A Phase 1 Study of CUDC-101, a multitarget inhibitor of HDACs, EGFR, and HER2, in combination with chemoradiation in patients with head and neck squamous cell carcinoma

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Abstract

Purpose: CUDC-101 is a small molecule that simultaneously inhibits the epidermal growth factor receptor (EGFR), human growth factor receptor 2 (HER2), and histone deacetylase (HDAC) with preclinical activity in head and neck squamous cell cancer (HNSCC). The primary objective of this investigation is to determine the maximum tolerated dose (MTD) of CUDC-101 with cisplatin-radiation in the treatment of HNSCC.

Experimental Design: CUDC-101 monotherapy was administered intravenously thrice weekly (M/W/F) for a 1-week run-in, then continued with concurrent cisplatin (100 mg/m^2 every 3 weeks) and external beam radiation (70 Gy to gross disease) over 7 weeks.

Results: Twelve patients with intermediate or high risk HNSCC enrolled. Eleven were p16INKa (p16) negative. The MTD of CUDC-101 based combination therapy was established at 275

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mg/m^2/dose. Five patients discontinued CUDC-101 due to an adverse event (AE); only one was considered a dose limiting toxicity (DLT), at the MTD. Pharmacokinetic evaluation suggested low accumulation with this dosing regimen. HDAC inhibition was demonstrated by pharmacodynamic analyses in peripheral blood mononuclear cells (PBMCs), tumor biopsies, and paired skin biopsies. Paired tumor biopsies demonstrated a trend of EGFR inhibition. At 1.5 years of median follow-up, there has been one recurrence and two patient deaths (neither attributed to CUDC-101). The remaining 9 patients are free of progression.

Conclusions: CUDC-101, cisplatin and radiation was feasible in intermediate/high risk patients with HNSCC, with no unexpected patterns of AE. Although the MTD was identified, a high rate of DLT-independent discontinuation of CUDC-101 suggests a need for alternate schedules or routes of administration.

Keywords

CUDC-101; EGFR; HER2; HDAC; HNSCC; cisplatin

Introduction

It is estimated that there will be more than 50,000 cases of head and neck cancer diagnosed in 2014(1) in the US. While an increasing proportion of these cases are human papillomavirus (HPV)-associated oropharynx cancer(2) in non-smokers associated with good prognosis, locally advanced HPV-associated oropharynx cancer in past/current smokers (intermediate risk) and HPV-negative (high risk) HNSCC do not share this excellent prognosis(3) and are in need of new treatment paradigms.

HNSCC tumors induced by environmental carcinogens typically bear a high number of mutations(4, 5). Targeting more than one relevant pathway may provide a therapeutic advantage. The only validated molecular target in HNSCC to date has been the EGFR, but preclinical models indicate that up-regulation of parallel receptor tyrosine kinases such as HER3 and MET may be important mechanisms of resistance to EGFR targeting(6). Inhibition of HDACs may be an effective means to interrupt such compensatory up-regulation given the proposed synergy of HDAC inhibition with ErbB blockade(7). Further, epigenetic changes such as acetylation of histones and non-histone proteins impact chromatin structure, affecting gene expression and contributing to cancer initiation, progression and treatment resistance(8), and may be amenable to treatment with HDAC inhibitors.

EGFR is overexpressed in up to 90% of HNSCC tumors(9), and high EGFR expression correlates with increased risk of local-regional relapse and poor overall survival following conventional radiotherapy(10). Targeting EGFR with concurrent radiation improves outcomes when compared to radiation alone(11), but EGFR inhibition combined with cisplatin and radiation in unselected patients has not been shown to be additive, regardless of HPV status(12, 13). HER2 is overexpressed in 20–40% of HSNCC and is associated with chemotherapy-refractory disease(14, 15). Although high membranous HER2 expression is an independent poor prognostic indicator for disease-free survival of HNSCC(16), HER2 has not yet been evaluated as a predictive biomarker of HER2 inhibitor therapy. HDAC 1

and 2 expression in oral tongue cancers (which are generally HPV negative) is associated with worse outcome(17). Although clinical experience with HDAC inhibitors is not as extensive as that with dual EGFR/HER2 inhibitors, HDAC inhibitors radiosensitize tumor cells both in vitro and in vivo(18, 19); prior experience suggests that such agents are well tolerated during radiation therapy(20, 21).

