Palbociclib and cetuximab in platinum-resistant and in cetuximab-resistant human papillomavirus-unrelated head and neck cancer: a multicentre, multigroup, phase 2 trial

Douglas Adkins, Jessica Ley, Prakash Neupane, Francis Worden, Assuntina G Sacco, Kevin Palka, Juneko E Grilley-Olson, Ronald Maggiore, Noha N Salama, Kathryn Trinkaus, Brian A Van Tine, Conor E Steuer, Nabil F Saba*, Peter Oppelt**

Summary

Background Most head and neck squamous-cell carcinomas (HNSCCs) are driven by $p16^{INK4A}$ inactivation and cyclin D1 overexpression that results in hyperactivation of cyclin-dependent kinase 4 and 6 (CDK4/6), rather than by the human papillomavirus (HPV). Deregulated cyclin D1 expression also causes resistance to EGFR inhibitors. We previously reported that palbociclib (a selective CDK4/6 inhibitor) given with cetuximab (an EGFR inhibitor) was safe. The aim of this study was to establish the proportion of patients achieving an objective response with palbociclib and cetuximab in recurrent or metastatic HNSCC.

Methods We did a multicentre, multigroup, phase 2 trial to evaluate the activity of palbociclib and cetuximab in platinum-resistant (group 1) and cetuximab-resistant (group 2) HPV-unrelated HNSCC. The study was done across eight university sites in the USA. Eligibility required measurable disease (according to Response Evaluation Criteria in Solid Tumors, version 1·1 [RECIST 1·1]), Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, age of 18 years or older, and disease progression on platinum but cetuximab-naive (group 1) or disease progression on cetuximab (group 2). All patients received palbociclib orally (125 mg/day, on days 1–21) and intravenous cetuximab (400 mg/m² on cycle one, day 1, then 250 mg/m² once per week) in 28-day cycles. The primary endpoint was objective response (complete responses and partial responses per RECIST 1·1). Analyses were done per protocol. This trial was registered with ClinicalTrials.gov, NCT02101034, and is ongoing, but both groups are closed to accrual.

Findings Between Oct 19, 2015, and Nov 7, 2018, 62 patients were enrolled onto the trial: 30 patients were enrolled in group 1 and 32 in group 2. Median follow-up was 5·4 months (IQR 4·4–12·1) for group 1 and 5·5 months (4·3–8·3) for group 2. In group 1, of 28 evaluable patients, an objective response was achieved by 11 (39%; 95% CI 22–59). In group 2, of 27 evaluable patients, an objective response was achieved by five (19%; 6–38) in group 2. The most common grade 3–4 palbociclib-related adverse event was neutropenia (in 21 [34%] of 62 patients). No treatment-related deaths occurred.

Interpretation In patients with platinum-resistant or cetuximab-resistant HPV-unrelated HNSCC, palbociclib and cetuximab results in promising activity outcomes. Further studies of CDK4/6 inhibitors are warranted in HPV-unrelated HNSCC.

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*Joint senior authors

Division of Medical Oncology (Prof D Adkins MD, J Ley BS, K Palka MD, B A Van Tine MD, P Oppelt MD), **Biostatistics Shared Resource** (K Trinkaus PhD), **and Alvin J Siteman Cancer Center** (Prof D Adkins, B A Van Tine, P Oppelt), **Washington University School of Medicine, St Louis, MO, USA; Division of Oncology, University of Kansas School of Medicine, Kansas City, KS, USA** (P Neupane MD); **Department of Medicine, University of Michigan, Ann Arbor, MI, USA** (Prof F Worden MD); **University of California San Diego Moores Cancer Center, La Jolla, CA, USA** (A G Sacco MD); **Department of Medicine, St Louis University, St Louis, MO, USA** (K Palka MD); **Department of Medicine, Division of Hematology-Oncology, and Lineberger Comprehensive Cancer Center, University of North Carolina School of Medicine, Chapel Hill, NC, USA** (J E Grilley-Olson MD); **Department of Medicine, Wilmont Cancer Institute at the University of Rochester, Rochester, NY, USA** (R Maggiore MD); **Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Cairo University, Cairo, Egypt** (N N Salama PhD); **Department of Pharmaceutical and Administrative Sciences, St Louis College of Pharmacy, St Louis, MO, USA** (N N Salama); **and Winship Cancer Institute of Emory University, Atlanta, GA, USA** (C E Steuer MD, Prof N F Saba MD)

Introduction

Head and neck cancer is the sixth most common cancer globally,[1] and in 2016, more than 800 000 new cases occurred worldwide.[2] Half of these patients will develop recurrent or metastatic disease. Progress in the treatment of recurrent or metastatic head and neck cancer has been slow over the past decade. Since 2008, first-line treatment has been platinum-based therapy (ie, platinum, 5-flurouracil, and cetuximab as investigated in the EXTREME trial).[3] When our trial began in 2015, the only drug with regulatory approval for treatment of platinum-resistant head and neck cancer was cetuximab. The efficacy of cetuximab was modest, with an objective response achieved by only 13% of patients, median time-to-progression of 2·3 months, and overall survival of 6 months.[4] Nivolumab and pembrolizumab were each approved by the US Food and Drug Administration for this indication in 2015, and 2018, respectively.[5,6] These drugs inhibit PD-1, an important negative regulator of the effector phase of T-cell responses. These PD-1 inhibitors resulted in an objective response in 13–15% of patients, median progression-free survival of 2·0–2·1 months, and median overall survival of 7·5–8·4 months.[5,6]

Currently, effective therapeutic options for patients with cetuximab-resistant head and neck squamous-cell carcinomas (HNSCCs) are few. Traditional chemotherapy has marginal activity, with 6% of patients or fewer achieving a tumour response.[7] The most effective therapy for these patients might be pembrolizumab or nivolumab, which have resulted in responses in 11–16%

Correspondence to:
Prof Douglas Adkins, Division of Medical Oncology, Washington University School of Medicine, St Louis, MO 63110, USA
dadkins@wustl.edu

