Neoadjuvant and Adjuvant Nivolumab and Lirilumab in Patients with Recurrent, Resectable Squamous Cell Carcinoma of the Head and Neck

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ABSTRACT

Purpose: Surgery often represents the best chance for disease control in locoregionally recurrent squamous cell carcinoma of the head and neck (SCCHN). We investigated dual immune-checkpoint inhibition [anti–PD-1, nivolumab (N), and anti-KIR, lirilumab (L)] before and after salvage surgery to improve disease-free survival (DFS).

Patients and Methods: In this phase II study, patients received N (240 mg) + L (240 mg) 7 to 21 days before surgery, followed by six cycles of adjuvant N + L. Primary endpoint was 1-year DFS; secondary endpoints were safety, pre-op radiologic response, and overall survival (OS). Correlatives included tumor sequencing, PD-L1 scoring, and immunoprofiling.

Results: Among 28 patients, the median age was 66, 86% were smokers; primary site: 9 oral cavity, 9 oropharynx, and 10 larynx/hypopharynx; 96% had prior radiation. There were no delays to surgery. Grade 3+ adverse events: 11%. At the time of surgery, 96% had stable disease radiologically, one had progression. Pathologic response to N + L was observed in 43% (12/28): 4/28 (14%) major (tumor viability, TV ≤ 10%) and 8/28 (29%) partial (TV ≤ 50%). PD-L1 combined positive score (CPS) at surgery was similar regardless of pathologic response ($P = 0.71$). Thirteen (46%) recurred (loco-regional = 10, distant = 3). Five of 28 (18%) had positive margins, 4 later recurred. At median follow-up of 22.8 months, 1-year DFS was 55.2% (95% CI, 34.8–71.7) and 1-year OS was 85.7% (95% CI, 66.3–94.4). Two-year DFS and OS were 64% and 80% among pathologic responders.

Conclusions: (Neo)adjuvant N + L was well tolerated, with a 43% pathologic response rate. We observed favorable DFS and excellent 2-year OS among high-risk, previously treated patients exhibiting a pathologic response. Further evaluation of this strategy is warranted.

See related commentary by Sacco and Cohen, p. 435

Introduction

Despite multimodality curative approaches to treat patients with squamous cell carcinoma of the head and neck (SCCHN), locoregional recurrence (LRR) is not uncommon, affecting up to 50% of patients depending on individual clinical risk factors and mucosal subsites of disease (1, 2). This should be distinguished from a second head and neck primary, when feasible. Recurrent SCCHN contributes to significant morbidity and portends overall poor survival, reflecting a situation that is difficult to treat owing to the effects of prior therapy (surgery, radiation, and/or chemotherapy) on the delicate structures of the head and neck (3). An important part of the evaluation of LRR includes the anatomy involved, the volume of disease, and the proximity of recurrence to a previously irradiated area.

Individuals with LRR confined to the head and neck may derive benefit from salvage surgery and/or reirradiation (reRT) with or without radiosensitizing chemotherapy. Five-year survival outcomes for this recurrent population undergoing salvage surgery ranges from 11% to 40% in older studies (4–10). When selecting patients for salvage surgery, there are several factors linked with poor outcomes: a short initial disease-free interval (DFI), a hypopharyngeal recurrence, and those patients with significant medical comorbidities (11, 12). Following salvage resection, the addition of postoperative reRT might improve locoregional control (LRC) but has not been shown to improve overall survival (13).

Newer approaches have shown favorable safety and evidence of pathologic response when using immune-checkpoint inhibitors as neoadjuvant therapy prior to upfront, curative-intent surgery in resectable SCCHN (14–19). These early trials have collectively shown

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Translational Relevance

This open-label, single-arm, nonrandomized, multicenter phase II trial using neoadjuvant nivolumab and lirilumab before and after salvage surgical resection is, to our knowledge, the first study to evaluate immune-checkpoint blockade as a therapeutic strategy for locoregionally recurrent, surgically salvageable head and neck cancer. Our findings of substantial rates of pathologic response (43%), excellent safety and tolerability, and overall encouraging survival outcomes in heavily pretreated patients with locoregionally recurrent squamous cell carcinoma of the head and neck (SCCHN) highlight the promising activity of immune-checkpoint blockade in this setting regardless of PD-L1 status—particularly when considering the limitations of reirradiation. This approach warrants further investigation as a therapeutic strategy for recurrent, resectable SCCHN.

pathologic response rates approaching 50% using programmed cell death protein-1 (PD-1) inhibition alone or in combination, favoring two doses over one in the neoadjuvant setting (20)—with the randomized, placebo-controlled phase III KEYNOTE-689 study ongoing in this population (NCT03765918) to evaluate major pathologic response (MPR) and event-free survival.

We hypothesized that integrating a combined neoadjuvant and adjuvant immunotherapy strategy around salvage surgery for this high-risk population would improve outcomes. Building on prior available data that supported the role of the PD-1 inhibitor nivolumab in platinum-refractory, recurrent SCCHN (21), we combined this agent with the anti-killer immunoglobulin-like receptor (KIR) antibody lirilumab. Lirilumab blocks another negative immune-checkpoint receptor on the surface of natural killer (NK) cells, which are important in innate immunity. NK cells are heavily infiltrated in the SCCHN tumor microenvironment (TME) (22, 23), can coexpress PD-1, and further mediate cellular cytotoxicity (24). At the time this study was conceptualized, the combination of nivolumab and lirilumab preliminarily demonstrated a 24.1% (7/29) objective response rate in an early-phase study that included advanced SCCHN among other solid tumor patients (25). Based on these findings, we proposed a phase II study of (neo)adjuvant dual anti–PD-1/KIR immune-checkpoint blockade among recurrent, surgically resectable SCCHN patients to improve disease-free survival.

Patients and Methods

Trial design and patients

This was an open-label, single-arm, multicenter phase II trial conducted at the Dana-Farber Cancer Institute (DFCI; Boston, MA), Beth Israel Deaconess Medical Center (BIDMC; Boston, MA), and Boston Medical Center (BMC; Boston, MA). There was no randomization. Patients with pathologically confirmed locoregionally recurrent SCCHN arising from any primary mucosal subsite including oral cavity, oropharynx, larynx or hypopharynx were eligible if they had a DFI >8 weeks after completion of prior therapy, were 18 years or older, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, had adequate organ and bone marrow function, and were deemed a candidate for salvage surgery. Any human papillomavirus (HPV) or smoking status was permitted. Patients with oropharyngeal or unknown primaries were required to undergo p16 immunostaining and/or confirmatory HPV testing. Any prior treatment was permitted as part of curative-intent therapy (surgery, radiation, and/or chemotherapy). Individuals with a significant autoimmune condition or prior immunotherapy exposure were excluded. The study was approved by the DF/HCC institutional review board (IRB; 17-411) and at each participating site, conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines, and registered nationally (ClinicalTrials.gov NCT03341936). Written informed consent was obtained from all subjects prior to study registration.

