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Durvalumab plus cetuximab in patients with recurrent or metastatic head and neck squamous cell carcinoma: an open-label, non-randomized, phase-2 clinical trial

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Abstract

Purpose: The efficacy of cetuximab is poor in metastatic head and neck squamous cell carcinoma (HNSCC). Cetuximab initiates natural killer (NK) cell-mediated antibody-dependent cellular cytotoxicity, with resultant recruitment of immune cells and suppression of anti-tumor immunity. We hypothesized that adding an immune checkpoint inhibitor (ICI) could overcome this and lead to an enhanced anti-tumor response.

Patients and Methods: A phase II study of cetuximab and durvalumab in metastatic HNSCC was conducted. Eligible patients had measurable disease. Patients who had received both cetuximab and an ICI were excluded. The primary endpoint was objective response rate (ORR) by RECIST 1.1 at six months.

Results: As of April 2022, 35 patients enrolled, of whom 33 received at least 1 dose of durvalumab and were included in the response analysis. Eleven patients (33%) had received prior platinum-based chemotherapy, 10 an ICI (30%), and 1 patient (3%) cetuximab. ORR was 39% (13/33) with a median duration of response of 8.6 months (95% CI: 6.5, 16.8). Median progression-free and overall survivals were 5.8 months (95% CI: 3.7 to 14.1) and 9.6 months

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(95% CI: 4.8 to 16.3), respectively. There were sixteen grade 3 treatment-related adverse events (TRAEs) and one grade 4 TRAE, with no treatment-related deaths. Overall and progression-free survival did not correlate with PD-L1 status. NK cell cytotoxic activity was increased by cetuximab and further increased with the addition of durvalumab in responders.

Conclusions: The combination of cetuximab and durvalumab demonstrated durable activity with a tolerable safety profile in metastatic HNSCC and warrants further investigation.

Keywords

EGFR inhibitor; immunotherapy; metastatic; head and neck; cancer; phase-II

INTRODUCTION

Approximately 67,000 patients are diagnosed with head and neck squamous cell carcinoma (HNSCC) in the United States every year (1). Even though the incidence of smoking-related cancers is declining, human papillomavirus (HPV) associated cancers of the oropharynx continue to increase by about 1% annually (1). Historically, platinum-based chemotherapy was the cornerstone for recurrent and metastatic (R/M) HNSCC, (2–4). . Cetuximab, a human-mouse chimeric IgG1 monoclonal antibody that binds and inhibits the epidermal growth factor receptor (EGFR), improved overall survival (OS) in combination with radiation or cisplatin and 5-fluorouracil (5),(6) and was FDA-approved for R/M HNSCC. However, single-agent cetuximab, has shown poor overall response rates (<15%) with a response duration of <2–3 months (7).

Programmed cell death 1 (PD-1) inhibitors- nivolumab and pembrolizumab have since received FDA approval for R/M HNSCC (8,9) after platinum failure. Most recently, single-agent pembrolizumab when the combined positive score (CPS) for programmed death ligand-1 (PD-L1) is ≥1, or a combination of pembrolizumab, platinum agent, and 5-fluorouracil (5-FU) regardless of PD-L1 status has become the most accepted standard of care for patients with untreated and incurable R/M HNSCC (10). Despite recent advances and the availability of immune checkpoint inhibitors (ICIs) as a promising modality for R/M HNSCC, the prognosis remains poor, with an estimated median OS of fewer than 15 months and the overall response rate is low at <18% (8,10,11) necessitating exploration of novel therapeutic strategies and combinations.

Cetuximab exerts its principal effect by inhibiting EGFR signaling in cancer cells and simultaneously induces natural killer (NK) cell-mediated antibody-dependent cell cytotoxicity (ADCC) (12–15). In addition, cytokines secreted from activated NK cells increase CD-8+ T-cell mediated lysis of cancer cells and induce recruitment of other immune cells to the tumor microenvironment (14,16). However, cetuximab-mediated ADCC and immune stimulation also initiate a negative feedback loop of immunosuppression (increased expression of checkpoints on tumor or immune cells, recruitment of regulatory T-cells (T-regs), and myeloid-derived suppressor cells (MDSCs)) in the TME (17). Therefore, we hypothesized that combining an ICI and cetuximab would synergize, overcoming immunosuppressive effects and resistance, leading to an increase in overall response rate (ORR) and survival. Previously, trials combining cetuximab and PD-1 inhibitors have

shown encouraging response rates of up to 44% with pembrolizumab and cetuximab and 22% (in the previously treated cohort and 37% in the previously untreated cohort) with nivolumab and cetuximab (18,19). We conducted a trial in previously treated patients with R/M HNSCC, where instead a PD-L1 inhibitor, durvalumab was combined with cetuximab, thus making this unique compared to prior studies.

METHODS

This investigator-initiated phase-II study was a single-arm, open-label, nonrandomized trial that enrolled patients at the University of Cincinnati Cancer Center (UCCC). The study was conducted following the International Conference on Harmonization guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. The protocol (online supplement) was approved by the institutional review board, and patients provided written informed consent for participation. This study is registered with ClinicalTrials.gov, NCT03691714

Study Design and Participants

The treatment schema is described in Supplementary Figure 1. Patients were eligible for enrollment if they were at least eighteen years of age, had histologically or cytologically confirmed R/M squamous cell carcinoma of the oral cavity, oropharynx, paranasal sinuses, nasal cavity, hypopharynx, or larynx; deemed not to be candidates for curative intent therapy (i.e., surgery or radiation therapy), had an Eastern Cooperative Oncology Group (ECOG) performance status 0–2; had adequate bone marrow, renal and hepatic function; and were able and willing to provide written informed consent. Patients with salivary gland tumors and nasopharyngeal tumors were excluded from the study. Enrolled patients were allowed prior exposure to systemic therapy for R/M HNSCC, including cetuximab and ICIs. However, patients exposed to *both* cetuximab and ICIs were excluded, as well as those with an active autoimmune condition requiring systemic therapy and those with active and untreated CNS metastasis. Detailed eligibility criteria are provided in the protocol (online supplement).

