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REVIEW ARTICLE

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Programmed death 1 (PD-1) and ligand (PD-L1) inhibitors in head and neck squamous cell carcinoma: A meta-analysis

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Abstract

Background: PD-1 and PD-L1 inhibitors have emerged as promising treatments for patients with head and neck squamous cell carcinoma (HNSCC).

Methods: Systematic review and meta-analysis of PD-1 and PD-L1 inhibitors in HNSCC. Outcomes: median overall survival (mOS), median progression-free survival (mPFS), Response Evaluation Criteria in Solid Tumors (RECIST) and treatment-related adverse events (TRAEs).

Results: Eleven trials reported data on 1088 patients (mean age: 59.9 years, range: 18–90). The total mOS was 7.97 months (range: 6.0–16.5). Mean mPFS for all studies was 2.84 months (range: 1.9–6.5). PD-1 inhibitors had a lower rate of RECIST Progressive Disease than PD-L1 inhibitors (42.61%, 95% confidence interval [CI]: 36.29–49.06 vs. 56.79%, 95% CI: 49.18–64.19, $P < 0.001$). The rate of TRAEs of any grade (62.7%, 95% CI: 59.8–65.6) did not differ.

Conclusions: Meta-analysis shows the efficacy of PD-1 and PD-L1 inhibitors in HNSCC and suggests a possible difference in certain RECIST criterion between PD-1 and PD-L1 inhibitors. Future work to investigate the clinical significance of these findings is warranted.

KEYWORDS

antibodies, disease progression, head and neck neoplasms, humanized, meta-analysis, monoclonal, squamous cell carcinoma of the neck

INTRODUCTION

Head and neck cancers represent the 6th most common malignancy globally, of which approximately 90% of which are histologically classified as squamous cell carcinoma (HNSCC).[1,2] Despite efforts to increase public awareness of the modifiable and preventable risk factors for HNSCC (e.g., smoking, alcohol, human papillomavirus [HPV]), the incidence of certain types of HNSCC continue to rise.[3] Up to 66% of these patients are diagnosed at advanced stages (III or IV) and often suffer from significant morbidity and mortality related to the involved structures impacting speaking, chewing, swallowing, eating, drinking, breathing, and cosmesis.[4–6] The dogma of treating HNSCC typically consists of varying sequences and combinations of surgery, radiotherapy, and chemotherapy. Despite significant research and medical advances, the 5-year survival of HNSCC has not improved, and, at approximately 40%, is worse than that of many other cancers.[7–9] The need for new avenues of treatment with better tumor response and lower toxicity for patients with HNSCC is paramount.

Immunotherapy using immune checkpoint inhibitors (ICIs), particularly targeting the program cell death 1 (PD-1) and program cell death ligand 1 (PD-L1) axis, represents an emerging treatment strategy for HNSCC. The negative checkpoint of PD-1, PD-L1 and program cell death ligand 2 (PD-L2) plays a vital role for immune homeostasis, enabling peripheral tolerance to self-tissues. When PD-1 on T cells binds the target ligand (PD-L1 or PD-L2) on self-tissue, an inhibitory cascade is initiated to prevent autoimmune destruction. Malignant cells leverage this fail-safe mechanism to evade detection and subsequent destruction through upregulating their expression of PD-L1/2.[10–12]

Given the high prevalence of mutations favoring immune evasion in HNSCC,[13] incorporating ICIs to restore host immunologic response has been at the forefront of therapeutic strategy development for HNSCC.[14] The landscape of HNSCC treatment recently shifted in the wake of the KEYNOTE-048 trial.[15,16] Stratifying subjects according to Combined Positivity Score (CPS)—a measure of the extent of PD-L1-expressivity in tumor and surrounding stroma—showed that individuals with a CPS ≥ 1 demonstrated an improvement in overall survival with pembrolizumab monotherapy and chemo-immunotherapy compared with the standard of care (EXTREME regimen). Following FDA approval, standard of care for recurrent/metastatic (R/M) HNSCC now includes pembrolizumab in combination with platinum and fluorouracil, or pembrolizumab as monotherapy for individuals with CPS ≥ 1.

The development and evaluation of PD-1/PD-L1 inhibitors continues to progress, yet no prospective trials have compared the outcomes or toxicities of these various immunotherapies. It thus remains unclear whether choice of target on this checkpoint axis is biologically relevant for the HNSCC population. The goals of this meta-analysis are (1) to analyze the use of PD-1/PD-L1 inhibitors in HNSCC patients, (2) report their overall tumor responses and safety profiles, and (3) to compare the efficacy and toxicity of these agents.

METHODS

Search strategy

This meta-analysis was designed according to PRISMA guidelines.[17] Searches were undertaken in PubMed (NLM NIH), Scopus (Elsevier), Embase (Elsevier), Web of Science (Clarivate), and Cochrane Library (Wiley) from inception through May 10, 2019. Searches used a combination of subject headings (e.g., MeSH in PubMed) and keywords such as head and neck cancer, head and neck squamous cell carcinoma, oropharyngeal cancer, immunotherapy, program cell death 1 receptor/antagonist and inhibitor (Supporting Information Appendix 1). References were uploaded to EndNote (Clarivate Analytics) and screened for relevance (authors D. A. L. and J. J. P.).