Treatment and surgery

Participants received nivolumab (240 mg i.v.) followed by lirilumab (240 mg i.v.) one time on the same day between 7 and 21 days prior to their planned salvage surgery date. Each patient then underwent salvage resection, which was to occur no later than 4 weeks from study registration. A single dose of combination immunotherapy pre-op was chosen so as not to delay salvage surgery. The appropriate surgical procedure and neck management was at the discretion of the treating head and neck surgeon(s) and carried out based on pretreatment clinical and radiologic assessment. Patients remained eligible to continue on study regardless of salvage surgery margin status; but reexcision to clear margins was permitted if appropriate. Following salvage surgery, reRT or additional chemotherapy was not permitted on study. During the adjuvant phase, 3 to 8 weeks (timeframe selected to permit adequate post-op recovery) after salvage surgery, patients received nivolumab 240 mg i.v. on days 1 and 15 and lirilumab 240 mg i.v. on day 1 of a 28-day cycle for cycles 1 to 3, followed by nivolumab 240 mg i.v. and lirilumab 240 mg i.v. both on day 1 of a 28-day cycle for cycles 4 to 6. Adjuvant treatment continued for a maximum of six cycles or until disease recurrence, unacceptable toxicity, withdrawal of consent, or death.

Participants were premedicated with standard doses of diphenhydramine, famotidine, and acetaminophen prior to each dose of lirilumab to prevent an infusion reaction. Immunosuppressive medications and doses of corticosteroids >20 mg prednisone equivalent daily within 14 days of starting the study treatment pre-op were prohibited unless being used for immune-related toxicity management.

Efficacy and safety measures

Baseline tumor measurements were obtained within 28 days prior to study registration and performed prior to administration of any study agents. A PET-CT or contrast-enhanced CT imaging of the chest, abdomen, and pelvis was obtained at baseline to rule out distant disease. A contrast-enhanced neck CT or MRI was completed at the time of screening and then repeated 1 to 4 days prior to the planned salvage surgery date (window phase). Target lesions were assessed according to RECIST v1.1 criteria (26). Interval scans (contrast-enhanced neck CT or MRI and a chest CT) were performed every 8 weeks following salvage surgery or as clinically indicated while on adjuvant treatment. After first disease recurrence (locoregional or distant), survival status continued to be assessed every 12 weeks until death or 5 years from the salvage surgical date (whichever occurred first).

Pathologic specimens obtained at the time of salvage surgery were reviewed by two experienced head and neck pathologists (KW and VYJ) blinded to outcome data. Following routine grossing protocols and standard hematoxylin and eosin (H&E) slide preparation, final pathologic evaluation was standardized to document: maximum tumor size, depth of invasion (DOI) if available or applicable, degree of histologic differentiation, margin status (positive noted as involving

the tissue edge or inked margin), the presence or absence of lymphovascular and perineural invasion (LVI and PNI, respectively), and lymph node involvement with size and evidence of extranodal extension (ENE). HPV testing was performed if otherwise unknown and clinically appropriate. As previously described (14, 19), the percentage of nonviable and viable tumor (0–100%, increments of 5) was estimated with tumor regression score (1–3), density of tumor infiltrating lymphocytes (TIL; 1–3), along with the presence or absence of immune exclusion, fibroblastic giant cell reaction (FBGCR), necrosis, fibrosis, and tissue repair granulation or neovascularization. MPR and partial pathologic response (PPR) denoted ≤10% and ≤50% tumor viability in the surgical specimen after neoadjuvant nivolumab and lirilumab, respectively.

Safety evaluations at all study visits included laboratory and adverse event (AE) assessments adhering to NCI Common Terminology Criteria version 4 (CTCAE v4.0; ref. 27). For patients who developed grade 3 or intolerable grade 2 toxicity events, doses of nivolumab and lirilumab could be interrupted, delayed, or discontinued; treatment was resumed once laboratory criteria and attributable toxicities resolved to grade 2 or less. No dose reductions of either study agent were permitted. Patients with a delay in adjuvant treatment dosing >8 weeks were considered for study treatment discontinuation. Subjects were removed from protocol treatment if they developed grade 3 immune-related uveitis or pneumonitis, or any grade 4 toxicity (excluding electrolyte derangements, cytopenias, or elevated amylase or lipase values judged to be non-life-threatening).

Correlative biomarkers

Targeted tumor genomic sequencing of salvage surgical biopsy specimens (requiring four unstained formalin-fixed, paraffin-embedded tissue slides) was conducted using FoundationOne CDx (Foundation Medicine, Inc.) which is clinically and analytically validated for all solid tumors and interrogates 324 DNA genes [and microsatellite instability, tumor mutational burden (TMB) with importance in cancer medicine]. A small subset of patients had in-house targeted massively parallel tumor sequencing (OncoPanel version 3), which targets the full coding regions of 447 genes and selected intronic regions of 60 genes, as previously described (28, 29). This assay calculates TMB by determining the number of nonsynonymous somatic mutations per megabase (Mb) across all genes on the panel. The details of PD-L1 IHC analysis and multiparametric immunoprofiling on peripheral blood and tumor tissue (30, 31) are described in Supplementary Appendix SA.

Trial endpoints and statistical methods

The primary endpoint of the study was 1-year DFS from the time of salvage surgery. A 1-year DFS of 57% was the basis of the null hypothesis (7–9, 32, 33). If >37 DFS events were observed within the first 4 years of trial initiation (assuming $N = 54$ patients were accrued in 2 years and followed for additional 2 years), there was 81% power to say that the trial did not meet its primary endpoint. This design assumed a 30% reduction in hazard rate from 0.5621 to 0.3935 DFS events/person-year of follow-up and under an exponential distribution corresponded to targeting an improvement in 1-year DFS from 57% to 67.5% (using a one sided 10% type 1 error rate and Wald test). DFS was measured from the time of salvage surgery to the earlier of recurrence or death due to any cause. Participants alive without recurrence were censored at date of last disease evaluation. The primary efficacy population included all eligible patients who began protocol treatment.

A secondary endpoint was response rate at time of salvage surgery (ORR) according to RECIST v1.1. This was based on central blinded radiologic review (no confirmation of response required) of imaging before and after neoadjuvant nivolumab and lirilumab just prior to salvage surgery summarized as a proportion with a corresponding exact 95% confidence interval (CI). Additional secondary endpoints included OS from the time of salvage surgery to death due to any cause (participants alive without disease recurrence were censored at date of last follow-up), and safety and tolerability. The Kaplan–Meier method was used to estimate time-to-event endpoints with corresponding 95% CIs for the median or time-specific event time. Exploratory analyses evaluated subgroup analyses (cycles of adjuvant therapy, pathologic response, and margin status), the impact of tumor PD-L1 status (obtained both at the time of recurrence prior to study registration and at the time of salvage surgery), and tumor genomic sequencing parameters on response and survival. Paired tumor and peripheral blood immune profiling was also obtained. Cox proportional hazards models were used to estimate hazard ratios (HR) in subgroup analyses. Wilcoxon signed-rank test (paired) and Wilcoxon rank-sum test (independent) were used, as appropriate, to compare subgroups. Data as of May 2021 were analyzed.

Data availability

The human sequence data generated in this study are not publicly available due to patient privacy requirements but are available upon reasonable request from the corresponding author. Other data generated in this study are available within the article and its supplementary data files.

Results

Administrative summary

Between March 15, 2018, and May 29, 2020, 29 patients were enrolled to the study. Bristol Myers Squibb notified the study team that manufacturing of lirilumab stopped with planned expiration of drug supply in 2021; thus, the trial was closed to accrual early to ensure availability of both nivolumab and lirilumab to all study participants. The trial officially closed on October 30, 2020. All but 1 ($N = 28$) patient began protocol treatment and are included in analyses (one subject withdrew consent prior to receiving neoadjuvant study therapy; see CONSORT flow diagram).