Procedures

All study participants received an initial loading dose of cetuximab 400 mg/m2 intravenously (IV) alone, followed by 250 mg/m2 IV once weekly. Cetuximab was chosen to be administered first to capture patients who may develop an infusion reaction with cetuximab, a common occurrence in previous clinical trials (20). Durvalumab was administered at a 1500 mg fixed dose IV, starting with the weekly dose of cetuximab on the first day of each four-week cycle (Supplementary Figure 1). Cycles were repeated every 28 days until disease progression, unacceptable toxicity, or the physician or participant's decision to withdraw from the study. A fixed 500mg dose of cetuximab every 2 weeks was allowed once this had been approved by the FDA (21). Adverse events were documented using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5, with attribution to each study drug, details of which are available in the protocol provided with the online supplement.

Response was assessed using conventional imaging- CT scans or MRI of the neck and chest (abdomen and pelvis if indicated) every eight weeks regardless of interruptions in treatment or treatment delays. Blood correlative studies were obtained at the time of screening (before administration of either drug), after the loading dose of cetuximab, and after the first dose of durvalumab (Supplementary Figure 1). End-of-treatment visit for clinical evaluation and safety assessment was done twenty-eight days after (or within seven days before or after) the last dose of the study drug, and participants who had discontinued treatment on trial were followed up every 3 months for collection of survival outcomes data.

PD-L1 expression in archival or newly obtained, formalin-fixed tumor samples was assessed by immunohistochemistry (IHC) using the next-generation sequencing platform from CARISTM. Monoclonal antibodies used included 22c3 (n=26) (PD-L1 positive defined as a combined positive score (CPS) ≥1) and 28–8 (n=5) (PD-L1 positive defined as ≥1+ staining intensity and ≥1% of cells stained). The threshold to define tumor mutational burden-high (TMB-H) was greater than or equal to 10 mutations/MB based on the KEYNOTE-158 pembrolizumab trial (22). Where available, p16 status was determined by immunohistochemistry (IHC) according to standard pathologic scoring (moderate to strong cytoplasmic and nuclear staining in at least 70% of tumor cells).

Outcomes

The primary endpoint for this study was the ORR by 6 months, defined as the proportion of participants with a partial or complete response per RECIST(version 1.1) criteria (23). Secondary endpoints were progression-free survival (PFS), defined as the time from administration of the first dose of cetuximab to disease progression or death from any cause, whichever happened first or otherwise censored at the last date known alive; overall survival (OS), defined as the time from study enrollment to death from any cause or censored at the last date known alive; disease control rate by 6 months (defined as the proportion of participants with a partial or complete response and stable disease, duration of response (defined as the time from documentation of tumor response to disease progression); and safety and tolerability (defined as the occurrence of treatment-related adverse events per NCI-CTCAE version 5). Secondary safety endpoints were grade 3 and 4 adverse events and all grade (grade 1–5) adverse events. Exploratory endpoints were PD-L1 expression (utilizing combined positive score) and p16 status and their association with a response by 6 months, OS, and PFS.

Correlative studies' methodology, including PBMC isolation, storage, plasma isolation, flow cytometry, and Luminex, are included with the online supplement.

Natural Killer Cell Cytotoxicity Assay

PBMCs isolated and frozen from patient blood were thawed in a 36^{O}C water bath for 2min. Cells were washed in 5mL RPMI and spun at 400xg for 5min, Cells were resuspended in RPMI (Corning) + 10% FBS (Corning) at density of 1×10^6 cells per mL with 100U/mL IL-2 (Peprotech). PBMCs were allowed to rest overnight at 37^{O}C and 5% CO_2. NK cells were then isolated using CD56 negative selection (Stemcell) and co-cultured at a 1:5 ratio with CellTrace™ CFSE Cell Proliferation Kit stained Cal27 tumor cells for 4hrs. Culture

was then collected and stained for 7AAD (Biolegend) and analyzed on a flow cytometer (BD LSRFortessa, University of Cincinnati Department of Cancer Biology). NK-killed targets were determined by gating CFSE+ cells, then 7AAD+. Basal death (Cal27s with no NK cells) was subtracted to determine direct killing.

ELISA for cytokines:

Cytokine concentrations in the sample supernatants were determined by enzyme-linked immunosorbent assay (ELISA) using a Luminex assay (R&Dsystems, a bio-techne brand, Minneapolis, MN) according to the manufacturer's protocol and is also detailed in the online supplement.