Research in context

Evidence before this study

We searched PubMed for articles published in English from Jan 1, 2009, to Dec 1, 2018, with the terms "recurrent or metastatic" and "head and neck cancer" and "platinum" or "cetuximab"; our search yielded 139 items. When we began our study, the only regulatory-approved drug for treatment of platinum-resistant head and neck squamous-cell carcinoma (HNSCC) was cetuximab. Since then, the PD-1 inhibitors nivolumab and pembrolizumab have shown benefit in platinum-resistant disease. There were no regulatory-approved drugs for treatment of cetuximab-resistant disease, with only one drug class—the PD-1 inhibitors—showing clinically meaningful activity in this setting. We did a separate PubMed search for publications with the terms "CDK4/6" and "head and neck cancer"; 17 items were found. Most HNSCCs are unrelated to the human papillomavirus (HPV), and are driven by $p16^{INK4A}$ inactivation and cyclin D1 overexpression that cause hyperactivation of cyclin-dependent kinase 4/6 (CDK4/6), which drives the cell cycle and tumour growth. Deregulated cyclin D1 expression also causes resistance to EGFR inhibitors. These somatic genomic alterations pointed to inhibition of CDK4/6 as a potential targeted therapeutic strategy in HPV-unrelated HNSCC. The CDK4/6 inhibitor palbociclib arrests cell cycle progression by selective CDK4/6 inhibition and might also reverse intrinsic resistance to cetuximab by countering the actions of deregulated cyclin D1. The antiproliferative and antitumour effects of selective CDK4/6 inhibition have been demonstrated in HNSCC cell lines and xenografts. In HPV-unrelated HNSCC cell lines, the combination of palbociclib and an EGFR inhibitor synergistically reduced cell viability and ERK1/2 phosphorylation. Only one previous clinical trial evaluated a CDK4/6 inhibitor in HNSCC—a phase 1 trial, in which we showed that palbociclib given with cetuximab was safe and resulted in objective tumour responses in platinum-resistant and cetuximab-resistant HPV-unrelated HNSCC.

Added value of this study

To our knowledge, this is the first clinical study to assess the activity of a selective CDK4/6 inhibitor in HNSCC. This study showed that palbociclib in combination with cetuximab exhibited substantial antitumour activity in platinum-resistant (group 1) and in cetuximab-resistant (group 2) HPV-unrelated recurrent or metastatic HNSCC. In group 1, the proportion of patients achieving an objective response (39%) was greater than that observed with single-agent cetuximab, or with PD-1 inhibitors. The median overall survival of 9·5 months with palbociclib and cetuximab was better than that with cetuximab monotherapy. In group 2, 19% of patients achieved an objective response, the median duration of response was 6 months, and the median overall survival was 6·3 months. These data are similar to outcomes with PD-1 inhibitors. Concurrent treatment with palbociclib and cetuximab did not significantly alter the expected pharmacokinetics of either drug given as monotherapy. The results of this study support the hypothesis that inhibition of CDK4/6 is a relevant therapeutic strategy in HPV-unrelated HNSCC.

Implications of all the available evidence

The results of this trial warrant further studies evaluating CDK4/6 inhibitors in this disease. Several preclinical reports support combining CDK4/6 inhibitors with PD-1–PD-L1 or angiogenesis inhibitors to enhance antitumour activity. Our trial provides an important platform to evaluate the addition of other targeted agents to improve the efficacy of CDK4/6 inhibitors in HNSCC.

of patients and median overall survival of 6·9–8·0 months.[8,9] Novel treatment strategies are needed for patients with recurrent or metastatic HNSCC.

Most head and neck cancers are squamous-cell carcinomas (SCCs) caused by smoking, and are unrelated to the human papillomavirus (HPV). These cancers have a poorer prognosis than HPV-related disease. Current therapy does not target the underlying tumour biology of HPV-unrelated HNSCC—ie, unrestrained activation of the cyclin-dependent kinase 4 and 6 (CDK4/6) and cyclin D1 regulatory complex. This key event drives the cell cycle and tumour progression. The Cancer Genome Atlas showed that cell cycle deregulation is ubiquitous in HNSCC.[10] In HPV-unrelated disease, cell cycle deregulation is a result of deletion of the *CDKN2A* gene, which encodes the tumour suppressor $p16^{INK4A}$ protein (the inhibitor of CDK4/6), and amplification of the *CCND1* gene, which encodes the cyclin D1 protein (the activating regulatory subunit of the complex). Cetuximab inhibits the cell cycle by preventing dimerisation and activation of EGFR. The modest antitumour activity of cetuximab in HPV-unrelated HNSCC might be due to downstream hyperactivation of CDK4/6. Collectively, these data point to inhibition of CDK4/6 as a potential targeted therapeutic strategy to pursue in HPV-unrelated HNSCC.

Selective inhibition of CDK4/6, by palbociclib or abemaciclib, arrests the cell cycle and inhibits tumour growth in preclinical models of HNSCC. Abemaciclib had antiproliferative and antitumour effects in HNSCC cell lines and xenografts.[11] Palbociclib and an EGFR inhibitor synergistically reduced viability of HPV-unrelated HNSCC cell lines.[12] Palbociclib might also reverse resistance to cetuximab by countering the actions of deregulated cyclin D1.[13] We previously reported the results of a phase 1 trial that combined palbociclib with cetuximab.[14] The regimen was safe and tolerable. Objective tumour responses occurred in patients with platinum-resistant and cetuximab-resistant HPV-unrelated HNSCC.

On this basis, we did a multicentre, phase 2 trial of palbociclib in combination with cetuximab in

platinum-resistant (group 1) and cetuximab-resistant (group 2) HPV-unrelated HNSCC to assess the activity of this novel therapy in patients selected to most likely benefit from a CDK4/6 inhibitor. A 2017 report[15] showed that some cases of recurrent and metastatic HPV-related HNSCC can exhibit a genomic profile similar to HPV-unrelated disease. On the basis of these data, the trial also includes an ongoing third group that tests the activity of this regimen in patients with HPV-related cetuximab-resistant oropharynx squamous cell carcinoma (group 3). In this Article, we report the results of groups 1 and 2.

Methods

Study design and participants

We did a multicentre, multigroup, phase 1–2 trial at eight university sites in the USA. The phase 1 part of the trial was reported previously.[14] Phase 2 is a non-randomised three-group study. Group 3 is ongoing, having accrued 15 of the planned sample size of 24 patients; the data are not yet mature. The results of group 3 will be reported at a later date. The same study design and therapy was applied to all three groups, although patient selection criteria differed: group 1 included patients with HPV-unrelated platinum-resistant HNSCC without previous cetuximab for recurrent or metastatic disease; group 2 included patients with HPV-unrelated cetuximab-resistant HNSCC; and group 3 included patients with HPV-related cetuximab-resistant oropharynx squamous cell carcinoma.

