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Phase 2 trial of adjuvant nivolumab following salvage resection in patients with recurrent squamous cell carcinoma of the head and neck

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Abstract

PURPOSE: Loco-regional relapse in patients with head and neck squamous cell carcinoma (HNSCC) is common, approaching 50% for some subsites despite multi-modality therapy. Salvage surgery is the standard of care, but able to achieve durable control in only a minority of patients.

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Conflicts of Interest Statement:

Funding for this study was provided by Bristol Myers Squibb awarded to Drs. Wise-Draper and Haque. PD-L1 staining and TMB analysis was provided by Caris Life Sciences. The authors have no additional relevant conflicts of interest to disclose. Julie McGrath and Michael Korn are employees of Caris Life Science.

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While adjuvant RT or chemo-RT is offered to select patients, this approach can be prohibitively toxic. Given the activity and tolerability of PD-1 inhibitors in metastatic HNSCC, we investigated the safety and efficacy of adjuvant nivolumab after salvage surgical resection.

EXPERIMENTAL DESIGN: This was an open-label, multi-institutional phase-II clinical trial (NCT03355560). Patients with recurrent, resectable HNSCC were enrolled within 6 weeks of salvage surgery. Six 28-day cycles of adjuvant nivolumab were planned. The primary endpoint was 2-year disease free survival (DFS) >58%, based on an institutional historical control group of 71 recurrent HNSCC patients who underwent salvage surgery.

RESULTS: Between February 2018 and February 2020, 39 patients were enrolled. At a median follow-up of 22.1 months, 2-year DFS was 71.4% (95% CI 57.8-88.1) and the 2-year overall survival (OS) was 73% (95% CI 58-91.8). 3/39 (8%) patients experienced grade 3 treatment-related adverse events and 3/39 (8%) discontinued treatment due to side effects. 10/39 had locoregional recurrence, while 2/10 also had synchronous metastatic disease. There was no difference in DFS between PD-L1 positive and negative patients. There was a non-significant trend toward improved DFS in patients with high TMB (p=0.083).

CONCLUSION: Adjuvant nivolumab after salvage surgery in locally-recurrent HNSCC is well-tolerated and showed improved DFS compared to historical controls.

Introduction

Head and Neck Squamous Cell Carcinoma (HNSCC) is the sixth most common cancer worldwide. There will be an estimated 66,630 new cases of HNSCC in the United States in 2021, with an estimated 14,620 deaths [1, 2]. The global incidence of HNSCC is rising and anticipated to exceed 1 million new cases annually by 2030[1]. Although declining rates of tobacco use in high-income countries have led to a decrease in smoking-related HNSCC, the global incidence of HPV-related oropharyngeal cancers are on the rise[3]. The majority of patients with HNSCC present with locoregionally advanced disease (stage III-IV) requiring multimodality treatment that may include surgery, radiation, and chemotherapy. Despite intensive treatment, local recurrence after definitive therapy for advanced HNSCC remains common, with up to 50% of patients experiencing local or distant recurrence[4].

Treatment of locally recurrent HNSCC is challenging, highly morbid, and the outcomes remain poor. Re-irradiation is often not feasible as many patients have already received the maximum tolerated dose of radiotherapy to critical normal structures and treatment morbidity is significant[5]. For patients with resectable disease, salvage surgery is considered the standard of care, and the only curative option in many patients. Historically, however, salvage surgery achieves durable disease control in only 20-50% of patients[6-8].

We have previously reported that risk factors for HNSCC recurrence after salvage surgery are similar to established pathologic risk factors at initial diagnosis [9]. These pathologic risk factors include extra-nodal extension (ENE), positive surgical margins, perineural invasion (PNI), lymphovascular invasion (LVI). Involvement of 2 or more lymph nodes predicts poor outcome after first line treatment and portends poor outcome in the relapsed setting as well. The addition of adjuvant chemo-radiotherapy (CRT) after salvage surgery has been studied in randomized clinical trials, and while it results in improved local control rates, there is

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no overall survival (OS) benefit, and adjuvant CRT after salvage resection was associated with significantly increased morbidity [10, 11]. To date, there is no adjuvant treatment that has been shown to improve OS over salvage surgery alone. Therefore, this is a population with significant unmet need.

Immune checkpoint blockade with PD-1 inhibitors was approved for use in platinum-refractory recurrent metastatic HNSCC in 2016[12] and was approved for first-line recurrent and metastatic disease for PD-L1 positive patients in 2019[13]. PD-1 inhibitors have a favorable toxicity profile even in the heavily pre-treated recurrent HNSCC population[14]. Targeting the PD-1/PD-L1 axis in the definitive setting has the potential to improve local-control rates and decrease the occurrence of distant metastases by promoting immune surveillance of micrometastatic disease. Therefore, given the established clinical activity of PD-1 inhibitors in HNSCC and the unmet need for locally recurrent HNSCC, we designed a single-arm phase II study evaluating adjuvant nivolumab following salvage resection. Given that the current standard of care is observation, the optimal duration of adjuvant therapy in HNSCC is unknown. Two recent reports of adjuvant immunotherapy in the definitive and relapsed setting suggested 6 months of therapy may have clinical benefit[15, 16]. Therefore, 6 months duration of adjuvant therapy was chosen as likely to provide meaningful benefit while minimizing undue burden and risk of long-term toxicity for study participants.

