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Response rates and survival to systemic therapy after immune checkpoint inhibitor failure in recurrent/metastatic head and neck squamous cell carcinoma

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ABSTRACT

Objectives: Prior reports have demonstrated a potential enhancement in overall response rate (ORR) to chemotherapy after exposure to immunotherapy. The goal of this study was to evaluate the ORR and survival to chemotherapy and/or targeted therapy in head and neck squamous cell carcinoma (HNSCC) patients who progressed on immune checkpoint inhibitors (ICI).

Materials and Methods: We retrospectively collected clinical and pathologic data from patients with recurrent/metastatic HNSCC who progressed on ICI and subsequently received chemotherapy or targeted therapy. ORR was assessed by RECIST version 1.1. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method.

Results: A total of 43 patients met criteria for inclusion. The majority were male (91%) and former smokers (60%). Most patients received ICI as first-line (58.14%); the vast majority was platinum exposed (90.7%). The ORR to ICI was 21%. The ORR to systemic therapy before ICI was 47%, and the ORR after ICI failure was 42%. After progression on ICI, the median PFS and OS on the subsequent line of therapy were 4.2 and 8.4 months respectively.

Conclusion: In our cohort of recurrent/metastatic HNSCC patients, the ORR and OS to systemic therapy after progression on ICI were higher than historical controls for second-line or beyond. Further investigations are warranted to better characterize optimal sequencing and combination strategies.

Introduction

Squamous cell carcinoma of the head and neck (HNSCC) is a global health issue, responsible for more than 600,000 cases and 350,000 deaths annually [1,2]. The overall incidence of HNSCC has been declining over the past decades; however, an increase in specific sites (i.e., oral and oropharyngeal) has been described in recent years, more pronounced in young adults as a result of HPV infection [3–5]. The majority of HNSCC patients present with locoregionally-advanced disease; nonetheless, most patients will recur despite combined-modality definitive-intent treatment and will succumb as a consequence of disease, highlighting the need for strategies to improve patient outcomes

Abbreviations: CR, complete response; EGFR, epidermal growth factor receptor; HNSCC, head and neck squamous cell carcinoma; ICI, immune checkpoint inhibitor; ORR, overall response rates; OS, overall survival; PD-1, programmed-death receptor 1; PFS, progression-free survival; PR, partial response

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[6,7].

Platinum-based chemotherapy plus cetuximab was until very recently the standard first-line therapy for patients with recurrent/metastatic HNSCC, achieving median overall survival (OS) of 8–10 months [8,9]. After progression, single-agent treatment consisting of chemotherapy or the epidermal growth factor receptor (EGFR) inhibitor cetuximab led to overall response rates (ORR) of 5–15% and median OS of around 6 months [9,10]. Recently, the development of antibodies blocking the programmed death-1 (PD-1) receptor has changed the treatment paradigm for this patient population [11]. Nivolumab and pembrolizumab have been approved by the Food and Drug Administration (FDA) for recurrent/metastatic HNSCC patients previously treated with a platinum-containing regimen based on improved OS compared to single-agent cytotoxic therapy or cetuximab [10–13]. These agents have demonstrated an ORR of approximately 15%, with median PFS of 2 months and OS of 7.5–8.5 months [10,12]. While response rate is not high, they are notably durable and patients experience a better quality of live; nevertheless, most patients will not respond and all will eventually progress on ICI, and those with a good performance status, will ultimately receive chemotherapy and/or cetuximab as the next line of treatment.

Improvement in response to chemotherapy has been described following exposure to immunotherapy in multiple cancers. Initially, augmented responses to cytotoxic treatment were noted following vaccine-based immunotherapy in extensive-stage small cell lung cancer and glioblastoma multiforme [14–16]. Recently, emerging data suggest enhanced responses to chemotherapy following progression on ICI in non-small cell lung cancer (NSCLC) [17–20]. For illustration, data from our group published by Schvartsman et al. analyzed a cohort of 28 NSCLC patients receiving single-agent chemotherapy following ICI; the confirmed ORR was 29%, which is significantly higher than the 7% ORR to docetaxel in patients without prior exposure to ICI [18,21]. In the current ever-changing dynamic landscape of oncologic treatments, these data are valuable and can shed light on optimal sequencing strategies.

