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# Are immune checkpoint inhibitors ineffective in treating patients with head and neck squamous cell carcinoma aged 75 years or Older? A Meta-Analysis

Siqi Zhang [1], Mengge Zheng [1], Huimin Tian, Wenjia Liu, Zhenbang Feng, Shasha Xing, Fujun Han [*]

*Cancer Center, The First Hospital of Jilin University, 71 Xinmin Ave, Changchun, China*

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ABSTRACT

*Objectives:* The efficacy of immune checkpoint inhibitors (ICIs) is unclear in patients aged ≥ 75 years with head and neck squamous cell carcinoma (HNSCC). We conducted a systematic review and *meta*-analysis of randomized trials that compared ICIs with standard-of-care (SOC) therapy for recurrent/metastatic HNSCC.

*Materials and Methods:* PubMed, EMBASE, Web of Science, and ClinicalTrials.gov were searched for eligible trials. We evaluated the overall survival (OS) benefit of ICIs versus SOC according to patient age (<75 versus ≥ 75 years). The OS benefit was evaluated and compared between the age subgroups using hazard ratios (HRs). Data were pooled using a random-effects model.

*Results:* Five phase 3 trials involving 3437 patients were included. In patients aged ≥ 75 years (n = 207), ICIs did not improve OS compared to SOC (HR = 1.30, 95 % confidence interval [CI]: 0.93–1.81, $P = 0.127$). However, an improvement in OS was observed in patients aged < 75 years (n = 3230, HR = 0.90, 95 % CI: 0.83–0.99, $P = 0.025$). There is a significant difference in OS benefit between patients aged < 75 and ≥ 75 years (ratio of HR = 0.69, 95 % CI: 0.49–0.98, $P = 0.036$). Subgroup, *meta*-regression, and sensitivity analyses supported the reliability of the results.

*Conclusions:* Given the small sample size, our findings showing no improvement in OS suggest a lack of evidence to support the use of ICIs in patients with recurrent/metastatic HNSCC aged ≥ 75 years. Therefore, prospective studies are needed to clarify their efficacy among this age group.

## Introduction

Nivolumab and pembrolizumab are approved by the National Comprehensive Cancer Network (NCCN) guidelines as immune checkpoint inhibitors (ICIs) for the treatment of recurrent/metastatic head and neck squamous cell carcinoma (HNSCC), based on results reported in the following trials: CheckMate-141 [1], KEYNOTE-040 [2], and KEYNOTE-048 [3]. HNSCC is commonly diagnosed at an older age [4], with approximately 16.0 % of patients aged ≥ 75 years at diagnosis [4]. The efficacy of ICIs among patients in this age group remains unclear, as this demographic was underrepresented in KEYNOTE-040 (n = 31, 6.3 %) [5], KEYNOTE-048 (n = 43, 7.2 %) [6], and CheckMate-141 (n = 18, 5.0 %) [7].

Therefore, there is an urgent need to determine the efficacy of ICIs in elderly patients with HNSCC. The objective of this systematic review and *meta*-analysis of randomized controlled trials was to evaluate the overall survival (OS) benefit in patients aged ≥ 75 years with recurrent/metastatic HNSCC who received ICIs versus standard-of-care (SOC) therapy.

## Materials and Methods

This systematic review and *meta*-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [8]. The search process, data extraction, and risk of bias assessment were independently performed by at least two authors, and discrepancies were resolved through discussions among the

*Abbreviations:* CIs, confidence intervals; HNSCC, head and neck squamous cell carcinoma; HRs, hazard ratios; ICIs, immune checkpoint inhibitors; NCCN, National Comprehensive Cancer Network; OS, overall survival; SOC, standard-of-care.

* Corresponding author at: Cancer Center, First Hospital of Jilin University, 71 Xinmin Ave, Changchun 130021, China.
*E-mail addresses:* siqiz21@mails.jlu.edu.cn (S. Zhang), zhengmg21@mails.jlu.edu.cn (M. Zheng), tianhuimin@jlu.edu.cn (H. Tian), llwwjj890812@126.com (W. Liu), zhenbangfeng@jlu.edu.cn (Z. Feng), ellaxing1999@163.com (S. Xing), fujunhan@jlu.edu.cn (F. Han).
[1] These authors contributed equally to this work.