METHODS:

Study Design and Population:

This is an open-label multi-center single arm phase II clinical trial conducted at The University of Cincinnati Cancer Center (UCCC) in Cincinnati, Ohio and Karmanos Cancer Center in Detroit, Michigan. This study is registered with ClinicalTrials.gov, NCT03355560. The data cut-off date was October 22, 2021. The study is ongoing for follow-up but is no longer enrolling patients. This study was approved and monitored by the respective Institutional Review Boards and UCCC data safety and monitoring board and was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients were required to sign written informed consent.

The study included adults ≥18 years of age with histologically confirmed recurrence of HNSCC after definitive therapy with CRT or radiation alone. Patients were eligible if they had undergone salvage resection with curative intent. Other inclusion criteria included ECOG Performance Status ≤2, and normal organ function.

Patients were excluded from participating in the trial if they had not received radiation as part of their prior definitive treatment, had gross residual disease after salvage resection or evidence of distant metastatic disease. Patients with nasopharyngeal and sinonasal cancer were also excluded. Additional exclusion criteria included a personal history of autoimmune disease requiring systemic steroids, history of pneumonitis, and HIV. The full clinical protocol including all inclusion and exclusion criteria is available in the data supplement.

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Treatment and Assessments:

Patients were enrolled to the trial within six weeks of salvage surgery. The total planned dose of Nivolumab was 2880mg, which was given as 12 cycles of 240mg every 14 days or 6 cycles of 480mg every 28 days. Patients were assessed for toxicity prior to each cycle and dose interruptions or discontinuations due to treatment-related adverse events (TRAEs) were managed according to protocol (Supplement). Patients were monitored for recurrence by clinical exam including thorough ear-nose and throat exam every 3 months for a total of 2 years. Consistent with HNSCC standard-of-care, surveillance chest or whole-body imaging was not required unless there was clinical concern for recurrence.

Study End Points:

The primary endpoint of this study was disease free survival (DFS) at 2-years as measured from the time of treatment allocation to the first evidence of any tumor or death from any cause. All patients who received at least one dose of nivolumab were assessed for the primary efficacy endpoint of DFS at 2 years. Secondary endpoints included 1-year DFS, safety as determined by CTCAE v5.0 and ability to complete 6 cycles of adjuvant nivolumab.

The All-Patients-As-Treated population was used for safety analysis. Secondary safety endpoints were grade 3 and 4 adverse events and all grade (grade 1-5) adverse events. Anticipated adverse event rates were projected based on Checkmate 141 where 13% of patients experienced Grade 3 and 4 adverse events and 58% experienced adverse events of any grade[14].

Sample Size Determination and Statistical Analysis:

This single-arm two-stage design with time-to-event endpoints was used to test the null hypothesis that DFS at 2 years was less than or equal to 33% versus the alternative that DFS at 2 years >53%, by a one-sided, one-sample log-rank test. Wiith the power of 80% at a 5% significance level, a total of 39 patients would be required for this study considering a 10% drop-out rate. Predicted survival after salvage surgery was based on a historical control sample of 71 patients with recurrent HNSCC who underwent salvage surgery at the University of Cincinnati between 2008-2017. Patient characteristics of the historical sample were compared to the trial group by 2-sided Fisher’s exact test for all categorical variables and Wilcoxon rank-sum test for age (Supplemental Table 1).

OS was calculated from date of salvage surgery or date of first nivolumab (per protocol) and defined as being alive at the time of censoring. Patients were followed for survival for 2 years after the completion of therapy or if recurrent disease, indefinitely until study completion. The Kaplan-Meier method was used to analyze DFS (and OS), and the median DFS (and OS) with its associated 95% confidence intervals (CI) were calculated. All secondary endpoints were summarized using frequencies and proportions.

Biomarker Assessment:

Where available, p16 status was determined by immunohistochemistry (IHC) according to standard pathologic scoring (moderate to strong cytoplasmic and nuclear staining in at least

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70% of tumor cells). In-Situ hybridization for HPV High risk genotypes (16/18/31/33/51) was conducted by Cincinnati Children's Hospital Research Core. In-situ hybridization scoring was done by certified pathologist where any specific nuclear staining was considered positive. Where available, HPV16/18 was also detected using the Caris pipeline, which includes 39 unique baits to detect HPV16 and 50 unique baits to detect HPV18 out of a total of 2360 total pathogen baits. The threshold for positive is ≥100 reads for either HPV16 or HPV18.

Programmed death ligand-1 (PD-L1) testing of the recurrent tumor specimen by IHC was performed by Caris Life Sciences with monoclonal antibodies 22c3 (n=31), where PD-L1 positive was defined as a combined positive score (CPS) ≥1 and with 28-8 (n=3) where PD-L1 positive was defined as ≥1+ staining intensity and ≥1% of cells stained. The threshold to define TMB-high (TMB-H) was greater than or equal to 10 mutations/MB based on the KEYNOTE-158 pembrolizumab trial[17].

Surgical Pathology Risk Assessment:

Pathological features were assessed on the salvage surgical specimen. Positive surgical margin (defined as "ink on tumor") and extracapsular extension were considered high risk features. Other pathological features assessed included close surgical margins (defined as ≤5mm), perineural invasion, lymphovascular invasion, and >5 lymph nodes involved.