To the best of our knowledge, however, there is limited data analyzing the outcomes of patients receiving chemotherapy after exposure to ICI in patients with incurable HNSCC [22]. The goal of this study is to evaluate response rates and survival to systemic therapy in second-line or beyond in HNSCC patients who previously progressed on ICI, specifically anti-PD1.

Materials and methods

Patient selection and data collection

We retrospectively collected clinical data from patient's electronic medical records at MD Anderson Cancer Center (MDACC). Vital status and/or last contact date were updated on 4/11/2019. As inclusion criteria for the analysis, patients must have: (1) progressed on prior ICI for recurrent/metastatic HNSCC; (2) received systemic therapy after ICI progression; and (3) appropriate follow up with at least one restaging image to evaluate the efficacy of systemic therapy. ORR was assessed by an independent radiologist (JJ), using Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1) [23]. Confirmatory imaging was not mandatory. The study was approved by the MDACC Institutional Review Board (protocol PA17-0865).

Statistical analysis

Patient characteristics were summarized through descriptive statistics. OS was defined as the interval between the start date of systemic therapy and the date of death, and was censored at the last follow-up date for patients who were alive. Progression-free survival (PFS) was defined as the interval between the start date of systemic therapy and the date of progression or death, whichever occurred first, and was censored at the last contact date for patients who neither progressed nor died. Survival curves were estimated using the Kaplan-Meier method, and differences in survival among independent groups were assessed using Wald tests. Cox proportional hazards regression models were used to estimate effect sizes of risk factors. A forward stepwise model selection strategy setting a significance α level = 0.2 for inclusion was applied to obtain multivariable Cox regression models. Associations between two categorical variables were evaluated through Fisher's exact tests. Mc Nemar's exact test was used to compare response to ICI and response to other systemic therapy given after ICI. Statistical analyses were conducted in R version 3.4.2.

Table 1
Patient and tumor characteristics.

Patient Characteristics		N = 43
Gender, No. (%)		
	Male	39 (90.7)
	Female	4 (9.3)
Smoking, No. (%)		
	Former	26 (60.5)
	Never	16 (37.2)
	Current	1 (2.3)
Smoking (pack years), No. (%)		
	< 10	25 (58.1)
	> =10	17 (39.5)
	Unknown	1 (2.3)
Cancer site, No. (%)		
	Oropharynx	26 (60.4)
	Oral cavity	10 (23.2)
	Larynx	4 (9.3)
	Nasopharyngeal (WHO type I)	3 (6.9)
Oropharynx p16/HPV, No. (%)		
	Negative	5 (19.2)
	Positive	20 (76.9)
	Unknown	1 (3.8)
TNM Staging at diagnosis, No (%)	I ,II	2 (4.6)
	III	3 (6.9)
	IVA	23 (53.4)
	IVB	5 (11.6)
	IVC	9 (20.9)
	Unknown	1 (2.3)
Induction chemotherapy, No. (%)		
	No	24 (55.8)
	Yes	18 (41.9)
	Unknown	1 (2.3)
Definitive treatment		
Surgery, No. (%)	Yes	19 (44.2)
Radiotherapy +/− chemotherapy, No. (%)	Definitive	22 (51.2)
	Adjuvant	18 (41.9)
Concurrent agent, No. (%)	Plat	17 (39.5)
	Cetuximab	3 (6.9)
	Plat/tax	1 (2.3)
	Tax/cetuximab	1 (2.3)
Salvage surgery, No. (%)	Yes	11 (25.6)
Site of recurrence, No (%)		
	Loco-regional	36 (83.7)
	Lung	23 (53.5)
	Bone	11 (25.6)
	Liver	6 (13.9)
	Others	13 (30.2)

Abbreviations: HPV: human papilomavirus, Plat: platinum agents, Tax: taxanes, WHO: world health organization.

Results

Patients

A total of 43 patients who received systemic therapy after failure to ICI from Jan/2016 to Oct/2018 met eligibility criteria and were included in the analysis. Table 1 summarizes baseline patient

Table 2
Summary of therapies received.

