

# Efficacy and Safety of PD-1 Inhibitor-Based Treatment in Advanced Cervical Cancer

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## Abstract

**Background:** This meta-analysis aimed to assess the clinical efficacy and safety of PD-1 inhibitor-based treatment in advanced cervical cancer patients.

**Methods and Results:** PubMed and Web of Science were systematically searched for relevant studies. This meta-analysis comprises 14 studies involving 1504 patients. The pooled results of ORR (objective response rate) and DCR (disease control rate) are as follows, respectively: 1) 16% and 53% in patients who were treated with a PD-1 inhibitor; 2) 26% and 56% in patients who were treated with a PD-1 plus a CTLA-4 inhibitor; 3) 68% and 92% in patients who were treated with a PD-1 inhibitor plus an antiangiogenic agent. Patients treated with a PD-1 inhibitor, a PD-1 inhibitor plus an antiangiogenic agent, or single-agent pembrolizumab experienced  $\geq$  grade 3 adverse events at rates of 21%, 50%, and 10%, respectively.

**Conclusion:** Although the therapeutic efficacy of a PD-1 inhibitor plus an antiangiogenic agent is superior to PD-1 inhibitor monotherapy or the combination of a PD-1 and CTLA-4 inhibitor, this combination is more toxic than other treatment strategies. Further evidence from large-scale randomized controlled trials is needed to validate the current results. (**International Journal of Biomedicine. 2026;16(1):46-52.**)

**Keywords:** cervical cancer • immunotherapy • efficacy • safety

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## Abbreviations

**AEs**, adverse events; **DCR**, disease control rate; **ORR**, objective response rate; **OS**, overall survival; **PFS**, progression-free survival.

## Introduction

Cervical cancer remains a major public health problem in women. Increasing rates of human papillomavirus prophylactic vaccination and well-organized screening programs in recent years have led to a decline in the incidence and mortality of cervical cancer. However, globally, many women lack access to screening programs, prophylactic vaccines, and high-quality interventional treatments when required.<sup>1</sup>

For cervical cancer, different stages have different treatment options. Early-stage cervical cancer may be cured

by surgery with tailored adjuvant therapy. Although treatment strategies have continuously evolved over the past several years, the treatment choice for locally advanced cancer is quite limited, and the prognosis of recurrence or advanced cervical cancer remains dismal.<sup>2</sup> In this scenario, immunotherapy has attracted significant attention as a potential strategy to improve clinical outcomes of recurrence or advanced cervical cancer. Pembrolizumab was approved for the treatment of PD-L1-positive, persistent, recurrent, or advanced cervical cancer in 2020.<sup>3</sup>

To date, multiple clinical trials have been conducted to investigate the effect of PD-1 inhibitor-based immunotherapy in advanced cervical cancer, and some have reported final or midterm results.<sup>4,5</sup> There is still a lack of supported evidence

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that PD-1 inhibitor-based immunotherapy in advanced cervical cancer is effective and safe. Therefore, we conducted this meta-analysis of existing studies to assess the efficacy and safety of PD-1 inhibitor-based immunotherapy in patients with advanced cervical cancer.

## Patients and Methods

### Study Strategy

All relevant studies published before 12 Mar 2025 were identified through the electronic databases PubMed and Web of Science. The following terms were used as the specific search strategy: cervical and (serplulimab or balstilimab or pembrolizumab or camrelizumab or sintilimab or nivolumab or cemiplimab or PD-1 or immune checkpoint inhibitor) and (neoplasia or tumor or malignancy or cancer or carcinoma or neoplasm) and patients. Additionally, the reference lists of relevant articles were manually examined to identify further potentially relevant studies.

### Inclusion and Exclusion Criteria

The inclusion criteria were as follows: 1) The association between PD-1 inhibitor-based immunotherapy and efficacy/safety was investigated in prospective clinical studies or retrospective studies; 2) Sample size was greater than or equal to 20 patients; 3) The included patients confirmed with advanced/persistent/recurrent/metastatic cervical cancer; 4) The patients were treated with PD-1 inhibitor, both single-agent therapy or in combination with other agents; 5) Studies reported outcome, such as either efficacy and/or safety end points, including the ORR (objective response rate), DCR (disease control rate), PFS (progression-free survival), OS (overall survival), and adverse events (AEs) with 95% confidence interval (CI) or data to calculate them; 6) Literature in English was considered. If authors published several studies using the same data, the comprehensive or most recent study was included.