Data Availability:

Raw data for next generation sequencing, TMB calculation, PD-L1 staining, and HPV 16/18 analysis were generated in a core facility (Caris Life Sciences). Analyzed patient-level data is included in the data supplement table 4.

RESULTS:

Patients

Between February 2018 and February 2020, 39 patients were enrolled. The median interval between salvage surgery and first nivolumab dose was 55 days (7-75 days). Baseline characteristics of the study group are shown in Table 1. The median age was 68 years (49-85). The majority were male (69%) and white (87%). Most common primary disease sites included the larynx (41%) and oral cavity (36%) and majority had recurrent T3-T4 disease (51%). Of the 39 patients enrolled, 62% had a >10 pack year tobacco smoking history and 21% had a history of alcohol use. 18 (46%) patients had high-risk pathologic features (positive margins and/or ENE) at time of salvage surgery. 36 patients had p16 status evaluable, of which, 10 (28%) were positive. 34 patients had evaluable PD-L1 staining. 28 (72%) were positive (≥ CPS 1 by 22c3) or (≥1+ and ≥1% staining by 28.8).

Regarding prior therapies for HNSCC, all patients had received radiation in their prior treatment course and were not eligible for further radiation (Table 1). 16/39 (41%) of patients received prior surgery for their HNSCC. This included 11/14 oral cavity patients who received surgery +/− adjuvant RT or CRT and 1 patient who received definitive RT followed by salvage surgery prior to enrollment on this trial (Table S1). The oral cavity

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group included 5 patients who had more than one HNSCC surgery prior to the salvage resection in this study but all received RT prior to enrollment at some point.

For patients with laryngeal cancer, 14/17 (82%) had definitive CRT, while 3/17 (18%) received definitive RT. One patient treated with definitive RT had a salvage partial laryngectomy prior to enrollment on this trial, where he received a total laryngectomy. Similarly, for patients with oropharyngeal HNSCC, 4/8 (50%) received definitive CRT, 3/8 (37.5%) received definitive RT, and 1/8 (12.5%) received surgery followed by adjuvant CRT. 2 patients with oropharyngeal cancer that were treated with definitive RT and definitive CRT had a prior recurrence treated with salvage resection. One of these patients received a second course of adjuvant re-irradiation prior to subsequent salvage resection relevant to this study.

When comparing baseline demographics of our study group to the historical control group, the trial group was older (median age 68 years vs 61 years, p=0.0124) and had fewer patients with the intermediate risk factor close (≤5 mm) margins (25% vs 62%, p=0.0064). There were no significant differences in other baseline demographics or overall pathologic risk assessment (Table S2).

Efficacy

As of data cutoff (October 22, 2021) median follow up was 22.1 months. Among all patients included in the analysis (n=39), median 2-year survival was not reached, and the 2-year DFS rate from the time of surgery was 71.4% (95% CI 57.8-88.1%). This was significantly higher than the historical control group, whose 2-year DFS rate was 41% (95% CI 30.5-54.1%) (Figure 1a). 2-year DFS measured per-protocol from date of first nivolumab treatment was nearly identical at 71.37% (95% CI 57.8-88.8%) which was sufficient to reject the null hypothesis of 2-year DFS <38%. 2-year OS from the date of salvage surgery in the nivolumab-treated study group was 77.7% (95%CI 64.1-94.2%) was also longer than the historical control group where 2-year OS rate was 57.8% (95% CI 47.2-70.8%), though this did not reach statistical significance(p=0.1) (Figure 1b).

10 patients (26%) experienced recurrent HNSCC during the study follow up period. All 10 patients experienced locoregional failure while 2 patients also developed synchronous metastatic disease. In addition, one patient developed biopsy-proven metastatic non-small cell lung cancer. Among the 10 patients that recurred, 6 had high- risk pathologic features (either ENE or positive margins) at the time of salvage surgery. In contrast, 39% of patients without recurrence had high-risk pathologic features. 4 patients with recurrent disease displayed no high-risk pathologic features at recurrence however all 4 displayed one or more intermediate risk features including a close surgical margin (n=2), perineural invasion (n=2), lymphovascular invasion (n=3), and/or >2 lymph nodes involved (n=1). Site of disease, pathologic risk, PD-L1 status, and TMB for all patients that progressed while on study can be found in (Table S3).

Consistent with HNSCC standard-of-care, routine chest imaging for detection of asymptomatic pulmonary metastasis was not required. However, most patients had chest imaging performed during survival follow up. All patients who recurred locally had chest imaging. Among the 28 patients that were disease-free at the time of censoring, 5 patients

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had no chest imaging during study follow up. This includes 3 patients that withdrew consent early in the treatment course and 2 patients with oropharyngeal cancer that are alive and free of clinical evidence of disease. 9/28 (32%) disease-free survivors had negative chest imaging within 3 months of the reported disease-free analysis and 4/28 (14%) within 6 month of survival analysis. 10/28 (36%) had negative chest imaging that were >6 months prior to last survival assessment.