Treatment Characteristics		N = 43
Agent 1st line, No. (%)		
	ICI	25 (58.1)
	Plat/tax	9 (20.9)
	Plat/tax/EGFRi	4 (9.3)
	Plat/tax/5-fU	2 (4.6)
	Plat or tax + EGFRi	3 (6.9)
Agent 2nd line, No. (%)		
	ICI	17 (39.5)
	Plat/tax +/- EGFRi	11 (25.6)
	EGFRi	9 (20.9)
	Others	3 (6.9)
	Tax +/- EGFRi	3 (6.9)
Agent 3rd line, No. (%)		
	No agent given	24 (55.8)
	EGFRi	8 (16.2)
	Tax +/- egfr	4 (4.6)
	Other	3 (6.9)
	Plat/5-FU or egfr	3 (2.3)
	ICI	1 (2.3)
Agent 4th line, No. (%)		
	No agent given	42 (97.6)
	Plat/tax	1 (2.3)
Immunotherapy (ICI), No. (%)		
	Pembrolizumab	29 (67.5)
	Nivolumab	14 (32.5)
EGFRi prior to ICI, No. (%)		
	No	28 (65.1)
	Yes	15 (34.8)
EGFRi within 6 months of ICI, No. (%)		
	No	31 (72.0)
	Yes	12 (27.9)
Platinum prior to ICI, No. (%)		
	Yes	39 (90.7)
	No	4 (9.3)
Platinum within 6 months of ICI, No. (%)		
	Yes	26 (60.5)
	No	17 (39.5)

Abbreviations: EGFRi: EGFR inhibitor; ICI:immune checkpoint inhibitor, Plat: platinum agents, Tax: taxanes.

characteristics. The majority of patients were male (91%) and former smokers (60%). The median follow-up is 25.3 months and 72% of patients (31/43) died during the study period.

Systemic therapy in the recurrent/metastatic setting

Table 2 summarizes the lines of therapies received by patients.

Table 3
Overall response rate to therapy.

	ORR	N (43)
Systemic therapy before ICI, No. (%)		
	Partial response	7 (37.8)
	Progressive disease	4 (22.2)
	Stable disease	4 (22.2)
	Unknown	3 (16.6)
ICI, No. (%)		
	Partial response	9 (20.9)
	Progressive disease	27 (62.7)
	Stable disease	7 (16.2)
ORR to systemic therapy after ICI, No. (%)		
	Complete response	1 (2.3)
	Partial response	17 (39.5)
	Progressive disease	19 (44.1)
	Stable disease	6 (13.9)

Abbreviations: ICI:immune checkpoint inhibitor, ORR: overall response rate.

Fig. 1 demonstrates an interval event chart aligned by start date of first line therapy.

Chemotherapy and anti-EGFR in frontline

Overall, 18 patients received chemotherapy with or without an EGFR inhibitor (cetuximab or erlotinib) in first-line, before ICI, and 15 were evaluable for response. The ORR to frontline chemotherapy +/- EGFR inhibitor was 47% (Table 3), and the median PFS was 3.89 months (95% CI 2.56–6.97).

Immunotherapy

Twenty-nine patients (67%) received pembrolizumab, and 14 (33%) were treated with nivolumab. The majority of patients (58%, 25/43) received ICI in first-line; 90% were platinum-exposed, 60% platinum refractory, and 35% received an EGFR inhibitor before ICI. Of 14 patients who received nivolumab, 9 received concurrently a HPV16 peptide vaccine as part of a clinical trial [24]. The ORR to ICI was 21%. There was no difference in response rate based on prior EGFR inhibitor exposure ($p = 0.24$) or concurrent HPV16 vaccination ($p > 0.99$). Supplementary Table 1 shows the association between several patients' characteristics and overall response to ICI. There was a negative association between having loco-regional recurrence and response to anti-PD1 (OR = 0.13, 95% CI 0.02–0.77).

The median PFS on ICI was 2.79 months (95% CI: 2.23–4.11). Patients with an oropharynx primary had a more prolonged PFS (HR = 0.34, 95% CI: 0.18–0.67), while those with loco-regional

