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# A pilot study of cetuximab and the hedgehog inhibitor IPI-926 in recurrent/metastatic head and neck squamous cell carcinoma

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SUMMARY

*Background:* This phase 1, dose-finding study determined the safety, maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D), antitumor activity, and molecular correlates of IPI-926, a Hedgehog pathway (HhP) inhibitor, combined with cetuximab in patients with relapsed/metastatic squamous cell carcinoma of the head and neck.

*Patients and methods:* Cetuximab was given with a 400 mg/m$^2$ loading dose followed by 250 mg/m$^2$ weekly. IPI-926 was given daily starting two weeks after cetuximab initiation. A "3 + 3" study design was used. Prior therapy with cetuximab was allowed. Tumor biopsies occurred prior to cetuximab initiation, prior to IPI-926 initiation, and after treatment with both drugs.

*Results:* Nine patients were enrolled. The RP2D was 160 mg, the same as the single-agent IPI-926 MTD. Among 9 treated, 8 evaluable patients, the best responses were 1 partial response (12.5%), 4 stable disease (50%), and 3 disease progressions (37.5%). The median progression free survival was 77 days (95% confidence interval 39–156). Decreases in tumor size were seen in both cetuximab-naïve patients (one HPV-positive, one HPV-negative). The most frequent treatment-emergent adverse events were fatigue, muscle cramps, and rash. No DLTs were observed. Tumor shrinkage and progression free survival were associated with intra-tumoral ErbB and HhP gene expression down-regulation during therapy, supporting the preclinical hypothesis.

*Conclusion:* Treatment with IPI-926 and cetuximab yielded expected toxicities with signs of anti-tumor activity. Serial tumor biopsies were feasible and revealed proof-of-concept biomarkers.



## Introduction

Cetuximab is an anti-epidermal growth factor receptor (EGFR/ErbB) antibody whose efficacy in treating relapsed/metastatic head and neck squamous cell carcinomas (R/M HNSCC) is limited by inherent or acquired resistance [1]. Epithelial-to-mesenchymal transition (EMT) has been hypothesized as a possible cause for drug resistance and worse prognosis in HNSCC [2–4]. The Hedgehog signaling pathway (HhP) has been implicated in EMT [5]. In the HhP the sonic hedgehog (SHH) ligand activates a signaling cascade that leads to glioma-associated oncogene family zinc finger 1 (GLI1) expression, which in turn modulates numerous cancer target genes [5,6]. Expression of HhP and GLI1 is associated with poor response to radiation *in vivo* and worse prognosis in HNSCC patients treated with curative intent radiation therapy [7,8]. Preclinical data suggest that the hedgehog and EGFR pathways interact. EGFR and HhP signaling converge and/or synergize upstream of GLI1 through the MEK/ERK signaling pathway in cancer cells and during keratinocyte oncogenic transformation [9,10]. In patient-derived tumor xenografts (PDX) inhibition of the HhP with the novel HhP inhibitor IPI-926 (Infinity Pharmaceuticals, Boston, MA) caused tumors to have a more epithelial, EGFR-dependent phenotype [11]. When HhP inhibition was combined with

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cetuximab, tumors were eliminated in two cases and re-growth was significantly delayed in the other two cases [11]. Expression of EMT genes TWIST and ZEB2 was increased in sensitive xenografts, suggesting a possible resistant mesenchymal population [11]. Therefore, combined inhibition of EGFR with cetuximab and the HhP pathway with IPI-926 was a rational approach in patients with R/M HNSCC.

In the first-in-human, phase 1, single-agent study of IPI-926, the recommended phase 2 dose (RP2D) was 160 mg daily [12]. The most common adverse events (AEs) were fatigue, nausea, muscle spasms, liver function abnormalities, and alopecia [12]. Given the preclinical rationale for combining HhP and EGRF inhibition, we conducted an open-label, phase 1 study combining IPI-926 and cetuximab to determine the maximal tolerated dose (MTD)/RP2D, toxicity profile, antitumor activity, and molecular correlates in patients with R/M HNSCC (NCT01255800).