Correlates of survival

There was no significant difference in survival in study participants with or without high-risk pathologic features at the time of salvage surgery (DFS p=0.42; OS p=0.09) (Figure 2 a, b). Similarly, among the 36 patients with known P16 status, there was no significant difference between DFS or OS between P16 positive and negative patients (Figure 2 c, d). Where available, HPV In-Situ Hybridization was conducted to confirm HPV-related disease. There was less than 10% discordance between p16 and HPV status. 3 cases were P16 positive and HPV-ISH negative. One of these cases was positive for HPV16 by Caris analysis. For detailed results of P16, High-risk HPV-ISH, and HPV 16/18 analysis by Caris, see Supplementary Table S4.

34 patients had PD-L1 testing available for analysis. There was no significant difference in DFS (Figure 3a) between PD-L1 positive and negative patients (p=0.56). High expression of PD-L1 (CPS ≥10 or 3+ staining by 28.8) was likewise not predictive of DFS (Figure 3b) in the study population (p=0.31). We also assessed PD-L1 expression as a continuous variable. By Cox proportional hazard model, there was no significant correlation between PD-L1 score and DFS HR=1.01 (0.99-1.3, p=0.275) or OS HR=1.0 (95% CI 0.97-1.03, p=0.9781).

There was an indication of improved DFS in patients with high TMB but this was statistically non-significant (p=0.083), where remarkably the 9 patients with ≥10 mutations/MB did not recur during the follow up period (Figure 3c and d).

It was not the primary hypothesis of this study to detect survival differences among subsites of HNSCC and the study was too small to determine any subgroup effects. We saw no significant differences or patterns of recurrence among patients with laryngeal, oropharyngeal, or oral cavity tumors in our exploratory analysis (Figure S1).

Toxicity:

We assessed safety in all patients who received at least one dose of study drug. Adjuvant nivolumab after salvage surgery for recurrent HNSCC was well tolerated. 27/39 patients (69%) completed all planned cycles of nivolumab, 3/39 (7.6%) did not complete due to treatment related adverse events (TRAEs), 7/39 (18%) had progression of disease while on treatment, and 2 patients withdrew study consent prior to completion of adjuvant nivolumab Supplemental Figure 2.

31/39 (79.5%) patients experienced TRAEs, the most common of which were grade 1-2 hypothyroidism (13%), fatigue (31%), and pruritus (18%). Grade 3-4 TRAEs were rare, occurring in 3/39 (7.7%) patients and included diarrhea, mucositis, and arthralgia (Table 2). 3/39 (8%) required treatment discontinuation due to side effects. There were no grade 4

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or 5 TRAEs and no treatment-related deaths occurred during this study follow-up period. The majority (80%) of immunotherapy-related adverse events occurred during the first 3 cycles of nivolumab therapy, while new TRAEs decreased in subsequent cycles. One patient developed new onset arthralgia and myalgia in the 30 day post-treatment follow up window, otherwise, there were no delayed TRAEs or SAEs observed. A full list of all TRAEs may be found in (Table S5).

DISCUSSION:

The advent of immunotherapy has revolutionized the treatment paradigm of HNSCC and PD-1 inhibitors have significantly prolonged survival for recurrent and metastatic HNSCC patients undergoing palliative systemic therapy[18]. Recent studies have also shown a benefit to adjuvant PD-1 inhibitors when added to adjuvant RT or CRT in high-risk HNSCC patients in the first line setting[19-21]. Therefore, we hypothesized that adjuvant nivolumab after salvage surgery would improve the 2-year DFS and show a favorable toxicity profile similar to the metastatic setting. In this phase II single-arm study, we report that among 39 evaluable patients with locally-recurrent HNSCC undergoing curative intent salvage surgery and adjuvant nivolumab, there was a very favorable 2-year DFS rate of 71.4% (95% CI 57.8-88.1%) and the 2-year OS rate was 77.7% (95%CI 64.1-94.2%). We compared DFS and OS with a historical control sample with similar baseline characteristics (Table S1). The DFS and OS distributions were significantly higher when compared to the historical control sample where 2-year DFS and OS were 40.6% (95% CI 30.5-51.3) and 57.8% (95% CI 47.2-70.8%) respectively [9].

Secondary endpoint analyses included safety and the ability to complete all planned cycles of nivolumab. We found that adjuvant nivolumab was well-tolerated. Grade 3-4 events were rare (10%) and consistent with the grade 3-4 AE rate in the metastatic setting[12, 14]. 3 patients (8%) discontinued therapy due to immunotherapy-related adverse events. Of note, the patient with grade-3 diarrhea had a remote history of colitis of unknown etiology and the patient with grade-3 mucositis had a history of well-controlled oral lichen planus, suggesting possible risk factors for the development of these TRAEs.

We undertook multiple exploratory subgroup analyses to identify factors affecting survival after salvage surgery and adjuvant nivolumab. In contrast to our historical control cohort, we saw no significant difference in OS or DFS based on pathologic risk or P16 status, two of the most well-established prognostic indicators in HNSCC. Although this signal-finding study was not designed for subgroup analyses and therefore these results should be interpreted with caution, the similar improvement in survival among all risk groups and the overall tolerability of adjuvant PD-1 supports the inclusion of patients with a broad range of post-surgical risk factors in future phase III clinical trials of adjuvant immunotherapy in the salvage setting.