Patient and disease characteristics

The median age was 66 (range, 36–85) with the majority comprised of men (23, 82%), and most were current or former smokers (24, 86%; **Table 1**). Oral cavity, laryngeal, and oropharyngeal (9 each, 32%) primary tumors were equally common. Five of nine (56%) patients with oropharyngeal primary tumors were HPV-positive. Eighteen (64%) were clinically stage III or IV at initial diagnosis of primary disease. All but one patient (27, 96%) received prior head and neck radiation (this subject had declined adjuvant radiation for stage I initial disease prior to recurrence and trial enrollment) and most (19, 68%) had prior chemotherapy or prior surgery (15, 54%) as part of initial treatment. Median DFI prior to study entry was 3.4 years (range, 0.5–26.4), with 12 (43%) having experienced multiple local or regional recurrences (or a second primary) prior to study enrollment. At the time of evaluation for recurrence at trial entry, most had clinical stage T4 tumors (19, 69%) with overall stage III or IV disease most often (25, 89%) with 20 (71%) experiencing local recurrence, 3 (11%) regional or nodal recurrence, and 5 (18%) with both locoregional involvement. The median time from study registration to date of salvage surgery was 14 days (range, 7–28), whereas the median time from the

Table 1. Baseline patient characteristics.

Characteristic	Number of patients (%)[a] $N = 28$
Age, years	66 (36–85)
Gender	
Male	23 (82)
Female	5 (18)
Race and ethnicity	
White/Caucasian	26 (92)
Black	1 (4)
Other	1 (4)
ECOG performance status	
0	12 (43)
1	16 (57)
Smoking history	
Never	4 (14)
Former smoker (>10 pack-years)	22 (79)
Current smoker	2 (7)
Primary site of disease	
Oral cavity	9 (32)
Oropharynx	9 (32)
Larynx	9 (32)
Hypopharynx	1 (4)
Human papillomavirus (HPV) status, $N = 9$	
p16 positive (by IHC)	6 (67)
HPV ISH or PCR positive	5 (56)
Clinical stage[b] at initial diagnosis	
I	3 (11)
II	6 (21)
III	5 (18)
IV (A/B)	13 (46)
Unknown	1 (4)
Prior therapy for initial head and neck cancer diagnosis	
Prior surgery	15 (54)
Prior radiation	27 (96)
Prior chemotherapy	19 (68)
Median time from initial diagnosis to confirmed recurrence, DFI (in years)[c]	3.4 (0.5–26.4)
Recurrent tumor site	
Local	20 (71)
Regional lymph nodes	3 (11)
Both	5 (18)
Clinical staging[b] at recurrence prior to salvage surgery	
T0–2	6 (21)
T3	3 (11)
T4	19 (69)
N0–1	23 (82)
N2	2 (7)
N3	3 (11)
Stages I–II	3 (11)
Stage III	3 (11)
Stage IV (A/B)	22 (79)
Registration to salvage surgery (in days)	14 (7–28)
First dose of immunotherapy to surgery (in days)	13 (6–24)
Pathologic staging after salvage surgery[b]	
Stages I–II	9 (32)
Stage III	5 (18)
Stage IV (A/B)	14 (50)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IHC, immunohistochemistry; ISH, *in situ* hybridization; PCR, polymerase chain reaction; DFI = disease-free interval.

[a]Values are numbers and percentages, except age, median time to recurrence, first visit to surgery, and first dose of immunotherapy to surgery: noted as median and range in parentheses.

[b]American Joint Committee on Cancer (AJCC) 2017 8th edition staging utilized except for HPV^+ oropharynx cancers, which are reported using AJCC 2010 7th edition staging.

[c]If the patient experienced multiple recurrences prior to trial enrollment, the date of completing initial therapy to first recurrence event was recorded.

neoadjuvant dose of nivolumab and lirilumab to salvage surgery was 13 days (range, 6–24).

Efficacy outcomes

At a median follow-up of 22.8 months (range, 9.2–35.7), median DFS was 12.9 months (95% CI, 8.2–27.2+) with a 1-year DFS of 55.2% (95% CI, 34.8–71.7; **Fig. 1**). At the time of analysis, 15 DFS events had occurred with 13 patients (46%) experiencing recurrence (10 locoregional; 3 with distant disease). Median OS was not reached at the time of data cutoff, but 1-year OS was estimated at 85.7% (95% CI, 66.3–94.4) with 7 deaths observed among $N = 28$ patients. Two patients experienced death without recurrence: both endured prolonged hospitalizations after salvage surgery and subsequent clinical decline (**Table 2**). Patients who completed all 6 cycles of adjuvant immunotherapy (HR, 0.20; 95% CI, 0.07–0.56) had improved DFS. Although not statistically significant, those patients achieving a pathologic response (MPR or PPR) had improved DFS (HR 0.42; 95% CI, 0.13–1.33) whereas positive margins at salvage surgery predicted worse outcomes (HR 2.17; 95% CI, 0.69–6.84). DFS among the four patients with MPR at the time of surgery ranged from 3.6 to 27.2 months.

Efficacy: radiologic and pathologic response

Baseline head and neck imaging was compared with repeat scans just prior (1–4 days) to salvage surgery after the single dose of neoadjuvant nivolumab and lirilumab. Overall radiologic response (ORR) was stable disease among 27 (96%; 95% CI, 81.6–99.8%) with 3 (11%) experiencing tumor shrinkage (from −5.6 to −27.1%), and 1 (4%) demonstrating evidence of tumor progression (+36.8%) before surgery (**Fig. 2**). At the time of salvage surgery, 4/28 (14%) demonstrated an MPR to neoadjuvant therapy, whereas 8/28 (29%) demonstrated a PPR, consistent with a 43% overall pathologic response rate (10 in the primary recurrence site, 1 in neck nodes, 1 in both). Using previously defined cutoffs to assess pathologic tumor response (pTR; ref. 22) where (pTR)-1 is 10–49% and pTR-2 is 50% or greater, our cohort demonstrated 50% and 43% (totaling 93%) pTR-1 and pTR-2, respectively.

Combined positive score (CPS) for PD-L1 was reported among all salvage surgical specimens (following immunotherapy exposure) and at registration if a recurrent biopsy specimen was available for testing (23/28, 82%). Scores were similar between patients with MPR or PPR and those with less of a pathologic response to therapy when comparing surgical salvage specimens ($P = 0.71$) or baseline recurrence specimens ($P = 0.73$). Fifteen patients (54%) demonstrated evidence of pathologic downstaging (11 at the primary site; 4 in neck nodes) from their initial clinical and radiographic stage of recurrence to the time of salvage surgery pathologic assessment; 5/15 (33%) patients with pathologic downstaging also had MPR or PPR. Supplementary Table S1 provides detailed clinical staging and pathologic assessments on all subjects, whereas Supplementary Table S2 describes all pathologic response and immunologic data.

