 months	Camrelizumab + chemotherapy **VERSUS** Placebo + chemotherapy
Lv et al.[25]	Retrospective Study	2022	65 (60–69; IQR)	n = 96	Sintilimab	200 mg	platinum and taxanes followed by esophagectomy	Follow-up was routinely conducted every 3 months during the first 2 years after surgery, and then every 6 months after 2 years. Median follow-up was 8.9 months	efficacy and safety of **neoadjuvant sintilimab + chemotherapy** in resectable locally advanced ESCC.
Ma et al. [26]	Retrospective Study	2023	**Anti-PD-1 + Chemoradio** 68 (47–74) **Chemoradio** 70 (50–75)	**Anti-PD-1 + Chemoradio** n = 30 **Chemoradio** n = 51	Tislelizumab Camrelizumab, Pembrolizumab	200 mg	All patients received standard intensity-modulated radiotherapy (IMRT). TP (paclitaxel plus cisplatin or carboplatin, 3-week cycle); FP (5-fluorouracil plus cisplatin, 4-week cycle).	Median follow-up was 31.4 months.	tislelizumab, camrelizumab, pembrolizumab **VERSUS** Chemoradiotherapy
Mu et al. [27]	multicentre, phase 2 study	2021	63 (44–75)	n = 23	SHR-1316	10 mg/kg	SHR-1316 plus liposomal irinotecan and 5-fluorouracil	median follow-up duration was 15.2 months (14.2–16.2)	NA

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Table 1 (*continued*)

Study	Design	Year	Age	Sample size	Drug	Dose	Compound	Follow up duration	Comparison
Muro et al. [28]	RCT	2022	**pembrolizumab,** 67 (50–80) **chemotherapy,** 67 (41–84)	**pembrolizumab,** n = 77 **chemotherapy,** n = 75	Pembrolizumab	200 mg	paclitaxel 80–100 mg/m2 on days 1, 8, and 15 of each 28-day cycle or docetaxel 75 mg/m2 on day 1 of each 21-day cycle	NA	Pembrolizumab **VERSUS** Chemotherapy
Ohsawa et al. [29]	Retrospective Observational Study	2023	**Overall** 66.2 ± 9.2 **Nivolumab** 70.0 ± 8.3 **Taxane** 64.1 ± 9.0	**Total** = 171 **Nivolumab** n = 61 **Taxane** n = 110	Nivolumab	240 mg	Paclitaxel (100 mg/m2) was administered for 60 min once weekly for six weeks, followed by no treatment for one week (each cycle of seven weeks). Docetaxel (75 mg/m2) was administered for 60 min every three weeks (each cycle of three weeks) until disease progression or toxicity was observed	follow-up period of at least 15 months	Serplulimab + chemotherapy **VERSUS** Placebo + chemotherapy
Okada et al. [30]	RCT	2022		**Overall** Nivolumab (n = 171) Chemotherapy (n = 158) **Patients who survived for 3 years** Nivolumab (n = 23) Chemotherapy (n = 8)	Nivolumab	240 mg	100 mg/m2 of paclitaxel IV every week for 6 weeks, followed by 1 week off (each cycle was 7 weeks) or 75 mg/m2 of docetaxel IV every 3 weeks (each cycle was 3 weeks)	minimum follow-up period was 36.0 months	Nivolumab **VERSUS** Chemotherapy
Qiao et al. [31]	Retrospective Study	2022	**Camrelizumab + NeoadjuvantChemo** 64.15 ± 7.293 **NeoadjuvantChemo** 62.22 ± 7.136	**Total** n = 254 **Camrelizumab + NeoadjuvantChemo** n = 48 **NeoadjuvantChemo** n = 206	Camrelizumab	200 mg	platinum-containing double-drug chemotherapy regimen including paclitaxel, albumin-bound paclitaxel or docetaxel	NA	Camrelizumab + NeoadjuvantChemotherapy **VERSUS** Neoadjuvant Chemotherapy
Lee et al. [32]	Retrospective Study	2021	65 (39–85)	n = 58	Nivolumab	3 mg/kg	ESCC patients refractory/intolerant to at least one line of chemotherapy and who received nivolumab as a subsequent line of therapy were included.	median follow-up duration for overall survival was 13.8 months	NA
Shen et al. [33]	RCT	2022	**Tislelizumab** (62.0 (40–86)) **ICC** (63.0 (35–81))	**Tislelizumab** (n = 256) **ICC** (n = 256)	Tislelizumab	200 mg	paclitaxel, docetaxel, or irinotecan	median follow-up from random assignment to data cutoff or death, whichever came first, was 8.5 months (0.2–31.7 months) for tislelizumab and 5.8 months (0.0–30.8 months) for chemotherapy	Tislelizumab **VERSUS** Chemotherapy

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Table 1 (*continued*)