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authors.

*Selection Criteria and Search Strategy*

To be eligible for inclusion in this study, randomized controlled trials for recurrent/metastatic HNSCC had to meet the following criteria: 1) the experimental group was treated with ICIs that were administered either alone or combined (for example, anti-PD-1/anti-PD-L1 antibody plus an anti-CTLA4 antibody); 2) the therapy received by the control group must be SOC at the time of the trial design; and 3) the OS benefit was either directly reported in patients aged ≥ 75 years, or information was provided that could be used to calculate this outcome. We conducted a search for relevant trials in PubMed, ClinicalTrials.gov, Web of Science, and EMBASE (from database inception until April 9, 2023) using the search strategies outlined in the Supplementary Materials. Additionally, we manually searched the references of the retrieved reviews and primary articles to ensure comprehensive coverage of the clinical trials. To further ensure comprehensive coverage of the trial data, we manually searched the regulatory documents of the identified trials on the websites of both the US Food and Drug Administration [9] and the European Medicines Agency [10].

*Data Extraction*

The following data were extracted for each included trial: trial name; phase; randomization factors; therapy regimen; number of patients; clinical endpoints; inclusion criteria; patient age subgroups; number of OS events; duration of follow-up; median OS; and 1-year OS rate. Hazard ratios (HRs) with 95 % confidence intervals (CIs) were determined for OS benefit. Reported HRs were used and, if necessary, extracted from forest plots (CheckMate-651 and KESTREL) [11,12] using the Getdata Graph Digitizer (version 2.26). The 95 % CIs of the HRs, which were not reported in the KEYNOTE-048 trial [3], were calculated according to the method described by Tierney et al. [13].

*Risk of Bias Assessment*

Each included trial subgroup was assessed for risk of bias using the Cochrane risk of bias tool for non-randomized intervention studies [14]. This tool classifies a study as having a low risk of bias when the quality of the study is equivalent to that of a well-performed randomized controlled trial.

*Statistical analysis*

The OS benefit of ICIs versus SOC was evaluated in patients aged < 75 and ≥ 75 years. All participants in the included trials were categorized into three age groups: < 65, 65–74, and ≥ 75 years. In post-hoc analyses of three clinical trials (KEYNOTE-040, KEYNOTE-048, and CheckMate-141) [1–3], which met their primary endpoints, the HRs for OS benefit showed the same trend and did not differ obviously between patients aged < 65 years and those aged ≥ 65 years. Therefore, patients aged < 65 years and those aged 65–74 years were combined as a single group of patients aged < 75 years using random-effects models. Nonetheless, the difference in the OS benefit was also quantified between patients aged < 65 years and those aged 65–74 years.

The trial HRs for each age group were combined using the random-effects model, and the statistical power for detecting differences in OS benefit between ICI and SOC in the different age groups was assessed by a power analysis using the pwr.t.test in R statistical software, at a significance level of $P < 0.05$ [15]. To quantify differences in the OS benefit, the ratio of HRs [16] between patients aged < 75 years and those aged ≥ 75 years was calculated for each included trial. The ratios of HRs were then combined using random-effects models. The $I^2$ statistic and $\tau^2$ tests were used to investigate heterogeneities between the groups and between trials within the groups.

We performed a random-effects *meta*-regression analysis to assess the relationship between study-level covariates and HRs of ICIs versus SOC. The covariates included patient age (<75 versus ≥ 75 years), ICI agent (NCCN approved versus non-approved), treatment line (first versus subsequent), number of patients aged ≥ 75 years (<30 versus ≥ 30), and ICI regimen (monotherapy versus combined therapy). In addition, subgroup analyses were conducted to evaluate whether the differences in the HRs between patients aged < 75 and ≥ 75 years were dependent on these covariates. Sensitivity analyses were conducted by excluding one trial at a time to investigate whether the outcomes were statistically affected by any particular trial. We used funnel plots to visually present the possibility of publication bias and assessed the symmetry of the plots using linear regression tests. Statistical analyses were conducted using R software (version 3.5.2). We considered a two-sided *P*-value of < 0.05 to be statistically significant.