Safety and toxicity

There were no delays to salvage surgery (1 patient was out of the 21-day window due to scheduling reasons) among the cohort and therefore no toxicity from neoadjuvant immunotherapy leading to surgical delay. Fatigue was the most commonly reported AE (12, 43%), followed by hypothyroidism (7, 25%), elevated liver function tests (AST: 7, 25%; ALT: 5, 18%), and diarrhea (5, 18%; Supplementary Table S3). No grade 4+ AEs were observed; and no deaths occurred due to study treatment. Seventeen patients (61%) experienced a therapy dose delay during the adjuvant phase of treatment (details

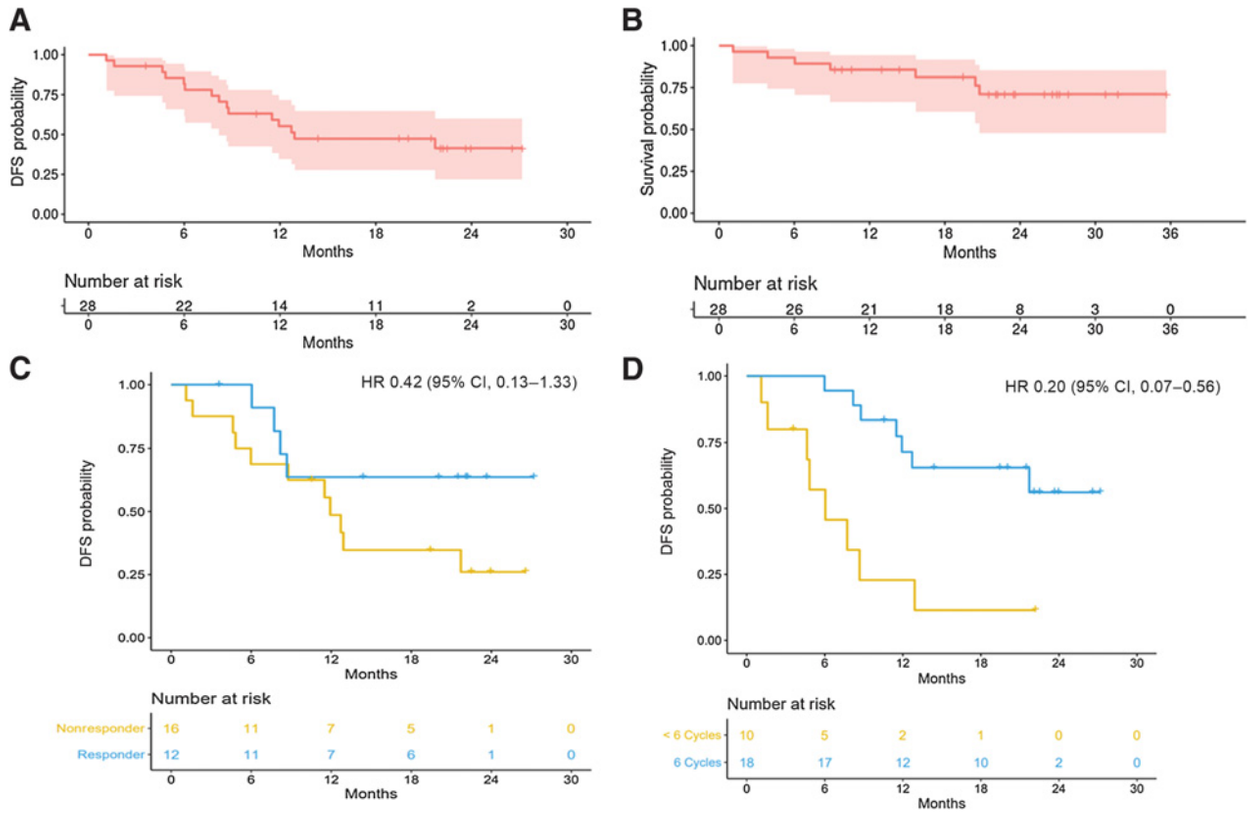

Figure 1.

Kaplan–Meier curves showing (**A**) DFS reported in months from the time of salvage surgery to the first of any disease recurrence, death, or censored at last follow-up. **B,** OS reported in months from the time of salvage surgery to death from any cause, or censored at last follow-up. DFS stratified by (**C**) pathologic response (PPR = partial pathologic response, ≤50% tumor viability; MPR = major pathologic response, ≤10% tumor viability) and (**D**) number of adjuvant cycles of immunotherapy received (maximum of 6).

in Supplementary Table S1). A grade 3 infusion reaction after lirilumab early in the study resulted in an amendment to require premedications prior to infusion in all subsequent patients. Grade 3 generalized muscle weakness and hyponatremia occurred in one patient each; the former noted in one subject resulting in prolonged hospitalization and overall clinical decline leading to death without disease recurrence.

Patterns of recurrence

Thirteen patients (46%) experienced recurrence while on study (**Fig. 3**). Median time from salvage surgery to recurrence (TTR, where deaths without recurrence are censored) was 21.7 months (95% CI, 8.8–27+). Five of 13 (38%) who experienced recurrence later died. Most (90%) with recurrence had oropharyngeal (6/13) or oral cavity (5/13) primary sites of disease. One had radiologic progression (+36.8%) after the single neoadjuvant dose of nivolumab and lirilumab. Three of the 13 were among the subgroup that demonstrated an MPR or PPR to neoadjuvant immunotherapy. Five (18%) patients among the entire cohort had positive margins at the time of salvage surgery (subsite: three oropharynx, two larynx), of which four of five (80%) later experienced disease recurrence. Four (14%) patients had pathologic ENE, of which three (75%) later recurred. In addition, 2 of 13 (15%) recurred while receiving adjuvant immunotherapy on study (both after cycle 4 of 6). Four patients among the entire cohort withdrew consent after salvage surgery and did not start any adjuvant immunotherapy (one of which had elected to come off study to pursue reRT with chemotherapy). Three of these four (75%) patients later experienced disease recurrence. Next-line therapy among the 13 patients with recurrence included: three receiving reRT with or without chemotherapy, five were treated on clinical trials, and two with platinum-taxane chemotherapy; three pursued hospice care.

Molecular correlates of response

All patients underwent targeted tumor genomic profiling of their surgical specimens. **Figure 4** shows the mutational landscape plot among the cohort separated by those who did and did not experience recurrence while on study. *TP53* was the most commonly observed mutation (86%), followed by *CDKN2A* (31%), *TERT* promoter (28%), and *PIK3CA* (21%). Median TMB was 4 (range, 1–11). Although commonly altered tumor genes among the patients with recurrence included *TP53* (70%) and *TERT* promoter (40%), there were no individual mutations occurring more frequently among those who recurred and the remainder of the cohort. Median TMB was similar among those who recurred and those who did not ($P = 0.73$). Additionally, 3/5 (60%) patients with HPV+ oropharyngeal tumors demonstrated a pathologic response.

Immunologic correlates of response

All but one patient (96%, 27/28) had paired peripheral blood sampling before and after immunotherapy exposure; but only six (21%) had paired fresh tissue biopsies before and after neoadjuvant

Table 2. Efficacy measures and reasons for treatment discontinuation.

