Received: 28 February 2024 | Accepted: 9 May 2024

DOI: 10.1002/lio2.1279

REVIEW

Laryngoscope Investigative Otolaryngology

The efficacy and safety of EGFR-TKI in recurrent/metastatic nasopharyngeal carcinoma patients: A systematic review and meta-analysis

Zeqi An MB | Libin He MB | Tuo Chen MB | Bosen Liang MB | Qiang Wu MD

Department of Otorhinolaryngology Head and Neck Surgery, Shenzhen University General Hospital, Shenzhen, China

Correspondence
Qiang Wu, Department of Otorhinolaryngology Head and Neck Surgery, Shenzhen University General Hospital, Shenzhen 518055, China.
Email: wuqiang1666@126.com

Funding information
Science, Technology and Innovation Commission of Shenzhen Municipality, Grant/Award Number: JCYJ20200109114244249

Abstract

Objectives: EGFR-tyrosine kinase inhibitor (TKI) is used to treat recurrent and metastatic nasopharyngeal carcinoma (rmNPC). This meta-analysis aims to study the efficacy and safety of EGFR-TKI in treating patients with rmNPC.

Methods: We conducted a systematic search of PubMed, Embase, and Web of Science up to November 2023, and included literature that met the criteria. We extracted objective response rate (ORR), disease control rate (DCR), median progression-free survival (mPFS), median overall survival (mOS), and adverse reaction-related events and performed meta-analysis using Stata 14.0.

Results: A total of nine articles were included. The summary results showed that the ORR for patients treated with EGFR-TKI for rmNPC was 38% (95% CI = 27%–49%), the DCR was 71% (95% CI = 61%–80%), the mPFS was 6.29 months (95% CI = 5.22–7.35), and the mOS was 15.94 months (95% CI = 14.68–17.20). The most common grade 3–4 adverse reaction events in these patients were mucositis, nasopharyngeal necrosis, and oral ulceration. We found an incidence rate of 49% (95% CI = 38%–61%) for grade 3–4 adverse events (AEs). The anti-PD1 combined with TKI treatment method is more effective than the EGFR-TKI alone for treating rmNPC.

Conclusion: The study shows that EGFR-TKI has good efficacy in treating rmNPC but does not translate into survival benefits and owns a high incidence of grade 3–4 AEs. More RCT trials are needed in the future to verify the efficacy of anti-PD1 combined with TKI treatment method.

KEYWORDS
anti-PD1, EGFR-TKI, immunotherapy, meta-analysis, nasopharyngeal carcinoma, systematic review

1 | INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a malignant tumor that is widely distributed in East and Southeast Asia. The main treatment method is radiotherapy, which is effective, but 30% of patients still experience local recurrence or metastasis, which is the main reason for the poor prognosis of NPC.[1] Currently, the standard first-line treatments for recurrent or metastatic nasopharyngeal carcinoma (rmNPC) include platinum-based chemotherapy and concurrent chemoradiotherapy,[2,3] with a median progression-free survival (mPFS) time of approximately

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
© 2024 The Author(s). *Laryngoscope Investigative Otolaryngology* published by Wiley Periodicals LLC on behalf of The Triological Society.

15 months and significant survival benefits. However, in cases where first-line treatment is ineffective, there is no standard second-line treatment option available, and patients who experience chemotherapy or PD-1 inhibitor treatment or a combination of the two often have limited treatment options. Although the FDA has approved pembrolizumab/nivolumab for second-line and later treatment, subsequent randomized trials have not found a significant difference in survival benefits compared to chemotherapy alone, with an objective response rate (ORR) of only about 20.5%. This has also led to a generally poor prognosis for patients with rmNPC. In addition, patients' physical condition often worsens after intensive chemotherapy, making it difficult for most patients to tolerate another round of conventional chemotherapy. Therefore, better treatment options are needed in clinical practice.

Currently, the main immunotherapy methods for NPC include immune checkpoint inhibitors and anti-EGFR therapy.[4,5] EGFR belongs to the receptor tyrosine kinase family and plays an important role in regulating the proliferation and survival of tumor cells. Upon ligand binding, EGFR is activated and forms homodimers or heterodimers, leading to the phosphorylation and activation of various downstream signaling pathways, such as cell differentiation, proliferation, and carcinogenesis.[6] The overexpression of EGFR in tumors has been shown to be significantly associated with angiogenesis and local metastasis. In most NPC patients, overexpression of EGFR has been observed, which is significantly associated with poor prognosis after radiotherapy.[7] Currently, angiogenesis is a mature target for the treatment of advanced NPC, and clinical trials have demonstrated that anti-angiogenic therapy can enhance the efficacy of immunotherapy. This approach has been approved by the FDA for the treatment of some advanced solid tumors, especially gastric cancer. EGFR-tyrosine kinase inhibitors (TKIs) are orally available inhibitors of epidermal growth factor receptor tyrosine kinase that act on VEGF. They selectively target the ATP binding site within the cells and have high affinity. Their effectiveness has been confirmed in various solid tumors,[8] and in recent years, their efficacy has also been reported in many head and neck tumors.[9] In fact, in recent years, trials of EGFR-TKIs (e.g., erlotinib, afatinib) in the treatment of rmNPC patients have shown promising results with a lower rate of grade 3–4 adverse reactions. Compared to the past, these new TKIs have more suitable pharmacological mechanisms, selectively targeting a single receptor kinase pathway and enhancing affinity for receptor binding, thus requiring lower concentrations to achieve inhibitory effects and resulting in fewer drug toxicities.

To evaluate the efficacy and safety of EGFR-TKI treatment in patients with rmNPC, we conducted this meta-analysis to evaluate its effectiveness compared to other current methods and provide more evidence for clinical treatment strategies and applications.