## Results

Five phase 3 trials (n = 3437 patients) were included. These comprised the EAGLE [17], KEYNOTE-040 [2], and CheckMate-651 [11] trials, as well as the KESTREL [12] trial arm, which compared durvalumab to cetuximab plus chemotherapy and the KEYNOTE-048 [3] trial arm which compared pembrolizumab to cetuximab plus chemotherapy (Table 1). The EAGLE [17] trial involved two comparisons (durvalumab with and without tremelimumab versus single-agent chemotherapy) that were analyzed separately. Figure 1 illustrates the trial selection process. The risk of bias analysis (Supplementary Table 1) yielded a moderate risk for all included trial subgroups.

In patients aged ≥ 75 years (n = 207), ICIs did not improve OS compared to SOC (HR = 1.30, 95 % CI: 0.93–1.81, $P = 0.127$). The power analysis showed that the study had a statistical power of 57.6 % to detect an effect size at a significance level of 0.05, which meant that approximately 350 patients would have been required to achieve a power of 80 % at the same significance level. However, ICIs resulted in an improvement in OS among patients aged 65–74 years (n = 958, HR = 0.84, 95 % CI: 0.71–0.99, $P = 0.033$) and a trend towards an improved OS in patients aged < 65 years (n = 2272, HR = 0.93, 95 % CI: 0.85–1.02, $P = 0.130$). There was a trend towards a statistical difference in OS benefit by age (*P* interaction = 0.068) (Figure 2). The pooled ratios of HRs (Supplementary Table 2) showed a similar OS benefit between patients aged 65——74 years and those aged < 65 years (ratio of HRs = 0.90, 95 % CI: 0.75–1.08, $P = 0.261$). The CI was sufficiently narrow to rule out any clinically meaningful differences in the OS benefit with high probability. Therefore, it was feasible to combine these two age groups for analytical purposes. ICIs improved OS compared to SOC in patients aged < 75 years (HR = 0.90, 95 % CI: 0.83–0.99, $P = 0.025$, Table 2). A statistical difference in OS benefit was observed between patients aged < 75 and ≥ 75 years (ratio of HRs = 0.69, 95 % CI: 0.49–0.98, $P = 0.036$). The heterogeneity between the included trials was assessed using the $I^2$ statistic and $\tau^2$ tests. The $I^2$ values ranged from 0 to 22 %, indicating minimal heterogeneity. Similarly, the $\tau^2$ values ranged from 0 to < 0.001, further supporting the absence of significant heterogeneity.

Among the covariates assessed, the *meta*-regression analysis showed that only patient age was a factor in determining the OS benefit of ICIs versus SOC (univariate HR = 1.43, 95 % CI: 1.02–2.01, $P = 0.040$; multivariate HR = 1.43, 95 % CI: 1.01–2.01, $P = 0.041$; Supplementary Table 3). In the subgroup analysis, the HRs for OS benefit ranged from 1.20 to 1.44 across all subgroups of patients aged ≥ 75 years, and the ratios of HRs for patients aged < 75 years versus those aged ≥ 75 years ranged from 0.63 to 0.75 among all subgroups (Table 2). Sensitivity analyses (Supplementary Figure 1) yielded results consistent with those of the main analyses. Funnel plots suggested the absence of publication bias (Supplementary Figure 2).

**Table 1**
Patient characteristics in the included trials.

| Trial | ICIs | Primary Endpoint | Inclusion Period | HR of OS, (95 %CI) | Patients (n) | Age, Years (n, %) | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | < 65 | 65–74 | ≥ 75 |
| Subsequent-line treatment | | | | | | | | |
| KEYNOTE-040 | Pembrolizumab | OS | 2014–2016 | 0.80 (0.65–0.98) | 495 | 332, (67.1) | 132, (26.7) | 31, (6.3) |
| EAGLE | Durvalumab | OS | 2015–2017 | 0.88 (0.73–1.10) | 489 | 340, (69.5) | 120, (24.5) | 29, (5.9) |
| EAGLE | Durvalumab + tremelimumab | OS | 2015–2017 | 1.06 (0.86–1.27) | 496 | 345, (69.6) | 127, (25.6) | 24, (4.8) |
| First-line treatment | | | | | | | | |
| KEYNOTE-048 | Pembrolizumab | OS | 2015–2017 | 0.83 (0.70–0.99) | 600 | 385, (64.2) | 172, (28.7) | 43, (7.2) |
| KESTREL | Durvalumab + tremelimumab | OS | 2015–2017 | 1.01 (0.84–1.28) | 410 | 265, (64.6) | 122, (29.8) | 23, (5.6) |
| CheckMate-651 | Nivolumab + ipilimumab | OS | 2016–2019 [a] | 0.94 (0.79–1.06) | 947 | 605, (63.9) | 285, (30.1) | 57, (6.0) |

Abbreviations: HR, hazard ratio; CI, confidence interval; ICI, immune checkpoint inhibitor; OS, overall survival.
[a] : https://classic.clinicaltrials.gov/ct2/show/record/NCT02741570.