The exclusion criteria were as follows: 1) Meeting abstracts, case reports, letters, reviews, and comments; 2) Duplicated publications; 3) Studies lacked the necessary data for analysis; 4) Ongoing clinical trials for which the results have not been published; 5) Animal studies.

**Table 1.**

### The clinical response.

Objective response rate	Events	No. of studies	Pooled RR (95%CI)	P	Effects model	Heterogeneity		Publication bias	
						I <sup>2</sup> (%)	Ph	Egger's	Begg's
PD-1 inhibitor	1004	10	0.16 (0.14-0.18)	0.000	Random	88.4	0.000	0.210	0.391
PD-1 inhibitor plus antiangiogenic agent	316	4	0.68 (0.63-0.73)	0.000	Random	87.0	0.000	0.089	0.025
PD-1 plus CTLA-4 inhibitor	180	2	0.26 (0.20-0.33)	0.000	Fixed	0.0	0.815	–	–
Pembrolizumab	410	5	0.16 (0.13-0.15)	0.000	Random	93.3	0.000	0.086	0.419
Disease control rate									
PD-1 inhibitor	945	9	0.53 (0.50-0.56)	0.000	Random	92.7	0.000	0.754	0.472
PD-1 inhibitor plus antiangiogenic agent	316	4	0.92 (0.89-0.95)	0.000	Random	66.9	0.028	0.089	0.118
PD-1 plus CTLA-4 inhibitor	180	2	0.56 (0.48-0.63)	0.000	Fixed	0.0	0.613	–	–
Pembrolizumab	351	4	0.50 (0.45-0.55)	0.000	Random	96.9	0.000	0.734	0.525
Nivolumab	45	2	0.56(0.17-0.94)	0.004	Random	87.8	0.004	–	–

### Data Extraction

Two investigators independently extracted data from the eligible articles according to the inclusion and exclusion criteria. A consensus was achieved for any discrepancies through discussion. The extracted data included basic information, such as first author, publication year, sample size, age, disease status, study type, intervention, recruitment, case review period, data cutoff, and follow-up time.

### Quality Assessment

We evaluated the quality of randomized controlled trials (RCTs) using the modified Jadad scale.<sup>6</sup> Methodological Index for Non-Randomized Studies (MINORS) criteria are used to assess the quality of comparative and non-comparative studies.<sup>7</sup> The retrospective studies without a comparison group were assessed by the JBI Critical Appraisal Checklist.<sup>8</sup>

### Statistical analysis

This meta-analysis was performed using Stata 12.0 (Stata Corporation). All results were reported as pooled RRs (risk ratios) and 95% CIs. The Cochran's Q test<sup>9</sup> and Higgins' I<sup>2</sup> statistic<sup>10</sup> were applied to assess the heterogeneity among the included studies. The chi-square *P*-value >0.10 or I<sup>2</sup> >50% suggested the existence of heterogeneity; a random-effect model was used; otherwise, the fixed-effect model was used. The effect size was reported as the 95% CI. Sensitivity analyses were performed to reflect the influence of individual data on the pooled results. Additionally, Begg's and Egger's tests were used to assess the potential publication bias of the enrolled studies. Values of *P*<0.05 were considered statistically significant.

## Results

### Study Selection and Characteristics

Supplementary Figure 1 shows the literature screening process. One retrospective study<sup>11</sup> and 13 prospective studies<sup>4,5,12-22</sup> with 1504 patients were included in this meta-analysis. The study by Lorusso et al.<sup>22</sup> included two cohorts by treatment; we treated this study as two reports in our analysis. The eligible studies were published from 2017 to 2025. The sample sizes ranged from 20 to 304. The general characteristics of each included study were described in Supplementary Table 1.

**Quality Assessment**

Supplementary Table 2 indicates the quality assessment of included studies. The retrospective study was assessed using the JBI Critical Appraisal Checklist and included in this study. Ten single-arm studies were evaluated using the MINORS index and scored 13-15 points, which were acceptable for the present meta-analysis. According to the Jadad scale, the included RCT studies were of high quality.

**Tumor Response**

The ORR and DCR were assessed according to Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). ORR included CR (complete response) and PR (partial response). DCR included CR, PR, and SD (stable disease). The pooled results of ORR and DCR were as follows, respectively: 1) 16% and 53% in patients who were treated with PD-1 inhibitor; 2) 68% and 92% in patients who were treated with PD-1 inhibitor plus antiangiogenic agent; 3) 26% and 50% in patients who were treated with PD-1 plus CTLA-4 inhibitor; 4) 16% and 56% in patient who were treated with single pembrolizumab (Figure 1b and Table 1).