Study	Design	Year	Age	Sample size	Drug	Dose	Compound	Follow up duration	Comparison
Song et al. [34]	RCT	2023	**Drug + Chemo** [64 (57–68)] **Placebo + Chemo** [64 (57–68)]	**Drug + Chemo** n = 368 **Placebo + Chemo** n = 183	Serplulimab	3 mg/kg	cisplatin (on day 1) and 5-fluorouracil (on days 1 and 2), once every 2 weeks	Tumor imaging scheduled once every 6 weeks for 48 weeks from randomization and every 12 weeks thereafter	Serplulimab + chemotherapy **VERSUS** Placebo + chemotherapy
Sun et al. [35]	RCTs	2021	**Pembrolizumab + chemotherapy** 64 (28–94) **Placebo + chemotherapy** 62 (27–89)	**Pembrolizumab + chemotherapy** (n = 373) **Placebo + chemotherapy** (n = 376)	Pembrolizumab	200 mg	chemotherapy (5-fluorouracil plus cisplatin)	median follow-up of 22.6 months	Pembrolizumab plus chemotherapy **VERSUS** chemotherapy alone
Takahashi et al. [36]	RCTs	2021	**Nivolumab** 65.0 (41–82) **Chemotherapy** 68.0 (33–80)	**Nivolumab** n = 136 **Chemotherapy** n = 138	Nivolumab	240 mg	paclitaxel or docetaxel	minimum follow-up period was 17.6 months	NA
Van Cutsem et al. [37]	RCT	2022	**Tislelizumab** (62.0 (40–86)) **ICC** (63.0 (35–81))	**Tislelizumab** (n = 256) **ICC** (n = 256)	Tislelizumab	200 mg	paclitaxel, docetaxel, or irinotecan	current study did not examine the longer-term effect of tislelizumab on HRQoL. It is possible that some later worsening was not captured or the failure to find differences between arms could be due to the shorter-term follow-up.	Tislelizumab **VERSUS** Chemotherapy
Wang et al. [38]	Single-center Retrospective Study	2023	**Overall** [61.78 (41–81)] **<80 % dose intensity** [62.80 (52–74)] **80–90 % dose intensity** [61.59 (47–81)] **90–100 % dose intensity** [60.79 (41–74)]	**Overall** n = 122 **<80 % dose intensity** n = 40 **80–90 % dose intensity** n = 37 **90–100 % dose intensity** n = 45	Tislelizumab	200 mg	Platinum-based chemotherapy regimen. Cisplatin combined with paclitaxel or abraxane	Median follow-up 13.76 months after esophagectomy	PD-1 inhibitor + different dose intensity neoadjuvant chemotherapy
Wang et al. [39]	Retrospective Study	2023	**Surgery alone** 60.6 ± 7.4 **NICT** 60.3 ± 7.3	**Total** = 137 **Surgery alone** n = 85 **NICT** n = 52	Sintilimab Pembrolizumab Camrelizumab	200 mg 200 mg 200 mg	Taxel paclitaxel, albumin-boundpaclitaxel, or docetaxel) + platinum-based (cisplatinum, carbopla-tin, nedaplatin, and lobaplatin) or albumin-bound paclitaxel plusfluorouracil (S1 and capecitabine)	For patients receiving NICT, the surgery was performed approximately 4–8 weeks after the end of the last neoadjuvant therapy if there were no surgical contraindications	Neoadjuvant immunotherapy combined with chemotherapy (NICT) **VERSUS** Surgery alone
Wei et al. [40]	Retrospective Study	2022	**Total (<65;** 44 (45.8), **≥65;** 52 (54.2)) **ICIs Group (<65;** 23	**Total** (n = 96) **ICIs Group** (n = 48)	Camrelizumab Tislelizumab Sintilimab	200 mg	platinum + paclitaxel	median follow-up time for surviving patients was 11.0 months	ICIs + CRT/CT **VERSUS** CRT/CT

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Table 1 (*continued*)

