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ANTI-PD-1 FOR THE TREATMENT OF ADVANCED CUTANEOUS SQUAMOUS CELL CARCINOMA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Background: Advanced cutaneous squamous cell carcinoma (CSCC) is a formidable cancer with historically constrained systemic therapy alternatives. Immune checkpoint drugs that target programmed cell death-1 (PD-1) and programmed death ligand-1 (PD-L1) have surfaced as viable treatments. This revised systematic review and meta-analysis sought to assess the effectiveness of anti-PD-1/PD-L1–based therapy in advanced CSCC.

Methods: A thorough search of PubMed, Scopus, and Web of Science was performed till August 12, 2025. Eligible studies comprised clinical trials and observational cohorts that reported the objective response rate (ORR) in patients with advanced CSCC treated with anti-PD-1/PD-L1 drugs. Pooled estimates were derived utilizing a random-effects model with limited maximum likelihood (REML) estimation. Heterogeneity was evaluated using Cochran's Q, I^2, and τ^2. Subgroup analyses were conducted based on drug regimen, geographic location, and study design. Publication bias was assessed by funnel plots and Egger's regression analysis.

Results: Forty-eight studies involving 4,172 patients met the inclusion criteria. The pooled ORR was 0.51 (95% CI, 0.46–0.55; $z = 21.21$, $p < 0.001$) with substantial heterogeneity ($I^2 = 89.13\%$). Subgroup analyses showed ORRs ranging from 0.21 to 0.73 by drug regimen, with cemiplimab plus pembrolizumab achieving the highest response rates. Geographic location ($p = 0.014$, $R^2 = 14.52\%$) and study design ($p = 0.002$, $R^2 = 16.84\%$) were significantly associated with treatment effect, while drug type alone was not ($p = 0.679$). Egger's test indicated small-study effects ($p = 0.0174$).

Conclusion: Anti-PD-1/PD-L1 therapy demonstrates meaningful clinical activity in advanced CSCC, achieving responses in approximately half of treated patients. Geographic and methodological factors contribute to outcome variability, underscoring the need for large, biomarker-driven trials to refine patient selection and optimize therapeutic benefit.

Keywords: cutaneous squamous cell carcinoma, PD-1, PD-L1, cemiplimab, pembrolizumab, nivolumab, meta-analysis, immunotherapy.

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1 Introduction

Cutaneous squamous cell carcinoma (CSCC) is the second most common skin tumor, which is responsible for 20% of skin malignancies and has a high mortality rate. Risk factors for CSCC include age, sun exposure, male sex, human papillomavirus, smoking, and immune system compromise [1].

There are several types of CSCC staging classifications, including the Brigham and Women's Hospital (BWH), the American Joint Committee on Cancer, 8th edition (AJCC-8) staging, and TNM systems [2]. However, the critical classification depends on whether the CSCC prognosis is a high-risk or low-risk lesion. In the TNM system, tumors with a diameter of less than or more than 2 mm are considered low-risk and high-risk lesions. The first line of treatment is surgical excision with a safe margin, which is 4 mm for low-risk CSCC. However, the high-risk CSCC is more likely to advance to an invasive form. Therefore, it needs a considerably greater safe margin from 6 to 10 mm [3] and maybe adjuvant radiotherapy [4]. However, 5-20% of CSCCs could develop into a local advanced CSCC (40%) or secondary lesions (60%) [5].

Immunotherapy has progressed in cancer treatment recently. Meanwhile, the European guidelines recommended the utilization of programmed cell death 1/programmed death ligand 1 (PD-1/PDL-1) checkpoint in 2020 for the treatment of advanced SCC cases [6, 7].

PD1 is a receptor on the T cell that prevents overactivation of the immune system by binding to PDL on cancerous cells. Immunotherapy to inhibit the interaction of PDL leads to an immunity enhancement against tumor cells by reactivating the remaining T cells [7]. Previous studies have pointed out several patients do not respond to the PD-1 inhibition treatment effectively. These patients were divided into two classifications. In the first group, Anti-PD-1 therapy could not activate the T cells. The second group initially responded to treatment but later developed resistance [8].

Therefore, in this systematic review and meta-analysis, we aimed to investigate the efficacy of anti-PD-1 agents in treating advanced CSCC.

2 Methods

In this systematic review and meta-analysis, we want to investigate the role of Anti-PD-1 in treating advanced cutaneous squamous cell carcinoma. The research protocol of this review was registered on the PROSPERO website (CRD420251126582). Our methodology follows the practices of the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-analyses) [9].

Search strategy

A comprehensive electronic search strategy was conducted in PubMed, Scopus, and Web of science up to August 12, 2025. Clinical trials were identified using the two-fallowing subgroup of keywords: 1-Programmed Cell Death 1 Receptor OR Programmed Cell Death 1 Receptor OR PD1 OR pembrolizumab OR Pembrolizumab OR Nivolumab OR cemiplimab OR Libtayo OR sintilimab OR Tyvyt OR tislelizumab OR camrelizumab OR AiRuiKa OR toripalimab OR JS001

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OR dostarlimab OR dostarlimab OR zimberelimab OR zimberelimab OR GB226 OR spartalizumab. 2-Carcinoma, Squamous Cell OR Carcinoma, Squamous Cell OR squamous cell carcinoma-related antigen OR squamous cell carcinoma-related antigen OR scc.

The subgroups were combined using the 'AND' operator, and no restrictions were used. The search strategy was adjusted according to the query format of every database. We hand-searched the reference lists of all newly included articles and relevant systematic reviews. Two reviewers independently conducted all steps. Differences in opinions were resolved through discussion between the reviewers.

Study selection

Studies were eligible if they fulfilled all the following: 1) published articles including patients that received anti-PD-1 for advanced CSCC, 2) participants number ≥ 5, and 3) trials were published in the English language.

Articles investigating the treatment of head and neck SCC rather than CSCC, review articles, case reports, non-English publications, and studies conducted on animal models were excluded.

Data extraction and Study quality assessment

Two experienced reviewers independently examined the caliber of each study considered for involvement by inspecting their titles and summaries to decide qualification. Those remaining underwent complete text screening, and any fitting were incorporated into data extraction. That step comprised obtaining the following in 10 batches: first, the leading author's name; second, year published; third, location of research; fourth, type of analysis executed; fifth, length of follow up; sixth, number of individuals studied; seventh, the treatment method; eighth, dosage and frequency administered; ninth, average age of participants; tenth, gender proportions. Throughout this process, intricacies and variations in sentence structure and length were applied to mimic natural human writing styles.