Eligible patients had recurrent or metastatic histologically or cytologically confirmed HNSCC, defined as distant metastases or inoperable local or regional recurrence (or both) in a previously radiated field. HPV-unrelated HNSCC was required for groups 1 and 2, defined as squamous cell carcinoma of the oral cavity, larynx, or hypopharynx, or $p16^{INK4a}$-negative squamous cell carcinoma of the oropharynx or level 2–3 neck node (occult primary). Patient selection was not determined by cyclin D1 or retinoblastoma protein (Rb) status. Patients in group 1 were required to have platinum-resistant HNSCC, defined as recurrent or metastatic disease, which progressed while on a platinum agent. For group 1, previous cetuximab for recurrent or metastatic disease was not permissible, although cetuximab given with curative intent was acceptable. Patients in group 2 had to have cetuximab-resistant HNSCC, defined as disease progression while on cetuximab. The protocol did not specify a limit in the interval from completion of previous platinum (group 1) or cetuximab (group 2) given for recurrent or metastatic disease. Additional inclusion criteria for both groups included age of at least 18 years, Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less, measurable disease per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1), adequate marrow and organ function (ie, absolute neutrophil count ≥1500 cells per μL, platelet count ≥100 000 per μL; creatinine and bilirubin <1·5×upper limit of normal [ULN]; and aspartate transaminase, alanine transaminase, and alkaline phosphatase <2·5×ULN), and QTc interval of less than 480 ms. Exclusion criteria included uncontrolled electrolyte disorders that could compound the effects of a QTc-prolonging drug or an uncontrolled intercurrent illness (ie, active infection, symptomatic congestive heart failure, or unstable angina pectoris). Full inclusion and exclusion criteria are available in the appendix (pp 31–34).

See Online for appendix

Tests required to determine eligibility included complete blood count, metabolic panel, pregnancy test (women), electrocardiogram (ECG), and CT scans of the neck and chest.

The study protocol was approved by the institutional review board at each of the eight participating sites. All patients provided written, signed, informed consent to participate. Independent data monitoring was done by the quality assurance committee of Washington University (St Louis, MO, USA).

Procedures

Palbociclib at 125 mg/day was administered orally or ingested with food on days 1–21 of each 28-day cycle. Capsule or liquid suspension formulations of palbociclib were available to patients based on their swallowing abilities. Cetuximab at 400 mg/m² was given intravenously on cycle one, day 1, then at 250 mg/m² once per week. Criteria to initiate subsequent cycles of cetuximab and palbociclib included an absolute neutrophil count of at least 1000 cells per μL, platelets of at least 50 000 cells per μL, and non-haematological toxicities of no more than grade 1. If not met, palbociclib was delayed by 1 week; however, cetuximab was continued. Palbociclib dose was adjusted for selected adverse events. Dose levels of palbociclib for modifications were 100 mg per day or 75 mg per day. A dose reduction was recommended for grade 4 neutropenia or thrombocytopenia, grade 3 neutropenia with infection or fever, or both, non-haematological toxicity of grade 3 or worse, or treatment delay more than 1 week because of persisting adverse event if recovery occurred within 2 weeks. Patients who required more than two dose reductions were treated with cetuximab alone. Doses omitted for adverse events were not replaced within the same cycle. Dose modifications of cetuximab were based on package insert guidelines.

Complete blood count and metabolic panel were done weekly during cycle one and every 4 weeks from cycle two onwards. Adverse events were monitored weekly and were graded using National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.0. Tumour response assessments were done every two cycles with neck and body CT using RECIST 1.1, assessed locally. Treatment continued until disease progression, death, intolerable adverse events, or patient withdrawal. Patient-reported quality of life was

monitored using the Functional Assessment of Cancer Therapy-Head and Neck (FACT-H&N), version 4, and the European Organisation for Research and Treatment of Cancer Quality of Life Questions-Core (EORTC QLQ-C30), version 3.[16,17] These quality-of-life assessments were administered at baseline and day 1 of cycles two to four, and six (appendix p 1).

Complete absence or low level of $p16^{INK4a}$ expression is a surrogate biomarker of HPV-unrelated HNSCC. Archival tumour tissue obtained at diagnosis or recurrence was used to assess $p16^{INK4a}$ expression by immunohistochemistry.[18] Archived tissue was not available for two patients. Tumours with no staining for $p16^{INK4a}$ were scored as negative and tumours with strong and diffuse (≥70%) $p16^{INK4a}$ staining were scored as positive. Tumours with focal $p16^{INK4a}$ staining were scored as negative if HPV-unrelated by in situ hybridisation or PCR methods. Additional biomarkers will be evaluated on archived tumour tissue and optional tumour biopsies. The results of the biomarker evaluation will be published at a later date.

Blood samples were collected to obtain pharmacokinetic variables on cycle one, days 15 and 22, before and after cetuximab, and on cycle two, days 15 and 22, when steady-state levels of palbociclib were expected.[19] Whole blood was collected before and immediately after palbociclib and cetuximab dosing, and at 1, 2, 4, and 8 h after dosing on cycle two, day 15, and before and after cetuximab dosing on cycle two, day 22. Plasma was analysed by PPD Laboratories (Wilmington, NC, USA) to determine the concentrations of palbociclib using a validated proprietary assay based on liquid chromatography–tandem mass spectrometry with a dynamic range of 1–250 ng/mL (AB Sciex API4000, Framingham, MA, USA). Serum was analysed by Wuxi (Shanghai, China) to establish the concentrations of cetuximab using an enzyme-linked immunosorbent assay. The standard curve detected lower and upper limits of calibration of 40 ng/mL and 4000 ng/mL of cetuximab, respectively. Pharmacokinetic data analysis was done on group 1 only; it was reasoned that pharmacokinetic data would not differ between the groups.

For **MultCLean Desktop software** see https://biostatistics.mdanderson.org/SoftwareDownload/

No major protocol deviations occurred. The protocol was amended several times over the course of the study: on Dec 21, 2015, to add optional tumour biopsy at disease progression, permit patients with HIV in group 2, and change exclusion criteria of previous malignancy from 5 years to 1 year; on June 7, 2016, to make administrative changes only; on Sept 6, 2017, to allow the suspension version of palbociclib to be used in patients unable to swallow the capsule; and on Oct 24, 2017, to add group 3 to the protocol.

Outcomes

The primary endpoint for each group was the proportion of patients achieving an objective response by RECIST 1.1 (the percentage of patients with complete and partial responses). When possible, tumour responses were confirmed at least 4 weeks later by repeat CT scans. Best overall response was recorded from the start of treatment to disease progression. Secondary endpoints were adverse events, progression-free survival, overall survival, and duration of response. Exploratory endpoints were pharmacokinetics and quality of life. Progression-free survival was the time from start of treatment to progression or death, whichever occurred first. Overall survival was the time from start of treatment to death from any cause. Duration of response was the time from achievement of first tumour response (complete or partial) to disease progression.