2 | MATERIALS AND METHODS

2.1 | Literature search strategy

This protocol was registered in PROSPERO (CRD42023449269) and was done on the basis of the PRISMA guidelines. By November 2023, we screened PubMed, Web of Science, and Embase for articles pertaining to the efficacy of EGFR-TKIs in the treatment of nasopharyngeal cancer. Specific search keywords and MeSH terms used were Nasopharyngeal Carcinoma, Carcinomas, Nasopharyngeal, Epidermal Growth Factor Receptor Tyrosine Kinase inhibitor, EGFR-TKI, Epidermal Growth Factor Receptor Tyrosine Kinase inhibitor, Apatinib, and Gefitinib. The whole search strategy is included above (Table S1 in Data S1). For all records, two authors independently screened title and abstracts to review the eligibility for selection, with contention being balanced through consensus by discussing or consulting a third researcher.

2.2 | Eligibility criteria

The inclusion criteria were: (1) the study participants were diagnosed with rmNPC in histological confirmation; (2) the use of EGFR-TKI alone or plus another therapy were included into treatment regimen; (3) the literature was published up to November 2023, covering the past decade to exclude the influence of previous drugs on the analysis results. The exclusion criteria were: (1) laboratory studies or animal studies; (2) studies enrolled too few patients (less than 15 patients); (3) comments, letters, meta-analysis, meeting abstracts, unavailable articles, books, and reviews.

2.3 | Data extraction

The extracted data included the author' s name, country, publication year, regimen, number of included cases, study type, ORR, disease control rate (DCR), mPFS, median overall survival (mOS), and adverse events (AEs; grade 3–5 AEs). Objective response comprised complete and partial responses, whereas disease control encompassed complete response, partial response, and stable disease. The basic information of the studies was extracted individually by two investigators (Z.A. and L.H.). Arguments between the researchers were settled through discourse or after consulting a third researcher.

2.4 | Quality and publication bias assessment

Two investigators assessed risk of bias (RoB) independently by using the ROBINS-I tool for non-randomized studies.[10] Disagreements between the investigators were resolved through discussion or after consulting a third researcher. In ROBINS-I, low, moderate, serious, or critical RoB in seven domains including confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of reported result were the evaluation of each study.[10] The RoB was then comprehensively evaluated in accordance with the scores assigned to these domains. As the included studies were all non-randomized controlled trials, we utilize Egger' s test to assess publication bias in the reported results.[11]

2.5 | Statistical analysis

We used Stata 14.0 software for statistical analysis, combining effect sizes and 95% confidence intervals (CIs) for ORR, DCR, mPFS, and mOS and the incidence of grade 3–4 AEs. Considering the presence of substantial heterogeneity in non-randomized controlled trials, a random-effects model was employed for meta-analysis, otherwise the fixed effects model was used. Subgroup and sensitivity analyses were carried out to probe the sources of heterogeneity, when the results showed high heterogeneity (I^2 > 50% or p < .1).

3 | RESULTS

We used PubMed, Web of Science, and Embase to search for eligible studies, and a total of 1450 articles were obtained through retrieval. There was a total of 838 studies, after removing duplicates and records marked as ineligible by automation tools; 809 studies were then excluded by examining the titles and abstracts of the articles based on eligibility criteria. We retrospected the whole texts of the residual 29 articles, and then eliminated 19 studies because there are 13 unavailable full texts and seven studies with an unmatched design. Finally, nine articles were included in the analysis eligibly (Figure 1).[12–20] Besides, the included nine articles were all assessed as low or moderate risk by ROBINS-I tool (Table S2 in Data S1).

3.1 | Characteristics of literature

There is a summary of baseline patient characteristics in Table 1. Two cohorts (patients with first-line platinum-resistant or PD-1 inhibitor resistant) each with different quantity of participants were incorporated into one of the picked articles. We deemed these cohorts to be representative of two independent studies, so 10 studies from 9 articles involved 416 participants ultimately in this protocol. All of them were non-randomized studies. Among the 416 patients included, four