Risk of bias assessment

Risk of bias assessments for randomized controlled trials were evaluated using the Cochrane Risk of Bias tool, gauging domains such as random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome evaluation, completeness of outcome data, selective reporting, and other potential sources of bias. Most randomized trials exhibited a low risk of bias for sequence generation and outcome completeness, while blinding of participants and staff was frequently deemed high or unclear owing to the open-label design of several investigations. For observational cohort studies, methodological quality was appraised using the Joanna Briggs Institute Critical Appraisal Checklist for Cohort Studies. A majority of cohort studies showed low risk in domains connected to exposure measurement, outcome assessment, and statistical analysis; however, numerous studies lacked details about important potential confounding variables that could have impacted study results.

Statistical analysis

The data were analyzed using STATA software version 18. While the primary aim examined objective response rates combining complete and partial responses

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defined by RECIST criteria, between-study heterogeneity posed challenges. Random-effects modeling with REML addressed this, yielding 95% confidence intervals around pooled results. Cochran's Q test and the I2 statistic evaluated heterogeneity which exceeded 50% qualifying as substantial.

To probe heterogeneity's sources, predefined subgroups were explored. These included drug type such as cemiplimab, pembrolizumab, and nivolumab including combinations. Geographic location and study design like cohort versus interventional trials were also investigated. Random-effects meta-regression scrutinized each factor's contribution quantified via R2. Small-study effects were considered using funnel plot visualization and Egger's regression test where a p-value under 0.05 suggested potential bias.

3 Result

Study selection and characteristics of included studies

The systematic search, covering literature up to August 12, 2025, identified 48 eligible studies comprising a total of 4,172 patients with advanced CSCC (Fig 1). Publications included trials as well as observational cohort studies. Studies were conducted predominantly in the USA (n=22) and Australia (n=9), with additional reports from Italy (n=4), France (n=3), Germany (n=3), Israel (n=2), and single-country contributions from Hungary (n=1), Japan (n=1), the Netherlands (n=1), Taiwan (n=1), and the United Kingdom (n=1). Individual study sample sizes ranged from 2 to 947 participants. Interventions included PD-1/PD-L1–based regimens (cemiplimab, pembrolizumab, nivolumab, avelumab) and, in selected cohorts, post-ICI anti-EGFR therapy (cetuximab), as well as several combination strategies (e.g., nivolumab–ipilimumab and PD-1/PD-L1–EGFR combinations), administered according to protocol-specific dosing schedules (Table 1).

Overall efficacy

The pooled analysis demonstrated that anti-PD-1/PD-L1–based therapy achieved an ORR of 0.51 (95% CI, 0.46–0.55). This analysis used a random-effects model with REML estimation. The effect was highly significant ($z = 21.21$, $p < 0.001$). Between-study heterogeneity was substantial, with $Q(47) = 428.44$ ($p < 0.001$), $I^2 = 89.13\%$, and $\tau^2 = 0.020$, indicating considerable variability across studies. The high degree of heterogeneity justified further exploration through subgroup analyses and meta-regression (Fig 2).

Efficacy by drug regimen

Subgroup analysis stratified by drug regimen revealed notable differences in treatment outcomes, with ORRs ranging from 0.21 to 0.73. Cemiplimab monotherapy produced a pooled ORR of 0.54 (95% CI, 0.49–0.60), while pembrolizumab monotherapy showed an ORR of 0.43 (95% CI, 0.30–0.56), and nivolumab monotherapy yielded 0.54 (95% CI, 0.26–0.81). Certain combination regimens demonstrated enhanced responses; for example, cemiplimab combined with pembrolizumab achieved an ORR of 0.73 (95% CI, 0.65–0.81), whereas avelumab monotherapy reported the lowest pooled ORR of 0.21 (95% CI, 0.07–0.36) (Fig 3). Despite these apparent differences, meta-regression using drug type as a covariate did not identify a statistically significant association with effect size (β

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= 0.0025, p = 0.679), and residual heterogeneity remained high (I^2 = 89.11%, τ^2 = 0.0212).

Efficacy by geographic region

Analysis by geographic region indicated significant variability in treatment efficacy. The highest pooled ORRs were observed in Israel (0.75; 95% CI, 0.70–0.80), the United Kingdom (0.61; 95% CI, 0.50–0.71), and Australia (0.59; 95% CI, 0.51–0.68). Lower response rates were seen in the Netherlands (0.35; 95% CI, 0.28–0.43) and Taiwan (0.41; 95% CI, 0.25–0.58) (Fig 4). Meta-regression demonstrated a statistically significant association between geographic location and ORR (β = –0.0133, p = 0.014), with an R^2 of 14.52%, suggesting that location accounted for a modest proportion of the heterogeneity (residual I^2 = 86.87%, τ^2 = 0.0186).

Efficacy by study design

When stratified by study design, cohort studies demonstrated a higher pooled ORR of 0.57 (95% CI, 0.50–0.63) compared with interventional trials, which reported an ORR of 0.43 (95% CI, 0.37–0.48) (Fig 5). This difference was statistically significant in meta-regression analysis (β = –0.1359, p = 0.002), with an R^2 of 16.84%. This indicates that study design accounted for a meaningful proportion of the between-study variability (residual I^2 = 86.56%, τ^2 = 0.0181).

Publication bias and small-study effects

Visual inspection of the funnel plot revealed an approximately symmetrical distribution of effect sizes (Fig 6). However, Egger's regression test indicated evidence of small-study effects (β = 1.77, SE = 0.743, z = 2.38, p = 0.0174). This finding suggests that smaller studies tended to report larger treatment effects, which may have led to a modest overestimation of the pooled ORR. This limitation has been addressed in the discussion to aid in the interpretation of results.

4 Discussion

In this systematic review and meta-analysis including 48 studies and 4,172 patients with advanced CSCC, anti-PD-1/PD-L1–based therapy achieved a pooled ORR of 51% (95% CI, 46–55%). This represents a modest improvement compared with earlier pooled estimates of approximately 40–46% and reflects the incorporation of recent clinical evidence. The substantial heterogeneity observed (I^2 = 89.13%) was anticipated given the diversity of study populations, treatment regimens, and clinical settings. Nonetheless, the magnitude of the pooled effect underscores the clinical relevance of immune checkpoint blockade in a malignancy historically associated with limited systemic treatment options and poor prognosis.