Study	Design	Year	Age	Sample size	Drug	Dose	Compound	Follow up duration	Comparison
			(47.9), **≥65;** 25 (52.1)) **Control Group** (**<65;** 21 (43.8), **≥65;** 27 (56.3))	**Control Group** (n = 48)					
Xia et al. [41]	Retrospective Single-arm Cohort Study	2022	**Total** 67.5 (59.0–71.0) **Partial Remission** 67.0 (59.0–70.8) **Stable Disease** 67.5 (62.0–72.3)	**Total** n = 66 **Partial Remission** n = 50 **Stable Disease** n = 16	Camrelizumab	200 mg	platinum + paclitaxel	Follow-up is based on the patient's regular admission to the hospital for examination and treatment, at least 3 months after surgery.	All participants receive the experimental treatment. There is no control group for comparison.
Xu et al.[42]	RCT	2023	**Drug + Chemo** [64.0 (59.0–68.0)] **Placebo + Chemo** [65.0 (58.0–70.0)]	**Total** = 649 **Drug + Chemo** n = 326 **Placebo + Chemo** n = 323	Tislelizumab	200 mg	Chemotherapy (platinum + fluoropyrimidine or platinum + paclitaxel)	Median 16.3 months tislelizumab group. 9.8 months placebo group	Tislelizumab + chemotherapy **VERSUS** Placebo + chemotherapy
Ebert et al. [43]	multicentre, open-label phase 2 trial	2022	**Nivolumab monotherapy** 72.5 (62–83) **Nivolumab + ipilimumab** 69 (55–84)	**Nivolumab monotherapy** (n = 22) **Nivolumab + ipilimumab** (n = 44)	Nivolumab	240 mg	Ipilimumab 1 mg/kg	Median follow-up was 6·8 months	Nivolumab monotherapy **VERSUS** Nivolumab + ipilimumab **VERSUS** Historical cohort receiving standard chemotherapy in the intention-to-treat population.
Zhang et al. [44]	Retrospective Observational Study	2022	**Median** 61 (44–74)	**Neoadjuvant + surgery** n = 20 **Chemoradio + Pembrolizumab** n = 22 **Chemo + Pembrolizumab** n = 15	Pembrolizumab	NA	chemotherapy (platinum and nab-paclitaxel) Radiotherapy was delivered by means of external-beam radiation	The median PFS and OS were not analyzed in this study as the follow-up time varied significantly.	Neoadjuvant + surgery **VERSUS** Chemoradio + Pembrolizumab **VERSUS** Chemo + Pembrolizumab

There was minimal heterogeneity (Q = 7.425; df = 11; p = 0.764; I^2 = 0.000; Tau^2 = 0.000).

5.3. Objective Response Rate

For ORR, the following PD-1 inhibitors were analyzed: Compound, Nivolumab, Pembrolizumab, Serplulimab, Sintilimab, and Tislelizumab. Analysis included 21 studies, of which 12 combined PD-1 inhibitors with chemotherapy and 9 used PD-1 inhibitors as monotherapy. The pooled odds ratio was 1.724 (95 % CI 1.554–1.913; Z = 10.289; p < 0.00001). There was some heterogeneity (Q = 56.976; df = 20; p < 0.00001; I^2 = 0.649; Tau^2 = 0.113).

5.3.1. Disease Control Rate

For DCR, the following PD-1 inhibitors were analyzed: Compound, Nivolumab, Pembrolizumab, Sintilimab, Tislelizumab. Analysis included 14 studies, the result was not significant, suggesting that PD-1 inhibitors do not demonstrate an advantage over chemotherapy in terms of disease control. The pooled odds ratio was 0.904 (95 % CI 0.784–1.043; Z = −1.381; p = 0.167). There was a high