Statistical Analysis

Analyses for evaluating ORR included participants who had received at least one dose of durvalumab following the loading dose of cetuximab. Those who received only the loading dose of cetuximab and died or withdrew from the study before receiving the first dose of durvalumab and did not have a scan to assess tumor response were excluded from the response analysis. However, for the secondary endpoints of PFS and OS, all enrolled participants (intention-to-treat population), who had received at least one loading dose of cetuximab (regardless of whether they were able to receive durvalumab) were included in the survival analysis. Similarly, if a patient had received the loading dose of cetuximab but died or withdrew from the study before durvalumab was started, they were included in the safety analyses as well. The null hypothesis for this study was that the ORR with durvalumab and cetuximab at a 6-month follow-up would not be higher than 14% (which was based on an assumed ORR of 14% with cetuximab (7). In our study, where we proposed to combine durvalumab and cetuximab, we expected to reach over 84% power to detect an ORR of 35% against a null overall response rate of 14%, using Simon's two-stage design method in power calculation. The Kaplan-Meier method was used to analyze PFS and OS, and the median PFS and OS with its associated 95% confidence interval (CI) were calculated. The secondary endpoint for adverse events was summarized using frequencies and proportions. The safety population included all participants who received at least one dose of durvalumab.

For the exploratory analyses, all statistics were performed in Prism V9. Two-way match ANOVA was utilized for time point analyses. One-way ANOVA analyzed responder comparisons. A type I error rate of 0.05 was used to determine statistical significance. All endpoint analyses were done in R version 4.2.1.

Data availability

Raw data are available as a supplementary table and are available upon request from the corresponding author.

RESULTS

Patients

Between October 2018 and October 2021, 35 patients were enrolled, of whom 33 received at least 1 dose of durvalumab (consort diagram; Supplementary Figure 2) and were included in response analysis. Data cutoff date for the analysis was April 8, 2022. Baseline demographics, information on the primary disease site, and type of prior therapies administered are shown in Table 1. The median age was 64 years (range 47–81 years), majority of patients were male (N=24; 68%) and white (N=33; 94%). Oropharyngeal (N=12; 35%) and oral cavity (N=11; 31%) were the most common primary sites. Among the twelve patients with oropharyngeal primaries, five (42%) were p16 positive. Majority of patients (54%) had received some form of systemic therapy for relapsed/metastatic HNSCC in the past. Eleven patients out of the 33 included in the response analysis (33%) had received prior platinum-based chemotherapy for R/M HNSCC, 10/33 patients (30%) had received an ICI, and 1/33 (3%) patients had received cetuximab in the past (Table 1). Archival tissue specimens were available from 31 (93%) patients for PD-L1 testing, of which 22 patients (71%) were PD-L1 positive.

Efficacy

The median duration of follow-up from the initiation of study treatment to data cutoff or death, whichever occurred first, was 7.5 months (range 1– 38.7 months). The primary endpoint of improved ORR was met in 13 of 33 patients available for efficacy analysis (39%) (Figure 1A, 1B), thus indicating that the null hypothesis could be rejected. Ten had a partial response (PR), and three had a complete response (CR). In addition, seven patients had stable disease (20%), and thirteen patients had progressive disease (39%) as their best response. Five patients discontinued treatment before the first follow-up scan could be performed (one due to an immune-related adverse event and three due to complications related to their cancer) and were classified as having progressive disease for this analysis. The median duration of response for patients who had a PR or CR was 8.6 months (95% CI: 6.5, 16.8) (Figure 1C). In these patients, the median time to first observed radiographic response was 1.91 months (range 1.8–9.3 months). Notably, four patients with a CR or PR continue to respond to the regimen at the 6-month follow-up time point (Figure 1C). The disease control rate (DCR) was 60% (20/33 patients). In the intention-to-treat population (35 patients), the median PFS was 5.8 months (95% CI: 3.7 to 14.1), and the median OS was 9.6 months (95% CI: 4.8 to 16.3). (Figure 1D, E).

Of note, amongst the 10 patients who had previously received ICI (pembrolizumab or nivolumab) for R/M HNSCC, three patients derived clinical benefit with the combination. These three patients had been treated with pembrolizumab, with a response lasting for 5 months (patient 1), 7 months (patient 2), and 5 months and 6 weeks (patient 3). Durvalumab and cetuximab in the current clinical trial were administered to them as the immediate next line of therapy and they attained stable disease as their best response. While there was no difference in the PFS or OS between patients who had received any prior systemic therapy or chemotherapy for R/M HNSCC (Supplementary Figures 3 and 4), the OS was better for

patients who had not received prior ICI (median OS 7.1 months; 95% CI: 2.8 to Not reached (NR) vs. 13.9 months; 95% CI: 4.8 to NR)). (Fig. 2A, B).

Safety

The median number of cycles administered for durvalumab and cetuximab were 3 (range, 0–26 cycles) and 4 (range, 0–26), respectively. A detailed summary of all adverse events is available in Supplementary Tables 1 and 2. For clear immune-related toxicities (eg. colitis) that were attributed to durvalumab, cetuximab was continued and vice versa. Most of these treatment continuation decisions were at the discretion of the treating investigator in consultation with the principal investigator. There were sixteen grade 3 treatment-related adverse events (TRAEs) and one grade 4 TRAE (Table 2). The most common TRAEs were dermatologic (acneiform rash) in 77% of patients, including one patient with grade 3 rash, fatigue in 46%, hypomagnesemia in 31 % (including one patient with grade 3 hypomagnesemia), and nausea in 31% of patients. There were no treatment-related deaths. Immune-related adverse events from durvalumab were seen in six patients (17%). They included grade 3 elevation of AST/ALT and bilirubin, grade 3 colitis, grade 3 hyperglycemia, diabetes ketoacidosis and acute kidney injury in the same patient, grade 3 pleural and pericardial effusions, grade 4 uveitis and grade 2 arthralgias. Of these, two patients discontinued treatment because of treatment-related adverse events (one due to grade 3 colitis and one due to grade 3 pleural and pericardial effusion). Dose reduction for cetuximab secondary to dermatological toxicity and fatigue was required in two (6%) patients.