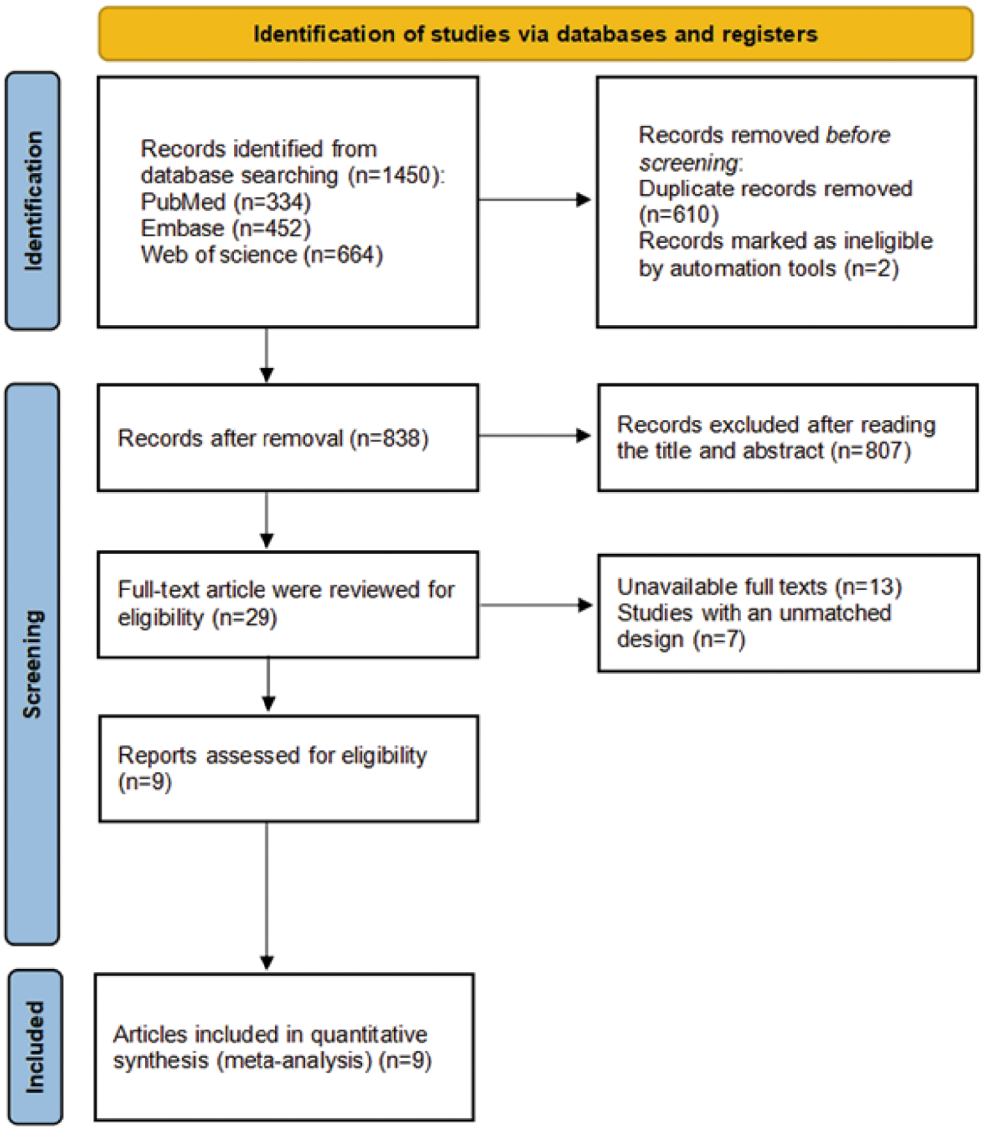

FIGURE 1 PRISMA flow diagram of the study selection process.

TABLE 1 Characteristics of literature.

Author	Year	Country	Study type	Population	Median age (years)	Sample size	Regimen	ORR (%)	DCR (%)	mPFS (months, 95% CI)	mOS (months, 95% CI)
Li et al.	2020	China	Single arm trial	Relapsed and refractory NPC	50	51	Apatinib	31.4	51.0	9 (5.2-12.8)	16 (9.3–22.7)
Ding et al(A).	2023	China	Single arm trial	rmNPC	Mean + SD	58	Camrelizumab + Apatinib	65.5	86.2	10.4 (7.2-13.6)	NR
Tang et al.	2023	China	Prospective trial	Platinum-refractory rmNPC	44	64	Apatinib + Capecitabine	39.1	85.9	7.5 (5.0-10.0)	15.7 (11.3–20.1)
Ruan et al.	2021	China	Prospective trial	rmNPC	48	33	Apatinib	36.4	54.5	5.0 (3.6-6.4)	16 (14.6–17.4)
Hui et al.	2018	China	Single Arm Trial	rmNPC	52	40	Axitinib	18.9	43.2	5 (3.9-5.7)	10.4 (6.8–19.0)
Ding et al(F).	2023	China	Simon two-stage designed trial	rmNPC	47	18	Camrelizumab + Famitinib	33.3	77.8	7.2 (3.5-14.2)	NR
Yuan et al.	2023	China	Cohort 1: single arm trial Cohort 2: single arm trial	Cohort 1: platinum-resistant rmNPC Cohort 2: platinum-resistant rmNPC	Cohort 1: 49 Cohort 2: 40	Cohort 1: 40 Cohort 2: 32	Cohort 1: Camrelizumab + Apatinib Cohort 2: Camrelizumab + Apatinib	Cohort 1: 65.0 Cohort 2: 34.4	Cohort 1: 80 Cohort 2: 68.8	Cohort 1: 12.6 (1.5–23.7) Cohort 2: 4.5 (3.7–5.4)	Cohort 1: NR Cohort 2: NR
Zhou et al.	2020	China	Retrospective trial	mNPC	48	41	Apatinib + S-1	34.1	80.1	9.7 (6.2–13.8)	22.1 (15.1–28.9)
Fang et al.	2023	China	Prospective trial	rmNPC	48	39	Anlotinib	20.5	71.8	5.7 (4.7–6.8)	NR

Abbreviations: DCR, disease control rate; mNPC, metastasis nasopharyngeal carcinoma; mOS, median overall survival; mPFS, median progression-free survival; NR, not reported; ORR, objective response rate; rmNPC, recurrent or metastatic nasopharyngeal carcinoma.

studies administrated EGFR-TKI monotherapy, with two using apatinib and the other two using axitinib and anlotinib. Among them, four studies involve treating patients with recurrent or metastatic nasopharyngeal carcinoma using a combination of TKI and anti-PD1 therapy, whereas two studies used a combination of TKI drugs and chemotherapy including apatinib plus capecitabine and apatinib combined with S-1.

3.2 | Efficacy

Based on results from 10 studies using the random-effects model, the ORR is 38% (95% CI = 27%–49%, I^2 = 80.6%) (Figure 2). The pooled DCR is 71% (95% CI = 61%–80%, I^2 = 80.3%) (Figure 3). Ten studies reported mPFS. The use of EGFR-TKI in rmNPC patients resulted in a mPFS of 6.29 months (95% CI = 5.22–7.35, I^2 = 79.1%) (Figure 4).