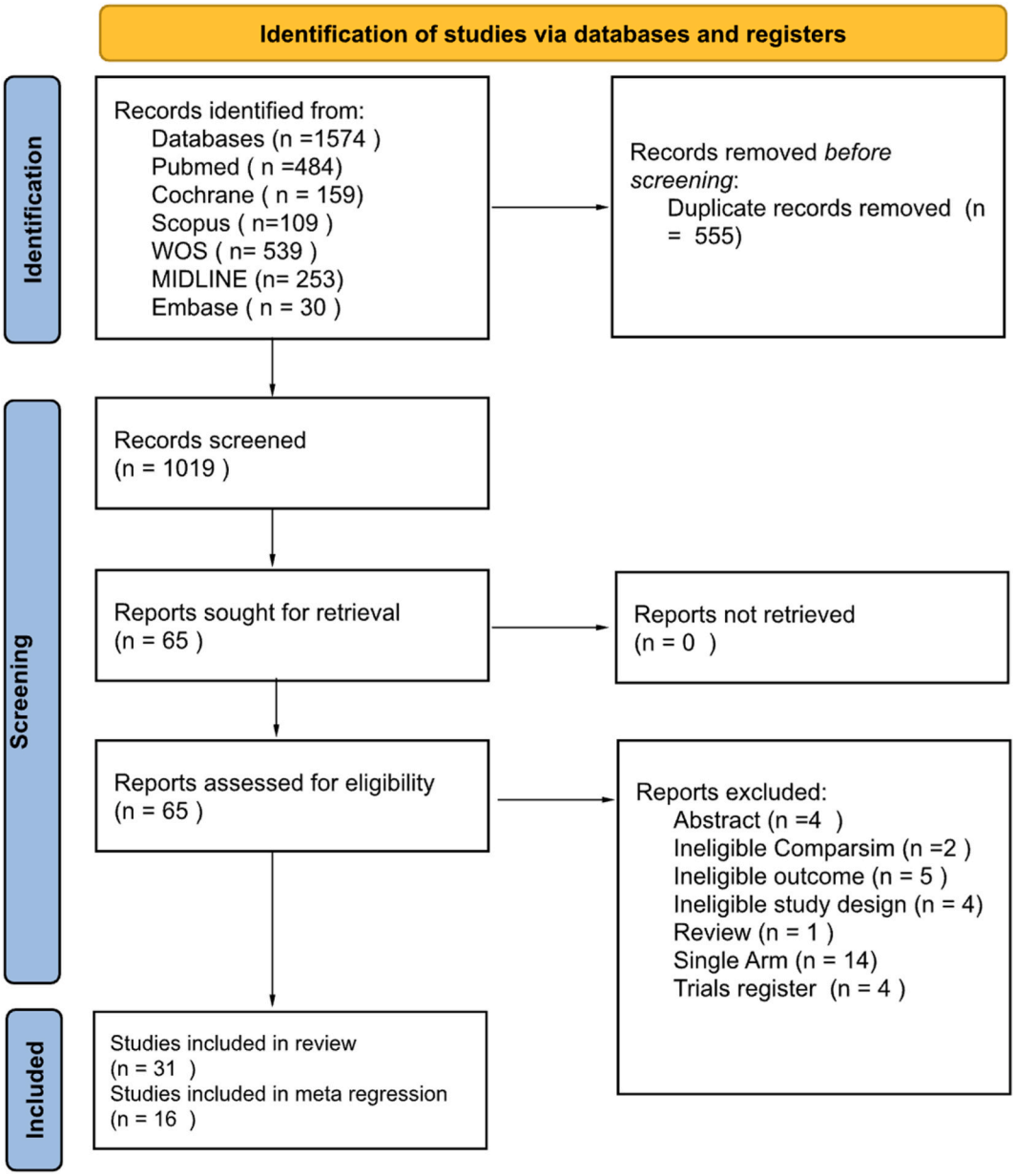


Fig. 1. Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) flow diagram of included studies.

level of heterogeneity (Q = 101.259; df = 13; p < 0.00001; I^2 = 0.871; Tau^2 = 0.519).

5.3.2. Adverse Effects and Safety Profile

Statistical analysis of the overall adverse effect and safety profile for PD-1 inhibitors suggest a significant reduction in the risk of adverse effects when using PD-1 inhibitors either alone or in combination with chemotherapy. The pooled odds ratio was 0.821 (95 % CI 0.734–0.918; Z = −3.454; p = 0.001). There is some heterogeneity observed (Q = 409.655; df = 26; p < 0.00001; I^2 = 0.937; Tau^2 = 1.340).

PD-1 versus Chemotherapy: our analysis of this subgroup included 12 studies, consisting of 5 studies with Grade 3-5 adverse effects and 7 studies with adverse effects of any grade. Findings suggest a significant lower likelihood of experiencing adverse effects with PD-1 inhibitors compared to chemotherapy. The pooled odds ratio was 0.594 (95 % CI 0.499–0.708; Z = −5.815; p < 0.00001). There is high heterogeneity between the studies (Q = 371.992, df = 11; p < 0.00001; I^2 = 0.970; Tau^2 = 3.250).

PD-1 and Chemotherapy: our analysis of this subgroup included 16 studies, consisting of 8 studies with Grade >3 adverse effects and 8 studies with adverse effects of any grade. Findings indicate that the combination of PD-1 inhibitors and chemotherapy does not significantly alter the risk of adverse effects. The pooled odds ratio was 1.064 (95 % CI 0.923–1.226; Z = 0.857; p = 0.391). There is low heterogeneity between the studies (Q = 21.655; df = 15; p = 0.117; I^2 = 0.307; Tau^2 = 3.250).

6. Discussions

The objective of our study was to evaluate the efficacy and safety of PD-1 inhibitors in the treatment of ESCC using 5 key outcomes: Overall Survival Rate (OSR), Progression-Free Survival (PFS), Objective Response Rate (ORR), Disease Control Rate (DCR), and Adverse Effects and Safety Profile. We analyzed 31 studies which consisted of a total 10, 681 patients. These included studies evaluated immunotherapeutic agents, such as Nivolumab, Pembrolizumab, and Camrelizumab, with or without chemotherapy. Overall, we demonstrated that PD-1 inhibitors, monotherapy or in combination with chemotherapy, significantly improves OSR, PFS, and ORR; and the overall Adverse Effects and Safety Profile were more favorable for PD-1 inhibitors. DCR did not display significant improvement with PD-1 inhibitors compared to chemotherapy. In OSR and PFS, these benefits largely remained consistent within the 6-month, 12-month, and 24-month subgroups.

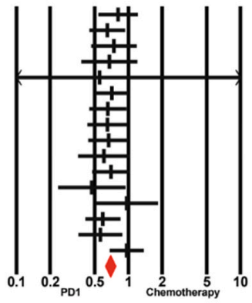
In agreement with the meta-analysis by Leone and colleagues, who reported a hazard ratio (HR) for OSR of 0.71 in favor of immunotherapy compared to chemotherapy (10 studies; 5257 patients), [45] our study also found a significant OSR improvement when immunotherapy was employed. Furthermore, Leone and colleagues examined PD-L1 expression. They found that the OSR was dependent on PD-L1 combined positive score status. This is reinforced by the meta-analysis of Yap and colleagues (9 studies; 4752 patients), who found a lack of OSR benefit for subgroups with low PD-L1 expression.[46]