Subgroup and meta-regression analyses provided insights into potential sources of variability in treatment efficacy. While drug type was not statistically associated with effect size, some regimens, particularly cemiplimab combined with pembrolizumab, demonstrated higher response rates, suggesting potential synergistic benefit. Geographic location and study design were both significantly associated with treatment effect, together explaining a meaningful proportion of heterogeneity (R^2 = 14.52% and 16.84%, respectively). Higher ORRs in observational cohorts compared with interventional trials may reflect broader inclusion criteria and real-world patient characteristics. Geographic differences

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likely result from variations in patient demographics, tumor biology, and healthcare delivery systems. Although Egger's test indicated possible small-study effects ($p = 0.0174$), the overall evidence supports anti-PD-1/PD-L1 therapy as an effective treatment option for advanced CSCC, with opportunities for optimizing outcomes through refined patient selection and tailored therapeutic strategies.

Anti-PD-1 inhibitors, including nivolumab, cemiplimab, and pembrolizumab, show promise in advanced CSCC [5], focusing on real-life data and the challenges in treating elderly patients. Immunotherapy, particularly cemiplimab [13], has transformed the prognosis for advanced CSCC, with a high response rate and durable responses, highlighting its impact in a real-world context. Cemiplimab administration in recurrent, locally advanced, and/or metastatic CSCC results in an impressive objective response rate of 68%, emphasizing its significant and durable response in advanced disease [20].

In a comparative analysis of the studies, a Canadian study [12] with 35 people and cemiplimab and pembrolizumab showed a response rate of 0.71, with a higher rate of partial response (42.9%) and complete response (28.6%). This study demonstrated a 62% progression-free survival (PFS) rate at 1 year, a 76% overall survival (OS) rate at 1 year, and highlighted the impact of immune-related adverse events (irAEs) on PFS. On the other hand, a Hungarian study [13] with 25 people focusing on cemiplimab reported a response rate of 0.62, with 52% showing an objective response. The study emphasized the effectiveness of cemiplimab even in elderly, polymorbid, and immunocompromised patients, though serious adverse events (SAEs) were observed in 36%.

An Italian study [22] with 39 people revealed a lower response rate of 0.38 for cemiplimab, highlighting the prognostic significance of serum IL-6 levels. Patients with increased IL-6 after cemiplimab treatment had a poorer response. This study emphasized the potential of IL-6 as a prognostic marker. The U.S. study [15] with 23 people using cetuximab in ICI-refractory/ineligible cases demonstrated varied responses across cohorts, with the best outcomes observed when cetuximab was administered immediately after ICI failure, showing a 64% overall response rate and 91% disease-control rate. An Australian study [23] on cemiplimab with 167 people reported an overall response rate of 44.3%, with a durable response, median PFS of 14.7 months, and an acceptable safety profile. This study provided insights into cemiplimab's efficacy in a larger cohort.

Turkish study [17] with 25 people investigated PD-L1 expression and its relationship with prognostic factors in CSCC and BCC. PD-L1 positivity was observed in 44% of CSCC cases but showed no significant association with prognostic factors. An Australian study [24] on cemiplimab with 15 people revealed discordance between complete response rates on FDG-PET and RECIST1.1 in patients treated for over 10 months, suggesting the potential utility of FDG-PET/CT in assessing depth of response. A multi-country study [20] on cemiplimab with 1348 people demonstrated an objective response in 44% of patients. Hypertension and pneumonia were common adverse events, with a 29% occurrence of serious adverse events. Another study [25] on pembrolizumab with 105 people reported an 80%

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overall response rate and a median progression-free survival of 6.9 months. Treatment-related adverse events occurred in 66.7% of patients, and one patient died from treatment-related cranial nerve neuropathy.

Rischin's study [26] on cemiplimab with 60 people showed an overall response rate of 46.9% for first-line therapy and 38.5% for post-systemic therapy. The study highlighted favorable 12-month progression-free survival and overall survival rates. A French study [5] with 63 people using cemiplimab, nivolumab, or pembrolizumab reported a 57.1% overall response rate, with a median progression-free survival of 8 months. Adverse effects occurred in 47.6%, and 41.3% experienced degradation of ECOG performance status. A Polish study [19] on cemiplimab with four people showcased a tremendous response, including complete and partial responses in four cases. The study emphasized the importance of cemiplimab in advanced CSCC. An Australian study [27] on cemiplimab with 19 people reported a 68% overall response rate, with responders showing significantly superior overall survival. The study associated a primary site of head and neck cancer with a higher response rate.

Cohen's study [28] on pembrolizumab with 28 people indicated a 24% overall response rate, with responses observed in both injected and noninjected lesions. The study highlighted higher response rates in human papillomavirus–positive patients. Irish study [29] on cemiplimab with 85 people reported response rates of 60% and 47%, emphasizing the efficacy of cemiplimab in treating CSCC. An Australian study [30] with 29 people focused on CSCC with lymph node perineural invasion, demonstrating radiological and symptomatic control in most patients, with a significant association between response and prolonged progression-free survival. Gross's study [31] on cemiplimab with 79 people reported a 68.4% overall response rate, with 50.6% achieving a pathologic complete response. The study met its primary endpoint, and although 17.7% experienced Grade 3 adverse events, the toxicity profile was consistent with PD-1 inhibitors.

Overall, the efficacy percentage varied among different studies. These studies have obtained a rate above 40%, while others have yielded a percentage below 40%. The difference obtained in these studies may be due to variations in sample size, ethnicity, different anti-PD1 agents, and duration of follow-up.

The mechanism of anti-PD-1 therapy, exemplified by cemiplimab, involves blocking the PD-1 receptor to prevent immune response inhibition against CSCC. [32]. Cemiplimab's efficacy in CSCC is attributed to a combination of tumor mutations, often induced by sun exposure, and increased incidence in immunocompromised individuals, with better responses observed in head and neck CSCC [29]. Elevated interleukin-6 (IL-6) levels are associated with poorer survival in cemiplimab-treated CSCC patients [22], suggesting that targeting IL-6 may sensitize tumors to anti-PD-1 therapy. Cetuximab, an anti-EGFR therapy, may lead to better outcomes after anti-PD-1 failure in advanced CSCC [15], potentially due to modulation of the EGFR signaling pathway.