CUDC-101 (7-(4-(3-ethylnylphenylamino)-7-methoxyquinazolin-6-yloxy)-N-hydroxyheptanamide) contains multiple pharmacophores within a small molecule and simultaneously inhibits HDAC, EGFR, and HER2 in the preclinical setting. It has potent anti-proliferative activity against cultured and implanted tumor cells that are not sensitive to agents that target HDAC, EGFR, and HER2 individually, and has activity in HPV-negative head and neck cancer cell lines(22). The maximum tolerated dose (MTD) of CUDC-101 as a single agent is 275 mg/m^2 (23). This multicenter phase 1 dose escalation trial was designed to evaluate the safety, tolerability, and MTD of CUDC-101 when administered with concurrent cisplatin and radiation in subjects with locally advanced, intermediate or high-risk HNSCC. A pharmacokinetic sampling scheme was designed to determine multiple relevant parameters of CUDC-101 and its metabolite, CUDC-101Met-M1. Finally, for proof of concept, paired tumor and skin biopsies were obtained to evaluate pharmacodynamic target inhibition by CUDC-101.

Methods

Patient eligibility

This was a multi-institutional phase 1 single arm dose-escalation trial. It was approved and activated by the Institutional Review Boards of all participating centers. Eligibility included patients with stage III/IV locally advanced HNSCC of the oral cavity, oropharynx, hypopharynx, and larynx and either 1) stage IV p16-positive tumor and > 10 pack years smoking history, or 2) stage III/IV p-16-negative tumor with evaluable disease by RECIST (version 1.1) criteria; no prior systemic therapy for the index cancer; age 18 years or greater; ECOG PS of 0–2; and adequate bone marrow function as denoted by ANC   1800/μL, platelets   100,000 μL, hemoglobin   8.0 g/dL, creatinine   1.5x upper limit of normal (ULN), total bilirubin   1.5x ULN, AST/ALT   2x ULN. Exclusion criteria included tumors of the nasopharynx and paranasal sinuses, and prior therapy targeted at EGFR, HER2, or HDAC for any indication. HPV status was determined by p16 immunohistochemistry. Patients were defined as HPV positive in the setting of strong and diffuse nuclear and cytoplasmic staining of p16 in   70% of tumor cells.

Clinical staging at presentation (within four weeks of the first administration of CUDC-101) included both anatomic (either CT or MRI, depending on the treating physician's preference) and functional (PET/CT) imaging.

Objectives and treatment administration

The principal objective of the trial was to determine the safety, tolerability, and MTD of CUDC-101 in combination with high dose cisplatin and external beam radiation for patients with locally advanced HNSCC. The secondary objectives were to evaluate the efficacy of

CUDC-101, cisplatin and radiation combination therapy; to assess the pharmacokinetics of CUDC-101; and to assess the pharmacodynamics of CUDC-101.

The initial dose of CUDC-101 for this clinical trial was 225 mg/m^2. This dose was chosen because it is 80% of the MTD established in the previous phase I mono-therapy trial with CUDC-101(23, 24). The second cohort was escalated to 275 mg/m^2; no escalation beyond the monotherapy MTD was planned. Doses of CUDC-101 were administered by intravenous (IV) infusion over 1 hour 3 times per week (Monday, Wednesday, Friday) for one week prior to the initiation of radiation and then as a part of combined modality treatment for weeks 1 – 7. Prior to the beginning of each treatment week, the following laboratory values were confirmed prior to therapy: ANC > 1,000 μL, platelets 50,000 μL, AST and ALT 5x ULN, bilirubin concentration 3x ULN, and normal serum potassium and magnesium (supplementation to maintain normal values allowed). Additionally, prior to every CUDC-101 administration the serum creatinine concentration was checked and dose modifications were applied. CUDC-101 was never administered on the same day as high dose (100 mg/m^2) cisplatin, which was administered on days 2, 23, and 44.