Our findings also partially align with the meta-analysis of Zhu and colleagues (5 studies; 1970 patients), who found that second-line

Fig. 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

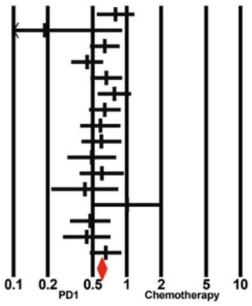
Overall survival rate (6 months)

Study name		Outcome	Statistics for each study					
			Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
Song 2023	PD1 wtih Chemotherapy	overall survival rate	0.808	0.544	1.199	-1.058	0.290	6 months
Doki 2022	PD1 wtih Chemotherapy	overall survival rate	0.648	0.452	0.928	-2.370	0.018	6 months
Luo 2021	PD1 wtih Chemotherapy	overall survival rate	0.743	0.470	1.174	-1.273	0.203	6 months
Lu 2022	PD1 wtih Chemotherapy	overall survival rate	0.676	0.384	1.191	-1.355	0.175	6 months
Ma 2023	PD1 wtih Chemotherapy	overall survival rate	0.552	0.022	13.980	-0.360	0.719	6 months
Sun 2021	PD1 wtih Chemotherapy	overall survival rate	0.710	0.507	0.995	-1.986	0.047	6 months
Xu 2023	PD1 wtih Chemotherapy	overall survival rate	0.655	0.451	0.951	-2.223	0.026	6 months
Kato 2019	PD1 alone	overall survival rate	0.651	0.434	0.975	-2.081	0.037	6 months
Ohsawa 2023	PD1 alone	overall survival rate	0.664	0.443	0.995	-1.982	0.047	6 months
Takahashi 2021	PD1 alone	overall survival rate	0.605	0.359	1.020	-1.885	0.059	6 months
Huang 2020	PD1 alone	overall survival rate	0.700	0.480	1.021	-1.850	0.064	6 months
Muro 2022	PD1 alone	overall survival rate	0.471	0.238	0.935	-2.152	0.031	6 months
Okada 2022	PD1 alone	overall survival rate	0.966	0.512	1.824	-0.106	0.916	6 months
Shen 2022	PD1 alone	overall survival rate	0.592	0.417	0.842	-2.922	0.003	6 months
Cao 2022	PD1 alone	overall survival rate	0.562	0.361	0.875	-2.553	0.011	6 months
Doki 2022	PD1 alone	overall survival rate	0.966	0.688	1.357	-0.198	0.843	6 months
			0.693	0.623	0.771	-6.728	0.000	



Overall survival rate (12 months)

Study name		Outcome	Statistics for each study					
			Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
Song 2023	PD1 wtih Chemotherapy	overall survival rate	0.794	0.547	1.154	-1.207	0.227	12 months
Ma 2023	PD1 wtih Chemotherapy	overall survival rate	0.189	0.040	0.899	-2.094	0.036	12 months
Sun 2021	PD1 wtih Chemotherapy	overall survival rate	0.638	0.478	0.853	-3.032	0.002	12 months
Xu 2023	PD1 wtih Chemotherapy	overall survival rate	0.447	0.326	0.611	-5.029	0.000	12 months
Doki 2022	PD1 wtih Chemotherapy	overall survival rate	0.658	0.482	0.899	-2.633	0.008	12 months
Luo 2021	PD1 wtih Chemotherapy	overall survival rate	0.777	0.559	1.079	-1.504	0.132	12 months
Lu 2022	PD1 wtih Chemotherapy	overall survival rate	0.639	0.469	0.871	-2.836	0.005	12 months
Kato 2019	PD1 alone	overall survival rate	0.584	0.393	0.868	-2.657	0.008	12 months
Ohsawa 2023	PD1 alone	overall survival rate	0.597	0.401	0.887	-2.555	0.011	12 months
Takahashi 2021	PD1 alone	overall survival rate	0.490	0.302	0.795	-2.887	0.004	12 months
Huang 2020	PD1 alone	overall survival rate	0.601	0.388	0.929	-2.289	0.022	12 months
Muro 2022	PD1 alone	overall survival rate	0.426	0.218	0.831	-2.502	0.012	12 months
Okada 2022	PD1 alone	overall survival rate	1.005	0.520	1.942	0.016	0.987	12 months
Shen 2022	PD1 alone	overall survival rate	0.475	0.318	0.709	-3.642	0.000	12 months
Cao 2022	PD1 alone	overall survival rate	0.443	0.275	0.711	-3.370	0.001	12 months
Doki 2022	PD1 alone	overall survival rate	0.650	0.477	0.887	-2.716	0.007	12 months
			0.604	0.548	0.665	-10.250	0.000	



Overall survival rate (24 months)