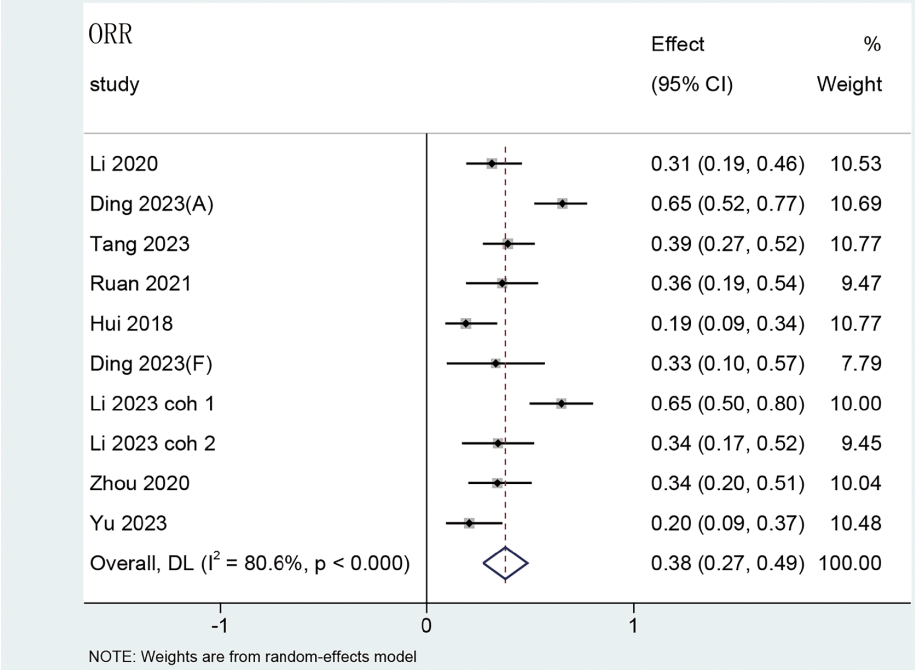

FIGURE 2 Forest plots of objective response rate (ORR) for the meta-analysis.

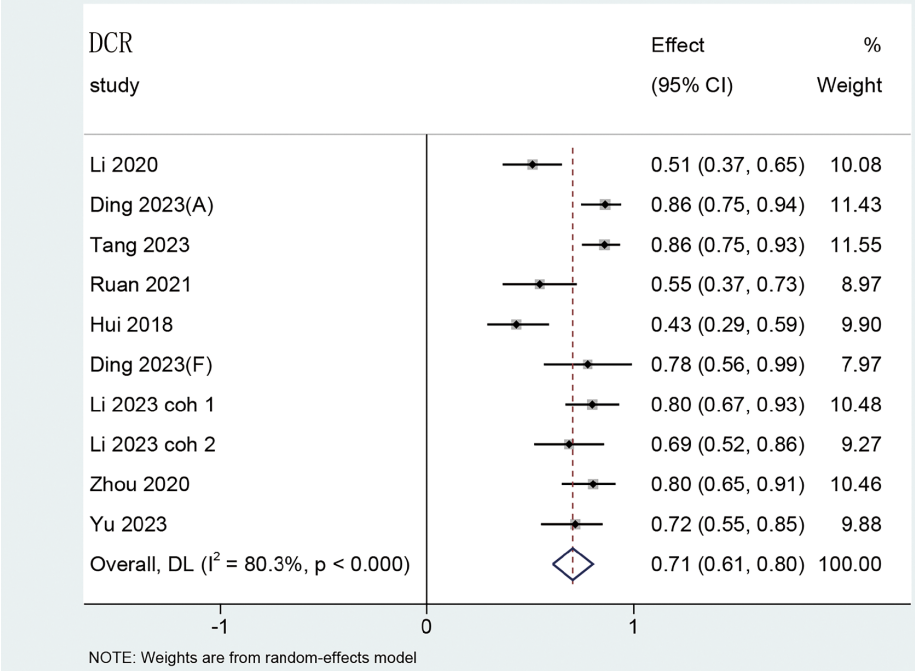

FIGURE 3 Forest plots of disease control rate (DCR) for the meta-analysis.

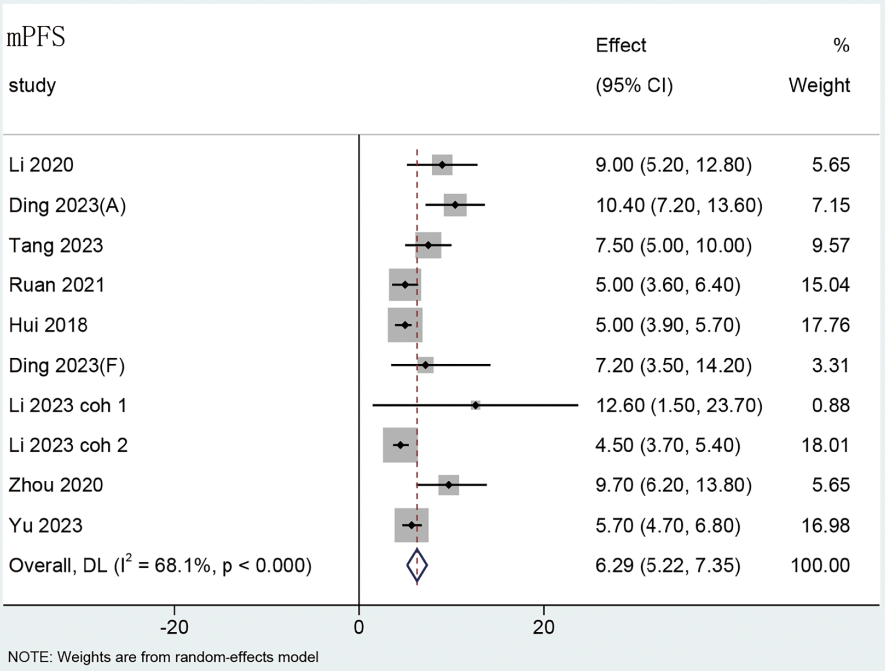

FIGURE 4 Forest plots of median progression-free survival (mPFS) for the meta-analysis.

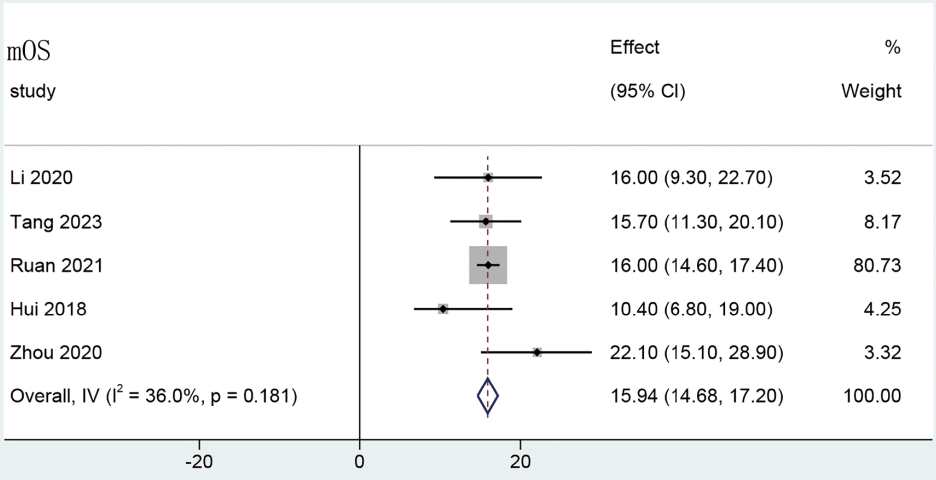

FIGURE 5 Forest plots of median overall survival (mOS) for the meta-analysis.