**Progression-Free Survival**

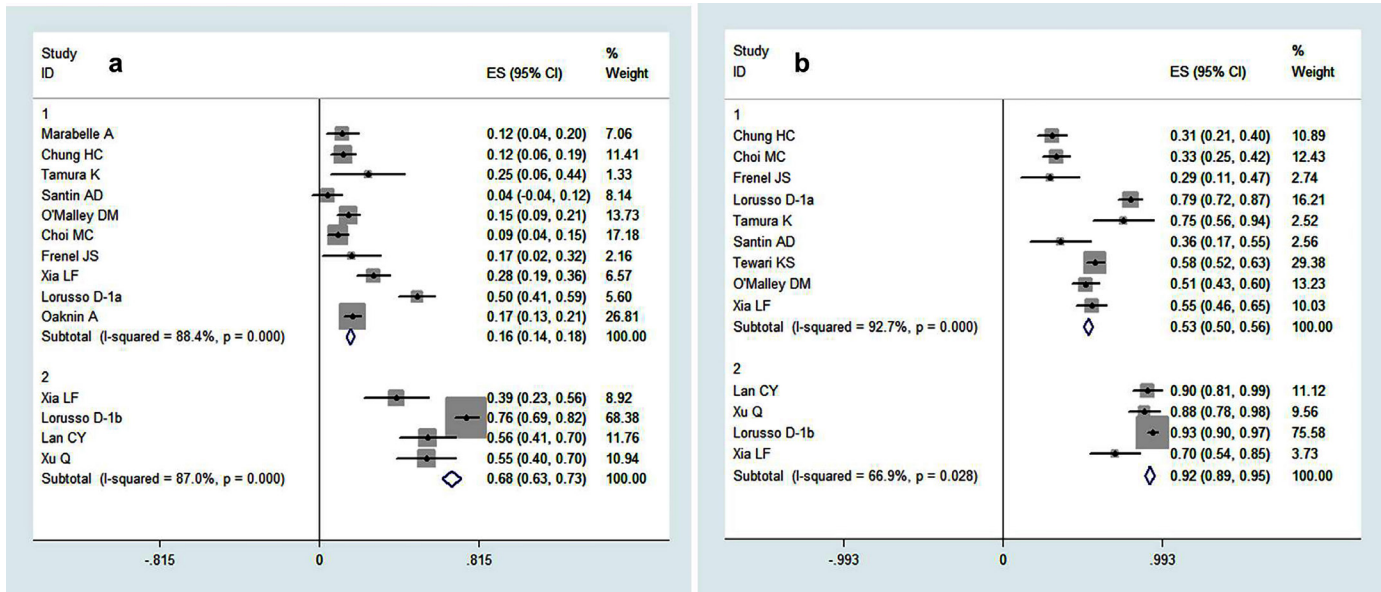
PFS was analyzed according to treatment agents. The pooled median PFS was 3.02 months in patients treated with a single PD-1 inhibitor, 2.91 months in patients treated with a single pembrolizumab, and 11.00 months in patients treated with a PD-1 inhibitor plus antiangiogenic agents (Table 2). Supplementary Table 3 shows the results of the pooled 6- and 12-month PFS rates.

**Overall Survival**

OS was also analyzed according to treatment agents. The pooled median OS was 11.66 months in patients treated with a single-agent PD-1 inhibitor, and 11.48 months in patients treated with a single-agent pembrolizumab (Table 2). The pooled 6- and 12-month OS rates are indicated in Supplementary Table 3.

**Safety**

The adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events. The results are indicated in Supplementary Table 4.



**Figure 1.** Pooled results of objective response rate (ORR) (a). <sup>1</sup>Patients were treated with a single anti-PD-1 antibody. <sup>2</sup>Patients were treated with an anti-PD-1 antibody plus antiangiogenic agent. Pooled results of disease control rate (DCR) (b). <sup>1</sup>Patients were treated with a single anti-PD-1 antibody. <sup>2</sup>Patients were treated with an anti-PD-1 antibody plus antiangiogenic agent.