Study name		Outcome	Statistics for each study					
			Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
Song 2023	PD1 wtih Chemotherapy	overall survival rate	1.100	0.400	3.023	0.185	0.853	24 months
Lu 2022	PD1 wtih Chemotherapy	overall survival rate	0.529	0.193	1.447	-1.241	0.215	24 months
Kato 2019	PD1 alone	overall survival rate	0.692	0.322	1.486	-0.945	0.345	24 months
Ohsawa 2023	PD1 alone	overall survival rate	0.586	0.343	0.999	-1.964	0.050	24 months
Takahashi 2021	PD1 alone	overall survival rate	0.888	0.364	2.164	-0.262	0.793	24 months
Muro 2022	PD1 alone	overall survival rate	0.657	0.222	1.946	-0.758	0.448	24 months
Okada 2022	PD1 alone	overall survival rate	0.373	0.157	0.884	-2.241	0.025	24 months
Shen 2022	PD1 alone	overall survival rate	0.372	0.131	1.060	-1.850	0.064	24 months
Ma 2023	PD1 wtih Chemotherapy	overall survival rate	1.146	0.418	3.142	0.264	0.791	24 months
Cao 2022	PD1 alone	overall survival rate	0.542	0.178	1.652	-1.077	0.282	24 months
Doki 2022	PD1 alone	overall survival rate	0.375	0.224	0.627	-3.741	0.000	24 months
Sun 2021	PD1 wtih Chemotherapy	overall survival rate	0.753	0.450	1.262	-1.076	0.282	24 months
Xu 2023	PD1 wtih Chemotherapy	overall survival rate	0.653	0.422	1.010	-1.915	0.056	24 months
Doki 2022	PD1 wtih Chemotherapy	overall survival rate	0.537	0.313	0.919	-2.266	0.023	24 months
			0.596	0.496	0.716	-5.514	0.000	

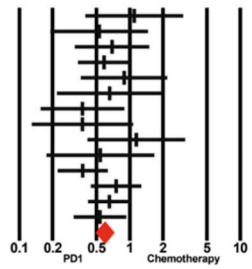


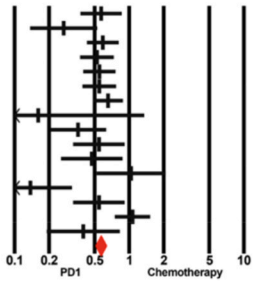
Fig. 3. Forest plot of comparison for Overall Survival Rate outcome at 6, 12, and 24 months.

PD-1 inhibitors significantly improved both OSR and ORR but did not lead to significant improvement in PFS.[47] In contrast to our study, where we observed a significant benefit in PFS.

Interestingly, Gao and colleagues conducted a Bayesian network meta-analysis (10 studies; 5250 patients) comparing different PD-1 inhibitors. They found that Toripalimab and Camrelizumab were the better agents in terms of OSR and PFS for advanced ESCC.[48] While our study did not compare different PD-1 inhibitors, the analysis by Gao et al. offers a potential avenue for future research.

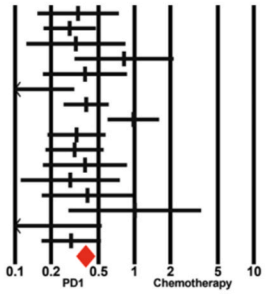
6 months progression free survival

Study name	Subgroup within study	Outcome	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
Song 2023	PD1 wtih Chemotherapy	Progression-Free Survival	0.569	0.380	0.852	-2.740	0.006	6 months
Li 2022	PD1 wtih Chemotherapy	Progression-Free Survival	0.268	0.138	0.520	-3.894	0.000	6 months
Lu 2022	PD1 wtih Chemotherapy	Progression-Free Survival	0.588	0.432	0.800	-3.374	0.001	6 months
Doki 2022	PD1 wtih Chemotherapy	Progression-Free Survival	0.523	0.377	0.727	-3.862	0.000	6 months
Xu 2023	PD1 wtih Chemotherapy	Progression-Free Survival	0.549	0.401	0.751	-3.753	0.000	6 months
Luo 2021	PD1 wtih Chemotherapy	Progression-Free Survival	0.548	0.394	0.761	-3.590	0.000	6 months
Sun 2021	PD1 wtih Chemotherapy	Progression-Free Survival	0.654	0.491	0.873	-2.884	0.004	6 months
Ma 2023	PD1 wtih Chemotherapy	Progression-Free Survival	0.161	0.019	1.340	-1.689	0.091	6 months
Shen 2022	PD1 alone	Progression-Free Survival	0.358	0.206	0.622	-3.644	0.000	6 months
Okada 2022	PD1 alone	Progression-Free Survival	0.544	0.327	0.903	-2.353	0.019	6 months
Takahashi 2021	PD1 alone	Progression-Free Survival	0.471	0.256	0.865	-2.428	0.015	6 months
Muro 2022	PD1 alone	Progression-Free Survival	1.039	0.524	2.060	0.110	0.912	6 months
Huang 2020	PD1 alone	Progression-Free Survival	0.137	0.060	0.313	-4.735	0.000	6 months
Kato 2019	PD1 alone	Progression-Free Survival	0.544	0.327	0.903	-2.353	0.019	6 months
Doki 2022	PD1 alone	Progression-Free Survival	1.069	0.756	1.511	0.377	0.706	6 months
Ohsawa 2023	PD1 alone	Progression-Free Survival	0.398	0.193	0.820	-2.498	0.012	6 months
			0.568	0.511	0.633	-10.357	0.000	