Efficacy measure	Number of patients, $N = 28$ (%)
Median follow-up (months, range)	22.8 (9.2–35.7)
Median DFS (months, 95% CI)	12.9 (8.2–27.2+)
Number of events	15 (54)[a]
One-year DFS (%, 95% CI)	55.2% (34.8–71.7)
Median OS (months, 95% CI)	NR
Number of events	7 (25)[b]
One-year OS (%, 95% CI)	85.7% (66.3–94.4)
Best ORR to neoadjuvant therapy[c]	
Complete response	0
Partial response	0
Stable disease	27 (96)
Progression of disease	1 (4)
Pathologic response to neoadjuvant therapy	
Major response (≤10% tumor viability)	4 (14)
Partial response (≤50% tumor viability)	8 (29)
Minor response (51%–100% tumor viability)	16 (57)
Reason for study treatment discontinuation	
Completed therapy	18 (64)
Toxicity	0
Noncompliance[d]	3 (11)
Physician discretion[e]	1 (4)
Withdrawal of consent[d]	4 (14)
Recurrence of disease	2 (7)
Death	0

Abbreviations: CI, confidence interval; NR, not reached; +, censored at last follow-up as of data cutoff.

[a]Includes deaths, 5 of 15 patients had recurrence and death whereas 2 of 15 experienced death without recurrence.

[b]Two of seven died without evidence of recurrence.

[c]Determined by RECIST v1.1.

[d]Seven patients with study visit noncompliance or withdrawal of consent were removed from study treatment after declining to return for their adjuvant infusions, citing distance from the institution and resource constraints, not toxicity.

[e]Patient elected to come off study treatment to pursue adjuvant concurrent reirradiation with chemotherapy post-op due to high-risk pathologic features.

immunotherapy for comparison. CD39 expression by TILs, NK T cells, and B cells in the TME increased after neoadjuvant nivolumab and lirilumab exposure, along with the proportion of $CD103^+$ NK cells. CD38 expression by $CD4^+$ and $CD8^+$ circulating peripheral T cells also increased after neoadjuvant immunotherapy exposure ($P < 0.05$; Supplementary Fig. S1). A decline in tumor TIM-3^+ $CD8^+$ T cells (HR 0.74) and total monocyte abundance (HR 0.71) predicted improved survival (DFS; $P < 0.05$). Elevated baseline expression of PD-1 by circulating peripheral $CD4^+$ and $CD8^+$ T cells, and a reduction in T-cell PD-1 (HR 0.88) over the course of immunotherapy treatment was also correlated with outcome (DFS, $P < 0.05$; Supplementary Table S4).

Discussion

To the authors knowledge, this represents the first report of immune-checkpoint inhibition as a therapeutic strategy for locoregionally recurrent, surgically salvageable head and neck cancer. The administration of neoadjuvant and adjuvant combined anti–PD-1/KIR immune-checkpoint blockade was both safe and well tolerated, with no delays to surgery and no patient discontinuing adjuvant therapy for toxicity.

We hypothesized that this (neo)adjuvant dual NK and T-cell immune-checkpoint inhibitor approach before and after salvage surgery would improve the 1-year rate of DFS among this high-risk population. Although the trial closed early due to discontinuation of the anti-KIR lirilumab, among the 28 evaluable subjects we report a 1-year DFS of 55.2% (95% CI, 34.8–71.7) with a favorable 1- and 2-year OS of 85.7% (95% CI, 66.3–94.4) and 71.1% (95% CI, 48–85.3) among the entire cohort, respectively. This high-risk group was composed of mostly former or current smokers, many with HPV-negative disease, with almost all (96%) having received prior head and neck irradiation and presenting with clinical stage IVA/B disease (79%) at the time of trial entry. Further, 43% had experienced a prior locoregional recurrence of their SCCHN before enrollment. Our estimated two-year OS outcomes were favorable compared with those reported in available series describing this population (two-year OS range, 50%–59%; refs. 4–6, 13). Recently presented data using adjuvant PD-1 blockade (nivolumab) for six months after salvage surgery (without neoadjuvant dosing) showed similar two-year OS estimates (34).

In this often multiply recurrent, surgically treated population, pathologic responses (≤50% tumor viability) occurred in 43% of patients receiving neoadjuvant immunotherapy. This is greater than pathologic response rates observed in other recent neoadjuvant studies using immune-checkpoint blockade among newly diagnosed head and neck cancers (14, 19) despite the fact that we adopted a more stringent definition of pathologic response in the present study. Emerging data are attempting to standardize immune-related pathologic response (irPR) reporting, but this has focused on previously untreated patient tumors (35). We acknowledge that prior treatments like radiation might have affected TME findings at salvage surgery. A longer time to surgery during the window phase (6–13 vs. 14–21 days) did not predict pathologic response, but emerging data suggest a second dose of neoadjuvant PD-1 blockade pre-op may increase rates of pTR (20). Of the 12 patients in our study who demonstrated MPR or PPR, only 3 of 12 (25%) later recurred (1 of the 3 had positive margins) and estimated 2-year DFS was 64% (95% CI, 29.7–84.5) and 2-year OS 80% (95% CI, 40.3–94.8) among this subgroup. Of note, five of these 12 individuals came off study before completing all adjuvant immunotherapy (after salvage surgery); one opted to pursue reRT and subsequently experienced concurrent locoregional and distant failure. It is important to recognize that three of four (75%) patients who elected to pursue observation or other treatments without starting any adjuvant immunotherapy later recurred. It is also worth noting that disease recurrence on study was uncommon among larynx and hypopharynx patients (2/10, 20%). These findings suggest that completing the six cycles of adjuvant immunotherapy treatment may be important, particularly for those individuals who demonstrated an initial pathologic response and in the setting of negative surgical margins. Among 10 patients who did not complete all six cycles of adjuvant therapy half had a pathologic response at salvage surgery, but some component of treatment bias must be acknowledged as this subgroup was comprised of many former or current smokers and nearly half had positive margins or ENE.

The question of reRT is challenging and treating physicians must weigh the anticipated morbidity of both the treatment and progression of locoregional disease. One aim of the present study was to determine if a favorable DFS could be achieved without the toxicity of reRT. The addition of postoperative reRT in combination with chemotherapy following surgical salvage has demonstrated some improvement in progression-free survival but not OS in one prospective trial (13), but grade 3–4 late toxicity was 39% at two years among the reRT arm. Some experts favor reRT among those with higher-risk postoperative