Interestingly, PD-L1 expression was not predictive of early disease progression after salvage surgery. In fact, of the 6 patients with very early recurrence of HNSCC (either on treatment or shortly after completion of adjuvant nivolumab) and evaluable PD-L1 staining, all 6 had PD-L1 positive disease and 4/6 had high PD-L1 expression (CPS ≥10 or 3+ staining by

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28.8) . The performance of PD-L1 as a predictive biomarker for PD-1 therapy in metastatic and recurrent HNSCC has been somewhat lackluster and, at best, context dependent[22]. Although we are cautious to over-interpret these findings in such few patients, we note that in a recent phase II study of neoadjuvant and adjuvant nivolumab and the anti-KIR antibody lirilumab following salvage resection in 28 high-risk HNSCC patients, there was likewise no significant correlation between PD-L1 positivity and DFS[16]. Together these data strongly suggest that PD-L1 expression may not be a useful marker of response to nivolumab in the adjuvant setting. While the search for molecular correlates of PD-1 response in both metastatic HNSCC and the adjuvant setting is ongoing, the 100% survival rate among TMB high (≥10 mutations/MB) in our study is an intriguing finding worthy of further investigation.

The patterns of recurrence in the study group were overall consistent with the known predilection of HNSCC to recur locally due to a field cancerization effect. We would, however, like to emphasize the very low rate of distant failures (seen in 2/39 patients) in this multiply recurrent HNSCC patient population. Although routine surveillance imaging for asymptomatic patients was not required per study protocol and done at the treating investigators discretion, at the time of analysis 46% of disease-free survivors had negative chest imaging in the previous 6 months and all patients had systemic imaging at time of progression. However, it should be noted that since this trial did not include standardized asymptomatic chest imaging, but rather relied on standard-of-care imaging which varies by institution and provider, patients with asymptomatic metastatic disease may have gone undetected. While this imaging approach is similar to our historical group and many published retrospective series, this remains a limitation.

Among the patients with recurrence, 9/11 (82%) experienced early progression—either while on adjuvant nivolumab therapy or within 6 months of completing therapy. This is not likely due to immunotherapy-induced hyperprogression, as we saw a similar rate of early recurrence in the historical group. Median OS among relapsed patients in this trial was 10 months. This pattern of early local recurrence emphasizes the primacy of local control in the relapsed HNSCC setting and raises the enthusiasm for ongoing trials investigating novel combinations with PD-1 inhibitors in salvage settings such as interstitial brachytherapy and intraoperative radiation during salvage surgery (NCT04340258 and NCT04754321). The addition of adjuvant RT, where tolerated, could provide additional local control and perhaps synergize with immunotherapy.

Limitations of the study include the single-arm design with the use of a historical control sample treated at our institution between 2008-2017. Although the groups were similar in most regards, the historical sample was significantly younger and had a higher incidence of close surgical margins. Most importantly, due to the treatment era of the historical data, p16 status is unknown for a significant number of historical control patients, and pathologic stage at recurrence for the control group is not available for comparison. In addition, the control sample evaluated all patients who underwent salvage surgery, whereas our study enrolled fit patients evaluated within 6 weeks of salvage surgery. Patients with surgical complications affecting performance status or with clinical evidence of disease progression were excluded from this study, perhaps resulting in an overall higher performance status

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study group. Finally, although the median follow-up of just over 2 years covers the time of highest risk for HNSCC recurrence, there are some late relapses which are not captured here.

Outcomes for recurrent HNSCC vary dramatically by study and subsite[23] with recurrent laryngeal cancers having superior survival to oral cavity and oropharyngeal cancers. The 2-year DFS of 71% we observed in our study population compares favorably to other published series who report 2-year DFS rates between 30-40%. A frequently sited 2017 retrospective by Hamoir et al. reported a 2-year DFS rate of 56% and found that oropharyngeal primary was an independent risk factor for failure of salvage surgery. In comparison to our study group, there were few oral cavity patients (4% v 36%) and 9% of patients had not received prior radiation.[24] A 2020 study by Patil et al. found a 2-year DFS rate of 50.9%, but importantly included 9 patients who underwent adjuvant radiation or chemotherapy following salvage resection[25]. A recent multi-institutional phase I/II trial evaluating the benefit of intraoperative CS-131 brachytherapy reported a historical control 2-year loco/regional DFS rate of 40%.[26]

Additional confounding factors which may limit the interpretation of the disease-free survival in the study population include a high rate (100%) of P-16 positive disease in the oropharynx patients. This has been associated with improved outcomes in both the primary and recurrent setting and HPV status was not assessed in either our control group or many benchmark historical series due to the lack of HPV testing in the treatment era.

Overall, this study suggests that adjuvant PD-1 inhibition after salvage resection is a well-tolerated approach which may improve outcomes for patients with locally recurrent HNSCC. Randomized controlled trials in this setting will be required to establish the clinical efficacy of adjuvant nivolumab after salvage surgery. Careful and thorough analysis of patient, pathologic, and molecular correlates of response in a larger patient cohort will further inform patient selection and rational combinations to improve local control.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Translational Relevance:

Outcomes for patients with locally-recurrent head and neck squamous cell carcinoma (HNSCC) remain poor. Although salvage surgery is currently the standard of care, surgery fails to achieve disease control in more than half of patients. To date, no adjuvant therapy has been shown to provide survival benefit after salvage resection. Here we report the results of a phase II open-labeled trial of adjuvant nivolumab after salvage resection for recurrent HNSCC. In this study, we found that adjuvant nivolumab was well-tolerated. 2-year disease-free survival after following adjuvant nivolumab was 71.4% (95% CI 57.8-88.1), which is significantly longer than a historical control sample with similar baseline characteristics. Further study in randomized controlled trials is warranted to establish clinical efficacy.