**Table 2.**  
**Median PFS and OS.**

Median PFS	Events	No. of studies	Pooled RR (95%CI)	P	Effects model	Heterogeneity		Publication bias	
						I <sup>2</sup> (%)	Ph	Begg's	Egger's
PD-1 inhibitor	456	5	3.02 (1.92-4.72)	0.000	Random	97.9	0.000	0.806	0.969
Pembrolizumab	351	4	2.91 (1.78-4.75)	0.000	Random	98.4	0.000	1.00	0.983
PD-1 inhibitor plus antiangiogenic agent	268	3	11.0(7.82-15.47)	0.000	Random	50.9	0.131	1.000	0.837
<b>Median OS</b>									
PD-1 inhibitor	665	5	11.66 (9.04-15.05)	0.000	Random	76.8	0.002	1.000	0.500
Pembrolizumab	351	4	11.48(7.84-16.81)	0.000	Random	81.7	0.001	1.000	0.387

### Sensitivity Analysis and Publication Bias

The sensitivity analysis was performed to assess the robustness of the results. For ORR (Supplementary Figure 2a) and DCR (Supplementary Figure 3a), the pooled results were not significantly affected by omitting trials one by one. This demonstrated that the results were robust and reliable.

To assess publication bias, funnel plots of studies reporting ORR (Supplementary Figure 2b) and DCR (Supplementary Figure 3b) were generated. Egger's and Begg's tests for ORR, DCR, PFS, OS, and AEs were performed to recognize publication bias in this study. No obvious publication bias was observed in the current study (Tables 1 and 2, Supplementary Tables 3 and 4).

### Discussion

Cervical cancer is the most common female gynecological malignancy. Although about 90% of early-stage patients can be cured through proper therapeutic strategies, the treatment for the advanced-stage patients still faces challenges.<sup>1</sup> The introduction of immunotherapy has revolutionized the treatment landscape in cervical cancer.<sup>23</sup> Study indicated that the expression level of PD-L1 in cervical cancer patients is relatively high, ranging from 34.4% to 96.0%, which suggests that cervical cancer patients can benefit from PD-1/PD-L1 inhibitors.<sup>24</sup> Nivolumab has been proven to have clinical activity in both PD-L1-positive and PD-L1-negative cervical cancer patients.<sup>5,25</sup>

Several strategies have been investigated to improve the clinical efficacy of PD-1 inhibitors, including combining them with other agents. Studies have demonstrated that the ability of antigen presentation was increased after the blockade of cytotoxic T-lymphocyte associated protein 4 (CTLA-4) axis, resulting in an expanded cytotoxic T-cell response.<sup>26</sup> Due to limited efficacy as monotherapy, CTLA-4 inhibitors were combined with other regimens in clinical trials. The combination of PD-1 and CTLA-4 inhibitors has a synergist effect on the activation of the antitumor immune response.<sup>4,5</sup> Studies suggested that anti-angiogenic agents may exert an immunostimulatory effect in the tumor microenvironment through multiple mechanisms.<sup>27,28</sup>

This meta-analysis systematically assessed the efficacy and safety of PD-1 inhibitor-based treatment in advanced cervical cancer. Thirteen clinical trials and one retrospective study, involving 1504 patients, were included. The results indicated that the clinical efficacy of a PD-1 inhibitor in combination with antiangiogenic agents was superior to PD-1 inhibitor monotherapy or to the combination of PD-1 and CTLA-4 inhibitors. Still, the combination of a PD-1 inhibitor plus antiangiogenic agents was more toxic.

Admittedly, our study has some limitations. First, the number of included studies was small, despite a comprehensive and systematic search of mainstream databases. Second, most of the studies included were non-controlled trials, and the sample sizes of some trials were limited; therefore, we cannot make a direct comparison to assess whether PD-1 inhibitor-based treatment has advantages. Therefore, more clinical studies are needed to validate the current results.

### Conflicts of Interest

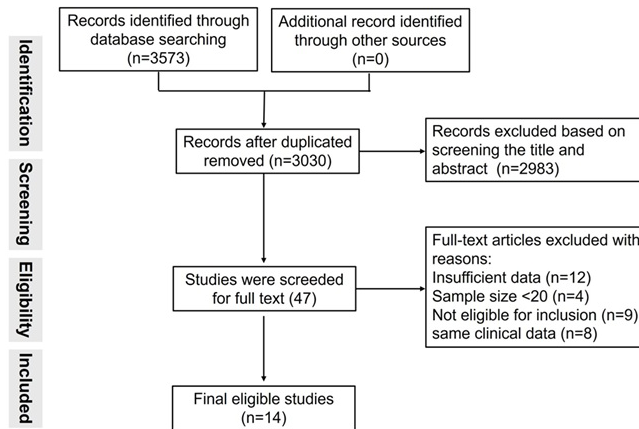
The authors declare that they have no competing interests.