Selection criteria

Inclusion criteria required the use of PD-1 or PD-L1 inhibitor monotherapy in HNSCC prospective trials. Exclusion criteria included (1) insufficient/not extractable data; (2) ongoing project; (3) cancer sites other than HNSCC and/or HNSCC data not extractable; (4) subgroup analysis of patients from a larger study; (5) retrospective design; (6) review article, letter to the editor, conference abstract, personal opinion, case report, or book chapter; (7) non-English. Articles were critically appraised to assess level of evidence using the Oxford Center for Evidence-Based Medicine criteria.[18]

Data extraction

Primary outcomes were median overall survival (mOS), overall survival (OS) rate, median progression-free survival (mPFS), and progression-free survival rate (PFS). Additional outcomes included tumor response per reporting the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1[19] and treatment-related adverse events (TRAEs) using the NCI Common Terminology Criteria for Adverse Events (CTCAE). RECIST objective response rate (ORR; the sum of patients who achieve complete or responses), stable disease (SD), and progressive disease (PD) rates were extracted. When part or all of the patient populations were reported in more than one publication, only the most comprehensive and updated study was included in the final analysis.

Statistical analysis

Meta-analysis evaluated RECIST data, OS, PFS, and TRAEs in PD-1 and PD-L1 inhibitors. Categorical variables were summarized by frequency and percentage. Continuous variables were summarized by mean ± standard deviation (or range for means of median values) or median and interquartile range (IQR: 25th and 75th) where appropriate. A meta-analysis of proportions was performed using MedCalc 19.0.4 (MedCalc Software bvba). This program lists the proportions (expressed as a

percentage), with their 95% confidence intervals (95% CI), found in the included studies. MedCalc uses a Freeman–Tukey transformation to calculate the weighted summary proportion under the fixed and random effects model. Under the fixed effects model, it is assumed that all studies come from a common population, and that the effect size (proportions) is not significantly different among trials. This assumption is tested by the "Heterogeneity test." If this test yields a low p value ($P < 0.05$), then the fixed effects model may be invalid. In this case, the random effects model may be more appropriate, in which both the random variation within the studies and the variation between the different studies is incorporated. Both models were used in this study. Finally, the Sterne and Egger tests were performed to further assess risk of publication bias.[20,21] Potential publication bias was evaluated by visual inspection of the funnel plot and Egger's regression test, which statistically examines the asymmetry of the funnel plot. In a funnel plot treatment effect is plotted on the horizontal axis and the standard error on the vertical axis.[22] The vertical line represents the summary estimated derived using fixed-effect meta-analysis. Two diagonal lines represent (pseudo) 95% confidence limits (effect ± 1.96 standard error) around the summary effect for each standard error on the vertical axis. These data show the expected distribution of studies in the absence of heterogeneity or selection bias. In the absence of heterogeneity, 95% of the studies should lie within the funnel defined by these diagonal lines. Publication bias results in asymmetry of the funnel plot. If publication bias is present, the smaller studies will show the larger effects. A $P < 0.05$ was considered to indicate a statistically significant difference for all statistical tests.

RESULTS

Search results and included studies

Database and reference searches identified 1125 publications. Title and abstract review identified 58 articles that discussed PD-1 and PD-L1 inhibitors and outcomes in HNSCC. Rationale for publication exclusion is shown in Figure 1.