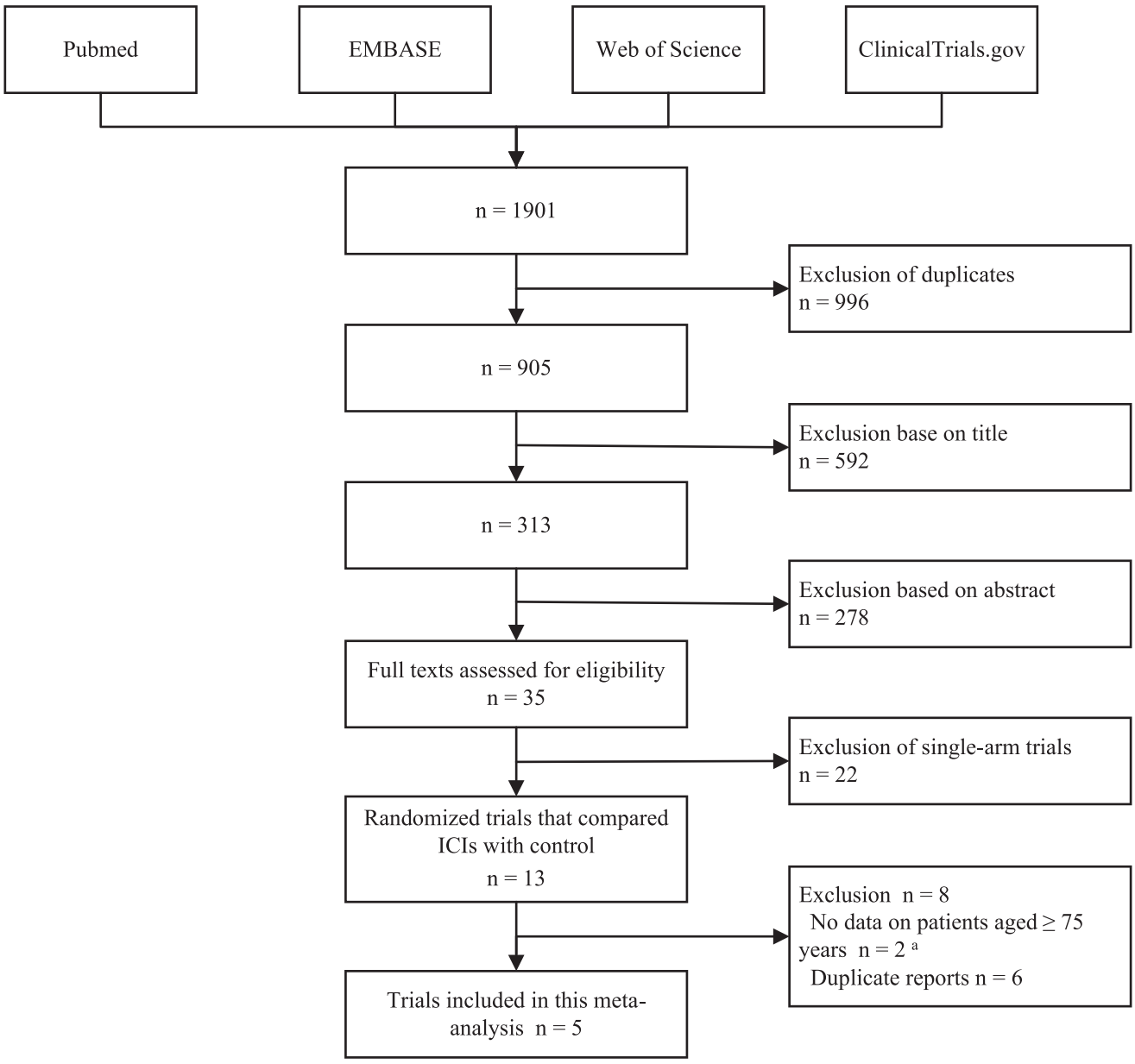


**Figure 1.** Flow chart showing inclusion and exclusion of trials. [a]: CheckMate-141 and the comparison of the durvalumab plus tremelimumab arm to the cetuximab plus chemotherapy arm in the KESTREL trial.