Cisplatin 100 mg/m^2 was administered every 3 weeks according to national guidelines. If during treatment it became apparent that cisplatin was resulting in unacceptable toxicity, the schedule and dose of cisplatin could be adjusted to 40 mg/m^2/week following discussion with the medical monitor. Pre-and post-cisplatin hydration was recommended as well additional IV hydration with normal saline (NS) 2–3x/week during therapy. Institutional guidelines for highly emetogenic regimens were followed with the administration of cisplatin.

A conventionally fractionated external beam radiotherapy regimen using intensity modulated radiation therapy (IMRT) was employed. Treatment of the low neck could be achieved with either a split-field matched to low anterior neck (LAN) technique or whole neck IMRT at the discretion of the treating radiation oncologist. Gross disease (both primary tumor and radiographically/clinically involved lymph nodes) was treated to a dose of 70 Gy with 2 Gy once daily fractions for a total of 35 treatment days. The elective neck(s) was treated to a dose of 56 Gy with 1.6 Gy once daily fractions in a dose-painting technique. A 63 Gy intermediate risk volume was optional. Institutions that chose to use image guided radiation therapy (IGRT) were permitted to decrease planning target volume (PTV) expansions to a minimum of 2.5 mm.

Dose escalation

A dose-limiting toxicity (DLT) was defined as a grade 3 non-hematologic toxicity that is considered a direct result of CUDC-101 therapy, excluding untreated nausea/diarrhea, dysphagia/weight loss or dermatitis/rash attributed to CUDC-101 and/or chemoradiation. Other DLTs included grade 4 dermatitis resulting in radiation break of > 4 days, grade 4 mucositis/esophagitis resulting in a radiation break of > 4 days, grade 4 neutropenia lasting > 7 days, and grade 4 thrombocytopenia (or grade 3 thrombocytopenia with bleeding).

The initial subject in each cohort was required to complete the 7 weeks of combined modality therapy prior to the enrollment of additional subjects in the cohort. All subjects in

the cohort were mandated to complete the 7 weeks of therapy prior to escalation to the next cohort. Dose escalation followed a classic 3 + 3 design, with expansion to 6 patients if one DLT was observed. If 2 subjects experienced a DLT at a certain dose level, then the MTD would be considered to be exceeded and an additional 3 subjects (total of 6) would be treated at the next lower dose level. The MTD was defined as the dose level immediately below that at which two or more subjects experience a DLT.

Dose modifications

CUDC-101 was held for grade 3–4 toxicities. If the delay was 2 consecutive CUDC-101 treatment days, treatment was resumed at the current dose level after improvement of the grade of toxicity. If the delay was > 2 days, treatment was resumed with a dose reduction. If toxicities continued at the reduced dose level, CUDC-101 was held indefinitely (i.e. only one dose reduction was permissible for each subject). To avoid any possibility of delaying the initial dose of cisplatin, subjects exhibiting an acute elevation of creatinine during the run-in phase of the trial (week −1: treatment with CUDC-101 alone) were discontinued from the trial and replaced. Acute creatinine increases were defined as a >2 x baseline increase in creatinine occurring within 48 hours of the first administration of CUDC-101 on day −7.

Response evaluation and follow-up

Evaluation of response was conducted by RECIST (version 1.1) and the principal investigator at each site recorded an 'Overall Clinical Response Assessment' for each patient, taking into account anatomic imaging, functional imaging (a PET/CT was required at 12 weeks after the completion of therapy), clinical examination and any post-treatment histology (i.e. both biopsy of suspicious imaging findings and attempts at surgical salvage at the primary site and/or neck). All sites provided extended follow-up on treated patients prior to manuscript submission.