## Patients and methods

### *Patients*

Inclusion criteria included patients with: histologically/cytologically confirmed R/M HNSCC; tumors amenable to biopsy; willingness to undergo three sequential tumor biopsies; measurable disease per RECIST 1.1; age $\geqslant$18 years, life expectancy >12 weeks; adequate hepatic, hematologic, and renal function; Eastern Cooperative Oncology Group performance status (ECOG PS) of $\leqslant$2; ability to swallow whole pills; previous treatment completed >4 weeks prior, and use of effective contraception. Prior treatment with cetuximab was allowed. Exclusion criteria included: presence of any medical/social factors affecting patient safety; pregnancy or breastfeeding; known human immunodeficiency virus; known or suspected clinically active brain metastases; venous thromboembolic disease that was symptomatic or diagnosed within the previous month; baseline QTcF >450 ms (men) or >470 (women); concurrent use of strong inducers or inhibitors of CYP3A4, PgP inhibitors, or medications that prolong the QTcF interval; and/or history of hypersensitivity reactions to cetuximab. The institutional review board granted approval and written informed consent was mandatory.

### *Design*

This was an open-label, dose escalation study of orally administered daily IPI-926 in combination with cetuximab given in 28-day cycles. On C1D0 patients underwent a tumor biopsy and aspiration. Cetuximab was administered at 400 mg/m$^2$ IV on C1D1 and then 250 mg/m$^2$ IV weekly thereafter. Cetuximab was administered first to allow patients to receive an FDA-approved therapy earlier in their treatment course. Patients underwent a tumor biopsy on C1D14. IPI-926 was administered by mouth starting on C1D15 and continued once daily by mouth thereafter. Patients underwent a third biopsy on C2D14-21. Patients who developed a cetuximab-rash were treated per local standard of care

### *IPI-926 dose escalation*

IPI-926 was administered at 130 or 160 mg daily to cohorts of 3 or more patients each using a standard "3 + 3" design. The 130 mg starting dose was chosen as representing the first dose level down from the established single-agent MTD of 160 mg in order to maximize safety. Each cohort initially enrolled up to 3 patients. Patients were considered evaluable for efficacy if they received at least four weeks of therapy unless the reason for not doing so was a dose limiting toxicity (DLT) or other IPI-926-related toxicity. Non-evaluable patients were replaced. If none of the first 3 evaluable patients experienced a DLT, then the dose of IPI-926 was escalated; if no more than 1 DLT was observed in the first 3 evaluable patients, the cohort was expanded to 6 patients. A dose was considered not tolerated if the observed rate of DLT in at least 6 patients was 33%. Patients were evaluated for efficacy by imaging using RECIST 1.1 every 8 weeks by imaging. Patients with stable disease or better received repeat cycles of treatment until progressive disease, unacceptable toxicity, or withdrawal of consent.

### *Safety monitoring*

Safety assessments included: vital signs, laboratory assessments, and physical exams. Adverse events were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.02. DLT included $\geqslant$grade 3 non-hematologic events considered possibly, probably, or definitely related to the combination study drug treatment, excluding untreated nausea, vomiting, or diarrhea.

### *Biopsy protocol and tissue analysis*

Two tumor tissue core biopsies were collected using standard practices by interventional radiology and samples were transferred directly to 10% formalin for processing. One fine needle aspirate (FNA) was deposited directly into RLT lysis buffer for RNA isolation (Qiagen) using the manufacturers protocol. RNA sequencing was performed on fresh or flash frozen FNA material. Tissue samples were cut and stained with hematoxylin-eosin (H/E) and by immunohistochemistry (IHC) that has been previously described [11]. HPV status was determined by *in situ* hybridization.

### *Statistics*

Sample size was determined empirically, based upon a 3 + 3 escalation design. Descriptive statistics were used for analyses of safety and tumor response. The bioinformatics strategy for RNAseq Analysis was previously reported [13].

## Results

### *Demographics and baseline characteristics*

Patient demographics and baseline characteristics are described in Table 1. Nine patients were enrolled and eight received therapy with both drugs ($N$ = 3 [130 mg], $N$ = 6 [160 mg]). The median age was 57 years and most patients were heavily pretreated. Most patients (77.8%) had received a prior EGFR-targeted therapy. A small majority of patients were HPV-positive (55.6%) and both local–regional and distant relapses were represented.

### *Dose and escalation safety*

IPI-926 dosing started at 130 mg and was escalated to 160 mg (single-agent MTD). No DLTs were seen in either of the 2 dose-escalation cohorts. Patients receiving at least one dose of either drug were evaluated for safety ($N$ = 9). The most frequent all-grade treatment emergent AEs attributed to IPI-926 were nausea (33%), muscle cramps (22.2%), and fatigue (22.2%) (Table 2). The most common all-grade treatment emergent AEs attributed to cetuximab were mucocutaneous (Table 2). One patient in the 160 mg cohort had a grade 3 infusion reaction to the loading dose of cetuximab and was replaced. Four patients experienced a total of four serious adverse events (SAEs); all were deemed due to concurrent illness or disease under study. One patient died while