Seven studies reported mOS and the pooled mOS was 15.94 months (95% CI = 14.68–17.20, I^2 = 36.0%) (Figure 5).

3.3 | Safety

All patients participating in clinical trials have experienced at least one drug-related adverse reaction, with the most common AEs being hand-foot syndrome, hypertension, and proteinuria. We conducted a meta-analysis of four studies that reported grade 3–4 adverse reactions and found a total incidence rate of 49% (95% CI = 38%–61%) (Figure 6). All grade 3–4 adverse reactions are summarized in Table S3 in Data S1. The most common grade 3–4 AEs are mucositis, nasopharyngeal necrosis, and oral ulcers, which is also the reason why the dose of TKI is reduced due to adverse reactions. Only one case of grade 5 adverse reaction was reported among the 416 patients, and

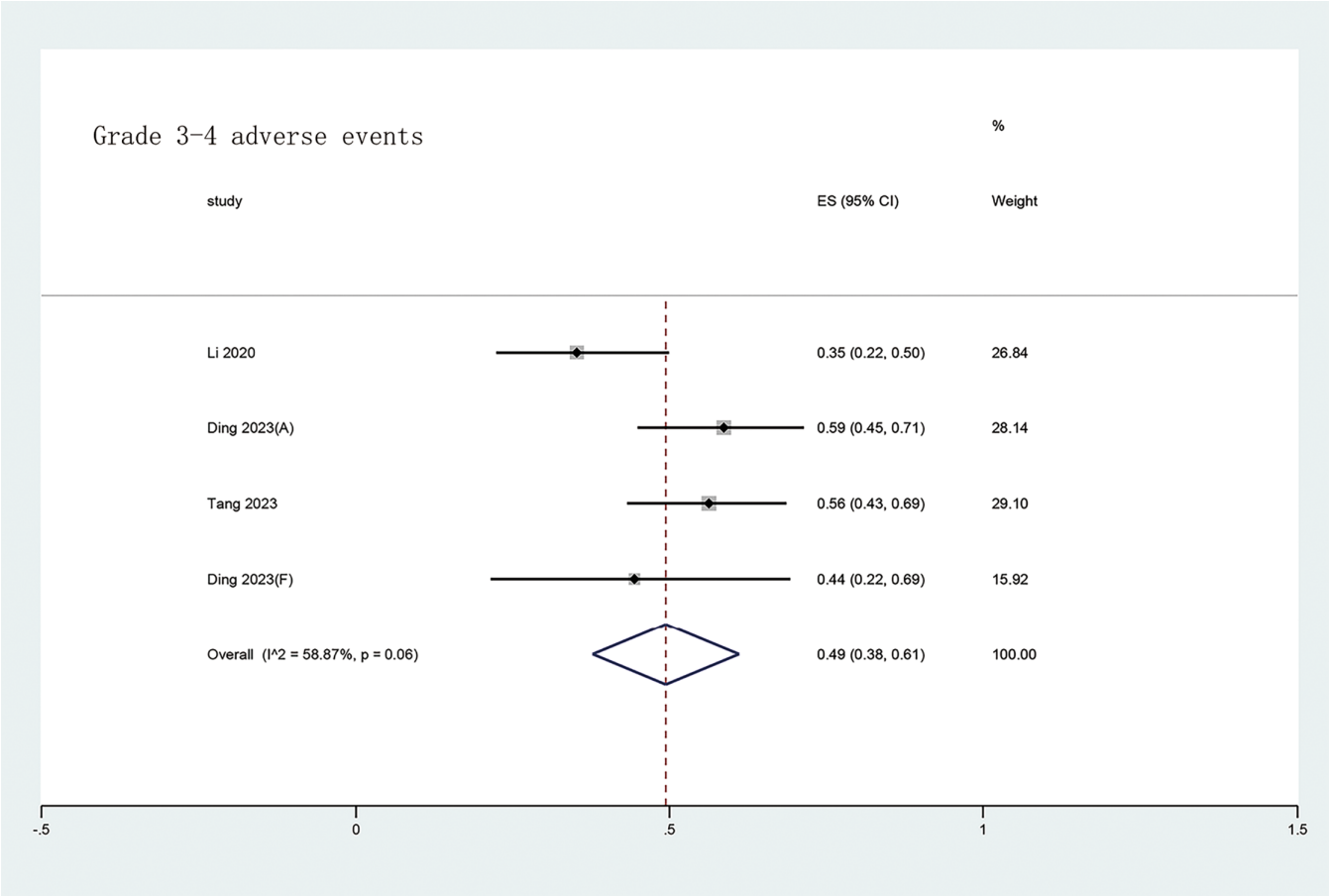

FIGURE 6 Forest plots of the incidence of grade 3–4 events.

TABLE 2 Subgroup analysis.

Subgroup	Included studies	ORR			DCR			mPFS		
		ES (95% CI)	I^2	*p*	ES (95% CI)	I^2	*p*	ES (month, 95% CI)	I^2	*p*
Study protocol										
EGFR-TKI monotherapy	3	0.26 (0.18–0.34)	22.1%	0.278	0.55 (0.43–0.67)	60.3%	0.056	5.41 (4.58–6.25)	37.4%	0.188
Anti-PD1 + TKI	4	0.51 (0.34–0.68)	76.6%	0.005	0.81 (0.74–0.88)	6.7%	0.360	7.72 (3.63–11.81)	79.6%	0.002
TKI + chemotherapy	3	0.37 (0.27–0.47)	0.0%	0.619	0.84 (0.77–0.92)	0.0%	0.5	8.16 (6.08–10.25)	0.0%	0.343

Abbreviations: DCR, disease control rate; ES, effect sizes; mPFS, median progression-free survival; ORR, objective response rate; TKI, tyrosine kinase inhibitor.

one patient died of grade 5 adverse reaction cerebral infarction in Ruan's study.