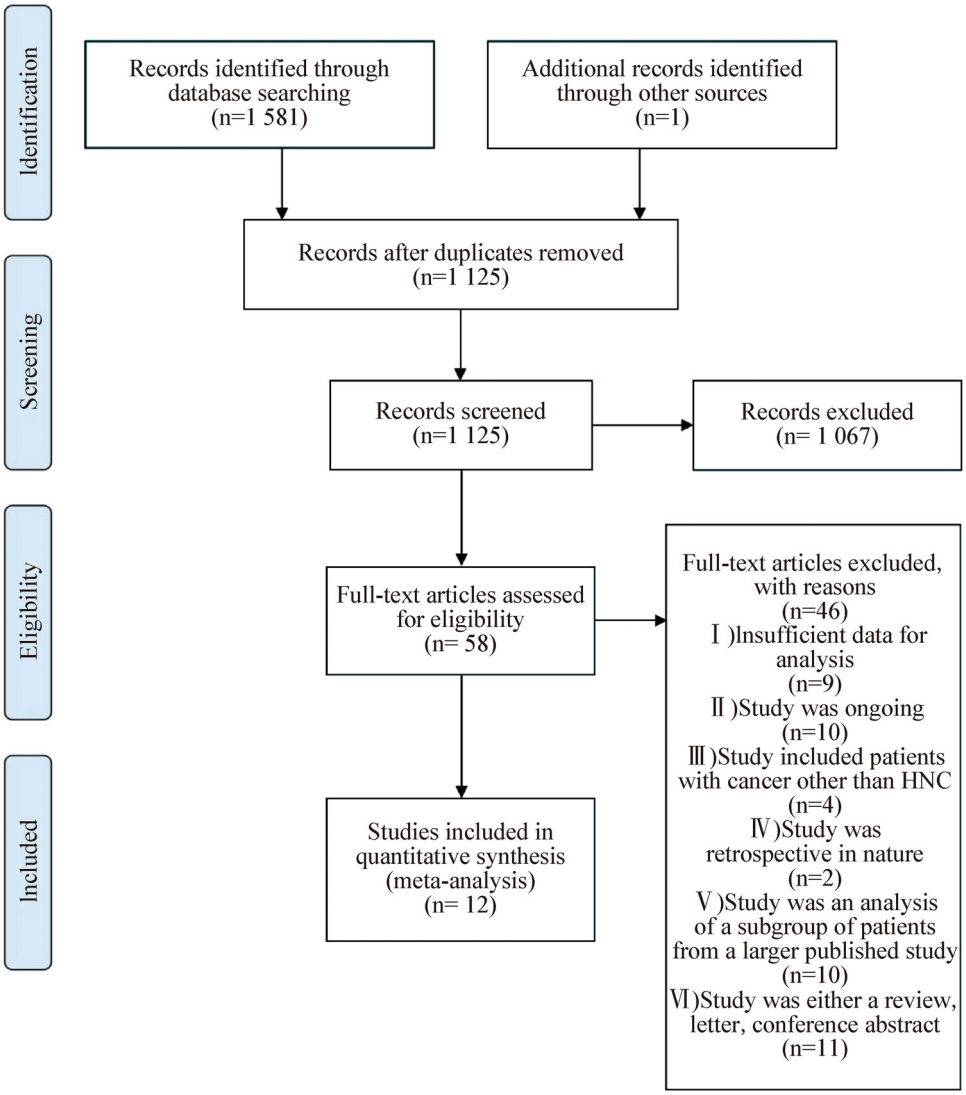

FIGURE 1 PRISMA diagram

TABLE 1 Characteristics of included studies

Author (year)	Study design	OLE	Investigational drug	Drug target	Setting	NCT #
Cohen (2019)	RCT	1b	Pembrolizumab	PD-1	Multinational	NCT02252042
Ferris (2018)[a]	RCT	1b	Nivolumab	PD-1	Multinational	NCT02105636
Gillison (2018)[a]	RCT	1b	Nivolumab	PD-1	Multinational	NCT02105636
Mehra (2018)[b]	NA[b]	2b	Pembrolizumab	PD-1	Multinational	NCT01848834
Bauml (2017)	Prospective single-arm	2b	Pembrolizumab	PD-1	-	NCT02255097
Hsu (2017)	Phase Ib	2b	Pembrolizumab	PD-1	Multinational	NCT02054806
Chow (2016)	Prospective single-arm	2b	Pembrolizumab	PD-1	USA and Israel	NCT01848834
Ferris (2016)	RCT	1b	Nivolumab	PD-1	Multinational	NCT02105636
Seiwert (2016)	Phase Ib	2b	Pembrolizumab	PD-1	USA and Israel	NCT01848834
Zandberg (2019)	Prospective single-arm	2b	Durvalumab	PD-L1	Multinational	NCT02207530
Colevas (2018)	Prospective single-arm	2b	Atezolumab	PD-L1	Multinational	NCT01375842
Siu (2018)	RCT	1b	Durvalumab	PD-L1	Multinational	NCT02319044

Abbreviations: NA, not applicable; NCT, National Clinical Trial; OLE, Oxford Level of Evidence; PD-1, program death receptor 1; PD-L1, program death ligand 1; RCT, randomized control trial; -, not available.

[a]This trial is a follow-up study of Ferris (2016) and does not present data on new subjects.

[b]This trial is a follow-up study of both Seiwert (2016) and Chow (2016) and does not present data on new subjects.

Study characteristics

The 12 publications that met inclusion criteria contained data from nine unique cohorts (Table 1). Studies featured both PD-1 inhibitors (pembrolizumab and nivolumab) and PD-L1 inhibitors (durvalumab and atezolizumab). Two publications which reported 1-[23] and 2-year[24] follow-up data of an index study (CheckMate-141)[25] were ultimately deemed relevant for inclusion as they collectively presented a complete data set. Similarly, one publication[26] presented a pooled analysis after long-term follow-up of two unique populations originally reported separately[27,28] but emanating from the same trial (KEYNOTE-012). Data from these articles were collapsed into single representative entries, merging data where appropriate and replacing previous data with updated findings. Altogether, this yielded eight evaluable data sets. Sterne and Egger testing suggested little relationship between the sample size of these studies and their effect sizes indicating less likelihood of publication bias ($I^2 = 0\%$, 95% CI: 0.00–60.37, $P < 0.49$).