Correlative analysis:

Post hoc correlative analysis included an association of PD-L1 status with PFS and OS. Of the 31 patients who had PD-L1 status available, tumors from six (19%) were from metastatic/recurrence site, four (12%) were from nodes and the remaining 21 (69%) were from the primary lesion. PD-L1 was positive in 11 out of 13 patients who had a partial or complete response to the combination (all three patients who had a complete response were PD-L1 positive) (Figure 3A). There was no statistically significant difference between median PFS in PD-L1 negative versus positive patients (2.99 months (95% CI: 1.8 to NR) and 8.3 months (95% CI: 3.7 to NR)). (Supplementary Figure 5A). Similarly, median OS was also not significantly different between the two groups (4.8 months (95% CI: 3.5 to not reached) in PD-L1 negative vs. 13.9 months (95% CI: 7.1 to 21) in PD-L1 positive) (Supplementary Figure 5B).

Four patients (11%) were p16 positive, while the remaining 31 (89%) patients either had p16 negative tumors or non-oropharyngeal tumors where p16 status was unavailable. Of the p16 positive tumors, one patient with oropharyngeal cancer had a PR. (Figure 3B). Of the thirteen responders, p16 was unknown in six patients. In the remaining seven, p16 was negative in all but 1 patient. Also noteworthy was that the majority of the p16 negative responders had oral cavity cancers (one p16 negative responder had a laryngeal primary). (Supplementary Figures 6A and 6B).

Evaluation of TMB was done in 27 (77%) patients and revealed that two patients who derived clinical benefit from the regimen (one with CR and one with SD) had a high TMB (>10 mutations/MB). The remaining patients had a low TMB, including the remaining 11 patients with clinical benefit to the durvalumab/cetuximab combination.

Flow cytometry analysis of the NK cells in the NK cell assay revealed a significant increase in the NK cytotoxic activity upon treatment with cetuximab, which was further enhanced in some patients upon the addition of durvalumab, though not significantly (Figure 4), especially in patients who derived clinical benefit (described as responders; included patients with PR, CR, and SD). Patients with progressive disease had the lowest NK cell cytotoxicity.

Cytokine analysis by Luminex showed that cetuximab alone decreased pro-tumorigenic IL-6 levels and increased IP-10 (Supplementary Figure 7A and 7B); however, these cytokines were not significantly changed between responders (those with CR, PR, SD) and non-responders. The full panel of tested cytokines, shown in Supplementary Figure 7C, did not significantly change upon administration of either drug and was not different between responders and non-responders.

DISCUSSION

This study presents safety and efficacy data from a phase II clinical trial combining cetuximab and the PD-L1 inhibitor durvalumab in R/M HNSCC. The ORR of 39% with the combination, including three patients who had a CR, is promising with improvement over the published response rates with ICIs or cetuximab administered as single agents (7–9).

Our data adds to the previous studies that have explored EGFR inhibition in combination with ICIs in R/M HNSCC. While previous studies utilized PD-1 inhibitors, ours is the first to combine a PD-L1 inhibitor with cetuximab, thus making this unique. Moreover, we allowed patients who had previously been treated with both chemotherapy and an ICI (>50% of patients had been treated with either or both drugs). The previously published phase II trial that evaluated the combination of pembrolizumab and cetuximab, which resulted in an ORR of 45% and a median OS of 18 months (18). Importantly, in this study, 88% of the included patients had not received any systemic therapy in the R/M setting, which may account for the superior response rate compared to our study. Subsequently, another phase II study of 24 ICI naïve patients evaluated the efficacy of the EGFR inhibitor, afatinib, in combination with pembrolizumab in patients with platinum-refractory recurrent metastatic HNSCC (24) and reported an ORR of 41.4%. In the treated cohort of the phase II trial combining nivolumab and cetuximab, the ORR was lower at 22% (19). Some differences in outcomes could be driven by the differences in how adverse events and dose reductions were handled between each study. Regardless, our study, where we report an ORR of 39% in previously treated patients with R/M HNSCC, not only adds to the previous literature on this combination but also presents proof of concept for efficacy of a PD-L1 inhibitor when combined with cetuximab.

Previously, durvalumab has been evaluated in a large phase-III trial, where patients previously treated with multiple lines of therapy (n=736) were randomized in a 1:1:1 manner to receive durvalumab, durvalumab plus the CTLA-4 inhibitor- tremelimumab or standard of care chemotherapy (cetuximab, a taxane, methotrexate, or a fluoropyrimidine) (25). The ORR (17.9% for durvalumab, 18.2% for durvalumab plus tremelimumab, and 17.3% for standard chemotherapy regimens) and the 12-month OS rates (37.0% vs. 30.4% vs. 30.5% for durvalumab, durvalumab plus tremelimumab, and standard-of-care chemotherapy, respectively) were not significantly different between the groups. However, here we demonstrate that the combination of a PD-L1 inhibitor with the EGFR monoclonal antibody, cetuximab, is just as likely to lead to a clinical benefit as are the PD-1 inhibitors. Further, since we report clinical benefit in patients who had previously been treated with an ICI, this combination may be considered for patients previously treated with an ICI. This is important to consider with the approval of pembrolizumab alone or in combination with chemotherapy in the frontline setting in R/M HNSCC. While the combination of pembrolizumab and cetuximab has been incorporated in guidelines (26), durvalumab and cetuximab may be a useful addition, especially in those who have already received prior systemic therapy.

