International Platform of Registered Systematic Review and Meta-analysis Protocols



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# Efficacy of Immune checkpoint inhibitors in the Treatment for head and neck cancer patients: A Systematic Review and Network meta-analysis

INPLASY202470073

doi: 10.37766/inplasy2024.7.0073

Received: 20 July 2024

Published: 20 July 2024

Li, J; Rahman, NA; Mohamad, S; Yang, G; Zhao, CX.

**Corresponding author:**
Caixia Zhao

zhaocaixia@sxmu.edu.cn

**Author Affiliation:**
School of Dental Sciences, Universiti Sains Malaysia, Health Campus, 16150, Kubang Kerian, Kelantan, Malaysia.

## ADMINISTRATIVE INFORMATION

**Support -** Universiti Sains Malaysia Research University Grant (1001/PPSG/8012345).

**Review Stage at time of this submission -** Completed but not published.

**Conflicts of interest -** None declared.

**INPLASY registration number:** INPLASY202470073

**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 20 July 2024 and was last updated on 20 July 2024.

## INTRODUCTION

**Review question / Objective** Checkpoint inhibitors have significantly improved outcomes in a number of malignancies. To determine the most effective course of treatment for head and neck squamous cell carcinoma (HNSCC), we evaluated the efficacy of several therapeutic approaches based on immune checkpoint inhibitors (ICIs).

**Condition being studied** HNC currently ranks seventh in the world in 2021, and 1.5% of cancer cases in the US mortality from related tumors, which includes cancer of the mouth, lip, nose, oropharynx, throat, and nasopharynx. Furthermore, 95% of instances of HNC are head and neck squamous cell carcinoma, or HNSCC. Risk variables for HNSCC consist in age, sex, diet, oral infection, history of infection with human papillomavirus or Epstein-Barr virus, and tobacco and alcohol use. The treatment procedure for HNSCC patients depends on the disease stage, the existence of lymph node metastases, distant metastases, anatomical site, and surgical accessibility. Treatment for HNSCC is complex and subtype-dependent, which typically involves surgical resection of the tumor followed by ionizing radiation (IR) therapy or chemoradiotherapy. On the other hand, short survival and locally progressed or metastatic disease affect about 60% of HNSCC patients. In less than three years, over fifty percent of HNSCCs experience tumor metastasis and recurrence.

Immune checkpoint inhibitors (ICIs) have shown encouraging efficacy in treating patients with HNSCC, particularly those who have advanced following treatment grounded on platinum. For advanced HNSCC patients, novel immunotherapy agents—antibodies that target the PD-1/PD-L1 system—offer improved effectiveness and relatively less poisonousness as compared to standard therapies. Initial immune checkpoint inhibitors (ICIs) licensed to treat HNSCC resistant to platinum, recurrent or metastatic are the monoclonal antibodies the anti–PD-1

pembrolizumab plus nivolumab. Pembrolizumab was cleared for use in the initial line of treatment for patients whose tumors have a PD-L1 CPS of ≥ 1% as per the outcomes of KEYNOTE-048 research, either together with cisplatin/5-fluorouracil alone or with chemotherapy. By inhibiting inhibitory signals via PD-1/PD-L1 pathway, these immunotherapeutic drugs enhance the immune system's reactivity. But in fact, access to these regimens is limited to 5 % globally and the overall response is still limited.
Although ICIs are now used to treat R/M HNSCC patients that already got systematic chemotherapy, there is currently little pertinent data available. As far as we are aware, there has only been one NMA comparing ICIs to other systemic treatments for advanced head and neck cancer. The other NMA, which included five RCTs Keynote 040 and 048, Eagle, Checkmate 141, Condor, compared anti-PD-1 to anti-PD-L1 therapies in HNSCC. However, as more clinical research is ongoing, new ICIs were involved in the treatment of HNSCC such as ipilimumab. Added assessments are required because there aren't enough head-to-head comparative trials to figure out whether ICIs-based treatment strategies—monotherapy and combination therapy—offer the highest level of efficacy. Whether employed as monotherapies, ICI combination therapies, or in conjunction with other anticancer treatments like chemotherapy or radiation therapy in HNSCC, the goal of this research is to provide insight on efficacy, survival advantages, and potential future difficulties of ICIs.

## METHODS

**Participant or population** The participants were adult patients (≥18 years old) diagnosed with HNC based on pathological results.

**Intervention** The intervention was ICIs of any format.

**Comparator** Chemotherapy, radiotherapy, ICIs therapy that different from intervention.

**Study designs to be included** The study type was an RCT, blind or not.

**Eligibility criteria** The exclusion criteria consisted of the following: (1) studies that were not published in either English; (2) studies that were reviews, study protocols, conference abstracts or duplicate publications; (3) research for which the complete text was lacking; plus (4) research that provided unextractable or insufficient data for further analysis.

**Information sources** We looked through the databases of Embase, PubMed, and the Cochrane Library to find publications on immune checkpoint inhibitor therapy for HNSCC up until April2024.

**Main outcome(s)** The outcome contains OS and/or PFS.

**Quality assessment / Risk of bias analysis** Applying "Cochrane Collaboration tool for assessing the risk of bias in randomized trials," two investigators (J.L. and CX. Z.) evaluated the danger of prejudice in the chosen research. Each study's bias risk was evaluated separately by two investigators. All investigators came to a consensus to settle disagreements.

**Strategy of data synthesis** The R 4.4.2 “gemtc” package was utilized for the data analysis. For all included studies, measurement of the impact size was done using the Hazard Ratio and 95% CI. The pre-iteration and iteration count for network meta-analysis were set at 20,000 and 100,000, respectively. The Rank Probability function was used to create therapeutic impact probability ranking diagrams.

**Subgroup analysis** None.

**Sensitivity analysis** Not appliable.

**Country(ies) involved** Malaysia, China.

**Keywords** HNSCC, immune checkpoint inhibitor, PD-1, PD-L1, network meta-analysis.

**Contributions of each author**
Author 1 - Jiao Li.
Author 2 - Nurhayu Ab Rahman.
Author 3 - Suharni Mohamad.
Author 4 - Guang Yang.
Author 5 - Caixia Zhao.