Patient characteristics

Data was provided for 1088 individuals. A total of 877 (80.6%) patients received a PD-1 inhibitor (pembrolizumab, $n = 637$; nivolumab, $n = 240$), and the remaining 211 (19.4%) received a PD-L1 inhibitor (durvalumab, $n = 179$; atezolizumab, $n = 32$). All subjects had advanced and/or R/M HNSCC. The majority were male ($n = 883$, 81.2%). Mean of median ages was 59.89 years (range 18–90) in Table 1. Primary tumor location was reported in 826 (75.9%) patients. The most common location was the pharynx ($n = 420$, 50.5%); specifically reported subsites include oropharynx ($n = 259$, 31.1%); nasopharynx ($n = 39$, 4.7%) and hypopharynx ($n = 29$, 3.5%) in Table 2. HPV status was evaluated in 667 (61.3%) patients and was positive in 243 patients (36.4%). Of the 259 oropharyngeal tumors, HPV status was specifically reported in only 20% of patients, of which approximately 60% were HPV+. Of 1007 tumors (92.6%) assessed for PD-L1-expressivity, 747 (74.2%) were positive. The number of prior treatments received for R/M HNSCC ranged from 1 to >5 prior treatments.

Clinical activity

Mean of median follow-up was 10.07 months (range: 0–32.0). The total mOS was 7.97 months (range: 6.0–16.5) in Table 3. The mOS for PD-1 inhibitors was 8.29 months (range: 8.0–16.5) and was 6.59 months (range: 6.0–7.1) for PD-L1 inhibitors. Mean mPFS for all studies was 2.84 months (range: 1.9–6.5); PD-1 inhibitors 3.0 months (range: 2.1–6.5), PD-L1 inhibitors 2.12 months (range: 1.9–2.6).

Total OS was 55.17% (95% CI: 49.44–60.83) at 6 months, 30.67% (95% CI: 18.69–41.14) at 12 months, 12.07% (95% CI: 3.40–25.05) at 18 months, 9.54% (95% CI: 2.63–20.12) at 24 months and 2.89% (95% CI: 0.22–0.845) at 30 months (Figure 2). PD-1 inhibitors had a higher rate of overall survival at 6 months (58.93%, 95% CI: 50.45–67.15 vs. PD-L1: 49.77%, 95% CI: 24.88–56.66; $p = 0.019$) and at 18 months (16.40%, 95% CI: 2.93–37.79 vs. PD-L1: 7.11%, 95% CI: 0.21–22.54; $P < 0.001$), but not at 12 months. There was insufficient survival data extending

TABLE 2 Oncologic characteristics

	Author (year)	N	Male (%)	Median age, years (range)	Primary tumor site, n (%)									HPV status, all subsites, n (%)			PD-L1 status[a], n (%)		
					PH	OP				NC	OC	LA	OT						
						All	Eval	HPV +	HPV−					Eval	+	−	Method	+	−
PD-1	Cohen (2019)	247	207 (84)	60 (55–66)	--	NA	NA	NA	NA	--	--	--	--	--	61 (--)	--	CPS > 1%	196 (79)	50 (20)
	Ferris (2018)[b]	240	197 (82)	59 (29–83)	92 (38)	NA	NA	NA	NA	0	108 (45)	34 (14)	6 (3)	120	64 (53)	56 (47)	CPS > 1%	96 (40)	76 (31)
	Mehra (2018)[b]	192	159 (83)	60 (20–84)	97	76	NA	NA	NA	12	28	18	37	--	45	--	CPS > 1%	152 (81)	36 (19)
	Bauml (2017)	171	138 (81)	61 (33–90)	108 (63)	100	NA	NA	NA	1 (1)	28 (16)	30 (18)	0	168	37 (22)	131 (78)	CPS > 1%	140 (82)	26 (15)
	Hsu (2017)	27	21 (78)	52 (18–68)	27 (100)	NA	NA	NA	NA	0	0	0	0	--	--	--	CPS > 1%	27	--
PD-L1	Zandberg (2019)	112	80 (71)	60 (24–84)	40 (36)	40	37	20	17	0	47 (39)	15 (13)	1 (1)	99	34 (34)	65 (65)	TC > 25%	111	0
	Colevas (2018)	32	27 (84)	62 (32–78)	23 (72)	18	16	12	4	0	7 (22)	2 (6)	0	28	13 (46)	12 (43)	IC > 5%	25 (78)	7 (22)
	Siu (2018)	67	54 (81)	62 (23–82)	33 (49)	25	NA	NA	NA	0	15 (22)	17 (25)	0	67	18 (27)	49 (73)	TC < 25%	0	65

Abbreviations: CPS, combined positive score; Eval, evaluable; IC, area of tumor area positive for immune cells; LA, laryngeal; NA, not available; NC, nasal cavity; OC, oral cavity; OP, oropharyngeal; OT, other; PH, pharyngeal; TC, tumor cell staining; --, not reported or not tested.