The adverse event profiles when combining durvalumab and cetuximab were within reasonable limits, and side effects were as expected from the two individual drugs. The most common TRAEs were dermatologic (acneiform rash), fatigue, hypomagnesemia, and nausea. In a previous study by Sacco *et al* (pembrolizumab+ cetuximab), (18) oral mucositis was the most common grade 3–4 TRAE, while we observed oral mucositis in only three patients (all with grades 1–2). Grade 3 skin-related toxicity was comparable in the two studies (6% in the study by Sacco *et al*, 2% in ours. Similar to our study, the study reported recently by Chung *et al* (nivolumab+ cetuximab), did not report any grade 3–4 oral mucositis in either cohort and reported a higher grade 3 skin toxicity in 9% and 14% of the enrolled patients in the 2 cohorts respectively. Overall, like previous studies, the combination was safe and well tolerated.

Exploratory analysis of PD-L1 status showed that despite no survival difference between PD-L1 positive or negative patients, most of the responders were PD-L1 positive (83%), and all of the patients who achieved a CR had PD-L1 combined positive score >1. The lack of survival difference between the PD-L1 positive or negative patients could be due to the small cohort size in our study. Previous studies reported higher response rates and better survival when using ICIs in patients with PD-L1 positive tumors (10,27). Importantly, we noted that two responders to durvalumab and cetuximab were PD-L1 negative; thus, raising the question if there are additional tumor characteristics that are responsible for a response requiring evaluation in larger studies.

Although, we cannot reliably ascertain the association of outcomes with p16 from our study due to the small number of patients with p16-positive tumors (n=4), it is important to underline that previous studies, including a meta-analysis have shown better efficacy of the combination of an EGFR inhibitor with an ICI in terms of better ORR and 1-year OS rate than an ICI monotherapy regimen in HPV-negative disease (28). Moreover, EGFR inhibitor monotherapy, either cetuximab or afatinib, has also resulted in lower efficacy

in HPV-positive than HPV-negative disease in previously published clinical trials of R/M HNSCC (29–31). A higher number of p16 negative patients in our study may explain the high response rate to the combination of cetuximab and durvalumab. This and prior data thus highlight that tumor HPV status should be considered in the design of future trials utilizing cetuximab with an ICI in R/M HNSCC.

From flow cytometry, it was evident that NK cellular cytotoxic activity increased upon treatment with cetuximab, which was further increased upon the addition of durvalumab, especially in patients who responded to the combination, although we acknowledge that peripheral NK cell cytotoxic activity may not be reflective of NK cell infiltration and activity in the tumor. NK cell-mediated ADCC from cetuximab is well known, and trials are underway to enhance the efficacy of NK cell function with cetuximab by combining with agents such as immunogenic cytokines (eg.IL-12) (32). Our findings support an approach to enhance the innate immunity of a tumor with cetuximab, followed by targeting the suppressive tumor microenvironment with an ICI to sustain greater anti-tumor effects of the NK cells.

Our study has limitations. The open-label design and the non-randomized single-arm nature of this clinical trial with a small number of patients from a single enter warrants evaluation of the combination of durvalumab and cetuximab in a larger phase-III randomized trial for confirmation of results. A follow-up of six months was chosen as previous studies have shown that patients with R/M HNSCC tend to relapse within this time window. However, we did note responses that lasted beyond six months. Furthermore, five patients who discontinued treatment before the first follow-up scan were counted as having progressive disease, which may have affected the results.

In conclusion, we present promising data from a phase-II clinical trial, which is unique from previous studies in that this is the first study reflecting the efficacy of a PD-L1 inhibitor in combination with cetuximab in R/M HNSCC. With an impressive response rate of 36% and durable responses, the study adds to the avenue of “chemotherapy-free” options. It provides evidence for use even in patients who have previously been treated with chemotherapy and or immune checkpoint-based therapies. Our correlative studies provide evidence of a higher response rate but similar overall survival between PD-L1 positive and negative patients. Further evaluation of this combination in a large phase-III trial is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Translational Relevance:

Outcomes for patients with recurrent and metastatic head and neck squamous cell carcinoma (HNSCC) remain poor. Although strides have been made with development of new drugs, including targeted therapies and immune checkpoint inhibitors, overall response rates with single agents remain <20%. Here we report the results of a phase II open-labeled trial of the combination of the epidermal growth factor receptor (EGFR) inhibitor, cetuximab and programmed death ligand-1 (PD-L1) inhibitor, durvalumab in patients with recurrent and metastatic HNSCC. The combination led to an overall response rate of 36%, with a median duration of response of 8.61 months and was well tolerated. Natural-killer cell cytotoxic activity was increased after cetuximab administration, which was further increased with the addition of durvalumab in patients who responded. Further study in a randomized controlled clinical trial is warranted to establish clinical efficacy.