Statistical analysis

The study design for group 1 was based on an objective response with cetuximab monotherapy being achieved in 13% of patients with platinum-resistant recurrent or metastatic HNSCC.[4] For group 2, the proportion of patients achieving an objective response with cetuximab-resistant HNSCC with therapy was not well defined. One report[4] documented no objective responses in patients treated with platinum and cetuximab after disease progression on single-agent cetuximab. The proportion of patients achieving an objective response with other agents available at that time and in this setting were unknown. Therefore, in group 2, we expected the proportion of patients achieving an objective response with available therapies to be less than or equal to the objective response of 13% with cetuximab-naive recurrent or metastatic HNSCC treated with cetuximab.[4] For each group, an objective response in 26% or more of patients with palbociclib and cetuximab treatment was considered clinically significant and warranted further investigation. Moreover, in a previous study, 46% of patients treated with cetuximab monotherapy had grade 3 or 4 adverse events,[4] and no significant increase in the adverse events of study patients was considered acceptable. Using these values, a Bayesian sequential rule was used to monitor the proportion of patients achieving an objective response and adverse events.[20] Adverse event monitoring boundaries were computed using MultCLean Desktop, version 2.1.0, developed by MD Anderson Quantitative Research Computing). The Bayesian algorithm used to generate boundaries has been published.[20] In a sample of 30 patients in each group, an objective response in four or more patients would support the alternative hypothesis and an objective response in three or fewer would support the null hypothesis. The acceptable maximum number of patients in each group who had grade 3 or 4 adverse events was 19.

Patients were evaluable for objective response and duration of response, unless they came off study before the first tumour response assessment because of adverse events or early death (in the absence of disease progression). All patients were evaluable for adverse events, progression-free survival, and overall survival.

The Kaplan-Meier product-limit method was used to estimate survival endpoints. Overall survival times were censored at the time of last follow-up for patients who were alive or who were lost to follow-up. Progression-free survival times were censored at the time of last imaging assessment for patients who were alive without disease progression or when lost to follow-up. The proportion of patients in each group who had grade 3 or 4 treatment-related adverse events were reported with 95% CIs. In group 2, a post-hoc subgroup analysis was done to assess survival outcomes between patients treated with previous cetuximab monotherapy or cetuximab in combination with chemotherapy. Patients who completed the baseline quality-of-life assessment were evaluable for quality of life. Quality-of-life data were collected until patients went off study, died, or were otherwise unable to respond, so more than 98% of missing values are explicitly related to the qualities being measured. Imputation is difficult and can be unreliable given that missingness that is not at random. The current sample sizes and study designs did not allow adequate multiple imputation under these circumstances. For this reason, quality-of-life results are presented in a descriptive fashion and represent the responses of patients while on study treatment. Patients were evaluable for pharmacokinetics and $p16^{INK4a}$ expression if these analyses were done. Details of the quality of life and pharmacokinetic analyses can be found in the appendix (pp 1–2). We also did a post-hoc analysis to evaluate whether selected pharmacokinetic parameters of palbociclib were associated with the activity endpoints. Statistical analyses were done using SAS (version 9.4), and STAT (version 14.2).

This study is registered with ClinicalTrials.gov, number NCT02101034.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all data in the study. The corresponding author had final responsibility for the decision to submit for publication.

Results

Between Oct 19, 2015, and Nov 7, 2018, 62 patients were enrolled onto the trial: 30 in group 1 and 32 in group 2 (table 1). The most common primary tumour sites were the oral cavity and larynx. Most patients (50 [81%] of 62) had received one or two lines of previous therapy for recurrent or metastatic disease. In group 1, the median interval from previous platinum treatment to enrolment was 0·5 months (IQR 0·3–1·0). In group 2, the median interval from previous cetuximab treatment to enrolment was 1·3 months (IQR 0·5–3·2). 26 (81%) of 32 patients in group 2 were enrolled in the trial within 4 months of disease progression on previous cetuximab. 11 patients in group 2 had been treated with previous single-agent cetuximab, but only one had achieved a tumour response. 36 (58%) of 62 patients were treated with immunotherapy (PD-1 or PD-L1 inhibitor): 17 before enrolment (two in group 1 and 15 in group 2), two before and after study (one in group 1 and one in group 2), and 17 after removal from the study (ten in group 1 and seven in group 2). The median duration of immunotherapy was 1·9 months (IQR 1·3–2·7). Tumour response to immunotherapy occurred in four (11%) of the patients treated with immunotherapy (two in group 1 and two in group 2). Archival tumour tissue was obtained at diagnosis from ten patients and at recurrence in 50 patients. Archival tissue was not available for two patients. Expression of $p16^{INK4a}$ in tumour was negative in 51 (85%) of 60 patients and focally positive, but HPV in situ hybridisation or PCR negative, in nine (15%) of 60 patients (data not shown). These findings are consistent with HPV-unrelated disease.

	All patients (n=62)	Group 1 (n=30)	Group 2 (n=32)
Age, years	66 (58–70)	67 (61–71)	63 (56–68)
Sex			
Male	44 (71%)	23 (77%)	21 (66%)
Female	18 (29%)	7 (23%)	11 (34%)
ECOG performance status			
0	15 (24%)	9 (30%)	6 (19%)
1	42 (68%)	20 (67%)	22 (69%)
2	5 (8%)	1 (3%)	4 (12%)
Smoking history			
Yes	50 (81%)	27 (90%)	23 (72%)
No	12 (19%)	3 (10%)	9 (28%)
Primary site			
Oral cavity	26 (42%)	14 (47%)	12 (38%)
Larynx	18 (29%)	8 (27%)	10 (31%)
Oropharynx	11 (18%)	4 (13%)	7 (22%)
Hypopharynx	3 (5%)	3 (10%)	0
Occult primary and neck node	4 (6%)	1 (3%)	3 (9%)
Site of recurrence			
Local or regional, or both	23 (37%)	6 (20%)	17 (53%)
Distant	13 (21%)	8 (27%)	5 (16%)
Both	26 (42%)	16 (53%)	10 (31%)
Curative therapy			
Cisplatin* plus radiotherapy	28/47 (60%)	10/22 (45%)	18/25 (72%)
Cetuximab† plus radiotherapy	5/47 (11%)	2/22 (9%)	3/25 (12%)
Radiotherapy alone	3/47 (6%)	0	3/25 (12%)
Surgery‡	17/47 (36%)	16/22 (73%)	1/25 (4%)
Metastatic disease at presentation	15 (24%)	8 (27%)	7 (22%)
Lines of previous therapy‡			
≥3	12 (19%)	4 (13%)	8 (25%)
2	22 (35%)	11 (37%)	11 (34%)
1	28 (45%)	15 (50%)	13 (41%)

(Table 1 continues on next page)