[a]Various methodologies reported in the included studies; if more than one methodology was reported, CPS ≥ 1 was determined to indicated positivity.

[b]Data from most recent study are presented here; if data in most recent study was not specifically reported, then data from prior studies are reported.

TABLE 3 Patient summary of treatment duration and outcomes

Author (year)		N[a]	Median time to response, m (range)	Median duration of response, m (range)	Median OS, m (95% CI)	Median PFS, m (95% CI)	RECIST outcomes				
							CR	PR	SD	PD	ORR
PD-1	Cohen (2019)	247	4.5 (2.3–6.4)	18.4 (5.8–18.4)	8.4 (6.4–9.4)	2.1 (2.1–2.3)	4	32	56	108	36
	Ferris (2018)[b]	240	2.1 (1.8–7.4)	9.7 (2.8–32.8+)	7.7 (5.7–8.8)	2.0 (1.9–2.1)	7	25	55	99	32
	Mehra (2018)[b,c]	192	2.0 (2.0–17.0)	NR (2+–30+)	8.0 (6.0–10.0)	2.1 (1.9–2.1)	8	26	33	93	34
	Bauml (2017)	171	2 (2.0–5.0)	8 (2.0–12.0)	8.0 (6.0–11.0)	2.1 (2.1–2.1)	1	27	33	87	28
	Hsu (2017)	27	1.9 (1.4–16.4)	17.1 (4.8–22.1+)	16.5 (10.1–NR)	3.7 (2.1–13.4)	0	7	14	6	7
PD-L1	Zandberg (2019)	112	2 (1.6–9.2)	10.3 (NA)	7.1 (4.9–9.9)	2.1 (1.9–3.7)	1	17	7	58	18
	Colevas (2018)	32	NA	7.4 (4.7-45.8)	6.0 (0.5–51.6+)	2.6 (0.5–48.4)	0	7	6	13	7
	Siu (2018)	67	4.1 (2.0–6.0)	NA	6.0 (4.0–11.3)	1.9 (1.8–2.0)	0	6	4	42	6

Abbreviations: CI, confidence interval; CR, complete response; m, months; NA, not available or not reported; NR, not reached; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progress-free survival; PR, partial response; RECIST, Reporting the Response Evaluation Criteria in Solid Tumors; SD, stable disease.

[a]Only *N* for monotherapy of interest included within.

[b]Data presented from most recent study when available: for Ferris (2018) includes Ferris (2016)/Gillison (2018), for Merhra (2018) includes Seiwert (2016)/Chow (2016) or from whichever article solely presents the data.

[c]Study reported responses from central review as well as confirmed/unconfirmed responses per investigator assessment. Central review confirmed responses are reported here.

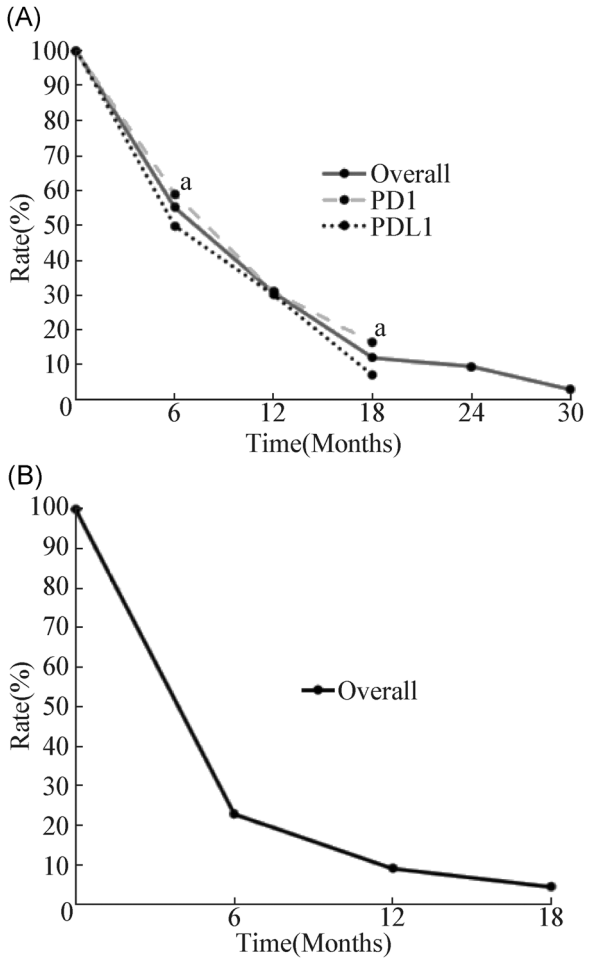

FIGURE 2 Comparisons of overall survival and progression-free survival between PD-1 inhibitors and PD-L1 inhibitors. (A) Overall survival for all patients (solid line), PD-1 inhibitors (dashed line) and PD-L1 inhibitors (dotted line). Note: there was insufficient survival data beyond 18 months to permit meaningful analyses between PD-1/PD-L1 inhibitors. [a]$p < 0.05$. (B) Progression-free survival for all subjects. PD-1, program cell death 1; PD-L1, programs cell death ligand 1