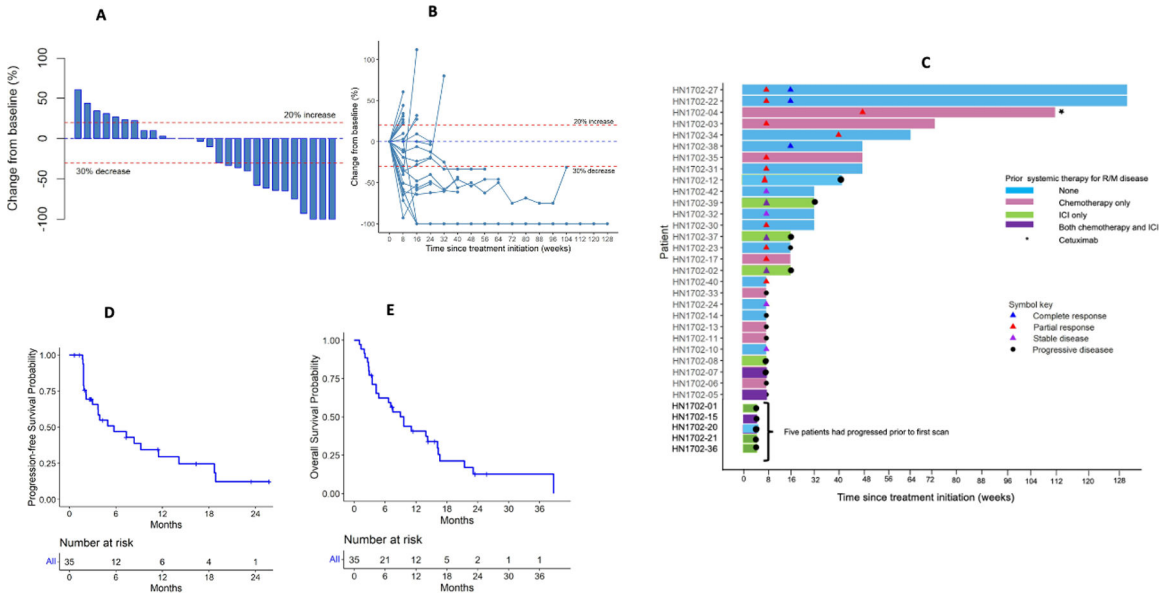

Figure 1. (A) Waterfall plot of best overall response; (B) Spider plot of overall response based on target lesions only and (C) Swimmer plot of patient response over time.

Overall response based on target and non-target lesions per RECIST 1.1 and observation time for 33 patients. For response plots, 33 of the 35 participants are included. Two patients were excluded from response evaluation as they did not receive at least one dose of durvalumab. Five patients discontinued treatment before the first follow- up scan could be performed (four due to complications related to their cancer and one due to an immune-related adverse event) and were classified as having progressive disease for the primary analysis of overall response rate and are not shown in this bar graph. Dashed lines at 20% increase: a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. Dashed lines at 30% decrease: a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. The swimmer's plots (1C) also show response distribution by prior systemic therapy administered prior to enrollment on this clinical trial in the relapsed/metastatic setting.

(D) Kaplan Meir curve to demonstrate progression-free survival for the intention to treat population (N=35)

(E) Kaplan Meir curve to demonstrate overall survival for the intention to treat population (N=35)

Abbreviations: R/M: relapsed/metastatic; ICI: immune checkpoint inhibitor

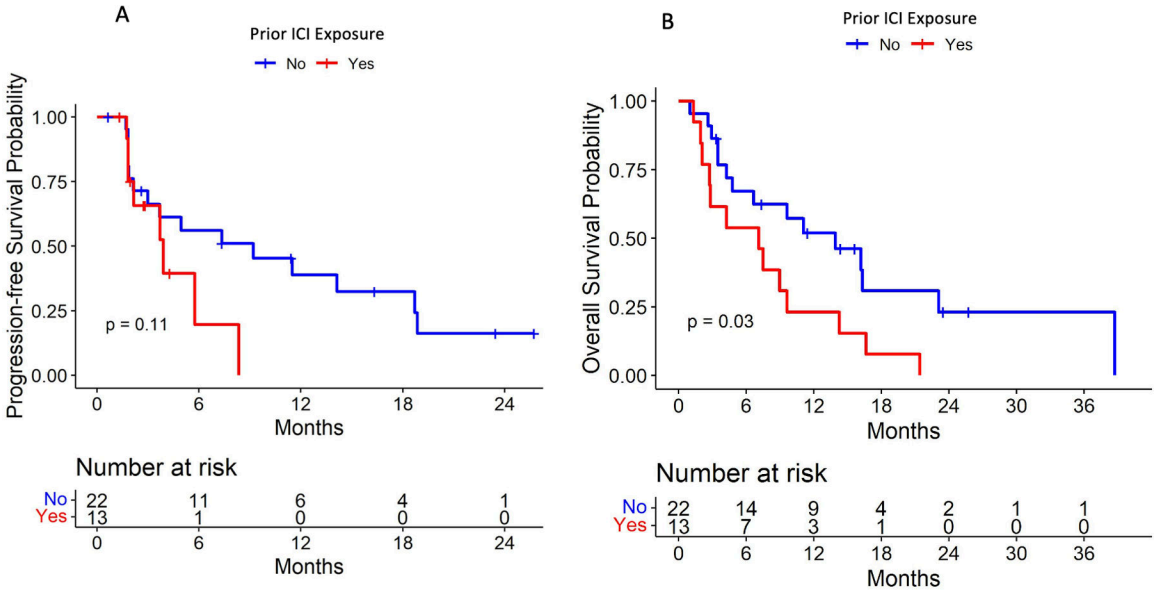

Figure 2. Comparison of outcomes between patients treated with prior immune checkpoint inhibitors (blue) vs. not (red)