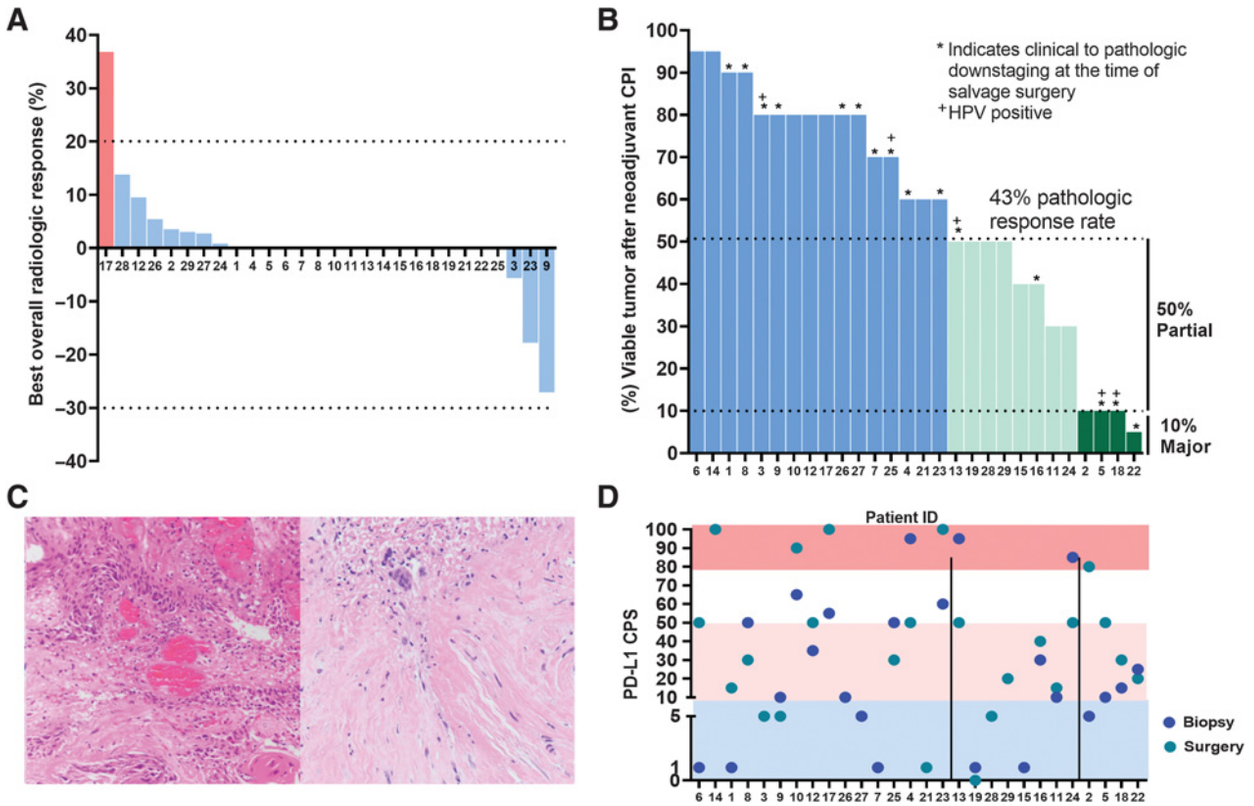

Figure 2.

A, Waterfall plot showing objective radiologic response rate to one dose of neoadjuvant nivolumab plus lirilumab in patients with relapsed, resectable SCCHN (RECIST v1.1). **B,** Viable tumor quantification (%) at the time of salvage surgery following neoadjuvant immunotherapy, arranged by degree of pathologic response (≤50%, partial response; ≤10% major response). HPV, human papillomavirus. **C,** Preimmunotherapy right posterior tongue biopsy (patient ID #22) showing keratinizing, invasive squamous cell carcinoma (200×; left) and a post-op hemi-glossectomy specimen with extensive fibrosis in the prior tumor bed with an area of necrosis and a few multinucleated giant cells noted in the upper left region (200×; right). **D,** Tumor and immune cell PD-L1 expression CPS in both the initial preimmunotherapy recurrence specimen and paired salvage tumor specimen, arranged by descending % tumor viability.

pathologic features (positive margins, ENE) after salvage resection citing a three-year locoregional control rate of 74% and three-year OS of 43% among prospective, well-selected cohorts (36, 37), but recognizing the risk of late toxicities (e.g., pharyngeal dysfunction, vascular compromise, tissue injury or necrosis) even with more modern RT planning and delivery techniques. However, a systematic review of 16 trials and over 500 patients receiving reRT reported a wider variation in two-year OS (24–81%) (38). It seems the dominant pattern of first-failure after reRT is LRR either alone or concurrently with distant failure (32). In the present study, using (neo)adjuvant immunotherapy 10 of 13 (77%) recurrences occurred locoregionally and the majority of patients with positive surgical margins at salvage surgery later recurred (4/5, 80%). The low rate of distant failure on study was notable; perhaps immune-checkpoint interactions in tumor-draining lymph nodes mitigates distant recurrence (39). An argument could be made to incorporate adjuvant reRT (with thoughtful consideration of dose, volume, and technique) in combination with immunotherapy to optimize locoregional control post-salvage surgery particularly among those with positive margins. The use of post-op reRT with immunotherapy is being explored in an actively accruing phase II trial (EA3191) supported by ECOG-ACRIN randomizing patients to reRT with pembrolizumab or platinum, or pembrolizumab alone in a similar population (NCT04671667).

One of our secondary objectives was to gauge the degree of radiologic response to a single dose of dual immune-checkpoint blockade prior to salvage surgery, recognizing the time from dosing to surgery was short at a median of about two weeks. The majority of patients had no appreciable change in tumor measurements by RECIST v1.1 and no objective radiologic responses were observed, but three had evidence of some volume regression (−5.6% to −27.1%; all at the primary site of recurrence, none at nodal sites), though none of these three patients had evidence of pathologic response and all later recurred. The one patient with +36.8% tumor growth during the window phase had no evidence of pathologic response, elected not to receive any adjuvant immunotherapy on study, and later recurred (arguing against any component of pseudoprogression). A recent study using neoadjuvant immune-checkpoint blockade (nivolumab with or without ipilimumab) for newly diagnosed oral cavity cancer reported evidence of radiologic regression (13%), but median time from treatment to surgery was longer at 19 days (14). Taken together, radiologic response did not correlate with pathologic response, except in the isolated case of disease progression during neoadjuvant treatment.

We used a number of correlative analyses to understand how patterns of PD-L1 expression, tumor genomic alterations, and paired tumor and peripheral blood circulating immune parameters

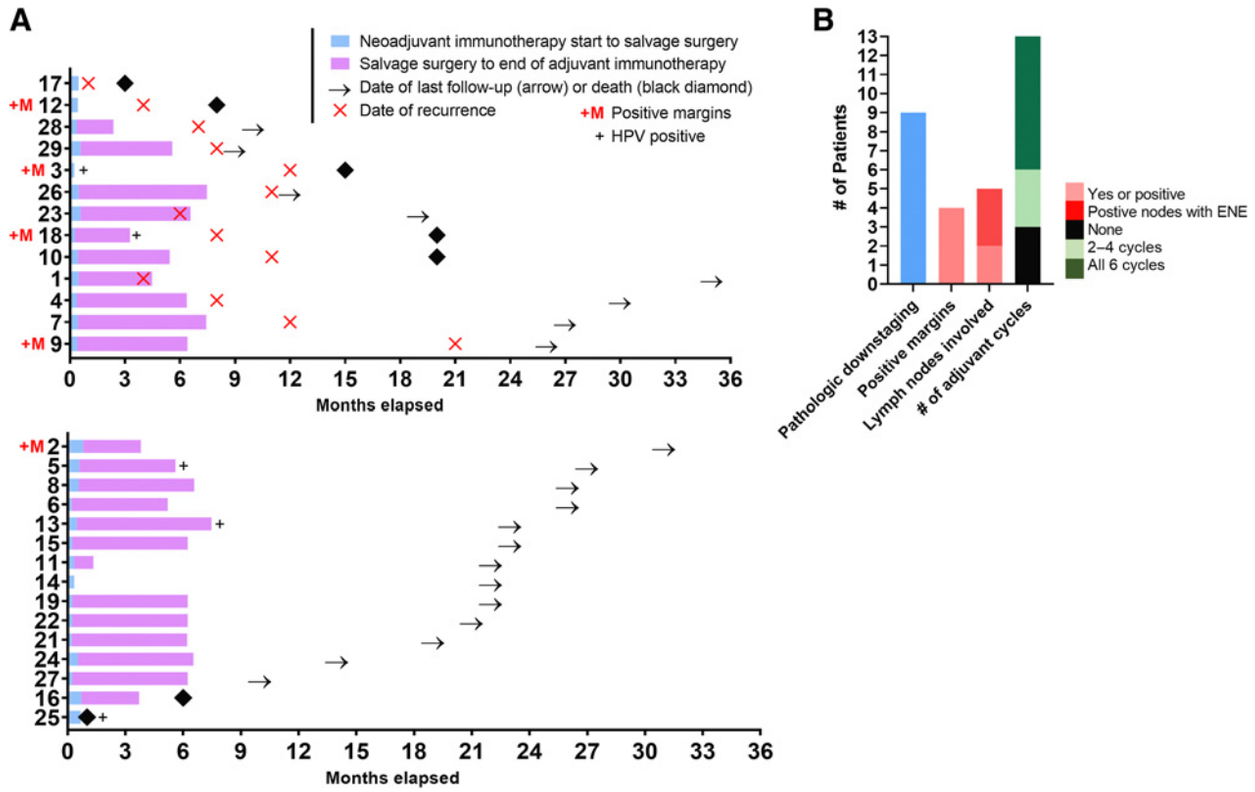

Figure 3.