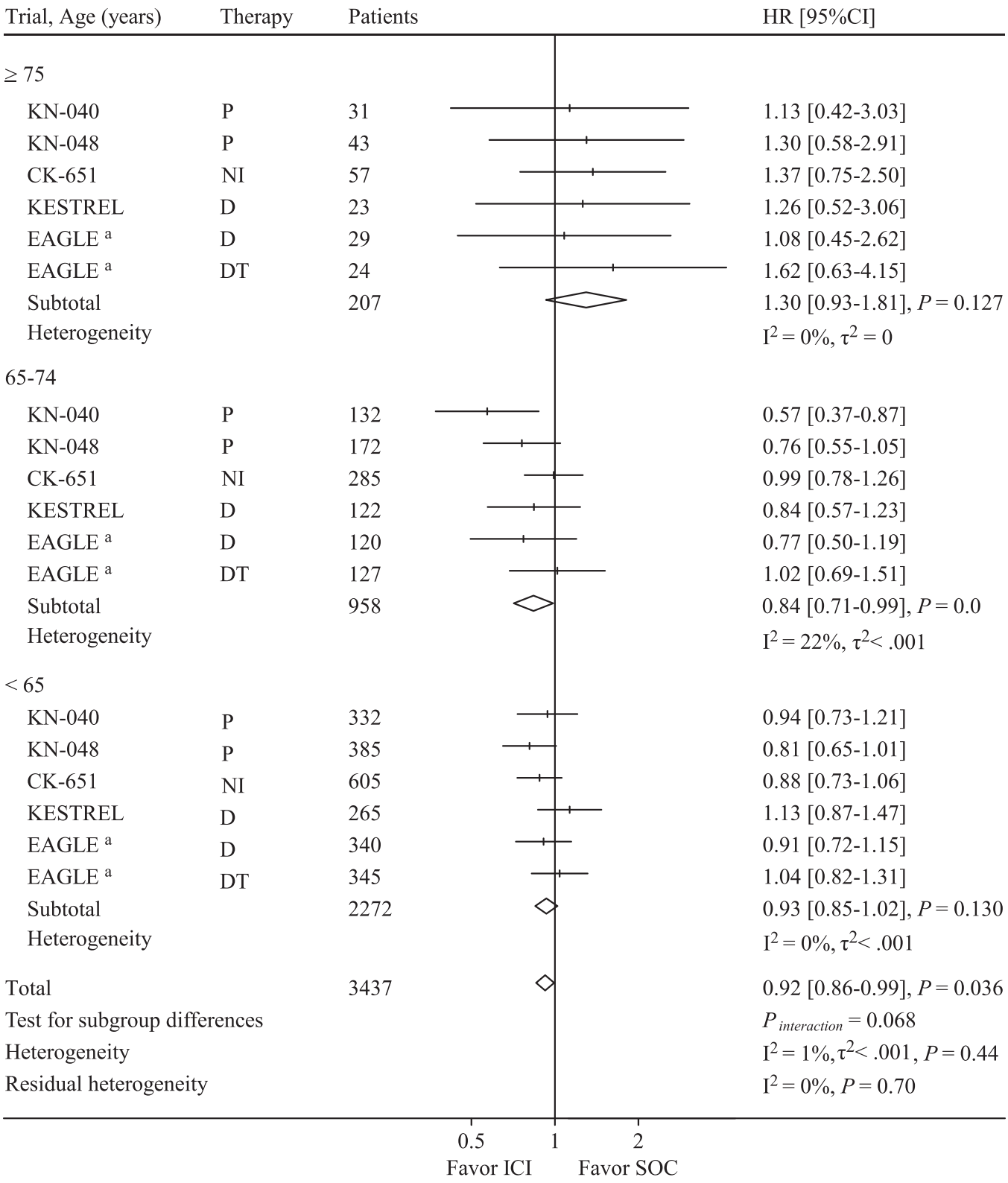


**Figure 2.** Overall survival benefit of ICI versus SOC therapy by age in patients with HNSCC. Abbreviations: CK, CheckMate; HNSCC, head and neck squamous cell carcinoma; HR, hazard ratio; ICI, immune checkpoint inhibitor; KN, KEYNOTE; NI, Nivolumab + Ipimumab; P, Pembrolizumab; SOC, standard-of-care therapy.[a]: The two comparisons, durvalumab (D) with and without tremelimumab (T) versus single-agent chemotherapy), were analyzed separately.

## Discussion

To the best of our knowledge, this is the first *meta*-analysis to examine the effectiveness of ICIs in the treatment of very elderly patients with recurrent/metastatic HNSCC. In clinical trials, the superior improvement in OS with ICI therapy to that with SOC therapy was found to be driven by patients aged < 75 years. For patients aged ≥ 75 years, the HR was 1.30, which failed to reach statistical significance. Nonetheless, the subgroup and sensitivity analyses yielded the HRs ranging from 1.20 to 1.44, and this narrow range of the HRs supports the

**Table 2**
Subgroup analyses of overall survival benefit of ICI versus SOC therapy among patients with HNSCC in different age groups.

| Subgroup | < 75 Years | | ≥ 75 Years | | < 75 *vs* ≥ 75 Years | |
|---|---|---|---|---|---|---|
| | HR (95 %CI) | *P* | HR (95 %CI) | *P* | Ratio of HRs (95 %CI) | *P* interaction |
| Overall | 0.90 (0.83–0.99) | 0.025 | 1.30 (0.93–1.81) | 0.128 | 0.69 (0.49–0.98) | 0.036 |