Pharmacokinetic/Pharmacodynamic Analysis

Plasma (3 mL) and urine samples were collected on days −7 (CUDC-101 alone) and day 43 to determine the following pharmacokinetic parameters of CUDC-101 and its metabolite CUDC-101Met-M1: clearance (CI), apparent volume of distribution at steady-state (Vd_{ss}), maximum concentration (C_{max}), time of maximum concentration (T_{max}), half-life ($T_{1/2}$), area under the curve ($AUC_{0\text{-inf}}$ and $AUC_{0\text{-t}}$) and other relevant parameters.

PBMCs were obtained prior to CUDC-101 administration and 60±30 minutes after the completion of CUDC-101 infusion on days −7, −3, and 43. Western blot analysis was conducted to evaluate the levels of acetylated histone H3 and histone H3 in PBMCs. Briefly, PBMCs were collected and isolated with BD Vacutainer® tubes according to manufacturer's instruction, and cryoperserved. PBMCs are recovered and batch analyzed by immunoblotting. Primary antibodies to detect acetylated histone H3 (06–599) and histone H3 (05–499) were obtained from Millipore. Secondary antibodies conjugated with fluorescent dye (926–32211 and 926–32210) were obtained from Li-Cor Biosciences. Blots were imaged and quantified with Odyssey® Infrared Imaging System. The ratios of acetylated histone H3 against total histone H3 were normalized to the pre-treatment baseline level of each patient on day −7.

Skin punch biopsies were obtained prior to and 60±30 minutes after completion of CUDC-101 IV infusion on days −7, −3, and 43. Within 2 minutes of collection, skin biopsies were fixed in 10% neutral buffered formalin for 6–24 hours and embedded in paraffin. Immunohistochemistry (IHC) staining was carried out on 5-μm sections of paraffin-embedded tissue at the Curis analytic lab. Antigen retrieval was performed by incubating slides in Target Retrieval Solution (Dako S1699) at 125°C for 30 seconds followed by 90°C incubation for 10 seconds. The antibodies used for detecting acetylated histone H3 were obtained from CST (9671) and Dako (K4002). Digital pathological quantification was performed with the Pannoramic NuclearQuant IHC quantification software as previously described(24). Briefly, more than 500 cells from 2 representative areas were evaluated on each slide. The histology score (H-score) was obtained by the formula: 3 x percentage of strongly staining nuclei + 2 x percentage of moderately staining nuclei + percentage of weakly staining nuclei, giving a range of 0 to 300.

Diagnostic archival tumor samples were obtained prior to CUDC-101 treatment. Fresh tumor biopsies were obtained 60±30 minutes after the completion of CUDC-101 IV infusion on day −5 or day −3 from subjects with at least 1 tumor lesion that was suitable for repeat biopsy. IHC staining for acetylated histone H3 was conducted using the same method as described in the skin biopsy method section above. For phosphorylated EGFR (pEGFR) IHC staining, antigen retrieval was performed by incubating slides in antigen retrieval solution (10mM Tris, 1mM EDTA pH 8.0, 0.05% Tween 20, pH9.0) at 95°C for 10 minutes followed by incubation at 90°C for 5 minutes. Anti-pEGFR Y1068 antibody was obtained from CST (3777), and the secondary antibody was obtained from Dako (K4002).

Fluorescent in situ hybridization (FISH) analysis was also conducted on tumor samples to evaluate EGFR and HER2 gene amplification status. FISH was performed with HER2 FISH pharmDx (Dako K5331) and EGFR/CEN-7 probe mix (Dako Y5500) according to manufacturer's protocol. Fluorescent signal was assessed under a Nikon Eclipse E800 microscope (Nikon). Greater than 50 cells were manually evaluated on each sample.

Statistical Analysis

The anticipated accrual to the trial was 12–22 subjects in the dose escalation phase and up to 10 subjects in the expansion cohort, excluding replacements. Thus, given the small sample size, it was anticipated that the statistical analyses would be primarily descriptive in nature, including incidences of adverse events, DLTs, estimates of pharmacokinetics, and descriptions of tumor and biomarker responses.