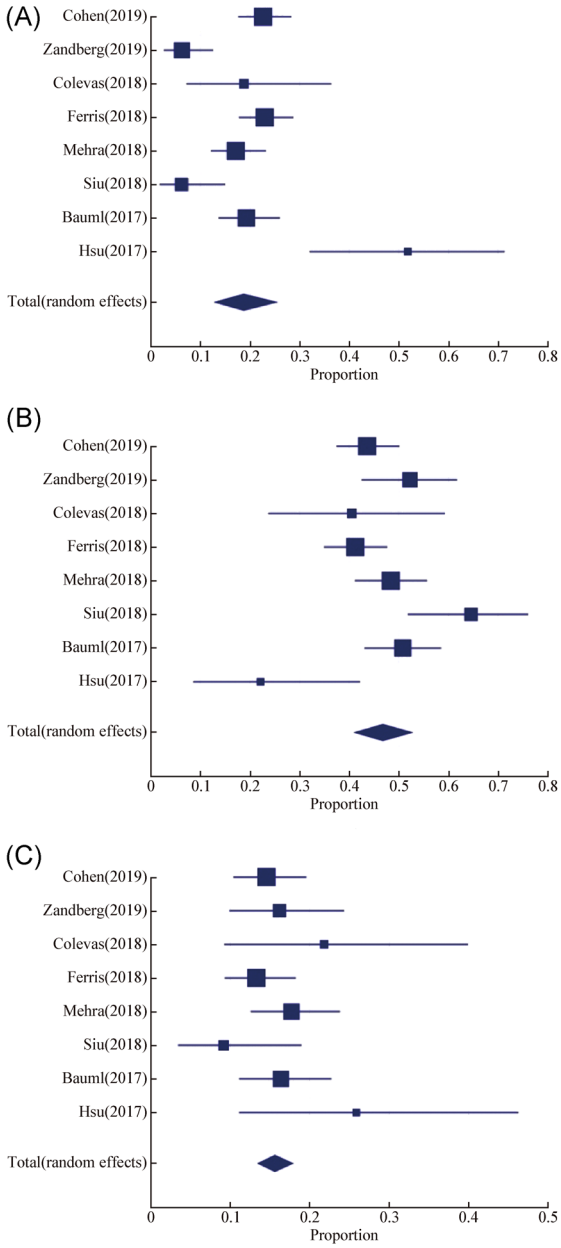

FIGURE 3 Forest plots of PD-1/PD-L1 RECIST outcomes. (A) RECIST stable disease (SD). (B) RECIST progressive disease (PD). (C) RECIST overall response rate (ORR). PD-1, program cell death 1; PD-L1, programs cell death ligand 1

beyond 18 months for meaningful subgroup comparisons. Total PFS was 22.84% (95% CI: 17.33–28.86) at 6 months, 9.14% (95% CI: 3.48–17.12) at 12 months and 4.40% (0.59–11.46) at 18 months, and did not differ between groups.

Seven studies reported median time to response (mean: 2.65 months, range: 1.4–17). Pooled ORR was 15.6% (95% CI: 13.5–17.9) with no difference between groups or individual agents (Figure 3). The overall rate of SD was 18.7% (95% CI: 12.9–25.2), with PD-1 inhibitors showing higher rate compared with PD-L1 inhibitors (23.2%, 95% CI: 17.8–29.1 vs. 8.4%, 95% CI: 5.0–13.0, $p < 0.001$). The overall PD rate was 46.8% (95% CI: 41.1–52.5); PD-1 inhibitors had a lower rate compared with PD-L1 inhibitors (44.1%, 95% CI: 38.4–49.8 vs. 54.32%, 95% CI: 47.34–61.17, $p = 0.007$). Mean of median duration of response from seven studies was 11.81 months (range: 2.0–45.8+).

Safety

Median duration of treatment was reported in 5 studies (mean = 2.96 months, range: 0–36+). Among 1081 evaluable patients, 12.8% (95% CI: 10.9–14.9) had Grade 3 or higher adverse events, and 62.7% (95% CI: 59.8–65.6) experienced an adverse event of any grade. There were no differences between groups or individual agents. The most commonly reported TRAEs were fatigue ($n = 170$, 15.7%), hypothyroidism ($n = 85$, 7.4%) and diarrhea ($n = 50$, 4.6%). Overall, 58 subjects (5.3%) withdrew due to TRAEs.