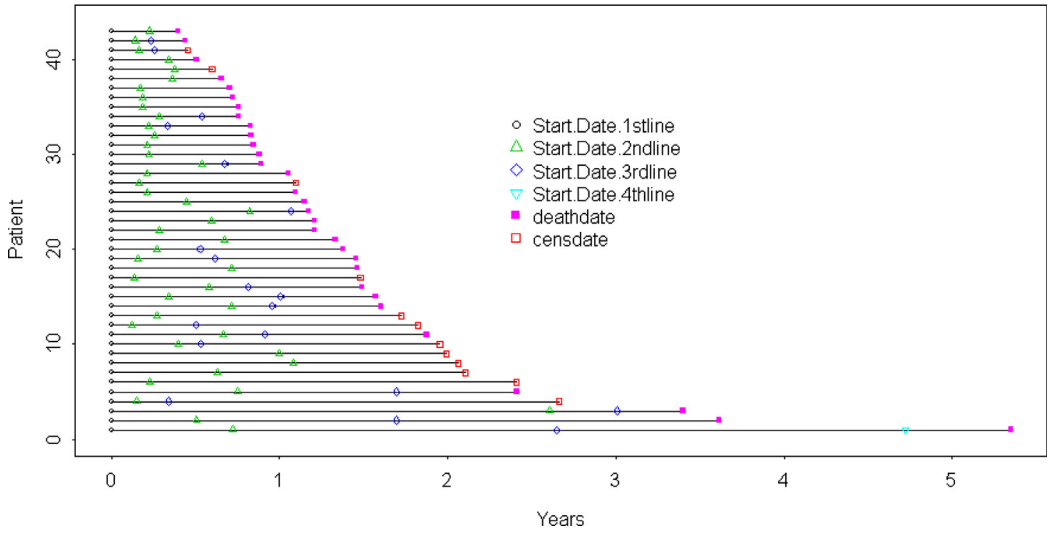

Fig. 1. Interval event chart aligned by start date of first treatment and sorted by time from start of first therapy to last date of contact.

recurrence had worse PFS (HR = 2.36, 95% CI: 1.02–5.44) (Supplementary Tables 2 and 3). There was no difference in survival between patients who received ICI or chemotherapy with or without EGFR inhibitor in the frontline setting (median OS from first line therapy was 16.5 months, 95% CI:13.8–28.9; p = 0.16).

Systemic therapy after immunotherapy

Sixteen patients (37.2%) received EGFR inhibitor alone, 14 (32.5%) received single-agent chemotherapy, 8 (18.6%) received chemotherapy plus anti-EGFR, and 5 (11.6%) received chemotherapy with other agents. The ORR to systemic therapy after ICI was 42% (18/43); 1 patient achieved a complete response and 17 patients a partial response (Table 3). The ORR to cetuximab as single agent after exposure to ICI was 37.5% (6/16 patients responded) and was comparable to the ORR of patients that received chemotherapy-containing regimens (p > 0.99). We also found no difference in ORR to systemic therapy following ICI based on prior concurrent HPV16 vaccination (p = 0.71). An association between response to immunotherapy and response to the subsequent systemic therapy was noted (OR = 3.25, 95% CI: 1–13.68, p = 0.049). Supplementary Table 4 shows the association between several patients' characteristics and overall response to post-ICI therapy.

The median PFS for systemic therapy after ICI failure was 4.24 months (95% CI: 2.63–5.19 months; Fig. 2A). Median OS from systemic therapy given after immunotherapy was 8.41 months (95% CI: 7.62–11.07 months; Fig. 2B). There was no difference in PFS or OS comparing patients that received single-agent cetuximab to patients that received treatment including chemotherapy (p = 0.78 and p = 0.22, respectively). Similar outcomes to subsequent systemic therapy were found when the nine patients who received an HPV16 therapeutic vaccine concurrently with ICI were excluded from the analysis.

Discussion

Anti-PD-1 checkpoint inhibitors have shown efficacy for treating recurrent/metastatic HNSCC; however, only approximately 15% of all patients achieve an objective response with monotherapy. Therefore, identifying the best sequencing and combination strategies is imperative.

Notable in our study are the ORR of 42% and OS of 8.41 months to systemic therapy administered after progression on ICI. These numbers compare favorably to the reported ORR and OS to second or third-line therapy in the pre- ICI era, and approached the outcomes seen with frontline chemotherapy with or without EGFR inhibitor in this cohort [11]. For illustration, the ORR to investigator-choice systemic therapy in platinum-refractory HNSCC was 5.1% in the control arm of Checkmate 141 [12].