Results

Patients

Twelve patients enrolled from November 2011 until October 2013. All but one patient was p16 negative. Four patients received treatment on the initial dose level (225 mg/m^2) and eight patients received treatment at dose level 2 (275 mg/m^2). Dose reductions of CUDC-101 were not necessary. The baseline characteristics of the patients are listed in

Table 1. Median age was 62 (range 52–71) and the majority of patients were male. The most common site was the oropharynx.

Safety of dose escalation

The phase 1 portion was completed and the MTD was defined per protocol. Although the regimen was feasible, the trial was discontinued prematurely before proceeding to a dose expansion cohort due to a high CUDC-101 discontinuation rate independent of DLT, prioritization of an oral formulation of CUDC-101 for clinical testing, and slow accrual.

Five patients (42%) discontinued CUDC-101 treatment due to an adverse event. The likelihood of discontinuation was higher among patients treated in the higher dose cohort (n = 4, 50% of patients in cohort) than the lower dose cohort (n = 1, 25% of cohort). Only one of these events (grade 3 renal injury in a patient treated on level 2) was considered a DLT. Two patients discontinued investigational therapy secondary to toxicity encountered during the run-in period (Table 2).

The single adverse event at dose level 1 was grade 2 joint pain and myalgia during the run-in with CUDC-101 alone, and thus a total of 4 patients were treated at dose level 1. No DLT was noted among the 3 patients who received combination therapy at dose level 1. Eight patients received therapy at dose level 2 with CUDC-101 at a dose of 275 mg/m^2. One DLT, a grade 3 renal injury, was noted during week 1 at dose level 2. Both cisplatin and CUDC-101 were discontinued; radiation was continued and completed in 42 days. Other AEs resulting in discontinuation of CUDC-101 were grade 1 blood creatinine increase (n=1), grade 5 cardiac failure (n=1), and grade 3 infusion site extravasation (n=1). Per protocol definition, the CUDC-101 dose of 275 mg/m^2 was declared the MTD. However, the high, DLT-independent discontinuation rate of CUDC-101 warrants consideration of alternate schedules or routes of administration when determining further development.

All patients experienced at least one AE. Consistent with expected events in patients receiving high dose cisplatin and radiation, the AEs reported by 50% of subjects were fatigue (67%), stomatitis (67%), nausea (50%), and weight loss (50%). Most adverse events were mild or moderate (grade 1 or 2) in intensity. A total of 7 patients experienced a serious adverse event (SAE); five patients treated at dose level 2 (63%) and two patients treated at dose level 1 (50%). Five patients experienced an SAE considered related to any agent and two, both at dose level 2, experienced an SAE considered related to CUDC-101 (Table 3).

One patient expired during week five of combination therapy secondary to cardiac failure unrelated to trial drug or chemoradiation. A second death after completion of therapy was attributed to thromboembolic complications following a planned neck dissection, and not attributed to trial drug or chemoradiation.

Response Evaluation

Eleven (92%) patients had an overall clinical evaluation assessment form completed after therapy. Eight (67%) patients were evaluable per RECIST. Per protocol, the assessments of efficacy were made at 4 and 12 weeks after completion of combination therapy. Of the 11 patients with a post-treatment clinical assessment, 7 (63%) were considered improved with

therapy while 4 (37%) were considered stable. Similarly, among patients evaluable by RECIST, 5 (63%) demonstrated an objective response and 3 (37%) demonstrated stable disease.

Given the difficulty of assessing long-term disease control at 12 weeks after chemoradiation for poor prognosis tumors, more detailed follow-up was pursued and is listed in Table 4. Extended follow-up data demonstrated encouraging tumor control; although 3 patients were staged as stable following CRT, 90% of patients were progression free at a median of 1.47 (0.68 – 2.3) years of follow-up.