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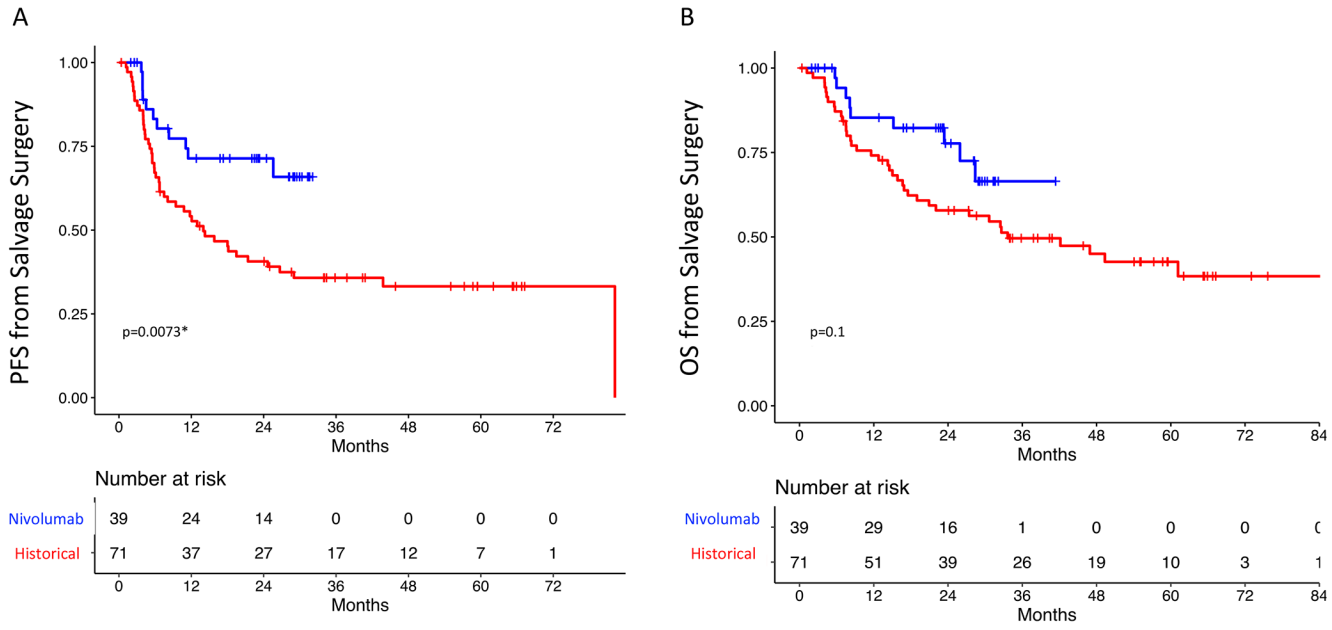

Figure 1. Survival Outcomes for Recurrent HNSCC Patients after Salvage Surgery

Kaplan-Meier curves showing disease-free survival (A) and overall survival (B) of the study group and historical controls measured in months from the date of salvage surgery to disease recurrence (A) or last known day alive (B). Subjects were censored at their last known medical contact. * Indicates statistical significance.