	All patients (n=62)	Group 1 (n=30)	Group 2 (n=32)
(Continued from previous page)			
Previous therapy§			
Platinum agent¶	55 (89%)	30 (100%)	25 (78%)‖
Interval since last dose, months	0·9 (0·5–2·4)	0·5 (0·3–1·0)	1·3 (1·0–5·0)
Best response**	18 (29%)	7 (23%)	11 (34%)
Immunotherapy††	19 (31%)	3 (10%)	16 (50%)
Interval since last dose, months	2·9 (0·7–6·4)	1·2 (0·5–1·8)	4·2 (0·9–9·9)
Best response**	3 (5%)	0	3 (9%)
Cetuximab‡‡	32 (52%)	0	32 (100%)
Given as monotherapy	11 (18%)	NA	11 (34%)
Best response**	1 (2%)	NA	1 (3%)
Given with chemotherapy	21 (34%)	NA	21 (66%)
Best response**	10 (16%)	NA	10 (31%)
Interval since last dose (months)	1·3 (0·5–3·2)	NA	1·3 (0·5–3·2)

Data are median (IQR), n (%), or n/N (%), unless otherwise stated. ECOG=Eastern Cooperative Oncology Group. NA=not applicable. *One patient received carboplatin with radiotherapy and is included here. †One patient received carboplatin, paclitaxel, and cetuximab with radiotherapy and is included here. ‡Patients who had surgery might also be included one of the other therapy groups (ie, if the patient received surgery followed by cisplatin plus radiotherapy). §For recurrent or metastatic disease. ¶ Two or more cycles of cisplatin ≥60 mg/m² per cycle or carboplatin area under the curve ≥4 per cycle. Exceptions: three patients in group 1 had radiologic disease progression after one cycle of carboplatin AUC 5. ‖Platinum was given before (n=1), with (n=18), or after (n=6) previous cetuximab. **Best response was measured as complete response or partial response. ††Pembrolizumab or nivolumab. ‡‡Six or more doses of cetuximab.

Table 1: **Patient, tumour, and previous treatment characteristics**

During cycles 1 and 2 for group 1, the median dose of palbociclib administered was 98% (IQR 91–100) and cetuximab was 100% (IQR 100–100). Dose reductions for palbociclib occurred in two (7%) of 30 patients in group 1 and four (13%) of 32 patients in group 2. Dose reductions for cetuximab occurred in one (3%) patient in group 1 and no patients in group 2. No patients in either group discontinued treatment for drug-related toxicity.

Median follow-up was 5·4 months (IQR 4·4–12·1) for group 1 and 5·5 months (IQR 4·3–8·3) for group 2. In group 1, 28 (93%) of 30 patients were evaluable for tumour response. Two patients were not evaluable because of early death or inability to measure the target lesion on the post-treatment non-contrast CT scan. Of 28 evaluable patients, an objective response occurred in 11 (39%; 95% CI 22–59). The best response observed was complete response in three patients (11%), partial response in eight (29%), stable disease in 14 (50%), and progressive disease in three (11%). Ten (90%) of the 11 responses were confirmed by repeat scan 1 month later (per RECIST 1.1). A decrease in the sum of the target lesions occurred in 19 patients (68%; figure 1). The median duration of response was 4·0 months (IQR 1·8–5·6). Only one (9%) of the 11 patients with tumour response had received previous immunotherapy.

In group 2, 27 (90%) of 32 patients were evaluable for tumour response. Five patients were non-evaluable because of the following events that occurred before the first assessment: comorbidity-related death (n=2), patient withdrawal (n=2), or non-treatment-related adverse event (n=1; *Clostridium difficile*-induced colitis) resulting in withdrawal. Of 27 evaluable patients, objective responses occurred in five (19%, 95% CI 6–38). The best tumour response observed was complete response in one (4%) patient, partial response in four (15%), stable disease in 13 (48%), and progressive disease in nine (33%). Four (80%) of the five responses were confirmed. A decrease in the sum of the target lesions occurred in nine (33%) of 27 evaluable patients (figure 1). The median duration of response was 6·0 months (IQR 2·0–15·5). Tumour response to study treatment occurred in four (17%) of 23 patients enrolled onto the trial immediately after disease progression on cetuximab. In the six patients enrolled in an interval greater than 4 months from disease progression on previous cetuximab, the objective response to palbociclib with cetuximab was partial response (n=1), stable disease (n=2), or progressive disease (n=3). Only one (20%) of the five patients with a tumour response had received previous immunotherapy.

In group 1, 26 progression-free survival events occurred (20 patients had disease progression and six died) and the median progression-free survival was 5·4 months (95% CI 3·4–7·0; figure 2A) and the median overall survival was 9·5 months (95% CI 5·3–16·5; figure 2B). 1-year overall survival was 36·5% (95% CI 18·0–55·3). At last follow-up (ie, Jan 4, 2019), ten patients were alive and four remained on study. 20 deaths occurred: 17 due to disease progression and three due to comorbidity or disease complication (ie, aspiration pneumonia, duodenal ulcer, or oral tumour bleed). In a post-hoc analysis, the median overall survival in patients treated with immunotherapy was 9·5 months (95% CI 2·9–14·5; n=13) compared with those patients not given immunotherapy (11·3 months, 2·1 to not reached; n=17). In group 2, 29 progression-free survival events occurred (25 patients had disease progression and four died) and the median progression-free survival was 3·7 months (95% CI 2·9–4·3; figure 2C) and median overall survival was 6·3 months (95% CI 4·9–10·0; figure 2D). 1-year overall survival was 28·1% (95% CI 11·5–47·6). At last follow-up, 12 patients were alive and one remained on study. 20 deaths occurred: 14 due to disease progression and six due to comorbidity or disease complication (ie, aspiration [n=3], myocardial infarction, stroke, and sepsis). In group 2, a post-hoc subgroup analysis was done to establish survival outcomes between patients treated with previous cetuximab monotherapy or cetuximab in combination with chemotherapy. In patients treated with previous cetuximab monotherapy (n=11), the median progression-free survival was

3·5 months (95% CI 1·3–4·4) and median overall survival was 5·7 months (95% CI 3·3–10·1). In patients who received previous cetuximab with chemotherapy (n=21), median progression-free survival was 3·8 months (95% CI 2·6–5·3) and median overall survival was 6·4 months (95% CI 5·0–16·1).

The most frequent adverse events are shown in table 2. 32 (52%, 95% CI 39–65) of 62 patients had grade 3 or 4 adverse events related to either study drug: 18 (60%, 41–77) of 30 in group 1 and 14 (44%, 26–62) of 32 in group 2. These data were below the predefined acceptable maximum number (19 per group) of patients who had grade 3 or 4 adverse events. The most common grade 3–4 palbociclib-related adverse event was neutropenia (in 21 [34%] of 62 patients; table 2). Three treatment-related serious adverse events occurred, all in group 1, and these were febrile neutropenia, fatigue, and infusion-related reaction. 26 (42%, 30–55) of 62 patients had grade 3 or 4 palbociclib-related adverse events. The most common adverse event attributed to palbociclib was myelosuppression. The most common adverse events attributed to cetuximab were rash and hypomagnesemia (table 2).