Pharmacokinetic evaluation

Plasma pharmacokinetic evaluations for CUDC-101 and its metabolite CUDC-101Met-M1 were performed on 12 patients on day −7 (first administration of CUDC-101 during run-in component) and 7 patients on day 43 (last administration of CUDC-101). Exposure to the parent compound, CUDC-101, was greater in all subjects when compared to its metabolite (data from metabolite not shown). Peak concentrations and exposure of CUDC-101 and its metabolite were similar between days −7 and 43, indicating a low probability of accumulation with this dosing regimen. There was no clear dose dependent increase in exposure or peak concentration, although this comparison is limited due to potential anomalous concentrations. Pharmacokinetic results are displayed in Table 5.

Pharmacodynamic evaluation

Post-treatment tumor biopsies were successfully obtained from five patients. IHC staining was performed on the post-treatment tissue together with associated pre-treatment archival tumor samples. Biomarker changes in 2 of the 5 pairs could not be evaluated due to the lack of phosphorylation and acetylation signal in the archival samples as a result of the age or condition of these samples. Phosphorylation on both Y1068 (Supplement Figure 1A) and Y1173 (data not shown) of EGFR was evaluated in 2 pairs due to limitation in the amount of tissue, and a trend of EGFR inhibition was observed. The HDAC inhibition, as evidenced by increased histone H3 acetylation, was observed from all 3 pairs of tumor biopsy (Supplement Figure 1B), paired skin biopsies from all 8 patients (Supplement Figure 1C), and paired PBMC samples from all 7 patients (Supplement Figure 1D). These results indicate that the doses delivered achieved a biologic effect.

Archival tumor sample FISH analysis detected EGFR amplification from 1 patient and HER2 polysomy in a small number of tumor cells in another patient (Supplement Figure 2).

The low numbers of patients and overall high degree of efficacy with the majority responding to CRT plus CUDC-101 precludes drawing any further conclusions about the association of either baseline levels or post-treatment changes of any of these markers with efficacy, even though a trend of higher histone H3 acetylation was observed in the PBMCs from patients with complete response (Supplement figure 3).

Discussion

This phase 1 trial intended to establish the MTD of CUDC-101 with concurrent high dose cisplatin and conventionally fractionated head and neck radiation. Although only 1 DLT at the previously established single agent MTD was encountered, this case of renal toxicity occurred despite lack of creatinine elevation during the monotherapy run-in, raising the possibility of additive toxicity. The trial was discontinued before proceeding to a dose expansion cohort due to the sponsor's prioritization of an oral formulation of CUDC-101 for further development. The established MTD of 275 mg/m^2 must be balanced against a slightly higher discontinuation rate of trial drug in dose level 2 (n=4, 50%) compared to dose level 1 (n=1, 25%). Although grade 3–4 AEs were reported for a high percentage (8/12) of patients, this represents an expected toxicity profile with concurrent cisplatin and radiation. Importantly, only two patients experienced SAEs attributable to CUDC-101. No extended radiation treatment breaks attributable to toxicity from the investigational product were encountered, suggesting that even in the setting of an SAE, delivery of CUDC-101 did not interfere with timely completion of radiation therapy. Pharmacokinetic data demonstrated similar peak concentrations and exposure of CUDC-101 and its metabolite at the beginning and end of therapy, suggesting minimal accumulation when administered according to the dosing schedule per protocol. Although pharmacodynamic studies were limited by patient refusal of repeat biopsy and limited pEGFR signal, available data demonstrated both EGFR and HDAC inhibition.

This phase 1 trial was an investigation of an intensification strategy – by deploying multi-pathway targeting for intermediate/high risk HNSCC that does not respond well to concurrent chemoradiation. Since the discovery of the prognostic importance of HPV association, investigations of other concurrent chemoradiation treatment intensification strategies have been retrospectively re-analyzed with respect to archived tumor HPV status. These have demonstrated that three commonly practiced modes of treatment intensification-docetaxel based induction chemotherapy[25] followed by chemoradiation, accelerated fractionation radiation with concurrent cisplatin[3], and concurrent cisplatin, radiation and cetuximab[12]-do not seem to produce satisfactory results in the treatment of intermediate/high risk HNSCC.