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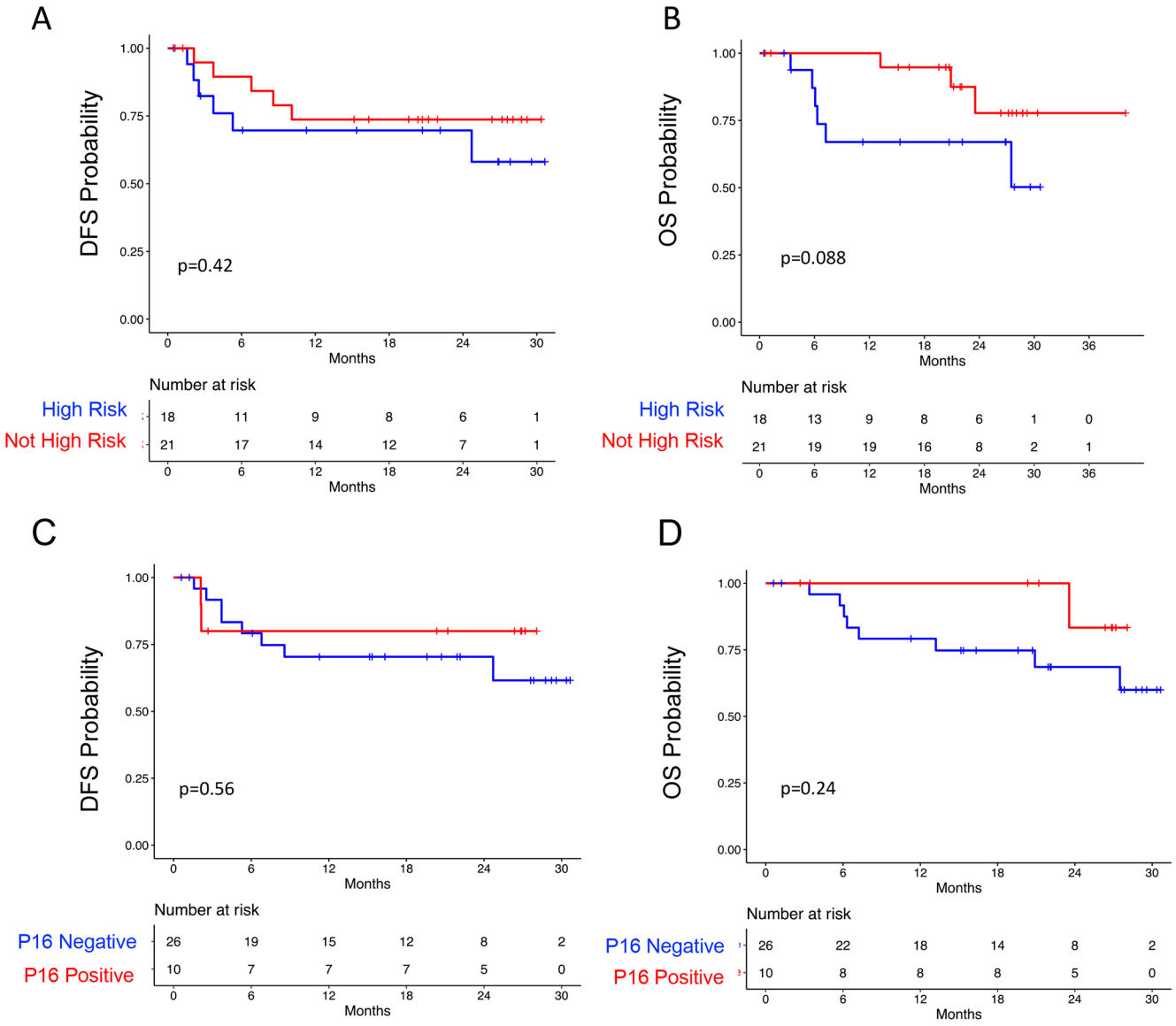

Figure 2. Survival Outcomes by Pathologic Risk and P16 Status

Kaplan-Meier curves showing disease-free survival (A) and overall survival (B) of the study group measured in months from the start of nivolumab therapy stratified by Pathologic Risk. (C and D) Disease free survival and overall survival of the study group stratified by P16 status.

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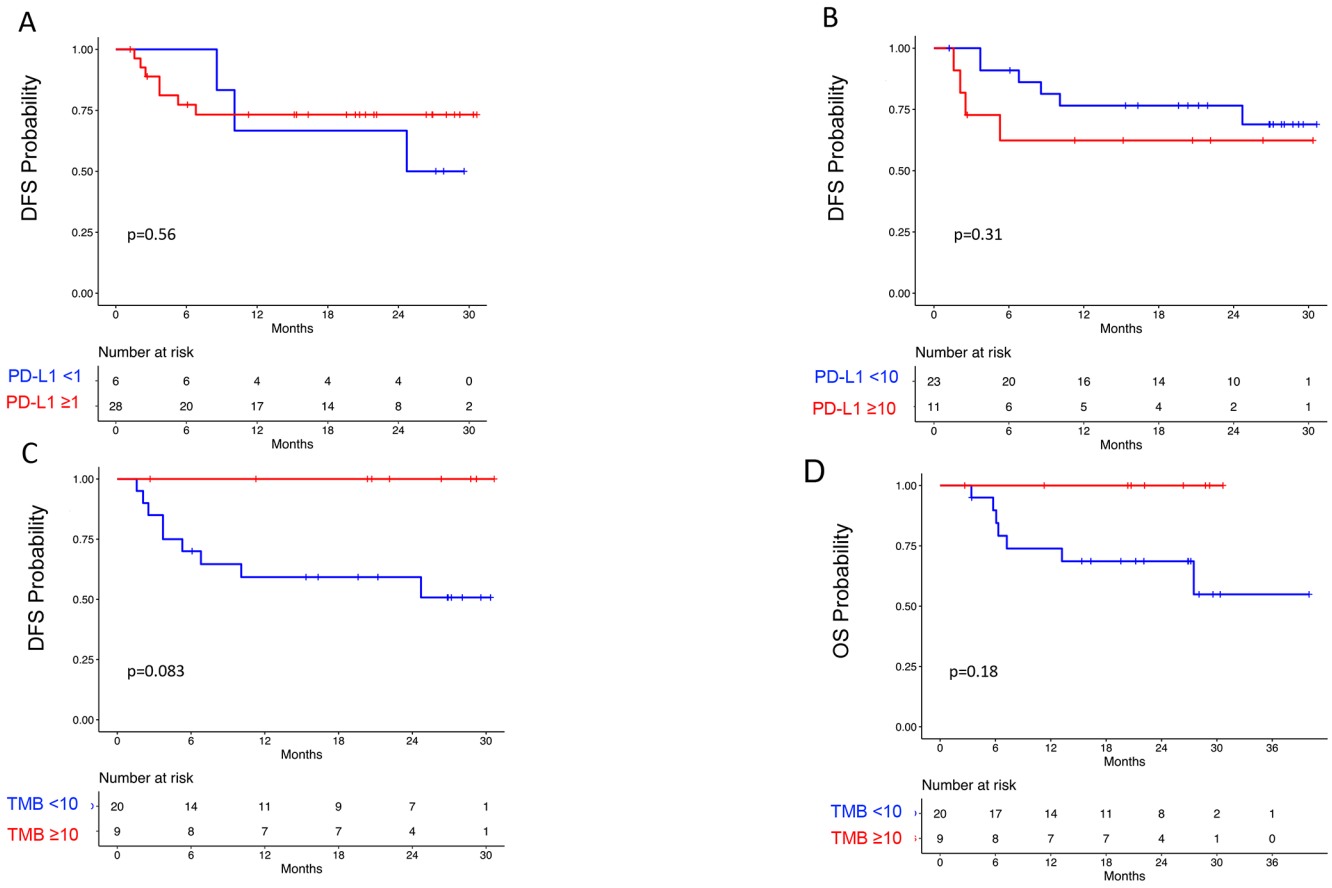