| Treatment lines | | | | | | |
| First | 0.89 (0.78–1.00) | 0.054 | 1.32 (0.87–2.02) | 0.194 | 0.68 (0.44–1.05) | 0.083 |
| Subsequent | 0.94 (0.81–1.08) | 0.367 | 1.25 (0.73–2.15) | 0.416 | 0.71 (0.40–1.25) | 0.237 |
| NCCN-approved | | | | | | |
| Yes | 0.79 (0.66–0.93) | 0.006 | 1.23 (0.66–2.29) | 0.517 | 0.63 (0.32–1.22) | 0.171 |
| No | 0.95 (0.86–1.04) | 0.253 | 1.32 (0.89–1.96) | 0.163 | 0.71 (0.47–1.07) | 0.106 |
| ICI regimen | | | | | | |
| Monotherapy | 0.85 (0.76–0.96) | 0.009 | 1.20 (0.77–1.86) | 0.425 | 0.71 (0.45–1.14) | 0.157 |
| Combined therapy | 0.96 (0.85–1.08) | 0.475 | 1.44 (0.87–2.39) | 0.160 | 0.66 (0.39–1.11) | 0.119 |
| Number of patients ≥ 75 years | | | | | | |
| < 30 | 0.97 (0.85–1.10) | 0.582 | 1.29 (0.77–2.17) | 0.338 | 0.75 (0.44–1.29) | 0.294 |
| ≥ 30 | 0.85 (0.75–0.98) | 0.021 | 1.30 (0.84–2.01) | 0.236 | 0.65 (0.41–1.03) | 0.064 |

Abbreviations: CI, confidence interval; HNSCC, head and neck squamous cell carcinoma;HR, hazard ratio; ICI, immune checkpoint inhibitor; NCCN, National Comprehensive Cancer Network; SOC, standard-of-care.

reliability of this finding. Notably, the number of patients aged ≥ 75 years (n = 207) was less than the required sample size (n = 350) needed to achieve a statistical power of 80 % at a significance level. Accordingly, there was a loss of statistical power to demonstrate a significant difference. Therefore, the efficacy of ICIs remains unclear in patients with recurrent/metastatic HNSCC aged ≥ 75 years.