12 months progression free survival

Study name		Outcome	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
Song 2023	PD1 wtih Chemotherapy	Progression-Free Survival	0.337	0.155	0.731	-2.752	0.006	12 months
Lu 2022	PD1 wtih Chemotherapy	Progression-Free Survival	0.286	0.175	0.468	-4.982	0.000	12 months
Ma 2023	PD1 wtih Chemotherapy	Progression-Free Survival	0.323	0.125	0.830	-2.348	0.019	12 months
Muro 2022	PD1 alone	Progression-Free Survival	0.818	0.318	2.104	-0.416	0.677	12 months
Okada 2022	PD1 alone	Progression-Free Survival	0.385	0.173	0.856	-2.339	0.019	12 months
Shen 2022	PD1 alone	Progression-Free Survival	0.073	0.017	0.311	-3.539	0.000	12 months
Sun 2021	PD1 wtih Chemotherapy	Progression-Free Survival	0.394	0.258	0.602	-4.306	0.000	12 months
Xu 2023	PD1 wtih Chemotherapy	Progression-Free Survival	0.980	0.602	1.595	-0.082	0.934	12 months
Doki 2022	PD1 alone	Progression-Free Survival	0.327	0.189	0.567	-3.981	0.000	12 months
Doki 2022	PD1 wtih Chemotherapy	Progression-Free Survival	0.315	0.182	0.546	-4.123	0.000	12 months
Kato 2019	PD1 alone	Progression-Free Survival	0.385	0.173	0.856	-2.339	0.019	12 months
Ohsawa 2023	PD1 alone	Progression-Free Survival	0.290	0.113	0.745	-2.570	0.010	12 months
Takahashi 2021	PD1 alone	Progression-Free Survival	0.403	0.169	0.962	-2.047	0.041	12 months
Li 2022	PD1 wtih Chemotherapy	Progression-Free Survival	1.008	0.283	3.591	0.012	0.991	12 months
Huang 2020	PD1 alone	Progression-Free Survival	0.031	0.002	0.525	-2.407	0.016	12 months
Luo 2021	PD1 wtih Chemotherapy	Progression-Free Survival	0.295	0.168	0.518	-4.255	0.000	12 months
			0.390	0.329	0.463	-10.819	0.000	



24 months progression free survival

Study name		Outcome	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
Song 2023	PD1 wtih Chemotherapy	Progression-Free Survival	2.022	0.283	14.471	0.701	0.483	24 months
Lu 2022	PD1 wtih Chemotherapy	Progression-Free Survival	0.326	0.034	3.153	-0.968	0.333	24 months
Ma 2023	PD1 wtih Chemotherapy	Progression-Free Survival	0.667	0.185	2.406	-0.619	0.536	24 months
Sun 2021	PD1 wtih Chemotherapy	Progression-Free Survival	0.112	0.026	0.488	-2.915	0.004	24 months
Xu 2023	PD1 wtih Chemotherapy	Progression-Free Survival	0.379	0.156	0.920	-2.144	0.032	24 months
Doki 2022	PD1 wtih Chemotherapy	Progression-Free Survival	0.291	0.079	1.066	-1.863	0.062	24 months
Muro 2022	PD1 alone	Progression-Free Survival	0.333	0.034	3.278	-0.942	0.346	24 months
Okada 2022	PD1 alone	Progression-Free Survival	0.291	0.079	1.074	-1.853	0.064	24 months
Shen 2022	PD1 alone	Progression-Free Survival	0.198	0.009	4.154	-1.042	0.297	24 months
Doki 2022	PD1 alone	Progression-Free Survival	0.224	0.063	0.795	-2.316	0.021	24 months
Kato 2019	PD1 alone	Progression-Free Survival	0.141	0.007	2.756	-1.291	0.197	24 months
Takahashi 2021	PD1 alone	Progression-Free Survival	0.326	0.013	8.076	-0.684	0.494	24 months
			0.332	0.213	0.517	-4.884	0.000	

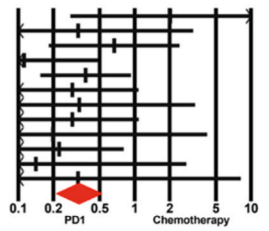


Fig. 4. Forest plot of comparison for Progression-Free Survival outcome at 6, 12, and 24 months.

Our study's adverse effects and safety profile was inconsistent with Lu and colleagues (6 studies; 3374 patients), who found that the incidence of adverse events was higher in the PD-1 inhibitors plus chemotherapy group, with no difference in grade 3 or higher adverse effects.[49] Whereas our analysis of the overall adverse effect and safety profile for PD-1 inhibitors suggest a significant reduction in the risk of adverse effects when using PD-1 inhibitors, alone or in combination with chemotherapy.