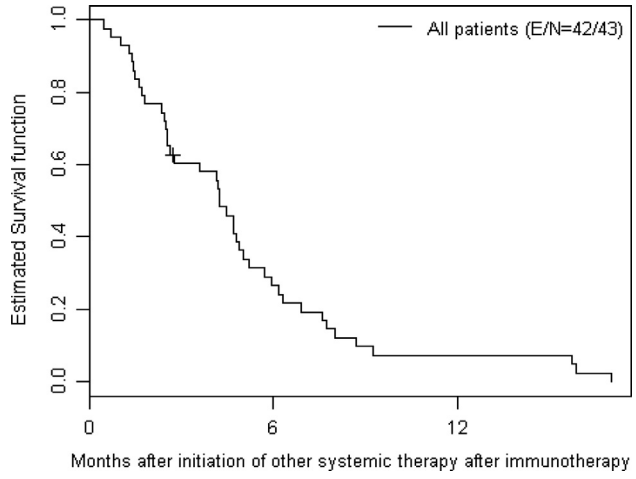

Fig. 2A. PFS from systemic therapy after ICI failure.

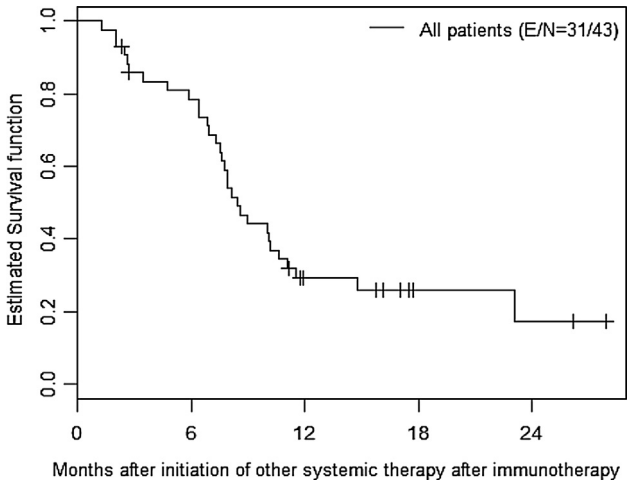

Fig. 2B. OS from systemic therapy after ICI failure.

We did not find a difference in response to ICI based on prior EGFR inhibitor exposure, in contrast with recently presented analysis from Checkmate 141 [25]. In this analysis, the magnitude of benefit of nivolumab in terms of response, compared to investigator's choice of chemotherapy, was greater in patients without prior cetuximab exposure [25]. In accordance with our data, experience with pembrolizumab in the KEYNOTE-012, KEYNOTE-040 and KEYNOTE-055 studies do no suggest a difference in benefit from pembrolizumab based on prior cetuximab exposure [10,26,27].

The mechanisms through which immunotherapies can act as chemosensitizing agents are not fully elucidated. Pre-clinical data has demonstrated that activated $CD4^+$ T-cells enhance chemotherapeutic tumor responses in xenograft models [28]. In this study, A375 melanoma or MDA-MB-231 breast cancer cell lines were injected subcutaneously into the flank of mice that were then randomized to receive ex-vivo activated human $CD4^+$ T-cells intratumorally or vehicle control, followed by chemotherapy starting 48 h later. Results demonstrated significant delay in tumor growth in mice that received intratumoral injection of $CD4^+$ T-cells as compared to mice treated with chemotherapy alone. It is reasonable to hypothesize that, in our study cohort, anti-PD-1 utilization led to increased intratumoral infiltration of activated T-cells that could have contributed to improving the response rates to the subsequent systemic therapy, which is further suggested by the positive association of ORR to ICI and ORR to the subsequent therapy [29]. Interestingly, prior reports in NSCLC failed to show correlation between response to ICI and response to the next line of chemotherapy [20]. Conversely, it can be postulated that the tumor shrinkage seen with systemic therapy after ICI might not represent the true objective response to the cytotoxic or targeted agent, and alternatively it could be a delayed tumor responses to ICI. In addition, given the long half-life of anti-PD1 antibodies, it is possible that therapeutic circulating levels were still present concurrently with the administration of subsequent systemic therapy, and, in this case, the enhanced responses could represent superiority of the combination of ICI with chemotherapy and/or targeted therapy rather than an optimal sequencing strategy. In fact, data from patients with melanoma suggests that chemoimmunotherapy after anti-PD-1 failure improved outcomes when compared to chemotherapy alone [30].

