**Protocol**

**Article Title:**

Systematic Review and Meta-Analysis on Efficacy and Safety of Cemiplimab in Locally Advanced and Metastatic Squamous Cell Carcinoma

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**Objectives**

1. To assess the real-world efficacy of cemiplimab in terms of response rates in patients with locally advanced or metastatic squamous cell carcinoma.
2. To assess the real-world safety of cemiplimab in terms of adverse events and serious adverse events in patients with locally advanced or metastatic squamous cell carcinoma.

**Search Strategies**

Electronic databases including Medline, ClinicalTrials.gov, Embase, and Cochrane Central Register of Clinical Trials were searched following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplemental Figure 1). The search terms used were “cemiplimab”, “programmed death ligand-1”, “libtayo” and “cutaneous squamous cell carcinoma”. English articles published until August 2023 were retrieved. Included articles were clinical trials, prospective or retrospective case series, conference abstracts and medical chart reviews on human subjects. Articles were screened independently by MJC and SA. Eligibility was assessed following full-text reading by MJC and SA. In case of disagreement, the senior dermatologist (PL) resolved conflicts.

Excluded criteria were studies investigating the use of cemiplimab for other types of squamous cell carcinoma, other types of cancers or non-cancerous conditions, studies investigating the use of other immunotherapeutic agents in combination with cemiplimab, studies reporting only pharmacokinetic/pharmacodynamic data or non-quantitative, studies providing only outcomes after surgery or radiotherapy and studies on cemiplimab used concurrently with additional treatments.

**Data Extraction**

MJC extracted data independently using a standardized Microsoft Excel form (Microsoft Corporation, Redmond, WA, USA). The following variables were extracted from every article: number of patients, medication, median follow-up and drug exposure in months, response rates, type of response, adverse effect (AE) rates.

**Risk of Bias**

The quality of evidence was assessed following the Oxford Centre for Evidence-Based Medicine levels1. Two authors independently reviewed publication biases, then conducted a joint evaluation. Any disagreements were resolved by the senior author (PL). To assess publication bias, we used funnel plots and the trim-and-fill method, which detects asymmetry in metrics from individual studies and imputes missing trials to correct biases. Heterogeneity was evaluated using forest plots and the I² statistic.

**Statistical Analysis**

Primary outcomes were overall response rates (ORRs) and complete response rates (CRRs). Data aggregation was conducted utilizing linear models, implementing fixed effects meta-analysis as the primary method for analysis previously reported2. ORR was defined as the proportion of patients with either partial or complete responses after receiving cemiplimab. CRR was defined as the percentage of patients with only complete responses.

Secondary outcomes were clinical benefit rates (CBRs), which were defined as the proportion of patients with stable disease and any type of responses (partial or complete).

To assess the safety of cemiplimab, the following AEs were collected: myocarditis, hypophysitis, pneumonitis, colitis, diarrhea, fatigue, nausea, constipation, rash, pruritus, maculopapular rash, vomiting, anemia, hypothyroidism. Data from different dosing regimens were merged.

Analyses were performed using R statistical software version 4.3.3 (The R Foundation for Statistical Computing, Vienna, Austria). Data aggregation was conducted utilizing linear models, implementing fixed effects meta-analysis as the primary method for analysis. As previously reported methodology, comparisons with Bayesian models with random-effects meta-analysis were performed as sensitivity analyses2.

**REFERENCES**

1 Howick, J., Chalmers, I.,  Glasziou, P.,  Greenhalgh, T., Heneghan, C., Liberati, A., Moschetti, I., Phillips, B., & Thornton, H. (2011). The 2011 Oxford CEBM Evidence Levels of Evidence (Introductory Document). Oxford Centre for Evidence-Based Medicine.

2 Nguyen A, Xie P, Litvinov I V., Lefrançois P. Efficacy and Safety of Sonic Hedgehog Inhibitors in Basal Cell Carcinomas: An Updated Systematic Review and Meta-analysis (2009–2022). *Am J Clin Dermatol* 2023; **24**:359–74.

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**Supplementary Figure 1.** PRISMA flow chart for the meta-analysis and systematic review