Figure 3: Disease-free Survival of the Study Group Stratified by PD-L1 Status and Tumor Mutational Burden.

Kaplan-Meier curves showing disease-free survival of the study group measured in months from the start of nivolumab therapy and stratified by PD-L1 expression (A) PD-L1 zero vs PD-L1 ≥1 (B) PD-L1 ≥10 vs all others. (C) disease-free survival and (D) overall survival of the study group stratified by tumor mutational burden ≥10 vs all others.

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Table 1.

Baseline Characteristics of the Study Group (n=39)

	No. (%)
Median Age y, (range)	68 (49 - 85)
Sex	
Male	27 (69)
Female	12 (31)
Race	
White	34 (87)
African American	3 (8)
Asian	2 (5)
Ethnicity	
Non-Hispanic	39 (100)
Smoking History (> 10 packs per year)	
Yes	24 (62)
No	15 (39)
Alcohol History (> 5 drinks per week)	
Yes	8 (21)
No	31 (78)
Primary Disease Site	
Larynx	17 (41)
Oral Cavity	14 (36)
Oropharynx	8 (20)
P16	
Positive	10 (28)
Negative	26 (67)
Unknown	3 (8)
Primary Therapy	
Definitive CRT	20 (51)
Definitive RT	7 (18)
Surgery + Adjuvant RT	8 (21)
Surgery + Adjuvant CRT	4 (10)
Prior Salvage Therapies	
Salvage Surgery	9 (23)
Re-irradiation	1 (3)
ECOG Performance Status	
0 – Fully active without restriction	14 (36)
1 – Activity restricted; ambulatory; “light work only”	21 (54)
2 – Ambulatory; all self-care; no work activities; up < 50% of waking hours	4 (10)
Pathologic Tumor Stage at Recurrence	

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	No. (%)
Tx	1 (3)
T0	1 (3)
T1	7 (18)
T2	10 (26)
T3	9 (23)
T4	11 (28)
Pathologic Nodal Stage at Recurrence	
Nx	4 (10)
N0	23 (59)
N1	5 (13)
N2	3 (8)
N3	4 (10)
M Stage at Recurrence	
M0	38 (97)
M1	1 (3)
Positive Margins	
Yes	10 (26)
No	29 (74)
Extranodal Extension	
Yes	11 (39)
No	28 (72)
Close Margins (<5mm)	
Yes	10 (25)
No	20(69)
Perineural Invasion	
Yes	13 (33)
No	26 (67)
Lymphovascular Invasion	
Yes	10 (26)
No	29 (74)
>2 Lymph nodes Involved	
Yes	3 (8)
No	36 (92)
Risk Stratification	
High Risk	18 (46)
Not High Risk	21 (54)
PD-L1 Positive	
Yes	28 (72)
No	6 (15)

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	No. (%)
Unknown	5 (13)

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Table 2.

Immunotherapy-related Adverse Events

	Grade 1-2	Grade 3-4	Any Grade
Any AE	31 (80)	3 (8)	31 (80)
Endocrine			
Hypothyroidism	5 (13)		5 (13)
Gastrointestinal Disorders			
Diarrhea	2 (5)	1 (3)	3 (8)
Mucositis oral		1 (3)	1 (3)
Nausea	2 (5)		2 (5)
General Disorders and Administration Site Conditions			
Chills	2 (5)		2 (5)
Edema limbs	2 (5)		2 (5)
Fatigue	12 (31)		12 (31)
Flu like symptoms	2 (5)		2 (5)
Investigations			
Weight loss	3 (8)		3 (8)
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	4 (10)	1 (3)	5 (13)
Myalgia	2 (5)		2 (5)
Nervous System Disorders			
Headache	2 (5)		2 (5)
Paresthesia	2 (5)		2 (5)
Respiratory, Thoracic and Mediastinal Disorder			
Cough	2 (5)		2 (5)
Skin and Subcutaneous Tissue Disorders			
Pruritis	7 (18)		7 (18)
Rash	7 (13)		7 (18)

Frequency of immunotherapy-related adverse events including grade 1-2 adverse events experienced by >5% of trial participants and all grade 3-4 immunotherapy-related adverse events. For a full list of all adverse events see supplemental table 5.