Recent analysis has suggested up-regulation and activation of HER2 in HNSCC cell lines that have developed cetuximab resistance secondary to prolonged exposure[15]. Although dual targeting agents (EGFR and HER2) are not efficacious as monotherapy[26] regardless of prior exposure to cetuximab, two separate trials demonstrated efficacy when combined with radiation[27], particularly among HPV negative patients[28]. Thus, it seems HER2 may be a target in intermediate and high risk head and neck cancer[29].

Epigenetic control of gene expression has been shown to play an important role in cancer initiation, progression, and resistance. Preclinical studies have demonstrated anticancer effects of HDAC inhibitors, with the greatest effects when used in combination therapy. HDAC inhibitors have also been shown to be effective radiation sensitizers in a variety of cancer cell lines while sparing normal tissues[30]. Preclinical studies with CUDC101 demonstrated reduced phosphorylation of Akt compared with erlotinib or suberoylanilide

hydroxamic acid (SAHA) alone(22). Further, trafficking of EGFR to the nucleus, and nuclear EGFR regulation of chromatin access may represent a mechanism of resistance to radiation that is of particular relevance in HPV-negative HNSCC(31, 32).

Although the protocol stipulated response assessment revealed that one-third of patients failed to achieve an objective response with combination therapy, the majority of non-responsive patients did not progress or relapse, emphasizing the difficulty of early clinical and radiographic assessment in this curative patient population(33). Only one recurrence has been encountered (a local recurrence marginal to the radiation field at 13 months after the completion of therapy in the sole patient that experienced a DLT) at a median follow-up of 1.5 years. Two patients have expired from intercurrent disease; neither death was thought to be secondary to combination therapy or its complications. Although this was a small phase 1 trial with a 1 year overall survival consistent with standard therapy(3), the relative lack of progression after therapy suggests that multi-pathway targeting warrants further investigation in patients with intermediate and high risk HNSCC, both as a means to improve cure and potentially as a mechanism for sparing acute and late toxicity from concurrent cisplatin and radiation(34).

In summary, this phase 1 trial showed that the combination of the EGFR/HER2/HDAC inhibitor CUDC-101 and conventional chemoradiation was tolerated at biologically efficacious doses. While the MTD was identified, a high rate of DLT-independent discontinuation of CUDC-101 suggests that alternate schedules or routes of administration may be preferable. Although not a planned objective, this trial showed the feasibility of conducting biomarker sample intensive phase 1 studies in the curative setting at experienced HNSCC academic sites.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

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Translational relevance statement

This trial evaluates the addition of a small molecule, CUDC-101, that simultaneously inhibits EGFR, HER2, and HDAC, to standard concurrent cisplatin-radiation in the treatment of HNSCC. Given the poor prognostic implications of EGFR, HER2, and HDAC overexpression, and the potential for HDAC inhibition to interfere with compensatory up-regulation of redundant receptor tyrosine kinases when the HER receptor family is inhibited, CUDC-101 is hypothesized to increase the efficacy of cisplatin-radiation. This phase I trial describes the initial tolerability of this regimen, confirms target inhibition, and identifies the MTD. Furthermore, this study demonstrates the feasibility of conducting fresh tissue-based pharmacodynamic studies in phase 1 trials in the curative setting with experienced HNSCC academic sites.

Table 1:

Patient characteristics

	225 mg/m^2 (n = 4)	275 mg/m^2 (n = 8)	Overall (n = 12)
Age (years)	60.5	63	62 (52 – 71)
Gender			
Male	4	5	9 (75%)
Female	0	3	3 (25%)
ECOG PS			
0	2	4	6 (50%)
1	2	4	6 (50%)
Primary tumor site			
Oropharynx	2	4	6 (50%)
Oral Cavity	0	2	2 (16.3%)
Larynx	0	2	2 (16.3%)
Hypopharynx	2	0	2 (16.3%)
Stage			
III	0	3	3 (38%)
IV	4	5	9 (72%)
HPV p16 status			11 (92%)
positive	0	1	1 (8%)
negative	4	7	11 (92%)