Patient-related quality of life was assessed using the FACT-H&N and EORTC QLQ-30 instruments. Completion rates at each assessment point are presented in the appendix (p 1). In groups 1 and 2, quality of life remained stable over the first six cycles of therapy across the three summary scales and five domains of the FACT-H&N assessment and the global health scale and five functional scales of the EORTC QLC-30 assessment (appendix pp 4–10). In each case, a global test indicated that there were no detectable changes over baseline (data not shown).

Pharmacokinetic analysis of palbociclib was done for 23 (77%) of the 30 patients in group 1. Pharmacokinetic analysis was not done because of early progression or death (four patients) or because of missing multiple doses (three patients). Additional details regarding pharmacokinetic analyses and mean observed palbociclib plasma concentrations over time are presented in the appendix (pp 18–19). Non-compartmental analysis was used to assess palbociclib pharmacokinetics (appendix p 3). Pharmacokinetic analysis of the intravenously administered cetuximab was done on 27 (90%) of the 30 patients in group 1. Pharmacokinetic analysis of cetuximab was not done in three patients because of early progression or death. The mean observed cetuximab serum concentrations over time are displayed in the appendix (p 18). Peak and trough serum concentrations of cetuximab and mean estimates for the zero order elimination rate constant during cycles 1 and 2 are shown in the appendix (p 19).

We did a post-hoc analysis to evaluate whether selected pharmacokinetic parameters of palbociclib were associated with the activity endpoints (appendix p 1). The peak drug concentration and area under the curve

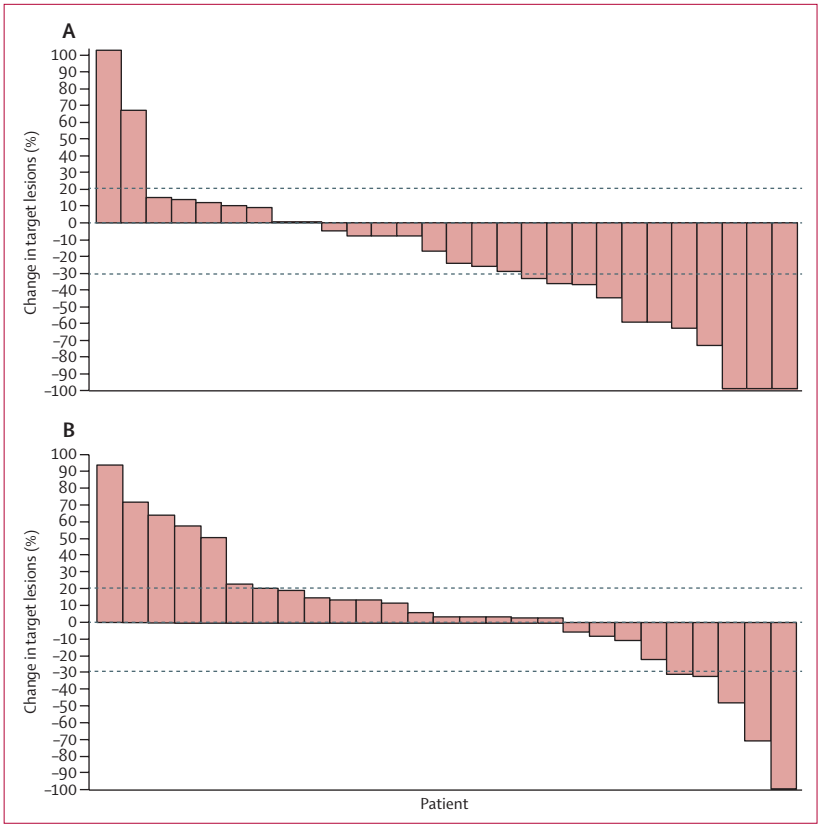

Figure 1: **Best response in sum of target lesions in individual evaluable patients for group 1 (A) and group 2 (B)**
Dashed lines represent partial response (≥30% decrease) and progressive disease (≥20% increase).

($AUC_{[0–24]}$) of palbociclib were not significantly associated with progression-free survival (p=0·80 and p=0·49, respectively) or overall survival (p=0·64 and p=0·93, respectively). Similarly, analysis of variance models found no association of the peak drug concentration or $AUC_{(0–24)}$ of palbociclib with best tumour response (p=0·20 for both pharmacokinetics; data not shown).

Discussion

To the best of our knowledge, this is the first trial to evaluate the activity of a selective CDK4/6 inhibitor in HNSCC. Palbociclib in combination with cetuximab exhibited substantial antitumour activity in platinum-resistant (group 1) and in cetuximab-resistant (group 2) HPV-unrelated HNSCC. The primary hypothesis of each group of the study was met. The proportion of patients achieving an objective response with palbociclib and cetuximab was 39% in group 1 and 19% in group 2. In platinum-resistant disease, the proportion of patients achieving an objective response with palbociclib and cetuximab was greater than that reported with single-agent cetuximab or PD-1 inhibitors.[4–6,21] In cetuximab-resistant disease, the proportion of patients achieving an objective response with palbociclib and cetuximab was similar to that reported with PD-1 inhibitors.[8,9] In group 2, tumour