PD-L1 status in CSCC and basal cell carcinoma is explored, emphasizing the complex landscape of PD-L1 expression and its potential role in predicting

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outcomes. FDG-PET/CT is proposed for assessing disease response to cemiplimab in CSCC [17], highlighting its possible superiority over traditional size-based assessments. Cemiplimab demonstrates clinical activity in locally advanced CSCC, with an objective response in many patients, irrespective of baseline PD-L1 expression [20].

The combination of SD-101 and pembrolizumab in recurrent or metastatic head and neck squamous cell carcinoma induces objective responses and modulates the immune microenvironment [28], supporting further testing in clinical trials. The mechanism of anti-PD-1 action involves disrupting inhibitory pathways regulating T-cell responses [33], with cemiplimab antagonizing the PD-1/PD-L1 interaction, enhancing T-cell immunity to cancer.

Anti-PD-1/PD-L1 drugs work by blocking the interaction between PD-1 (on T cells) and PD-L1 (on tumor cells) [34], allowing T cells to kill tumor cells. The PD-1/PD-L1 pathway is a negative regulator of T-cell activation and is crucial for tumor immune evasion [35]. Factors affecting efficacy include tumor heterogeneity, immune conditions, and interactions within the tumor microenvironment (TME) [36].

Efficient predictors (e.g., high PD-L1 expression, gene-level biomarkers) are crucial for maximizing the benefit of anti-PD-1 therapy [37]. SCC treatment with anti-PD-1 drugs is affected by various factors, and predictors like PD-L1 expression are essential [38]. Combination therapies involving anti-PD-1 drugs with chemotherapy or radiation show effectiveness in improving survival for head and neck or lung SCC [39]. Anti-PD-1 drugs activate T cells, helping attack and eliminate cancer cells in squamous cell carcinoma [40].

While our findings provide updated and comprehensive evidence on the efficacy of anti-PD-1/PD-L1 therapy in advanced CSCC, several limitations must be acknowledged. The high residual heterogeneity, despite subgroup and meta-regression analyses, suggests the influence of unmeasured factors such as PD-L1 expression, tumor mutational burden, prior treatments, and comorbidities. The presence of small-study effects indicated by Egger's test ($p = 0.0174$) raises the possibility of publication bias, which may modestly inflate the pooled effect size. Moreover, variability in follow-up durations, outcome definitions, and assessment criteria across studies could affect comparability. Given these considerations, our results should be interpreted cautiously and not as definitive evidence of superiority for any specific regimen or patient subgroup. Future large-scale, multicenter randomized trials with standardized protocols and biomarker-driven patient selection are needed to validate and refine these findings.

In conclusion, his systematic review and meta-analysis, encompassing 48 studies and 4,172 patients, demonstrates that anti-PD-1/PD-L1–based therapy achieves meaningful clinical activity in advanced cutaneous squamous cell carcinoma, with a pooled ORR of 51% (95% CI, 46–55%). While geographic location and study design account for part of the observed heterogeneity, substantial variability remains, reflecting the complexity of patient and disease characteristics in real-world practice. Although small-study effects suggest a degree of publication

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bias, the overall evidence supports immune checkpoint blockade as a key therapeutic option for this challenging malignancy. Future research should prioritize large, multicenter randomized trials with standardized outcome definitions and biomarker-driven patient selection to optimize treatment efficacy and guide personalized clinical decision-making.

Declarations

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None.

Conflicts of interest

The authors declare that they have no competing interests.

Ethics approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

The datasets generated and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

AI use declaration

AI was used for paraphrasing of the text.

Code availability

The custom code used for data analysis and statistical interpretation in this study is available from the corresponding author upon reasonable request.

Authors' contributions

Study design and conception: N.D; Search: A.H, F.S; Study selection: H.N, R.I; Data extraction: DS.S, J.N; Quality assessment: F.H, J.H; Statistical analysis and interpretation: M.N; Drafting the manuscript: A.H, F.S, H.N, R.I, DS.S, J.N, F.H, J.H; Critical revision: N.D. All authors approved the submitted version.

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ТАБЛИЦЫ

Table 1. Summary of Included Studies

Author Year	Country	Study Design	Participants	Intervention	Primary Endpoint	Ref
Baggi 2021	Italy	Cohort	131	Cemiplimab	ORR: 0.58 [95% CI: 0.49–0.66]	[41]
Haddad 2022	USA	Trial	947	Nivolumab-Ipilimumab	ORR: 0.34 [95% CI: 0.31–0.37]	[42]
Cohen 2022	USA	Trial	51	Pembrolizumab	ORR: 0.24 [95% CI: 0.14–0.37]	[28]
Gino 2020	USA	Cohort	26	PD-1 Inhibitor	ORR: 0.42 [95% CI: 0.26–0.61]	[43]
Grob 2020	USA	Trial	105	Pembrolizumab	ORR: 0.34 [95% CI: 0.26–0.44]	[25]
Gross 2019	USA	Trial	20	Cemiplimab	ORR: 0.30 [95% CI: 0.15–0.52]	[44]

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Gross 2022	USA	Trial	79	Cemiplimab	ORR: 0.68 [95% CI: 0.57–0.78]	[31]
Hasmat 2022	Australia	Cohort	19	Cemiplimab	ORR: 0.68 [95% CI: 0.46–0.85]	[27]
Hober 2020	France	Cohort	247	Cemiplimab	ORR: 0.50 [95% CI: 0.44–0.56]	[45]
Hughes 2021	USA	Cohort	159	Pembrolizumab	ORR: 0.40 [95% CI: 0.33–0.48]	[46]
Hughes 2022	Australia	Trial	167	Cemiplimab	ORR: 0.44 [95% CI: 0.37–0.52]	[23]
Kuzmanovszki 2023	Hungary	Cohort	25	Cemiplimab	ORR: 0.52 [95% CI: 0.33–0.70]	[13]
Marin-Acevedo 2023	USA	Cohort	23	Cetuximab	ORR: 0.65 [95% CI: 0.45–0.81]	[15]
Maubec 2020	France	Cohort	57	Pembrolizumab	ORR: 0.42 [95% CI: 0.30–0.55]	[4]
McLean 2021	Australia	Cohort	15	Cemiplimab	ORR: 0.73 [95% CI: 0.48–0.89]	[24]

