

# INPLASY

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## Comparing the efficacy of immune checkpoint inhibitors plus other treatments as the first-line treatment for recurrent or metastatic squamous cell carcinoma of the head and neck: a protocol for network meta-analysis of phase III trials

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## ADMINISTRATIVE INFORMATION

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**Review Stage at time of this submission** - Data extraction.

**Conflicts of interest** - None declared.

**INPLASY registration number:** INPLASY202370009

**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 03 July 2023 and was last updated on 03 July 2023.

## INTRODUCTION

**Review question / Objective** Head and neck squamous cell carcinomas (HNSCC) rank as the sixth most prevalent kind of cancer that can affect the larynx, hypopharynx, oropharynx, nasopharynx, oral and nasal canals, and paranasal sinuses, among other localizations of the upper aerodigestive tract and has poor prognosis. In the recent decade, US Food and Drug Administration has approved two PD-1 inhibitors, nivolumab and pembrolizumab in which pembrolizumab in combination with chemotherapy showed higher OS in the overall population. Recently, the accrual phase of the KESTREL phase III study, which compared EXTREME to durvalumab with or without tremelimumab for patients with platinum-sensitive recurrent or metastatic (R/M) HNSCC, but did not reveal a statistically significant OS advantage. This network

meta-analysis aims to compare the effectiveness of immune checkpoint inhibitors as first-line therapy in recurrent or metastatic squamous cell carcinoma of the head and neck patients in order to support evidence-based treatment choices.

**Condition being studied** Recurrent or metastatic squamous cell carcinoma of the head and neck.

## METHODS

**Search strategy** A systematic literature search will be performed on the electronic databases of PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials from inception to May 2023 using terms of: “head and neck carcinoma”, “head and neck cancer”, “head and neck neoplasm”, “immune checkpoint inhibitors”, “PD-1/PD-L1”. The study type will be focused on phase III randomized controlled trials (RCTs),

studying first-line treatment with any single-agent or combination. Searching details are documented in supplementary materials.

**Participant or population** patients with recurrent or metastatic squamous cell carcinoma.

**Intervention** Immune checkpoint inhibitors plus other treatments.

**Comparator** placebo or chemotherapy or standard of c.

**Study designs to be included** Phase III randomized controlled trials.

**Eligibility criteria** Criteria for eligible studies are (1) studies designed in phase III randomized controlled trials (RCTs); (2) treatment includes two or more arms, with at least one arm utilizing immune checkpoint inhibitors; (3) the study shall be published reports providing outcomes of OS, PFS, and ORR in the intention-to-treat (ITT) population; (4) no limitations of the publication language, year or stage etc. Studies that don't meet these criteria will be excluded.

**Information sources** PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials.

**Main outcome(s)** The primary outcome comparisons will be OS and PFS.

**Quality assessment / Risk of bias analysis** We will assess the risk of bias of each RCT included with the Cochrane Risk of Bias Tool. Trials' risk of bias will be assessed as "low", "high" or "ambiguous" under the evaluation of seven aspects: random sequence generation, blinding of participants and personnel, allocation concealment, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias.

**Strategy of data synthesis** We will conduct the Bayesian NMA using the "JAGS" and "GEMTC" packages in R-studio Version 1.3.959 (<https://rstudio.com/>) for Markov Chain Monte Carlo stimulation. The model will be run with 150 000 iterations and a burn-in of 10 000 samples and a thinning interval of 1. Node splitting analysis will be used to evaluate both direct and indirect comparisons.

The primary outcome comparisons will be OS and PFS. The secondary outcomes will be ORR and adverse events of any grade. The effect size that we are synthesizing are HRs for OS and PFS. For the trails whose HRs are missing, we will use

GetData Graph Digitizer (version 2.26; <http://getdata-graph-digitizer.com/download.php>) to quantify the Kaplan-Meier (KM) curve and reconstruct (using R-studio) the individual patient data (IPD), then we will recalculate the HRs from the IPD. The odds ratio for ORR and AEs will be synthesized. Then, the network graph will be generated with R to illustrate the comparative efficacy of different arms. Furthermore, we will calculate the surface under the cumulative ranking (SUCRA) probabilities to rank different arms. Pairwise meta-analysis will be implemented using the "meta" package for the same intervention from different trials. For heterogeneity analysis, we will use I<sup>2</sup> test. Results with I<sup>2</sup> <25 % indicate low heterogeneity, 25 % < I<sup>2</sup> < 50 % mean a moderate, and 50 % < I<sup>2</sup> reveal a high heterogeneity.

**Subgroup analysis** Subgroup analyses for each biomarker will be planned on the basis of the country in which the study was conducted, stage of pancreatic cancer, cut-off level, risk factors of head and neck cancer and risk of bias.

**Sensitivity analysis** The sensitivity analysis was performed by repeating the network meta-analysis including high-risk studies. If the estimated effect was significantly influenced, Inconsistency between direct and indirect comparisons was evaluated using nodesplit approach.

**Country(ies) involved** China.

**Keywords** HNSCC; immune checkpoint inhibitors; network meta-analysis.

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