3.4 | Subgroup analysis

To gain a deeper understanding and address the problem of high heterogeneity in the results, we divided the included studies into several subgroups according to the study protocol and performed statistical analysis to aggregate ORR, DCR, and mPFS for each subgroup (Table 2) (Figures S1–S3 in Data S1). In the grouping based on the study protocol, the treatment efficacy results summarized using anti-PD1 plus TKI group were ORR: 51% (95% CI = 34%–68%), DCR: 81% (95% CI = 74%–88%), and mPFS: 7.72 months (95% CI = 3.63–11.81). The treatment efficacy results summarized using chemotherapy plus TKI group were ORR: 37% (95% CI = 27%–47%), DCR: 84% (95% CI = 77%–92%), and mPFS: 8.16 months (95% CI = 6.08–10.25). The efficacy of these two treatment regimens was higher than

that of TKI alone, and of course, the efficacy results of these two treatment groups were also higher than the overall summary results, indicating better treatment effects. Our subgroup analysis also found that there was no significant difference in the efficacy of anti-PD1 plus TKI treatment for rmNPC compared to TKI plus chemotherapy group on the basis of the current integrated results of included studies.

3.5 | Publication bias and sensitivity analysis

In this protocol, Egger' s test indicated that the *p* value was .96 for ORR. As a result, no publication bias was detected in the studies incorporated into our analysis. Owing to the high heterogeneity, we conducted a sensitivity analysis (Figure S4 in Data S1), which indicated that the pooled ORR, DCR, and mPFS were relatively stable and not significantly influenced by the exclusion of any individual study. However, we found that the combined results of grade 3–4 AEs were greatly affected by the exclusion of Li' s study, suggesting that this study was a major source of heterogeneity in the grade 3–4 adverse reaction outcomes.

4 | DISCUSSION

There is currently no clear standard for patients who have failed in first-line treatment of NPC. For these patients, the most common treatments are chemotherapy or immunotherapy and the EGFR-TKI drug is currently among the most utilized immunotherapy drugs following failure of first-line treatment. In our systematic review and meta-analysis of 10 studies, the ORR, DCR, mPFS, and mOS for TKIs as the treatment of the rmNPC were found to be 38% (95% CI = 27%–49%), 71% (95% CI = 61%–80%), 6.29 months (95% CI = 5.22–7.35), and 15.94 months (95% CI = 14.68–17.20), respectively. It is significantly better than the outcome of using chemotherapy alone (ORR: 21%, mPFS: 6.1 months). However, the results of our meta-analysis indicate that TKI treatment is correlated with a greater incidence of grade 3 and 4 adverse drug events. The current research scheme and clinical experience suggest that TKI dose reduction is recommended to mitigate the impact of adverse reactions on patients. Nasopharyngeal necrotic hemorrhage is the most common reason for dose reduction or even drug discontinuation in the trial. This may be attributed to the heightened angiogenesis of NPC itself and complications arising from first-line radiotherapy.[21] Even if the dosage needs to be reduced due to adverse reactions, our meta-analysis results for TKIs as the treatment of the rmNPC indicate that the efficacy of TKI is comparable to PD1, another mainstream drug currently available. In some cases, TKI's efficacy is even superior. In addition, almost all drug-related AEs could be controlled through dose reduction.[22]

The study design we included in our research involved a much lower dosage of TKI than what is typically used in other cancer treatments. For instance, the initial dose of apatinib for gastric cancer is 850 mg,[23] whereas most of the studies we included used a dosage of around 500 mg. In trial design, it is important to consider the different drug absorption rates for each type of cancer and whether combination therapy will increase the probability of adverse drug events. Furthermore, it is not necessarily true that the larger the dosage used in a trial, the better the efficacy. Zhou's research suggests that a low dose of TKI combined with chemotherapy also has a certain therapeutic effect. Compared to other similar treatment regimens, the effect is not significantly different, and the adverse reactions are greatly reduced. There is no negative impact on the therapeutic effect of chemotherapy combined with TKI treatment. Similar evidence has also appeared in lung cancer. Corral's RCT study confirmed that patients who continued to use dacomitinib with dose adjustments guided by tolerability did not show a significant difference in mPFS and mOS compared to the original control group.[24]

A higher level of effectiveness is achieved through the utilization of a combination therapy consisting of chemotherapy and TKI. This combination therapy has an ORR of 37%, a DCR of 84%, and a mPFS of 8.16 months, all surpassing the outcomes observed with monotherapy alone. According to other studies on NSCLC tumors, this phenomenon may be attributed to the fact that both drug resistance mechanisms are mutually affected.[25] EGFR-TKIs inhibit EGFR and HER2, preventing the activation of downstream signaling pathways, and arresting the cell cycle at the G2/M phase.[26] This leads to an increased rate of apoptosis and inhibits DNA damage repair,[27] thereby enhancing the sensitivity of tumor cells to radiotherapy and chemotherapy. The development of resistance during drug treatment is mainly related to the high heterogeneity of NPC itself, and patients may simultaneously have multiple resistance mechanisms.[28] This may be due to mutations in the nuclear localization signal (NLS) of EGFR (mNLS), which prevent the translocation of EGFR to the nucleus, releasing EGFR-induced resistance to chemotherapy, especially resistance to cisplatin. Therefore, real-time genetic testing for tailored and more personalized treatment may be a new direction in the future. Following progression, additional therapeutic medications may be required, or existing drugs may need to be changed based on new cellular gene sequencing results. However, the current progress in molecularly targeted therapy for NPC lags behind, posing a challenge to patient treatment and the development of new drugs to combat drug resistance.[29]