Recently, the final analysis of the KEYNOTE 048 phase III study investigating pembrolizumab single agent or the incorporation of pembrolizumab to platinum and 5-fluouracil (5-fu) versus platinum, 5-fu and cetuximab (EXTREME regimen) in front-line were presented in abstract form [31,32]. The results showed improved outcomes for platinum/5-fu/pembrolizumab versus EXTREME and non-inferiority of

pembrolizumab single agent compared to EXTREME in the overall population. In patients with PD-L1 expression in at least 1% of the tumor cells, lymphocytes or macrophages (combined proportion score/ CPS ≥ 1%) pembrolizumab single agent was superior to EXTREME. This study led to the FDA approval of two new first line therapies for HNSCC: pembrolizumab for patients with CPS ≥ 1% and platinum/5-fu/pembrolizumab irrespective of PD-L1 status. Since 85% of recurrent/metastatic HNSCC patients have a CPS ≥ 1% and due to the better toxicity profile and more durable response with pembrolizumab single agent as compared to chemotherapy plus pembrolizumab, we believe that a large proportion of HNSCC patients will still be receiving single agent anti-PD1. It will be interesting to learn if some of the benefit of pembrolizumab in front-line is indeed due to an improved response to the subsequent line of therapy, and wheter a higher activity of further chemotherapy or cetuximab will be seen after combination of chemotherapy with anti-PD1.[32]

Our results are in concordance with recent reports of higher response rate to salvage cytotoxic therapy after ICI use. In NSCLC, three retrospective studies have demonstrated unexpectedly high activity of salvage chemotherapy after immunotherapy [17–19]. Moreover, Saleh et al. reported in abstract form the ORR to salvage chemotherapy after exposure to ICI (including anti-PD-1, anti-PD-L1, anti-CTLA-4, and anti-KIR) in patients with advanced HNSCC in four French centers. In his cohort of 82 patients, the confirmed ORR to chemotherapy was 30%, including 3 complete responses. Taxane-based regimens were the most frequently used after progression on ICI (56%), and half of the patients received combined cetuximab therapy at salvage [22]. In addition, prospective data from the KEYNOTE-024 study also suggests that immunotherapy followed by chemotherapy is a better treatment sequence than the opposite. In this trial, patients with PD-L1 positive advanced NSCLC were randomized to either frontline pembrolizumab or carboplatin plus pemetrexed, with cross-over allowed at the time of progression [33]. A recent updated report demonstrated that the PFS2 (combined PFS for the first- and second-line therapy) for first-line pembrolizumab followed by chemotherapy was significantly improved when compared to that of frontline cytotoxic treatment followed by immunotherapy (18.3 vs 8.4 months, $p < 0.01$] [34]. Notable and novel in our study is the high observed ORR to cetuximab monotherapy after ICI failure; this distinguishes our results from the above-mentioned data in NSCLC and from the french study in HNSCC, which exclusively evaluated response to chemotherapy. Our results suggest that the mechanism through which response to chemotherapy is increased extends to EGFR inhibition or, alternatively, a different sensitization to anti-EGFR coexists.

Limitations of our study include the small sample size, the inclusion of a heavily selected cohort of patients, lack of control group, and the retrospective nature of the study. Moreover, the inclusion of nine patients that received concurrent HPV16 vaccination could be a confounder, however, our analysis did not show differences in ORR, PFS, or OS when HPV16 vaccinated patients were excluded. Furthermore, the inclusion criteria of patients that received therapy after ICI progression may inevitably select for those with more indolent disease and better performance status. Notwithstanding, it is anticipated that additional therapy similar to that received by our cohort will be only offered in clinical practice to patients that maintain appropriate performance status, and therefore our study provides an estimate of the real-world ORR in this setting.

To our knowledge, we provide the first report of increased response rates and encouraging OS to systemic therapy given after exposure to anti-PD-1 in a cohort of HNSCC patients from the USA. With immunotherapy being increasingly incorporated as a standard treatment for advanced HNSCC, further examination of the chemosensitizing effects of ICI have the potential to contribute for the development of novel therapeutic strategies, with optimization of sequencing and combination regimens incorporating the growing number of cytotoxic, targeted, and immunotherapy agents available.

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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.2019.104523.

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