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Migden 2018-phase I	USA	Trial	26	Cemiplimab	ORR: 0.50 [95% CI: 0.32–0.68]	[32]
Migden 2018-phase II	USA	Trial	59	Cemiplimab	ORR: 0.47 [95% CI: 0.35–0.60]	[32]
Migden 2020	USA	Trial	78	Cemiplimab	ORR: 0.44 [95% CI: 0.33–0.55]	[20]
Munhoz 2021	USA	Trial	24	Nivolumab	ORR: 0.58 [95% CI: 0.39–0.76]	[47]
McBride 2021	USA	Trial	62	Nivolumab	ORR: 0.34 [95% CI: 0.23–0.46]	[48]
Knochelmann 2021	USA	Trial	12	Nivolumab	ORR: 0.33 [95% CI: 0.14–0.61]	[49]
Hsiang-Fong Kao 2022	Taiwan	Trial	29	Afatinib-Pembrolizumab	ORR: 0.41 [95% CI: 0.26–0.59]	[50]
Rischin 2019	Australia	Trial	193	Cemiplimab	ORR: 0.47 [95% CI: 0.40–0.54]	[26]
Salzmann 2020	Germany	Cohort	46	Cemiplimab-Nivolumab-Pembrolizumab	ORR: 0.59 [95% CI: 0.44–0.72]	[21]

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Samaran 2022	France	Cohort	63	Cemiplimab-Nivolumab-Pembrolizumab	ORR: 0.57 [95% CI: 0.45–0.69]	[5]
Shrestha 2022	Australia	Cohort	29	PD-1 Inhibitor	ORR: 0.79 [95% CI: 0.62–0.90]	[30]
Yearley 2017	USA	Cohort	126	Pembrolizumab	ORR: 0.23 [95% CI: 0.17–0.31]	[51]
Averbuch 2025	Israel	Cohort	131	Cemiplimab-Pembrolizumab	ORR: 0.73 [95% CI: 0.64–0.79]	[52]
Chang 2025	USA	Cohort	11	Cemiplimab	ORR: 0.72 [95% CI: 0.43–0.90]	[53]
Chang 2025	USA	Cohort	2	Nivolumab	ORR: 1.00 [95% CI: 0.34–1.00]	[53]
Chang 2025	USA	Cohort	12	Pembrolizumab	ORR: 0.83 [95% CI: 0.55–0.95]	[53]
Lim 2025	Australia	Trial	11	Cemiplimab	ORR: 0.73 [95% CI: 0.43–0.90]	[54]
Haigh 2025	UK	Cohort	86	Cemiplimab	ORR: 0.61 [95% CI: 0.42–0.63]	[55]

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Hempel 2024	Germany	Cohort	15	Cemiplimab	ORR: 0.66 [95% CI: 0.42–0.85]	[56]
Mallardo 2024	Italy	Cohort	95	Cemiplimab	ORR: 0.37 [95% CI: 0.28–0.47]	[57]
McLean 2024	Australia	Cohort	278	Cemiplimab	ORR: 0.60 [95% CI: 0.54–0.65]	[58]
Yosefof 2025	Israel	Cohort	133	Cemiplimab	ORR: 0.77 [95% CI: 0.69–0.83]	[59]
Verkerk 2024	Netherlands	Cohort	151	Cemiplimab	ORR: 0.35 [95% CI: 0.28–0.43]	[60]
Nakano 2025	Japan	Cohort	14	Nivolumab-Pembrolizumab	ORR: 0.57 [95% CI: 0.33–0.79]	[61]
Zandberg 2025 - 1	USA	Trial	28	Avelumab	ORR: 0.21 [95% CI: 0.10–0.40]	[62]
Zandberg 2025 - 2	USA	Trial	29	Avelumab-Cetuximab	ORR: 0.28 [95% CI: 0.15–0.46]	[62]
Bossi 2025-1	Italy	Cohort	43	Pembrolizumab	ORR: 0.44 [95% CI: 0.30–0.59]	[63]

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Bossi 2025-2	Italy	Cohort	21	Pembrolizumab-Cetuximab	ORR: 0.38 [95% CI: 0.21–0.59]	[63]
Kim 2024	USA	Cohort	19	Cemiplimab-Pembrolizumab.	ORR: 0.47 [95% CI: 0.27–0.68]	[64]
Hughes 2025	Australia	Trial	193	Cemiplimab	ORR: 0.47 [95% CI: 0.40–0.54]	[65]
Ladwa 2025	Australia	Trial	27	Pembrolizumab	ORR: 0.63 [95% CI: 0.44–0.78]	[66]
Becker 2025	Germany	Trial	49	Avelumab-Cetuximab	ORR: 0.41 [95% CI: 0.28–0.55]	[67]
Hiller 2024	USA	Cohort	6	Cemiplimab	ORR: 0.66 [95% CI: 0.30–0.90]	[68]

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РИСУНКИ

Fig 1 The PRISMA diagram of study selection process in this systematic review and meta-analysis