In comparison, the academic community has proposed a promising approach involving the simultaneous use of antiPD1 and TKI inhibitor therapy, which has indeed yielded better results. This approach has shown an aggregated ORR of 51%, a DCR of 81%, and a mPFS of 7.72 months. The satisfactory efficacy combined with an increased response rate translates well into an improvement in progression-free survival. This may be because a significant body of evidence demonstrates that low-dose EGFR-TKI can effectively modulate the immunosuppressive microenvironment within tumors, leading to a more homogeneous distribution of tumor vessels.[30,31] This modulation facilitates the polarization of macrophages from an immunosuppressive M2-like phenotype to an immunostimulatory M1-like phenotype, and enhances infiltration by CD4+ and CD8+ T-cells.[32,33]

These mechanisms contribute to combating resistance to PD1 therapy and improving the immune environment to support immune checkpoint inhibitor therapy.[22] Currently, a clinical trial is underway that combines chemotherapy, TKI, and anti-PD1 simultaneously, and it has also demonstrated satisfactory efficacy. These three therapies can mutually mitigate the inhibitory effect of drug resistance mechanisms. This could also be a new approach to clinical trials in the future. The ongoing phase 2 clinical trial by Ma (NCT05807880) is investigating the combined treatment of anlotinib, camrelizumab, and capecitabine for rmNPC. The new trial results from this study are highly anticipated. The ORRs of the two experiments conducted by Ding's team were 65.5% and 33.0%, respectively, whereas the DCRs exhibited a generally similar trend. The findings also indicate that, for patients with rmNPC, apatinib has a more positive drug response, such as reducing the size of tumors more and providing greater relief from clinical symptoms. This suggests that apatinib may be a promising therapeutic option for rmNPC patients. Meanwhile, Li's cohort 2 trial, conducted in PD1-resistant patients, revealed similar findings to those observed with TKI monotherapy. The combination of anti-PD1 and TKI in such patients yields limited efficacy and an unfavorable prognosis, thus necessitating further elucidation into the underlying causes and potential solutions. Although all four studies use anti-PD1 combined with TKI for the treatment of rmNPC, the differences in patient characteristics (e.g., significant variations in prior treatments received by the patient population) and drug dosages have resulted in significant differences in mPFS and mOS in the clinical trial results, contributing to the high heterogeneity of this subgroup. Despite the current findings that the treatment efficacy of using anti-PD1 and TKI regimens is not significantly different from TKI combined with chemotherapy, with more clinical trials underway, the heterogeneity of this approach is expected to decrease, leading to a clearer understanding of treatment efficacy. We look forward to comprehensive and precise clinical trial results from ongoing trials, such as Cai's open-label phase II study (NCT04996758) using toripalimab and anlotinib in combination for patients with rmNPC who have failed first-line platinum-based chemotherapy.

The novelty of this article is that, to our knowledge, it is the first systematic review study to analyze and demonstrate the efficacy of anti-PD1 and TKI combination therapy for rmNPC, and to update the latest data on TKI efficacy evaluation from the past 3 years. This meta-analysis of drug efficacy provides more valuable references for clinical doctors to assess patients and customize treatment plans.

Our study also has some limitations. The literature we included were all non-randomized controlled trials and some studies had small sample sizes with limited statistical power, so we could not discuss more factors that affect the outcome. The studies we included were all non-randomized controlled trials, which resulted in high heterogeneity of the results.

5 | CONCLUSION

The study shows that EGFR-TKI has good efficacy in treating rmNPC but does not translate into survival benefits and owns a high incidence of grade 3–4 AEs. More RCT trials are needed in the future to verify the efficacy of anti-PD1 combined with TKI treatment method and assess the minimum effective dose for combination therapy, with better clinical benefits associated with less likelihood of grade 3–4 AEs.

ACKNOWLEDGMENTS

This research was supported by the grants from Science, Technology and Innovation Commission of Shenzhen Municipality (JCYJ20200109114244249).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ORCID

Zeqi An https://orcid.org/0009-0007-5805-2320
Qiang Wu https://orcid.org/0000-0002-4093-2334

REFERENCES

1. Chen YP, Chan ATC, Le QT, Blanchard P, Sun Y, Ma J. Nasopharyngeal carcinoma. *Lancet*. 2019;394:64-80.
2. Zhang L, Huang Y, Hong S, et al. Gemcitabine plus cisplatin versus fluorouracil plus cisplatin in recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 trial. *Lancet*. 2016;388(10054):1883-1892.
3. Li WF, Chen NY, Zhang N, et al. Concurrent chemoradiotherapy with/without induction chemotherapy in locoregionally advanced nasopharyngeal carcinoma: long-term results of phase 3 randomized controlled trial. *Int J Cancer*. 2019;145:295-305.
4. Li WT, Duan XB, Chen XX, et al. Immunotherapeutic approaches in EBV-associated nasopharyngeal carcinoma. *Front Immunol*. 2023;13:1079515.
5. Chen XS, Liang RB, Zhu XD. Anti-EGFR therapies in nasopharyngeal carcinoma. *Biomed Pharmacother*. 2020;131:110649.
6. Sabbah DA, Hajjo R, Sweidan K. Review on epidermal growth factor receptor (EGFR) structure, signaling pathways, interactions, and recent updates of EGFR inhibitors. *Curr Top Med Chem*. 2020;20:815-834.
7. Hui EP, Chan ATC, Pezzella F, et al. Coexpression of hypoxia-inducible factors 1α and 2α, carbonic anhydrase IX, and vascular endothelial growth factor in nasopharyngeal carcinoma and relationship to survival. *Clin Cancer Res*. 2002;8:2595-2604.
8. Lin YS, Qin SK, Li ZY, et al. Apatinib vs placebo in patients with locally advanced or metastatic, radioactive iodine-refractory differentiated thyroid cancer: the REALITY randomized clinical trial. *JAMA Oncol*. 2022;8:242-250.
9. Liu ZJ, Zheng ZZ, Dong LH, et al. Efficacy and safety of apatinib in patients with recurrent or metastatic head and neck squamous cell carcinoma: a retrospective multi-center study. *Sci Rep*. 2022;12(1):18327.
10. Sterne JAC, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919.
11. Sterne JAC, Sutton AJ, Ioannidis JPA, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*. 2011;343:d4002.
12. Li L, Kong F, Zhang L, et al. Apatinib, a novel VEGFR-2 tyrosine kinase inhibitor, for relapsed and refractory nasopharyngeal carcinoma: data from an open-label, single-arm, exploratory study. *Investig New Drugs*. 2020;38:1847-1853.
13. Ding X, Zhang WJ, You R, et al. Camrelizumab plus apatinib in patients with recurrent or metastatic nasopharyngeal carcinoma: an open-label, single-arm, phase II study. *J Clin Oncol*. 2023;41:2571-2582.