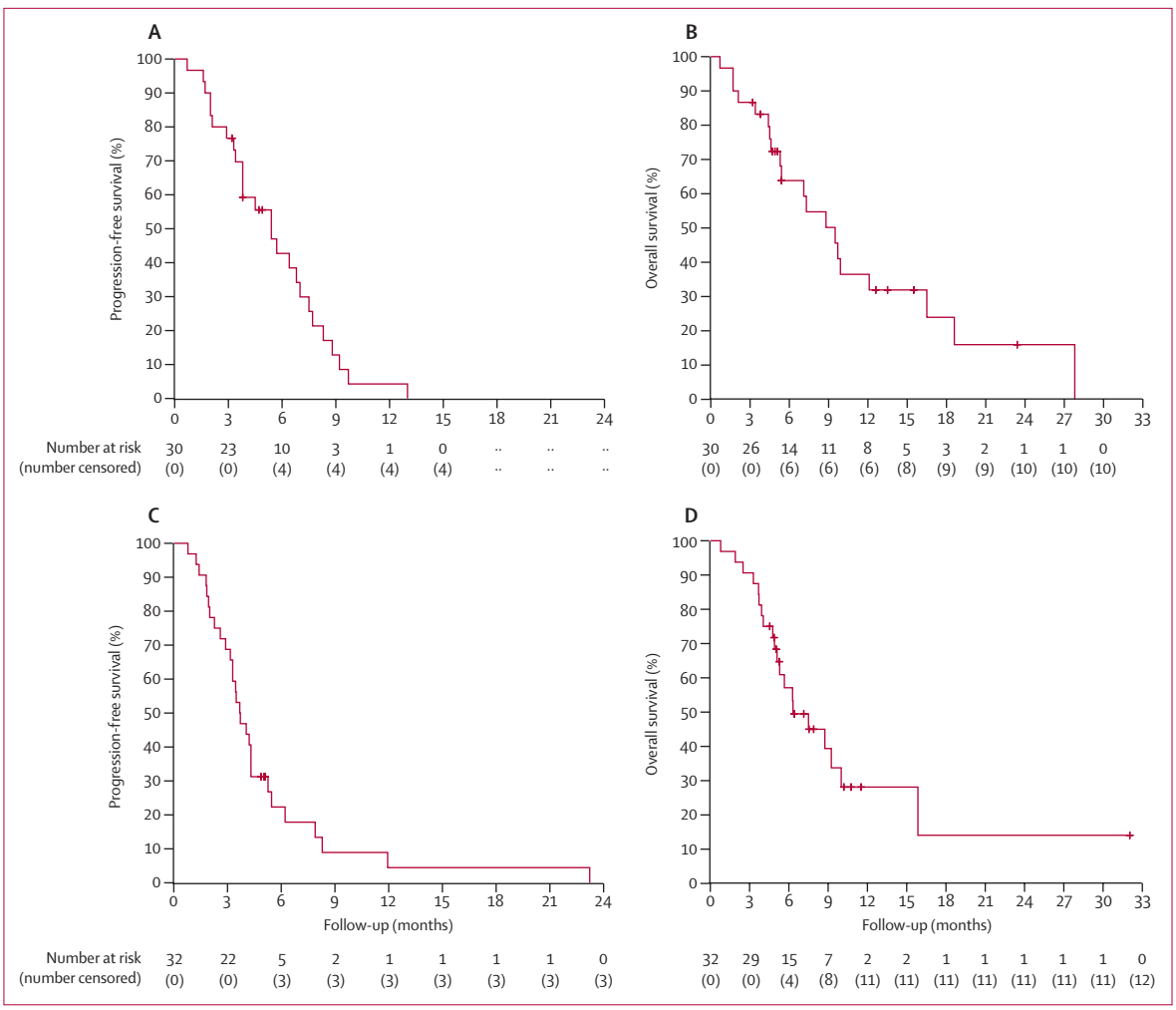

Figure 2: **Kaplan-Meier curves**
Progression-free survival for group 1 (A) and group 2 (C). Overall survival for group 1 (B) and group 2 (D). Crosses denote censored patients.

responses to palbociclib and cetuximab given immediately after disease progression on single-agent cetuximab are consistent with an independent effect of palbociclib or palbociclib-mediated restoration of cetuximab benefit. As seen in a post-hoc group 2 subgroup analysis, there were no significant differences in outcomes with study treatment between those patients who had been previously treated with cetuximab monotherapy and those with previous cetuximab with chemotherapy.

In our trial, the median duration of response with palbociclib and cetuximab was 4 months in group 1 and 6 months in group 2. By contrast, the median duration of response with PD-1 inhibitors was longer: 18·4 months in platinum-resistant disease and 8 months in cetuximab-resistant disease.[6,8] However, the median progression-free survival with palbociclib and cetuximab was 5·4 months in group 1 and 3·7 months in group 2. In comparison, the median progression-free survival with PD-1 inhibitors was approximately 2 months in platinum-resistant disease and 2·1 months in cetuximab-resistant disease.[5,6,8] Although the duration of response was longer with PD-1 inhibitors, progression-free survival was longer with palbociclib and cetuximab than with PD-1 inhibitors. This result might be because of the higher proportion of patients achieving an objective response with palbociclib and cetuximab than with PD-1 inhibitors.

The median overall survival in group 1 was 9·5 months, which was longer than expected in similar patients treated with single-agent cetuximab (6 months).[4,21] However, two issues confound the interpretation of overall survival in group 1. First, group 1 included only patients with poor-prognosis HPV-unrelated disease, whereas trials of cetuximab also included patients with good-prognosis HPV-related disease. For this reason, overall survival in group 1 would be expected to be worse than the historical control if palbociclib did not add a survival benefit. Second, 13 patients on group 1 received immunotherapy before or after trial participation, and might have had a delayed survival benefit from the immunotherapy. However, the median overall survival was shorter in