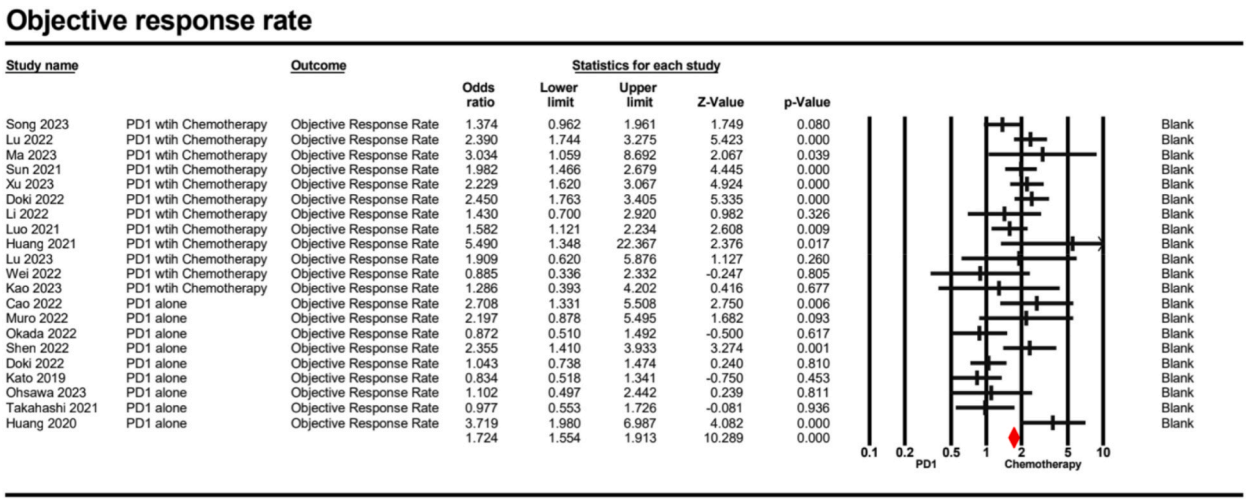


Fig. 5. Regression analysis of Objective Response Rate; A) Regression of Log odds ratio on compound or alone. B) Regression of Log odds ratio on Drug. C) Regression of Log odds ratio on Dose.

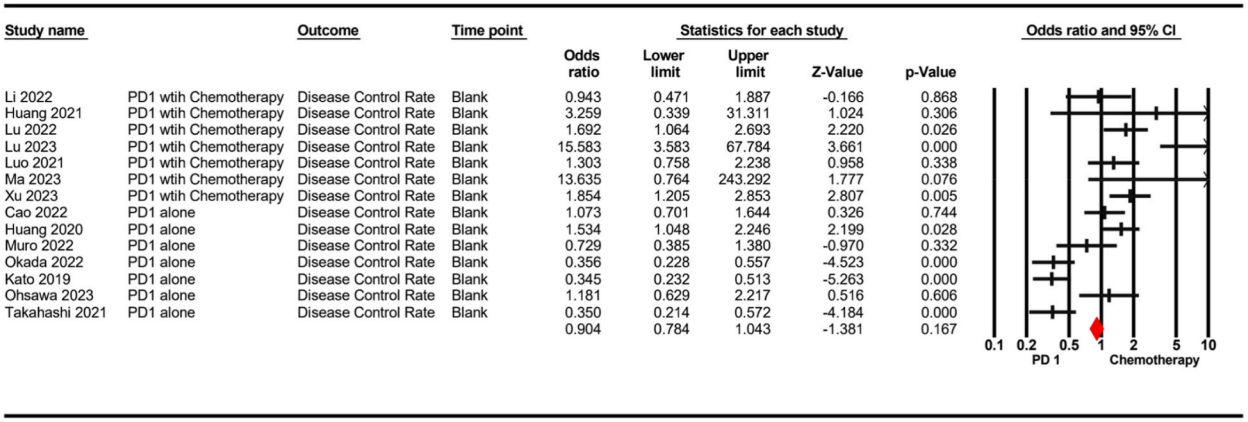


Fig. 6. Forest plot of comparison for Disease Control Rate outcome.

7. Conclusions

In conclusion, in this meta-analysis of published trials evaluating PD-1 inhibitors in ESCC, we demonstrate that PD-1 inhibitors, as monotherapy or in combination with chemotherapy, significantly improves OSR, PFS, and ORR in patients with ESCC. These advantages are consistent over different time points (6, 12, and 24 months). We also note a significant difference in adverse effects and safety profile. These findings indicate that PD-1 inhibitors can be considered as another option in the treatment of ESCC, though future research is warranted to understand the long-term outcomes and integration into current treatment regimes.

CRediT authorship contribution statement

F.A. Ameer: Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Formal analysis, Conceptualization. **Armand G:** Writing – original draft, Software, Resources, Formal analysis, Data curation. **Ahmed Ibrahim:** Software, Methodology, Investigation, Formal analysis, Data curation. **Ali Saad Al-Shammari:** Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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