14. Tang LQ, Li XY, Li ZM, et al. The efficacy and safety of apatinib plus capecitabine in platinum-refractory metastatic and/or recurrent nasopharyngeal carcinoma: a prospective, phase II trial. *BMC Med*. 2023;21(1):94.
15. Ruan XL, Liang JH, Pan YF, et al. Apatinib for the treatment of metastatic or locoregionally recurrent nasopharyngeal carcinoma after failure of chemotherapy: a multicenter, single-arm, prospective phase 2 study. *Cancer*. 2021;127:3163-3171.
16. Hui EP, Ma BBY, Loong HHF, et al. Efficacy, safety, and pharmacokinetics of axitinib in nasopharyngeal carcinoma: a preclinical and phase II correlative study. *Clin Cancer Res*. 2018;24:1030-1037.
17. Ding X, Hua YJ, Zou X, et al. Camrelizumab plus famitinib in patients with recurrent or metastatic nasopharyngeal carcinoma treated with PD-1 blockade: data from a multicohort phase 2 study. *EClinicalMedicine*. 2023;61:102043.
18. Yuan L, Jia GD, Lv XF, et al. Camrelizumab combined with apatinib in patients with first-line platinum-resistant or PD-1 inhibitor resistant recurrent/metastatic nasopharyngeal carcinoma: a single-arm, phase 2 trial. *Nat Commun*. 2023;14(1):4893.
19. Zhou LY, Lin J, Wu G, Chen J, Huang X, Zhang S. Safety and feasibility of low-dose apatinib combined with S-1 as the second-line therapy or beyond in Chinese patients with pulmonary and hepatic metastasis of nasopharyngeal carcinoma. *Drug Des Devel Ther*. 2020;14:1257-1262.
20. Fang Y, Su N, Zou QH, et al. Anlotinib as a third-line or further treatment for recurrent or metastatic nasopharyngeal carcinoma: a single-arm, phase 2 clinical trial. *BMC Med*. 2023;21(1):423.
21. Kamba T, McDonald DM. Mechanisms of adverse effects of anti-VEGF therapy for cancer. *Br J Cancer*. 2007;96:1788-1795.
22. Yi M, Jiao DC, Qin S, Chu Q, Wu K, Li A. Synergistic effect of immune checkpoint blockade and anti-angiogenesis in cancer treatment. *Mol Cancer*. 2019;18(1):60.
23. Li J, Qin SK, Xu JM, et al. Apatinib for chemotherapy-refractory advanced metastatic gastric cancer: results from a randomized, placebo-controlled, parallel-arm, phase II trial. *J Clin Oncol*. 2013;31:3219-3225.
24. Corral J, Mok TS, Nakagawa K, et al. Effects of dose modifications on the safety and efficacy of dacomitinib for EGFR mutation-positive non-small-cell lung cancer. *Future Oncol*. 2019;15:2795-2805.
25. Mi YJ, Liang YJ, Huang HB, et al. Apatinib (YN968D1) reverses multidrug resistance by inhibiting the efflux function of multiple ATP-binding cassette transporters. *Cancer Res*. 2010;70:7981-7991.
26. Brands RC, Müller-Richter UDA, De Donno F, et al. Co-treatment of wild-type EGFR head and neck cancer cell lines with afatinib and cisplatin. *Mol Med Rep*. 2016;13:2338-2344.
27. Hsu SC, Miller SA, Wang Y, Hung MC. Nuclear EGFR is required for cisplatin resistance and DNA repair. *Am J Transl Res*. 2009;1:249-258.
28. Li XX, Guo YL, Xiao MM, Zhang W. The immune escape mechanism of nasopharyngeal carcinoma. *FASEB J*. 2023;37:e23055.
29. Huang HG, Yao YY, Deng XY, et al. Immunotherapy for nasopharyngeal carcinoma: current status and prospects (review). *Int J Oncol*. 2023;63(2):97.
30. Yuan M, Zhai YR, Men Y, et al. Anlotinib enhances the antitumor activity of high-dose irradiation combined with anti-PD-L1 by potentiating the tumor immune microenvironment in murine lung cancer. *Oxid Med Cell Longev*. 2022;2022:5479491.
31. Huang YH, Yuan JP, Righi E, et al. Vascular normalizing doses of antiangiogenic treatment reprogram the immunosuppressive tumor microenvironment and enhance immunotherapy. *Proc Natl Acad Sci USA*. 2012;109:17561-17566.
32. Du Four S, Maenhout SK, Niclou SP, Thielemans K, Neyns B, Aerts JL. Combined VEGFR and CTLA-4 blockade increases the antigen-presenting function of intratumoral DCs and reduces the suppressive capacity of intratumoral MDSCs. *Am J Cancer Res*. 2016;6:2514-2531.
33. Peng F, Chen M. Antiangiogenic therapy: a novel approach to overcome tumor hypoxia. *Chin J Cancer*. 2010;29(8):715-720.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: An Z, He L, Chen T, Liang B, Wu Q. The efficacy and safety of EGFR-TKI in recurrent/metastatic nasopharyngeal carcinoma patients: A systematic review and meta-analysis. *Laryngoscope Investigative Otolaryngology*. 2024;9(3):e1279. doi:10.1002/lio2.1279