DISCUSSION

This meta-analysis investigated both the collective and comparative efficacy and safety of PD-1 and PD-L1 inhibitors in the treatment of HNSCC. The first included trial was published in 2016, more than half a decade after FDA approval of the first ICI.[28] Herein, in KEYNOTE-012, patients who were PD-L1 biomarker-expressive received a body-weight dosing regimen of pembrolizumab, which was well-tolerated and demonstrated clinically significant antitumor activity. Since then, a comprehensive effort from numerous studies has supported a shift in standard of care for patients with R/M HNSCC to include pembrolizumab.[29] PD-L1-expressivity by CPS is now the first required biomarker analysis for specific therapy selection in HNSCC. Shortly after the results from KEYNOTE-012 and KEYNOTE-055 were published, the Check-Mate-141 study introduced the next PD-1 inhibitor, nivolumab, for the treatment of R/M HNSCC.[25] This landmark investigation demonstrated significantly improved mOS, longer mPFS and fewer TRAEs in biomarker-unselected patients with platinum-refractory R/M HNSCC.[25] As a result, head and neck surgeons and oncologists alike recognized PD-1 inhibitors as important therapeutics with potential to further improve treatment paradigms of HNSCC. Trials utilizing PD-L1 inhibitors for HNSCC were first published in 2018; these agents remain under investigation in HNSCC and additional data will be forthcoming.

The present study also showed a possible difference in antitumor activity and OS between these agents. Compared with PD-1 inhibitors, PD-L1 inhibitors had a higher overall rate of disease progression (PD) and a lower rate of disease stability (SD). PD-1 inhibitors demonstrated a statistically significant higher rate of OS at 6 and 18 months, with no observed difference at 12 months. To our knowledge, the present study is the first comparison of these drugs in the treatment of HNSCC, and also the first reported data in any patient population to suggest a possible difference in response rates among PD-1 and PD-L1 inhibitors. Previous meta-analyses among patients with non-small-cell lung cancer (NSCLC) did not identify any differences in OS between these classes, yet did not perform any analyses on RECIST criteria.[30–32] Our results concur with a recent meta-analysis of the efficacy and toxicity of PD-1 and PD-L1 inhibitors in HNSCC.[33]

While there is no currently established evidence to support the preferential selection of PD-1 inhibitors over PD-L1 inhibitors in unselected patients, Pillai et al.[30] postulate that antibodies directed against PD-L1 on neoplastic and native cells alike still permit engagement of PD-L2 with PD-1 expressed on T lymphocytes. Investigators have started to explore the role of PD-L2 expression in attenuating the blockage response in patients with HNSCC, with one study showing a high correlation between PD-L1 and PD-L2 expression.[26] Further, recent reports suggest that cis-interactions of PD-L1 with CD80 on the tumor surface limit the signaling capacity of PD-L1; therefore, targeting PD-L1 could be less effective if a high proportion of PD-L1 on the tumor is already bound to CD80.[34] Deeper understanding of the underlying mechanisms of these agents is crucial for selecting appropriate treatment.

Further objectives of the present study were to assess treatment safety and toxicity. Approximately 62% of patients who received PD-1/PD-L1 inhibition experienced a TRAE of any grade, with less than 14% of patients experiencing a TRAE ≥ grade 3. Treatment-related death ranged from 0% to 3.70% of patients in PD-1 trials, and 0%–1.49% of patients in PD-L1 trials, suggesting that risk of death due to treatment with these ICIs remains relatively low. These figures are consistent with other large studies.[30,35] In a large meta-analysis of patients with NSCLC, PD-1/PD-L1 inhibitors demonstrated a more favorable toxicity profile with fewer TRAEs compared with traditional chemotherapy.[36] However, the mechanism of immune activation inherent to PD-1/PD-L1 inhibition results in a unique toxicity profile: by inhibiting the self-regulatory abilities of the immune system in the periphery, these drugs can incite lymphocytic infiltration into nearly any tissue, subsequently precipitating an autoimmune-like response.[35,37–40] The gastrointestinal tract, skin, liver, and endocrine glands are the most commonly affected organs from these immune-related adverse events (irAEs).[38,40] The most commonly reported TRAEs in the present study were fatigue, hypothyroidism, and diarrhea—findings reinforced by other large meta-analyses.[35,37] Our data did not reveal any differences in toxicity between PD-1 and PD-L1 inhibitors, which aligns with previous studies among NSCLC patients.[30,32] However, Sun et al.[31] reported a lower frequency of irAEs in patients treated with PD-L1 inhibitors, further supporting the theory of limited axis inhibition with PD-L1 inhibitors.

There are several limitations to the present meta-analysis. First, by virtue of study design, individual patient data was not available. Several essential metrics such as original tumor stage, biopsy confirmation of HNSCC, and classification of local versus regional versus distant metastasis were inconsistently reported. Furthermore, exact duration, sequence dosage of treatments and extent of surgeries were also not included for individual patients. The substantial variability of number and types of previous treatments among these patients is yet another limitation. Gillison et al.[23] stratified outcomes based on the number of previous treatments received, comparing these groups with standard of care but not head-to-head. Further, these data are currently only generalizable to patients with R/M HNSCC; therefore, future studies of the impact of ICIs for patients with primary untreated and resectable locoregional disease will be informative to understand the benefit for a wider range of disease manifestations. There are several ongoing trials using neoadjuvant PD-1 inhibitors for HNSCC, probing the idea of an expanded future role for immunotherapy.[41,42] Nevertheless, a balancing strength of this study is that most included trials were multinational and representative of a diverse global population of individuals with R/M HNSCC.