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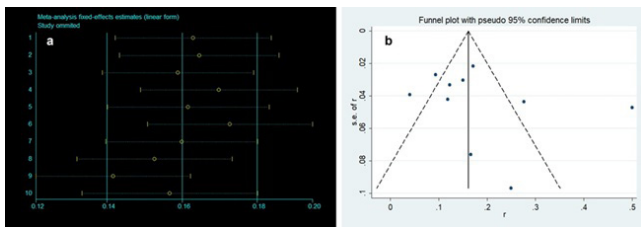
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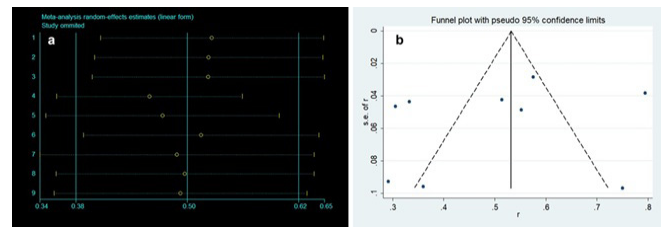
Supplementary Material



Supplementary Figure 1. Flow chart of the study selection process.



Supplementary Figure 2. Sensitivity analysis and publication bias. (a) Sensitivity analysis for ORR. (b) Funnel plot of ORR.



Supplementary Figure 3. Sensitivity analysis and publication bias. (a) Sensitivity analysis for DCR. (b) Funnel plot of DCR.

Supplementary Table 1.

The characteristics of all included studies.

Author	Year	Age	Study type	Sample size	Recruitment/ case review period	Data cutoff	Follow-up (months)	Intervention
Marabelle A et al.	2020	61(55-68)	phase II	75	Jan 15, 2016, to Jun 25, 2019	Jun 27, 2019	37.1 (IQR 35.0-38.3)	Pembrolizumab
Chung HC et al.	2019	46(24-75)	phase II	98	Jan27, 2016, to Aug 18, 2016	Jan 15, 2018	10.2(0.6-22.7)	Pembrolizumab
O'Malley DM et al.	2022	50(24-76)	phase II	125	Aug 27, 2018, to May 7, 2020	Apr 29, 2021	21(11.8-32.1)	Balstilimab plus zalifrelimab
Xu Q et al.	2022	53(36-67)	phase II	42	Dec 2019 to Dec 2020	Jul 13, 2021	10.9 (0.03-19.2)	Sintilimab plus anlotinib
O'Malley DM et al.	2021	53(25-81)	phase II	161	Nov 20, 2017, to Apr 16, 2020	Feb 11, 2021	14.6(9.9-38.8)	Balstilimab
Choi MC, et al.	2020	53(28-79)	retrospective	117	Jan 2016 to March 2020	31 Mar, 2020	4.9 (0.2–35.3)	Pembrolizumab
Frenel JS et al.	2017	42(26-62)	phase Ib	24	NA	NA	11.0(1.3-32.2)	Pembrolizumab
Zhao YY et al.	2023	53(20-81)	phase Ib	55	March 2020 to July 2021	Mar 31, 2021	89.5	PSB205 (QL1706)
Santin AD et al.	2020	45	phase II	25	May 2015 to June 2016	NA	32 (2-41.5)	Nivolumab
Tamura K et al.	2019	50(32-68)	phase II	20	NA	Aug 18, 2017	8.6 (1.4-13.7)	Nivolumab
Oaknin A et al.	2025	18.2(6.0-38.2)	phase III	304	Jul 2017 to Aug2020	Apr 20, 2023	47.3	Cemiplimab
Xia L et al.	2023	51 (31-75)	phase II	105	Jun 11, 2020, to Apr 29, 2021	Apr 29, 2022	16.9 (6.3-18.4)	Zimberelimab
Lorusso D et al. (1a)	2025	52.5 (30-82)	phase III	112	Nov 20, 2018, to Jan 31, 2020	Oct 3, 2022	39.1 (32.1-46.5)	Pembrolizumab
Lorusso D et al. (1b)	2025	51 (25-82)	phase III	196	Nov 20, 2018, to Jan 31, 2020	Oct 3, 2022	39.1 (32.1-46.5)	Pembrolizumab plus bevacizumab
Lan C et al.	2024	51 (33-67)	phase II	45	Jan 21 to Aug 2019	Jul 31, 2023	NA	Camrelizumab plus apatinib