A, Swimmer plot showing 13 of 28 evaluable patients with evidence of biopsy-proven recurrent disease (above) and $N = 15$ without recurrent disease (below) after (neo)adjuvant immunotherapy followed by salvage surgery and adjuvant immunotherapy for up to six cycles with anti–PD-1/KIR combination therapy. Each row or bar represents an individual study patient with their time from the start of immunotherapy to date of salvage surgery indicated. The time from surgery to the end of up to six cycles of immunotherapy (28-day cycles) is displayed. Positive margin status at the time of salvage surgery (with tumor on ink) is noted. HPV (human papillomavirus)-positive disease is denoted by a "+." The date of biopsy-proven recurrence (if applicable) is plotted along with last known follow-up (censored) or date of death. **B,** Clinicopathologic features of individuals experiencing recurrence ($N = 13$) sorted by pathologic downstaging from pre-op (clinical stage) to post-op (pathologic stage), margin status (positive defined as tumor on ink), lymph node status (ENE = extranodal extension) if sampled, and number (#) of adjuvant cycles of immunotherapy received post-op (six total cycles were planned; 28-day cycle length).

affected response and survival. Owing to tissue availability, we assessed tumor and immune cell PD-L1 expression primarily at the time of salvage surgery but we observed differences in PD-L1 CPS scores between paired pretreatment and posttreatment specimens after a single dose of neoadjuvant immunotherapy. This could reflect sample heterogeneity, assay differences, or changes to the TME after the window phase of treatment. However, median PD-L1 CPS scores at baseline or at salvage surgery were similar regardless of whether the patient demonstrated a pathologic response (12.5 vs. 35, $P = 0.73$; 35 vs. 30, $P = 0.71$) or experienced recurrence (25 vs. 10, $P = 0.49$; 40 vs. 30, $P = 0.54$). Although data in the advanced, platinum-refractory setting portends improved survival with the use of nivolumab in those with PD-L1 expression ≥1% (21), our findings suggest that pathologic response may be more predictive than PD-L1 status in the surgical salvage disease setting. TMB was also similar regardless of recurrence status (5 vs. 5.2, $P = 0.73$). Molecular profiling showed similar mutation rates among commonly altered genes in head and neck cancer (40), with *TP53* and *TERT* promoter observed in at least 30% of those who developed recurrence. Peripheral blood flow before and after immunotherapy demonstrated reduced PD-1 expression on circulating $CD4^+$ and $CD8^+$ T cells, and reduced CD158/CD158b expression on NK/NK T cells that can be attributed to on-target binding effects from nivolumab and lirilumab exposure, respectively. Increases in CD38 expression by circulating $CD4^+$ and $CD8^+$ T cells may reflect a more Th1-polarized phenotype systemically following immunotherapy exposure. Among a subset of patients ($N = 6$) with paired tumor and peripheral blood samples obtained before and after immunotherapy, increased CD39 and CD69 (activation markers) expression on T cells, NK T cells, and B cells was observed in the TME.

Our collective findings suggest that there may be a role for (neo) adjuvant immunotherapy in surgically salvageable SCCHN patients with high-risk disease. Although speculative, those patients with HPV-negative tumors, a smoking history, and higher-risk mucosal subsites (hypopharynx and oral cavity) may have the most to gain from this approach regardless of PD-L1 status. Although PD-1 blockade is approved alone or in combination with platinum-based chemotherapy in the recurrent, metastatic setting (41), future approval of immune-checkpoint inhibitors in the pre-op or neoadjuvant setting among patients undergoing curative-intent surgery for SCCHN would complicate retreatment or rechallenge with immunotherapy in future settings (such as at the time of relapse or recurrence). Further, whether neoadjuvant immunotherapy and