The observed differences between PD-1 and PD-L1 inhibitors also warrant further discussion. Although there were more favorable RECIST-defined antitumor response rates for PD-1 inhibitors, included studies fail to report a specific basis for which target lesion(s) were selected for radiographic monitoring and reporting in determination of RECIST criteria. As noted previously, published results of PD-1 inhibitors in HNSCC preceded those of PD-L1, likely resulting in substantial differences in follow-up times and sample sizes. In addition, sample sizes were limited for trials investigating

durvalumab and atezolizumab (PD-L1 inhibitors), which may have influenced the difference in OS secondary to relatively immature survival data for PD-L1 inhibitors. Indeed, the two long-term follow-up publications exclusively reported individuals receiving PD-1 monotherapy. The durability of these responses is also uncertain, and these differences may conceivably converge with longer follow-up. Ultimately, the validity and clinical significance of these findings must be interpreted with caution until confirmed by prospective clinical trials and larger meta-analyses as more patient data becomes available.

The heterogeneity in primary tumor sites is another complexity present in HNSCC. Although the theory of field cancerization provides a reasonable framework for including most types of HNSCC in these trials, it is still possible that microenvironments within the head and neck region respond differently to these agents. One included study reported specific inclusion criteria based on PD-L1-expressive nasopharyngeal carcinoma, which has a unique etiopathogenesis.[43,44] Additionally, the simple dichotomy of PD-L1-expressivity reported herein fails to capture the dynamic nature of this metric. Included studies contained substantial methodological variability in their assessment and determination of PD-L1 expression, the magnitude of which has been shown to predict enriched responses in HNSCC.[15,27,45,46] The most commonly reported criterion was CPS ≥ 1, indicating positive expression. Other reported methods have variable predictive abilities for response, and include tumor cell staining (TC), tumor-infiltrating immune cell staining (IC), and tumor proportion score (TPS). One included investigation of durvalumab by Zandberg et al.[47] studied subjects strictly with TC ≥ 25%, possibly skewing our results by including a cohort of patients enriched for response. Given this heterogeneity, stratification by PD-L1 expression was excluded from the present analyses and has been reported elsewhere.[46] Therefore, we are unable to account for subtle differences in PD-L1-expressivity which may have unknowingly influenced these results.

Lastly, the present study is also subjected to heterogeneity with respect to HPV status. Although stratification according to HPV status was not part of the present analysis, several included studies reported an apparent association between HPV status and favorable outcomes for patients receiving nivolumab,[24] pembrolizumab,[27,28,48] and durvalumab,[47] but not for patients treated with atezolizumab.[49] Additionally, the number of patients tested for HPV status and subsite analysis was variable and methods and accuracy of HPV testing for non-oropharyngeal sites was not reported. Future studies that stratify these patients according to their PD-L1-expressivity, HPV status, primary tumor site, and other emerging factors would be beneficial in characterizing the intricate interaction of these variables within the HNSCC population.

CONCLUSION

These data represent early investigatory findings of treatment using PD-1 and PD-L1 inhibitors for HNSCC. PD-1 inhibition may be more effective in preventing disease progression and promoting disease stability than PD-L1 inhibition. The clinical significance of these differences is unclear given the size and heterogeneity of the patient population, and the results of cross-trial comparisons should be interpreted with caution. These agents are generally well tolerated, with fatigue being the most common TRAE. Further prospective clinical trials using these agents in clearly stratified patient populations, with correlative molecular and cellular markers, are needed to predict who might benefit from immunotherapy. This information may help generate hypotheses for improved immunotherapeutic paradigms for the significant proportion of patients who do not derive benefit from this treatment regimen in its current state.

AUTHOR CONTRIBUTIONS

Dylan A. Levy: conceptualization, data curation, formal analysis,writing original draft, review & editing. **Jaimin J. Patel:** conceptualization, data curation, formal analysis, writing original draft, review & editing. **Shaun A. Nguyen:** conceptualization, formal analysis,writing original draft, review & editing, supervision. **W. Nicholas Jungbauer:** writing, reviewing, editing, resubmission. **David M.Neskey:** supervision, writing: reviewing and editing. **Ezra E. W.Cohen:** writing: reviewing & editing. **Chrystal M. Paulos:** writing:reviewing & editing. **John A. Kaczmar:** supervision, writing: reviewing& editing. Hannah M. Knochelmann: writing: reviewing & editing.**Terry A. Day:** conceptualization, supervision, formal analysis, writingoriginal draft, review & editing.

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CONFLICTS OF INTEREST

The authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available via the databases referenced in the manuscript.

ETHICS STATEMENT

The authors state that the manuscript is the authors' own original work and has not been published elsewhere, nor is being considered for publication elsewhere. The paper reflects the authors' own research and analysis, and all authors have seen and take responsibility for the final manuscript.

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SUPPORTING INFORMATION

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

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