A) Progression-free survival and B) Overall survival comparison

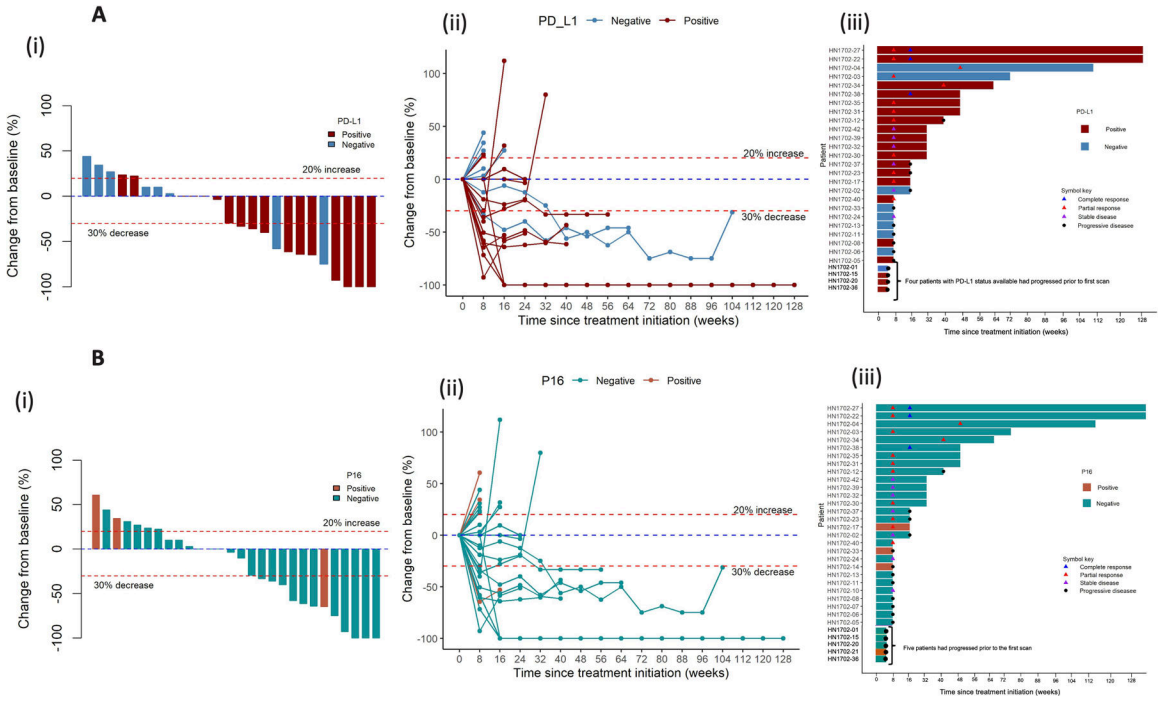

Figure 3A. Response assessment based on PD-L1 status.

(i) Waterfall plot of best overall response and (ii) Spider plot of overall response based on target lesions (iii) Swimmers plot pf response over time

3B. Response assessment based on p16 status. (i) Waterfall plot of best overall response and (ii) Spider plot of overall response based on target lesions (iii) Swimmer's plot of response over time

Overall response based on target and non-target lesions per RECIST 1.1 and observation time for 33 patients. For response plots, 33 of the 35 participants are included. Two patients were excluded from response evaluation as they did not receive at least one dose of durvalumab. Five patients discontinued treatment before the first follow- up scan could be performed (four due to complications related to their cancer and one due to an immune-related adverse event) and were classified as having progressive disease for the primary analysis of overall response rate. 29 of the 33 patients included had PD-L1 status available and were included in this analysis. Dashed lines at 20% increase: a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. Dashed lines at 30% decrease: a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

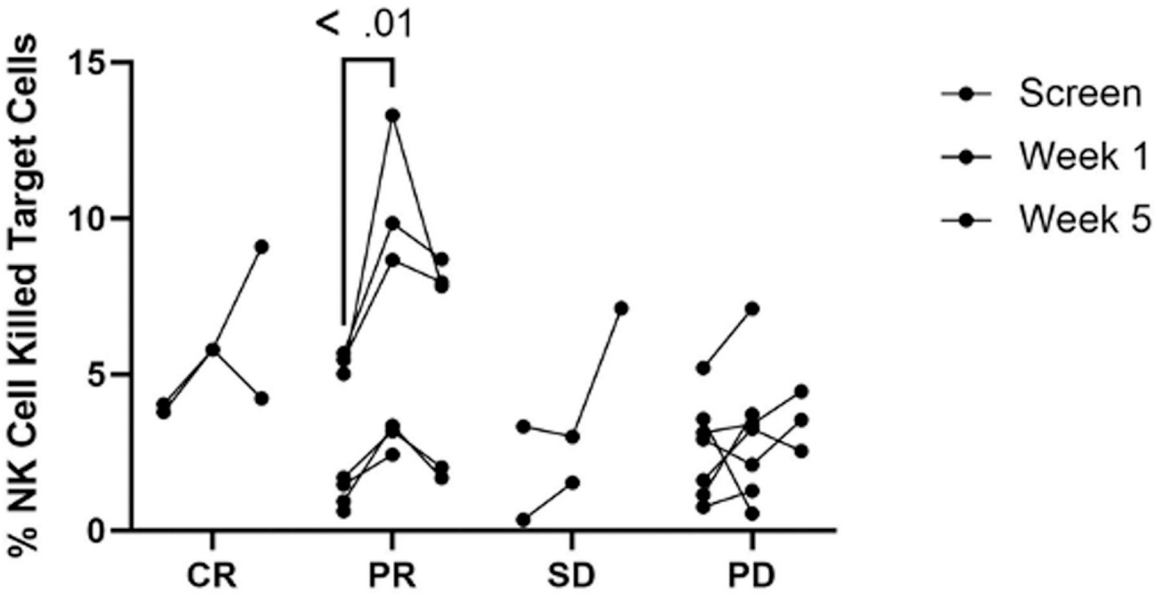

Figure 4. Cetuximab and Durvalumab increase NK Cytotoxic Activity:

NK cells were isolated from peripheral blood from patients on trial either before treatment, at 1 week (after cetuximab administration) and at week 5 (after the combination of cetuximab and durvalumab). Patient NK cellular cytotoxicity was compared between those with CR, PR, SD (those with clinical benefit) or progressive disease (PD) at the three-time points.