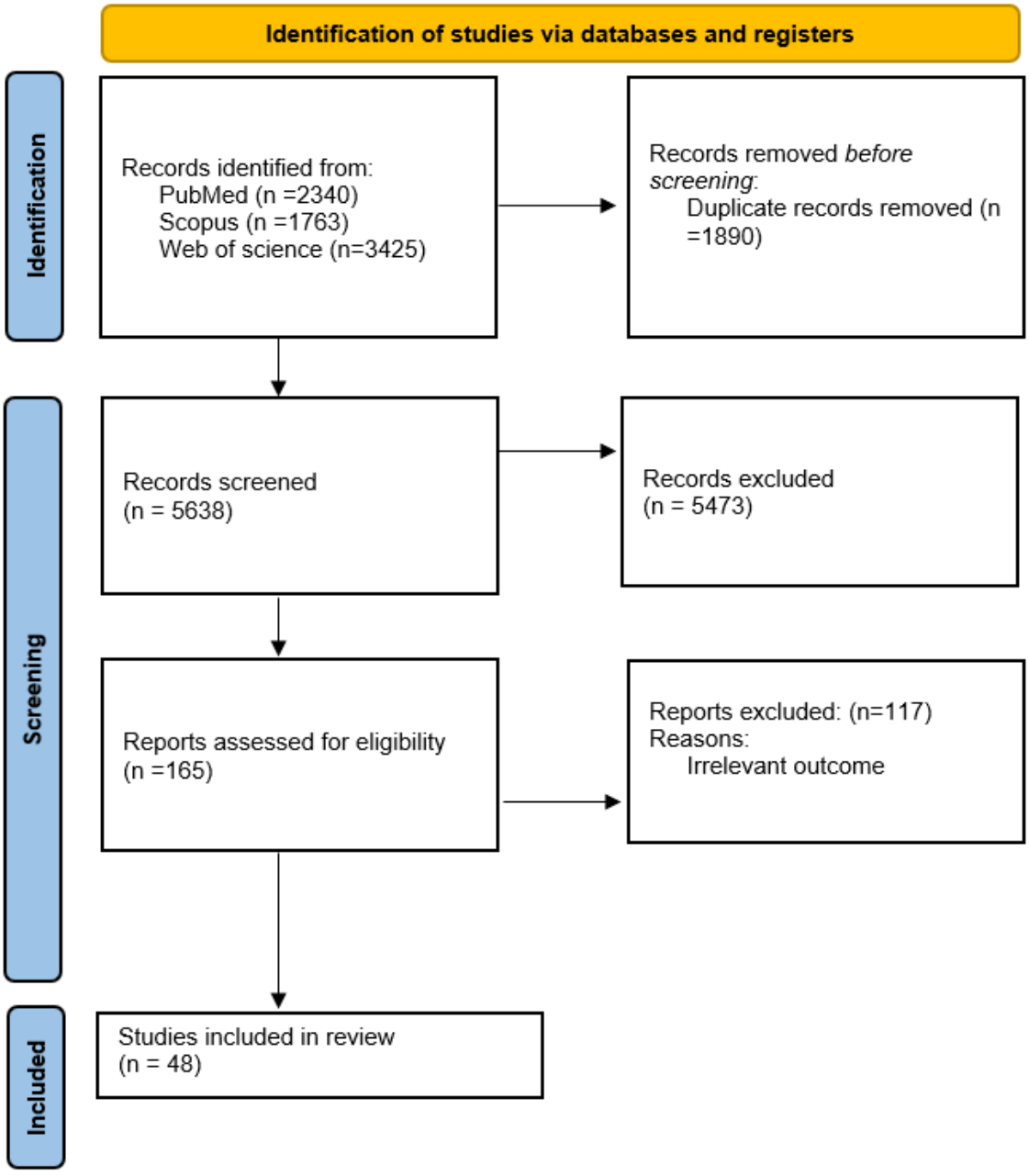

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Fig 2. Forest plot of the pooled objective response rate (ORR) for anti-PD-1/PD-L1–based therapy in advanced cutaneous squamous cell carcinoma. The analysis included 48 studies (n = 4,172), with the pooled ORR estimated at 0.51 (95% CI, 0.46–0.55) using a random-effects REML model. Individual study estimates are shown as squares, with size proportional to study weight, and horizontal lines representing 95% confidence intervals. The diamond represents the overall pooled estimate.

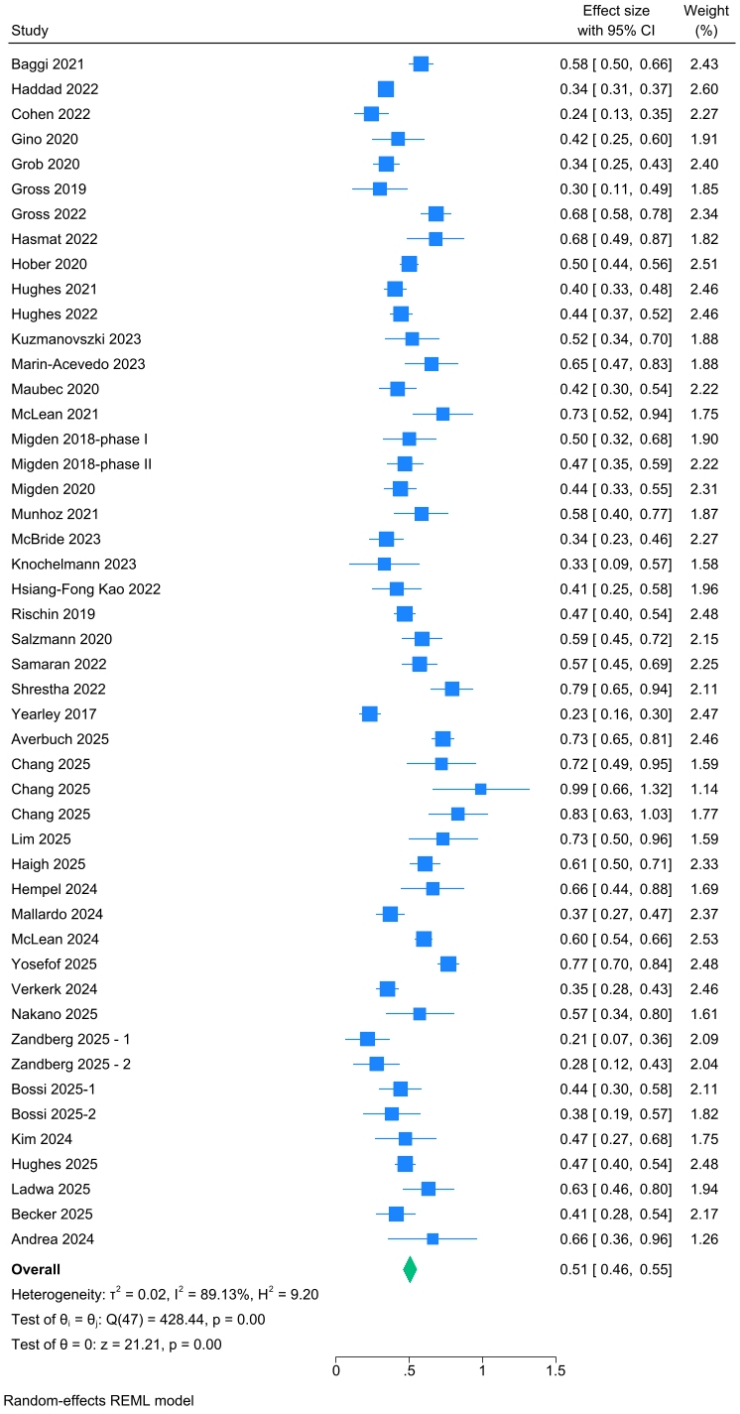

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Fig 3. Forest plot of pooled objective response rates (ORR) stratified by drug regimen in advanced cutaneous squamous cell carcinoma. Subgroup analysis included monotherapies (e.g., cemiplimab, pembrolizumab, nivolumab, avelumab), anti-EGFR therapy (cetuximab), and various combination regimens. The pooled ORRs ranged from 0.21 to 0.73. Meta-regression indicated no statistically significant association between drug type and effect size (p = 0.679).