**Supplementary Table 2.****Quality assessment.**

JBI Critical Appraisal Checklist for included retrospective study											
Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Overall appraisal
Choi MC et al. (2020)	yes	yes	yes	unclear	yes	yes	yes	yes	yes	yes	included
B. MINORS index for included non-randomized studies											
Study	I	II	III	IV	V	VI	VII	VIII	Total		
Marabelle A et al. (2020)	2	1	2	2	2	2	0	2	13		
Lan CY et al. (2020)	2	1	2	2	2	2	2	2	15		
O'Malley DM et al. (2022)	2	1	2	2	2	2	0	2	13		
Tamura K et al. (2019)	2	1	2	2	2	2	2	2	15		
Chung HC et al. (2019)	2	1	2	2	2	2	2	2	15		
Xu Qet al. (2022)	2	1	2	2	1	2	2	2	14		
Zhao YY et al. (2023)	2	1	2	2	1	2	2	2	14		
O'Malley DM et al. (2021)	2	1	2	2	2	2	2	2	15		
Santin AD et al. (2020)	2	1	2	2	1	2	2	2	14		
Frenel JS et al. (2017)	2	1	2	2	1	2	2	2	14		
Xia LF et al. (2023)	2	1	2	2	2	2	0	2	13		
Lan CY et al. (2024)		2	1	2	2	1	2	2	14		
Jadad scale for included RCT study											
Study	Randomization		Concealment of allocation		Double blinding		Withdrawals and dropouts		Quality grade		
Tewari KS et al. (2022)	2		2		1		2		7		
Oaknin A et al. (2025)	2		2		1		2		7		
Lorusso D et al. (2024)	2		2		2		2		8		

Numbers I-VIII in the heading signify: I, a clearly stated aim; II, inclusion of consecutive patients; III, prospective collection of data; IV, endpoints appropriate to the aim of the study; V, unbiased assessment of the study endpoint; VI, follow-up period appropriate to the aim of the study; VII, loss of follow up less than 5%; VIII, prospective calculation of the study size.

Numbers Q1-Q10 in the heading signify: Q1: Were there clear criteria for inclusion in the case series? Q2: Was the condition measured in a standard, reliable way for all participants included in the case series? Q3: Were valid methods used for the identification of the condition for all participants included in the case series? Q4: Did the case series have consecutive inclusion of participants? Q5: Did the case series have complete inclusion of participants? Q6: Was there transparent reporting of the demographics of the participants in the study? Q7: Was there transparent reporting of clinical information of the participants? Q8, were the outcomes or follow-up results of cases clearly reported? Q9: Was there transparent reporting of the presenting site(s)/clinic(s) demographic information? Q10: Was the statistical analysis appropriate?

**Supplementary Table 3.****6-month and 12-month rates of PFS and OS**

6-month rate of PFS	Events	No. of studies	Pooled RR (95%CI)	P	Effects model	Heterogeneity		Publication bias		
						I <sup>2</sup> (%)	Ph	Begg's	Egger's	
Pembrolizumab	239	3	0.27 (0.21-0.32)	0.000	Fixed	0.0	0.579	0.296	0.480	
6-month rate of OS										
PD-1 inhibitor	259	4	0.66 (0.45-0.87)	0.000	Random	92.0	0.000	0.734	0.668	
Pembrolizumab	239	3	0.61 (0.36-0.85)	0.000	Random	93.3	0.000	1.000	0.943	
12-month rate of PFS										
PD-1 inhibitor	246	3	0.16(0.11-0.20)	0.000	Random	87.9	0.000	1.000	0.818	
12-month rate of OS										
PD-1 inhibitor	227	3	0.49(0.42-0.55)	0.000	Random	69.9	0.036	1.000	0.731	
PD-1 inhibitor plus antiangiogenic agent	72	2	0.67(0.57-0.78)	0.000	Random	58.6	0.120	–	–	

**Supplementary Table 4.****Treatment-related adverse events (AEs).**

Treatment	Events	No. of studies	Pooled RR (95%CI)	P	Effects model	Heterogeneity		Publication bias	
						I <sup>2</sup> (%)	Ph	Egger's	Begg's
PD-1 inhibitor	947	10	0.21(0.19-0.23)	0.000	Random	97.6	0.000	0.089	0.595
PD-1 inhibitor plus angiogenesis	779	4	0.50(0.47-0.53)	0.000	Random	98.7	0.000	0.734	0.408
Pembrolizumab	281	4	0.10(0.06-0.13)	0.000	Fixed	43.7	0.148	0.089	0.056