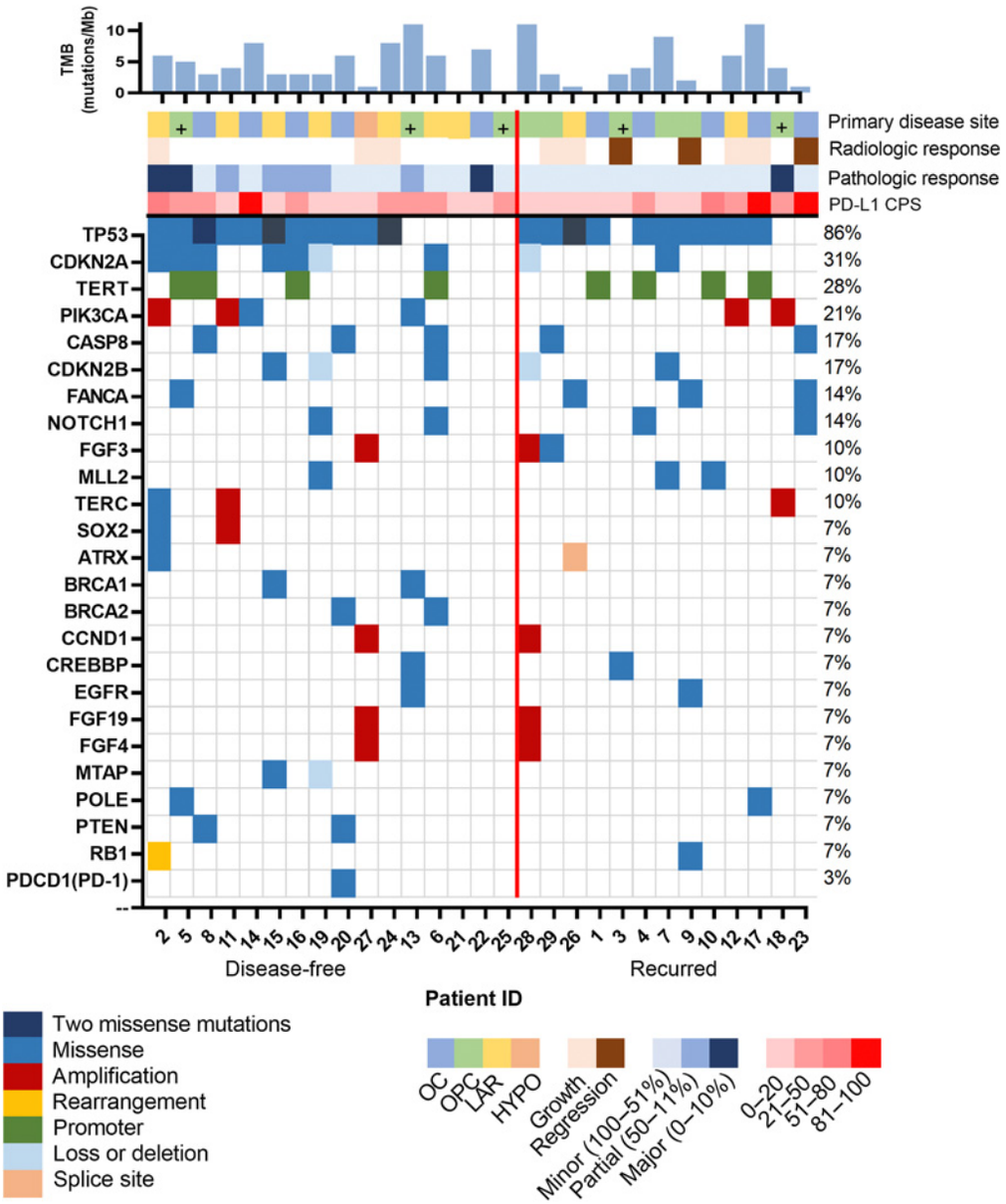

Figure 4.

Mutational landscape plot showing the most commonly mutated genes arranged by frequency (top to bottom). Each column represents an individual patient's tumor sample obtained at the time of salvage surgery, following neoadjuvant immunotherapy grouped from left to right based on disease status (disease-free or recurrence). The bar graph at the top of the figure shows TMB in mutations/Mb. The color-coded top row tiles indicate key clinicopathologic features, including primary site of initial disease (OC, oral cavity; OPC, oropharynx; "+" human papillomavirus positive; LAR, larynx; HYPO, hypopharynx), radiologic response to neoadjuvant immunotherapy prior to salvage surgery (RECIST v1.1), pathologic response graded by degree of viable tumor remaining in the surgical specimen (≤50%, partial response and ≤10% major response), and PD-L1 CPS determined from the salvage surgical specimen.

pathologic response may permit a deescalation or omission of post-op or adjuvant radiation and/or chemotherapy remains an unanswered question.

The authors acknowledge some limitations to the present study. We did not achieve our target accrual owing to discontinuation of lirilumab; therefore, further studies in this space will likely rely on PD-1 inhibition as a backbone for neoadjuvant therapy. Nonetheless, we demonstrate favorable two-year OS outcomes in this high-risk recurrent head and neck population treated with immunotherapy before and after salvage surgery despite similar DFS when considering a comparable historical population. We enrolled a mix of mucosal SCCHN subsites, which may have contributed to some variation in prognosis and outcomes, but almost all had high-risk disease features. We observed significant pathologic responses (<50% tumor viability) in nearly half of patients regardless of tumor PD-L1 score resulting in a two-year DFS of 64% and two-year OS of 80% among this subgroup. Disease recurrence was often locoregional and occurred in 46% of patients on study. Not completing all six monthly cycles of adjuvant

immunotherapy after salvage surgery was associated with worse outcomes. Combining adjuvant immunotherapy with reRT and extending the length of the adjuvant dosing phase (six months of adjuvant therapy was selected in the present study to promote subject adherence and minimize toxicity) may help further improve outcomes among those with the highest risk features in this critical population. These findings add to emerging data building on the role of neoadjuvant immunotherapy in head and neck cancer.

Authors' Disclosures

G.J. Hanna reports grants from Bristol Myers Squibb during the conduct of the study as well as grants and personal fees from Bicara, Exicure, Regeneron, BMS, and Sanofi Genzyme; grants from Gateway for Cancer Research, GSK, Kite Pharma, NantKwest/Altor Bioscience, and Secura Bio; and personal fees from Maverick and Merck outside the submitted work. V.Y. Jo reports "my spouse works as a Principal Scientist at Merck and Co for which he receives a salary, but his line of work in non-oncology has no relevant conflicts with this present study." J.H. Lorch reports grants and personal fees from Novartis and Bayer and grants from Bristol Myers Squibb and Takeda outside the submitted work. J.D. Schoenfeld reports grants from BMS during the conduct of the study as well as grants from Merck, BMS, Regeneron, and Debiopharm and personal fees from Genentech, Immunitas, Debiopharn, LEK, Catenion, ACI Clinical, Astellas, and Stimit outside the submitted work. R.B. Tishler reports other support from PSI, Enzychem, and Regeneron outside the submitted work. P.C. Everett reports other support from Dana-Farber/Harvard Cancer Center (DF/HCC) during the conduct of the study. A.M. Desai reports other support from BMS during the conduct of the study. R. Uppaluri reports other support from Merck Inc outside the submitted work. R.I. Haddad reports grants from BMS during the conduct of the study as well as grants and personal fees from Merck, BMS, Pfizer, GSK, Merck Serono, Eisai, Bayer, AstraZeneca, Kura, NCCN, Nanobiotix, ISA, and Mirati outside the submitted work. No disclosures were reported by the other authors.

Disclaimer

The study sponsor (Bristol Myers Squibb) reviewed the manuscript. The study sponsor had no role in the design and conduct of the study, collection, management, analysis and interpretation of the data, and no role in the preparation or approval of the manuscript or the decision to submit the manuscript for publication.

Authors' Contributions

G.J. Hanna: Conceptualization, resources, data curation, supervision, funding acquisition, validation, investigation, writing–original draft, project administration, writing–review and editing. **A. O'Neill:** Conceptualization, data curation, formal analysis, validation, methodology, writing–original draft, writing–review and editing. **K.-Y. Shin:** Data curation, formal analysis, validation, writing–review and editing. **K. Wong:** Resources, formal analysis, methodology, writing–review and editing. **V.Y. Jo:** Data curation, formal analysis, methodology, writing–review and editing. **C.T. Quinn:** Resources, data curation, writing–review and editing. **J.M. Cutler:** Resources, data curation, writing–review and editing. **M. Flynn:** Resources, data curation, investigation, project administration, writing–review and editing. **P.H. Lizotte:** Resources, data curation, software, formal analysis, validation, methodology, writing–review and editing. **D.J. Annino Jr:** Resources, data curation, writing–review and editing. **L.A. Goguen:** Resources, data curation, writing–review and editing. **J.I. Kass:** Resources, data curation, writing–review and editing. **E.M. Rettig:** Resources, data curation, writing–review and editing. **R.K.V. Sethi:** Resources, data curation, writing–review and editing. **J.H. Lorch:** Resources, data curation, writing–review and editing. **J.D. Schoenfeld:** Resources, data curation, writing–review and editing. **D.N. Margalit:** Resources, data curation, writing–review and editing. **R.B. Tishler:** Resources, data curation, writing–review and editing. **P.C. Everett:** Resources, data curation, writing–review and editing. **A.M. Desai:** Resources, data curation, writing–review and editing. **M.E. Cavanaugh:** Resources, data curation, software, formal analysis, investigation, methodology, writing–review and editing. **C.P. Paweletz:** Conceptualization, resources, software, supervision, investigation, writing–review and editing. **A.M. Egloff:** Resources, data curation, investigation, writing–review and editing. **R. Uppaluri:** Conceptualization, resources, data curation, supervision, investigation, methodology, writing–original draft. **R.I. Haddad:** Conceptualization, resources, data curation, supervision, investigation, methodology, writing–original draft.

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Note

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