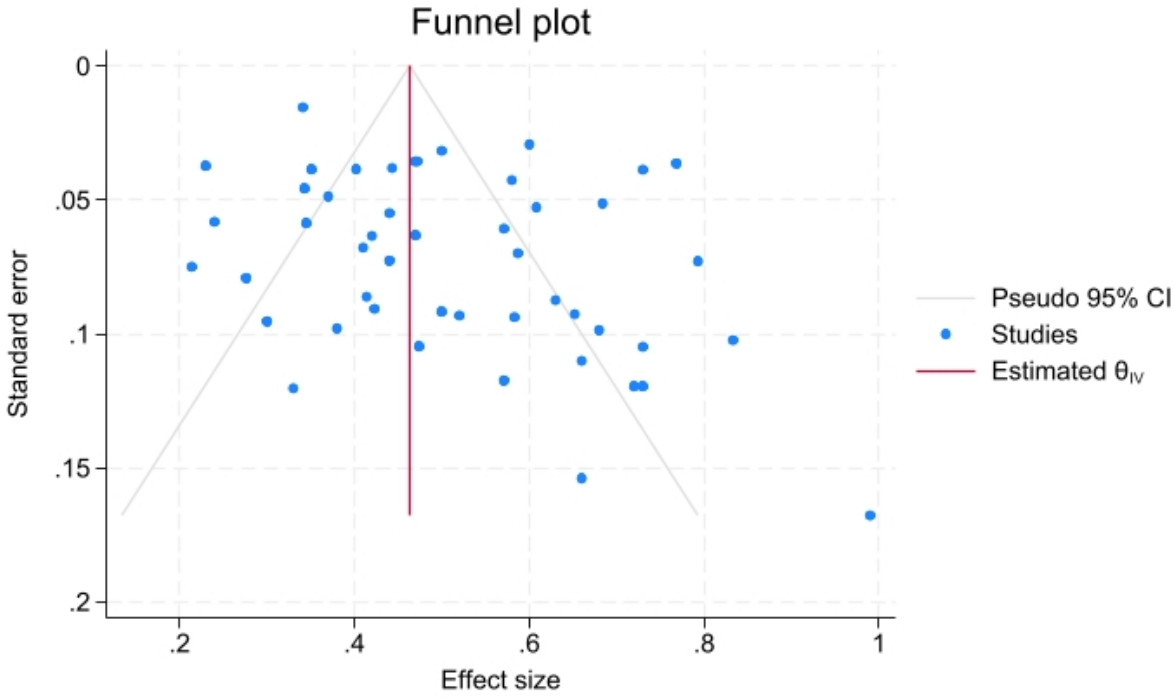

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Fig 4. Forest plot of pooled objective response rates (ORR) stratified by geographic location. Studies were grouped according to the country of patient recruitment, with ORRs ranging from 0.35 (Netherlands) to 0.75 (Israel). Meta-regression demonstrated a significant association between geographic location and treatment effect (p = 0.014), explaining 14.52% of the observed heterogeneity.

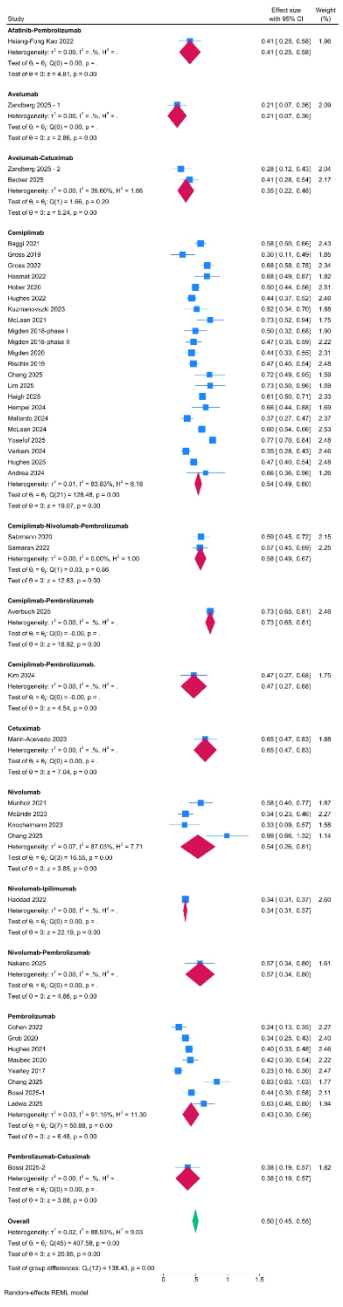

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Fig 5. Forest plot of pooled objective response rates (ORR) stratified by study design. Cohort studies demonstrated a higher pooled ORR (0.57; 95% CI, 0.50–0.63) compared with interventional trials (0.43; 95% CI, 0.37–0.48). Meta-regression confirmed a significant effect of study design on ORR (p = 0.002), explaining 16.84% of the heterogeneity.