Abbreviations: CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; NK: Natural Killer

Table 1.

Baseline characteristics.

All patients enrolled on clinical trial (N=35)	
Median age (years (IQR))	64 (47–81)
Sex (No.,%)	
Male	24 (68%)
Female	11 (32%)
Ethnicity (No.,%)	
White	33 (94%)
Black	2 (6%)
ECOG performance status[1] (No.,%)	
0 (fully active without restriction)	6 (17%)
1 (activity restricted; ambulatory; “light work only”)	22 (63%)
2 (Ambulatory; all self-care; up < 50% of waking hours)	7 (20%)
Smoking history (No.,%)	
Yes	28 (80%)
No	7 (20%)
Alcohol use (No., %)	
Yes	8 (23%)
No	27 (77%)
Primary tumor site (No., %)	
Oral cavity	11 (31%)
Oropharynx (HPV related)	4 (11%)
Oropharynx (non-HPV related)	7 (20%)
Oropharynx (HPV stats unknown)	1 (2%)
Larynx	11 (31%)
Paranasal sinus	1 (2%)
Exposure to prior systemic therapy for R/M disease (No., %) in patients included in response assessment	
None	15 (45%)
Yes	18 (54%)
Chemotherapy (No., %)[2]	
None	24 (67%)
Yes	11 (33%)
I**mmune checkpoint inhibitor** (No., %)*	.
None	23 (70%)
Yes	10 (30%)
Cetuximab (No., %)	
None	33 (97%)
Yes	1 (3%)
PD-L1 positive	
Yes	22 (63%)

All patients enrolled on clinical trial (N=35)	
No	9 (26%)
Unknown (not collected or insufficient tumor)	4 (11%)

[1] **ECOG** (Eastern Cooperative Oncology Group) performance status was designated 0 if fully active, able to carry on all pre-disease performance without restriction; 1, if restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; 2, if ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours; 3, if capable of only limited selfcare; confined to bed or chair more than 50% of waking hours, 4, if completely disabled and 5, if the patient was dead.

[2] Three patients had received both chemotherapy and an immune checkpoint inhibitor before trial enrollment

Abbreviations: IQR, interquartile range; No., Number; HPV, human papillomavirus; R/M, relapsed/metastatic; PD-L1, programmed death ligand-1; ECOG, Eastern Cooperative Oncology Group

Table 2.

All grade treatment-related adverse events (in >10% or >3 patients) if grade 1 or 2 and any grade 3 and 4 adverse events.

TRAE	Grade 1–2	Grade 3	Grade 4
Eye Disorders			
Blurred vision	0	1 (2%)	0
Uveitis	0	0	1 (2%)
Gastrointestinal Disorders			
Colitis	0	1 (2%)	0
Diarrhea	9 (26%)	0	0
Mucositis oral	3 (8%)	0	0
Nausea	11 (31%)	0	0
Oral pain	4 (11%)	0	0
Vomiting	5 (14%)	0	0
General Disorders and Administration Site Conditions			
Fatigue	16 (46%)	0	0
Localized edema (neck/face)	3 (8%)	1 (2%)	0
Immune System Disorders			
Infusion reaction (during cetuximab)	3 (8%)	0	0
Infections and Infestations			
Skin infection	3 (8%)	0	0
Investigations			
Alanine aminotransferase increased	0	1 (2%)	0
Alkaline phosphatase increased	0	1 (2%)	0
Aspartate aminotransferase increased	0	1 (2%)	0
Bilirubin increased	0	1 (2%)	0
Weight loss	3 (8%)	0	0
Metabolism and Nutrition Disorders			
Acidosis (diabetic)	0	1 (2%)	0
Anorexia	4 (11%)	0	0
Hyperglycemia	0	1 (2%)	0
Hypomagnesemia	11 (31%)	1 (2%)	0
Musculoskeletal and connective tissue disorders			
Myalgia	3 (8%)	0	0
Nervous System Disorders			
Headache	7 (20%)	0	0
Syncope	0	1 (2%)	0
Renal and Urinary Disorders			
Acute kidney injury	0	1 (2%)	0
Respiratory, Thoracic and Mediastinal Disorder			
Aspiration pneumonia	0	1 (2%)	0

TRAE	Grade 1–2	Grade 3	Grade 4
Pleural effusion	0	1 (2%)	0
Skin and Subcutaneous Tissue Disorders			
Dry skin	9 (26%)	0	0
Nail changes (nail loss, brittle nails, nail ridging)	3 (8%)	0	0
Pruritis	20 (57%)	0	0
Rash (acneiform)	27 (77%)	1 (2%)	0
Rash (maculopapular)	3 (8%)	0	0
Skin and subcutaneous tissue disorders- others (finger skin split/fissures)	5 (14%)	0	0
Vascular Disorders			
Thromboembolic event (PE, PAD, Stroke)		1 (2%)	0

Abbreviations: TRAE, treatment-related adverse events; PE, pulmonary embolism; PAD, peripheral arterial disease