Recently, the NCCN guidelines recommended pembrolizumab or nivolumab in combination with cetuximab as a treatment option for recurrent/metastatic HNSCC, irrespective of patient age [18]. These recommendations are based on two phase II trials [19,20], in which treatment efficacy was not specifically analyzed based on patient age. Subgroup analyses from the EXTREME trial, which led to the approval of cetuximab plus chemotherapy as first-line treatment for recurrent/metastatic HNSCC, suggested that the OS benefit of adding cetuximab were primarily observed in patients aged < 65 years [21]. Furthermore, a *meta*-analysis of five randomized trials has indicated that adding epidermal growth factor receptor inhibitors to either a chemotherapy or radiotherapy regimen did not improve OS in patients with HNSCC aged ≥ 65 years [22]. These findings, along with the results of our *meta*-analysis, raise concerns regarding the use of the combined use of ICIs and cetuximab in patients aged ≥ 75 years.

In clinical settings, treatment of patients with HNSCC aged ≥ 75 years relies on data derived from clinical trials primarily conducted in younger populations. However, it is crucial to recognize the impact of age-related changes on the efficacy and toxicity of ICIs. Compared with younger patients, older patients with HNSCC exhibit distinct characteristics, including a substantially higher female-to-male ratio [23,24], a notably higher prevalence of laryngeal and oral cavity carcinomas [25,26], progressive decline in multiple organ functions, reduced nutritional status, and decreased mobility. In addition, immune function gradually diminishes with age and chronic inflammatory responses persist [27]. Certain age-related changes can lead to modifications in the tumor immune microenvironment, as well as in the pharmacodynamics and kinetics [28], potentially impacting the efficacy of ICIs and increasing the risk of treatment-related toxicity in elderly patients. Our *meta*-analysis underscores the necessity of conducting prospective trials specifically designed for elderly patients, with a focus on age-specific assessments to elucidate the relationship between the efficacy and toxicity of ICIs and age-related changes. A comprehensive geriatric assessment, as recommended by the International Society of Geriatric Oncology [29], to evaluate elderly patients with cancer, could provide valuable insights by assessing age-related changes like life expectancy, comorbidities, performance and functional statuses, and psychosocial support.

One major limitation of our *meta*-analysis is the low statistical power, with only 57.6 % to detect a significant difference. This limitation can be primarily attributed to the under-representation of elderly individuals in the clinical trials included in our analysis. Additionally, our *meta*-analysis was unable to evaluate the efficacy of ICIs in patients with high PD-L1 expression or those with high tumor mutation burden owing to the lack of available data. Moreover, the absence of patient-level data made it impossible to account for potential confounding factors that could have led to biased outcomes. Furthermore, the utilization of predefined age stratification in the original trials prevented the evaluation of ICI therapy efficacy for different age cutoffs, possibly resulting in the failure to identify precise age cutoffs at which no survival benefit was obtained. Conducting a patient-level *meta*-analysis could offer insights to address these resolved issues, which are crucial for designing future clinical trials and evaluating the cost-benefit ratio. The latter is particularly important when planning a randomized phase III trial, considering that elderly age is often a barrier to treatment [30–32], and conducting clinical trials exclusively on patients aged ≥ 75 years can be costly. Therefore, it is urgent to establish international collaborations to facilitate data sharing for all relevant clinical trials to conduct a patient-level *meta*-analysis.

Other limitations of our *meta*-analysis were as follows: 1) the inclusion of clinical trials that failed to achieve their primary end points [5,11,17]. Nevertheless, this was considered reasonable, as the ICIs used in these trials exhibited antitumor activity. For example, the 1-year OS rates for durvalumab (37.0 %) in the EAGLE trial [17], nivolumab (36.0 %) in the CheckMate-141 trial [1], and pembrolizumab (37.0 %) in the KEYNOTE-040 [2] trial were comparable for patients with recurrent/metastatic HNSCC who had experienced progression after platinum-based treatment. 2) there were between-study heterogeneities regarding ICI regimens, programmed death-ligand 1 expression definition, and treatment lines.

## Conclusion

Our *meta*-analysis indicated that the use of ICIs was associated with an improved OS benefit compared to SOC therapy in patients aged < 75 years with recurrent/metastatic HNSCC. However, no improvement in OS was observed in patients aged ≥ 75 years. These findings highlight the need for further randomized clinical trials to determine the efficacy of ICIs in elderly patients with recurrent/metastatic HNSCC.

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## Declaration of competing interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

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*Notes*

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2023.106632.

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