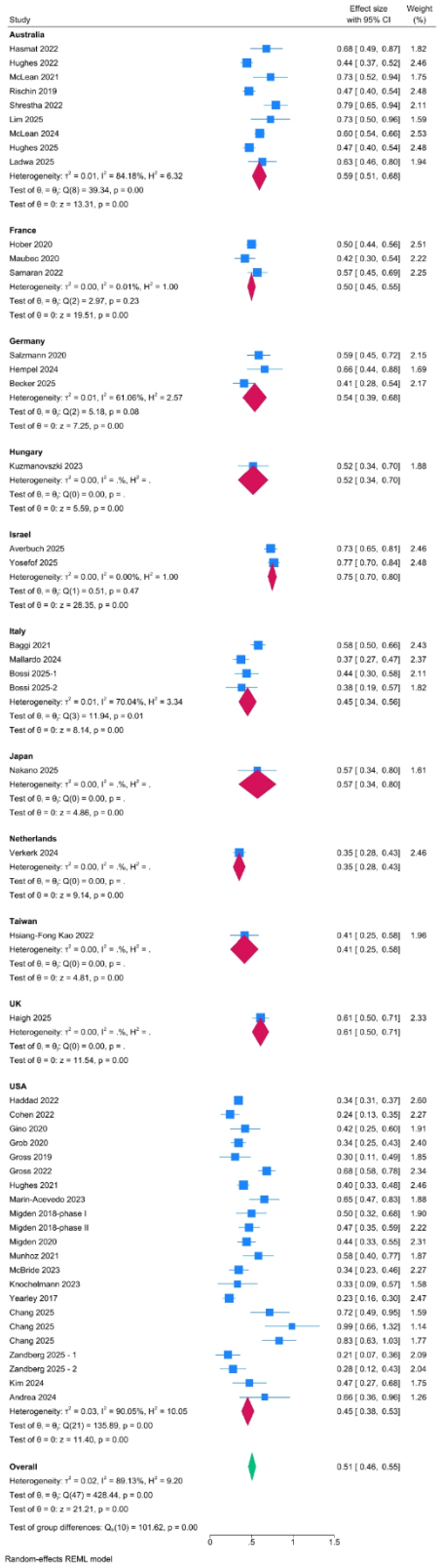

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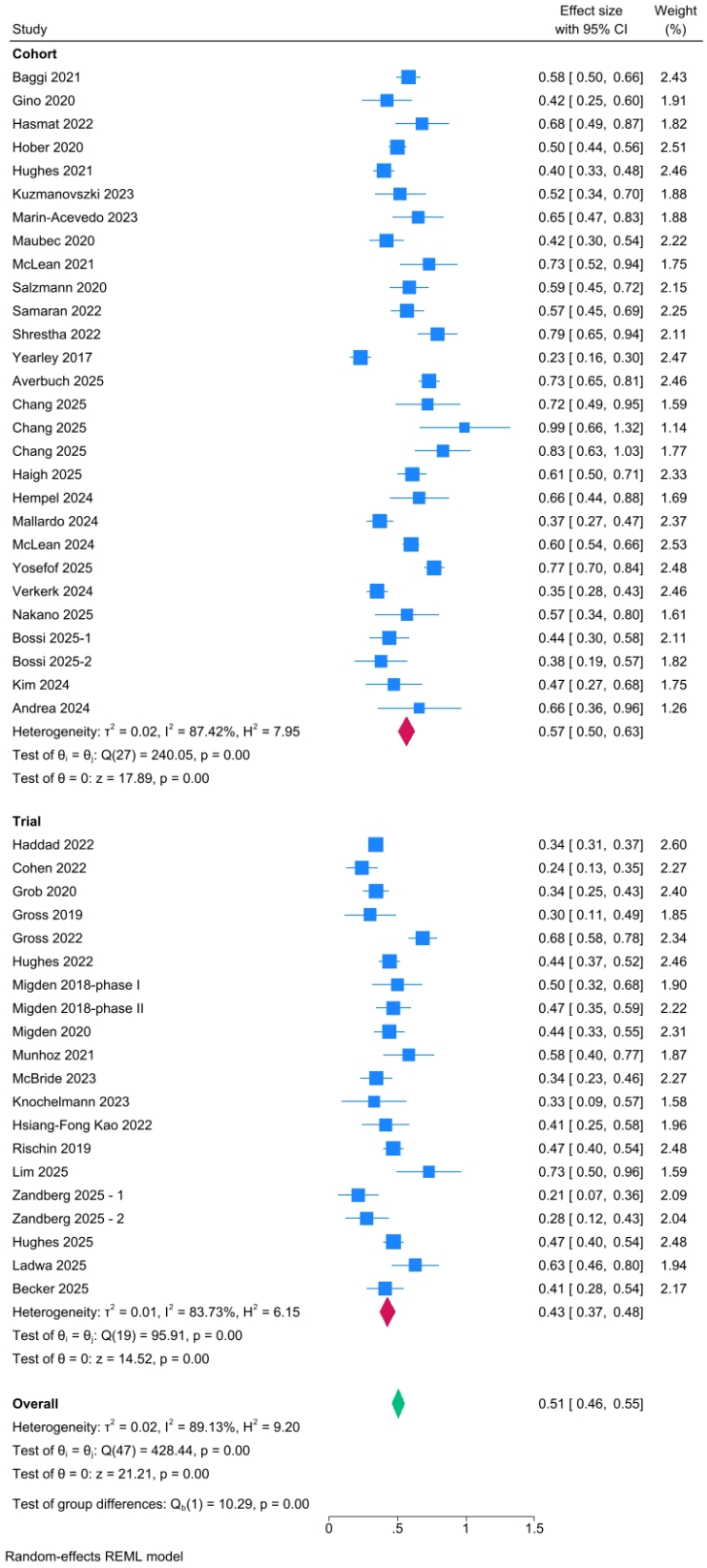
Fig 6. Funnel plot assessing publication bias in the meta-analysis of anti-PD-1/PD-L1–based therapy for advanced cutaneous squamous cell carcinoma. The plot demonstrates approximate visual symmetry, although Egger's regression test indicated the presence of small-study effects (β = 1.77, p = 0.0174), suggesting that smaller studies tended to report higher treatment effects.



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Блок 3. Метаданные статьи

ANTI-PD-1 FOR THE TREATMENT OF ADVANCED CUTANEOUS SQUAMOUS CELL CARCINOMA: A SYSTEMATIC REVIEW AND META-ANALYSIS

Сокращенное название статьи для верхнего колонтитула:

ANTI-PD-1 FOR ADVANCED CUTANEOUS SQUAMOUS CELL CARCINOMA

Keywords: cutaneous squamous cell carcinoma, PD-1, PD-L1, cemiplimab, pembrolizumab, nivolumab, meta-analysis, immunotherapy.

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