Table 2:

Treatment delivery

Parameter (n)	225 mg/m²	275 mg/m²	Overall
Pts with ≥ 1 dose any agent	(n = 4)	(n = 8)	(n = 12)
Week –1	4	8	12
Week 1	3	7	10
Weeks 2–5	3	6	9
Weeks 6–7	3	5	8
Combination treatment (median # doses)			
CUDC-101	19	14	15
Radiotherapy [o] (Gy)	32 (64)	33 (66)	32.5 (65)
Cisplatin (mg)	3 (479)	2 (358)	2 (394)
Reason discontinued any agent			
Withdrew consent	1	0	1
Toxicity [*]	1	3	4
Other	1	1	2

[*] Creatinine increased (2 patients), renal injury and pneumonia (1 patient each)

[o] Numbers reflect median RT fractions received on protocol. All living patients received 35 fractions.

Table 3:

SAEs related to any agent

SAE	Dose Level 1 225 mg/m^2	Dose Level 2 275 mg/m^2	Agent
Number of patients witd at least 1 SAE	**2 (50%)**	**3 (38%)**	
Failure to thrive	1 (25%)		Cisplatin/Radiation
Fluid overload		1 (25%)	Cisplatin
Hyperglycemic hyperosmolar nonketotic syndrome	1 (25%)		Cisplatin
Hypoxia		1 (25%)	Cisplatin
Pneumonia	1 (25%)		Cisplatin
Acute Kidney Injury [*]		1 (25%)	Cisplatin/CUDC-101
Stomatitis		1 (25%)	Cisplatin/Radiation/CUDC-101

[*] Regulatory submissions assigned two SAEs (Acute Renal Failure and Renal Injury) to the same patient. For clarity of reporting, this is presented as a single SAE of 'Acute Kidney Injury' per CTCAE v4.0.

Table 4:

Best overall response

Dose Level	Clinical Response Assessment (n = 11)	RECIST Assessment (n = 8)	Long Term Follow-up (n = 12) Median fu 1.47 (0.68–2.3) years
1	Improved: 3	Confirmed CR: 1	NED: 3
		Confirmed PR: 1	DID: 1
		SD: 1	
2	Improved: 4	Confirmed CR: 2	NED: 6
	Stable: 4	Unconfirmed CR: 2	Local Recurrence: 1
		SD: 1	DID: 1

RECIST: Response evaluation criteria in solid tumors, CR: Complete response, PR: Partial response, SD: Stable disease, NED: No evidence of disease, DID: Dead of intercurrent disease

Table 5:

Mean (CV%) Pharmacokinetics of CUDC-101

Day	Cohort/Dose (mg/m^2)	T_{max}[a] (h)	C_{max} (µg/mL)	AUC_{last} (h•µg/mL)	Half-Life (h)	Cl (L/h)	Vd_{ss} (L)
−7	1/225	0.542 (0.500–1.00)	13.1 (95.8)	9.92 (72.4)	2.83 (84.0)	56.3 (41.7)	26.6 (37.6)
43	1/225	1.25 (1.00–1.50)	8.89 (NA)	7.11 (NA)	3.91 (NA)	53.7 (NA)	54.4 (NA)
−7	2/275	0.500 (0.450–1.12)	7.89 (11.5)	8.00 (18.7)	2.88 (56.9)	63.7 (23.0)	42.3 (25.9)
43	2/275	0.742 (0.467–1.08)	7.82 (8.57)	7.77 (9.39)	6.41 (56.8)	61.0 (11.7)	76.0 (43.4)

AUClast= area under the plasma concentration-time curve from time 0 to time of last measurable plasma concentration calculated using the linear-up log-down trapezoidal rule; Cl=clearance; Cmax= maximum observed plasma concentration; %CV=coefficient of variation; NA=not available; PK=pharmacokinetic; Tmax= time of maximum concentration (h), obtained directly from the observed concentration versus time data; Vdss=volume of distribution at steady state.