	Grade 1–2	Grade 3	Grade 4	Grade 5
Palbociclib related				
Platelet count decreased	34 (55%)	8 (13%)	2 (3%)	0
Neutrophil count decreased	22 (35%)	19 (31%)	2 (3%)	0
White blood cell decreased	28 (45%)	17 (27%)	3 (5%)	0
Electrocardiogram QT corrected interval prolonged	6 (10%)	1 (2%)	0	0
Cetuximab related				
Acneiform rash	40 (65%)	0	0	0
Hypomagnesemia	18 (29%)	1 (2%)	0	0
Other adverse events				
Fatigue	32 (52%)	7 (22%)	0	0
Hypoalbuminemia	31 (50%)	2 (3%)	0	0
Anaemia	30 (48%)	17 (27%)	0	0
Hyponatremia	30 (48%)	1 (2%)	0	0
Hypertension	24 (39%)	3 (5%)	0	0
Nausea	24 (39%)	2 (3%)	0	0
Dysphagia	23 (37%)	4 (6%)	0	0
Dyspnoea	20 (32%)	3 (5%)	2 (3%)	0
Hypocalcaemia	19 (31%)	3 (5%)	1 (2%)	0
Lymphocyte count decreased	19 (31%)	18 (29%)	4 (6%)	0
Diarrhoea	18 (29%)	2 (3%)	0	0
Weight loss	16 (26%)	6 (10%)	0	0
AST increased	16 (26%)	0	0	0
Tumour pain	15 (24%)	3 (5%)	0	0
Constipation	15 (24%)	0	0	0
Cough	15 (24%)	0	0	0
Anorexia	14 (23%)	3 (5%)	0	0
Vomiting	14 (23%)	2 (3%)	0	0
Dry mouth	13 (21%)	0	0	0
Sinus tachycardia	12 (19%)	0	0	0
Alkaline phosphatase increased	12 (19%)	0	0	0
Hypokalaemia	11 (18%)	8 (13%)	2 (3%)	0
Hyperglycaemia	11 (18%)	9 (15%)	1 (2%)	0
Hypernatremia	10 (16%)	1 (2%)	0	0
Fever	10 (16%)	0	0	0
Dizziness	9 (15%)	2 (3%)	0	0
Hypercalcaemia	9 (15%)	0	1 (2%)	0
Dry skin	9 (15%)	0	0	0
Dehydration	8 (13%)	2 (3%)	0	0
Hypotension	8 (13%)	1 (2%)	0	0
Creatinine increased	8 (13%)	0	0	0
Trismus	7 (11%)	1 (2%)	0	0
ALT increased	7 (11%)	0	0	0
Elevated INR	6 (10%)	1 (2%)	0	0
Headache	6 (10%)	0	0	0
Paronychia	6 (10%)	0	0	0
Dysarthria	5 (8%)	1 (2%)	0	0
Hypophosphatemia	3 (5%)	6 (10%)	2 (3%)	0
Lung infection	1 (2%)	4 (6%)	0	2 (3%)
Febrile neutropenia	0	2 (3%)	0	0
Abdominal pain	0	2 (3%)	0	0
Colitis	0	1 (2%)	0	0
Tumour haemorrhage	0	1 (2%)	0	0
Haematuria	0	1 (2%)	0	0
Duodenal ulcer	0	1 (2%)	0	0
Oesophageal fistula	0	1 (2%)	0	0
Oral cavity fistula	0	0	0	1 (2%)
Sepsis	0	0	6 (10%)	0
Duodenal perforation	0	0	1 (2%)	0
Skin infection	0	4 (6%)	0	0
Tracheitis	0	1 (2%)	0	0
Aspiration	0	0	0	1 (2%)
Pleural effusion	0	1 (2%)	0	0
Pneumothorax	0	1 (2%)	0	0
Catheter-related infection	0	1 (2%)	0	0
Jejunal obstruction	0	1 (2%)	0	0
Mucositis oral	0	1 (2%)	0	0
Oral haemorrhage	0	0	0	1 (2%)
Death, not otherwise specified	0	0	0	3 (5%)
Infusion-related reaction	0	1 (2%)	0	0
Urinary tract infection	0	1 (2%)	1 (2%)	0
Respiratory failure	0	0	1 (2%)	1 (2%)

Data are n (%). The table shows grade 1–2 adverse events occurring in 10% or more of patients and all grade 3, 4, and 5 events. AST=aspartate aminotransferase. NA=not applicable. ALT=alanine aminotransferase. INR=international normalised ratio.

Table 2: **Adverse events across all cycles (for all patients, n=62)**

patients treated with immunotherapy (9·5 months) compared with those not given immunotherapy (11·3 months) in a post-hoc analysis. These data suggest that the longer than expected overall survival in patients on group 1 is not likely to be explained by immunotherapy alone, and might be due to palbociclib given with cetuximab.

Palbociclib and cetuximab were tolerable and safe to administer. Drug-related adverse events were similar to those expected for each drug.[4,19] 42% of patients had a grade 3 or 4 palbociclib-related adverse event. In comparison, drug-related adverse events of grade 3 or worse occurred in 6% of patients treated with cetuximab monotherapy, 36% with methotrexate, 40% with afatinib, and 11% with PD-1 inhibitors.[4,5,22] Drug delivery was favourable, with at least 98% of scheduled doses of palbociclib and cetuximab administered during the first two cycles. Notably, grade 3–4 rash was less frequent than expected,[3] the reason for which is unclear, but might be due to early implementation of antibiotics or the immune effects of CDK4/6 inhibition. Quality of life remained stable during therapy, further supporting the tolerability of the regimen.

Concurrent treatment with palbociclib and cetuximab did not significantly change the expected pharmacokinetics of either drug given as monotherapy. Palbociclib was slowly absorbed and eliminated and had a large volume of distribution, in line with a report[19] of palbociclib monotherapy. Peak and trough concentrations were similar to those with palbociclib monotherapy.[19] The average steady-state palbociclib concentration in our patients was well above that which significantly inhibited Rb phosphorylation and reduced tumour growth in mouse xenograft models.[19] As previously reported,[23] there was substantial interpatient variability of cetuximab concentrations in our study. However, the mean trough and peak concentrations of cetuximab were above the minimum threshold predictive of clinical benefit and similar to those reported for cetuximab monotherapy.[24]

Development of resistance to palbociclib and cetuximab, as reflected by failure to respond or response followed by progression events, eventually occurred in patients treated on this trial. Reported mechanisms of resistance to CDK4/6 inhibitors include alterations in CDK6, cyclin E, cyclin-dependent kinase 2, p21, p27, Rb, the phosphatidylinositol 3-kinase–mTOR pathway and the fibroblast growth factor receptor.[25] Several of these alterations are targetable with currently available drugs. Preclinical reports[15,26,27] support combining CDK4/6 inhibitors with angiogenesis or mTOR inhibitors to enhance antitumour activity.

Combinations of CDK4/6 inhibitors with immunotherapy might be synergistic. Preclinical reports[28–31] published in the past 3 years showed that combining CDK4/6 and PD-1 or PD-L1 inhibitors enhanced antitumour activity. CDK4/6 inhibition increased PD-L1 expression and tumour immunogenicity, promoted CD8 T cell-mediated killing of tumour cells, and suppressed regulatory T-cell proliferation.[28,29] Importantly, the addition of PD-L1 antibody to a CDK4/6 inhibitor enhanced tumour killing and regression.[28–31] The non-overlapping toxicity profile of these agents support that combinations would be tolerable. Our trial provides an important platform to evaluate combinations of immunotherapy with CDK4/6 inhibitors in HNSCC.

Our trial has some limitations. We used a single-group design to assess the activity of palbociclib and cetuximab. The results require validation in a controlled trial with a larger sample size. Additionally, the rationale for our study was based on the genomics of newly diagnosed HNSCC; however, the genomics of recurrent or metastatic disease remain poorly understood. Immunotherapy might not have affected the objective response or progression-free survival outcomes, but could have contributed to the overall survival outcome. The trial design did not allow us to assess whether antitumour activity of palbociclib occurred primarily through a direct effect or by reversal of primary cetuximab resistance. Tumour response could have occurred on rechallenge with cetuximab in cetuximab-resistant patients (group 2); however, the interval from previous cetuximab to enrolment was short (<4 months) in most (81%) patients. Moreover, an earlier report showed no objective responses with cetuximab and platinum in patients with cetuximab-resistant disease.[4] A delayed tumour response to previous immunotherapy might also have occurred while on the study; however, 14 of the 16 patients with a tumour response in groups 1 and 2 had not received previous immunotherapy.

In this multicentre, phase 2 trial, the combination of palbociclib and cetuximab exhibited substantial antitumour activity in platinum-resistant and in cetuximab-resistant HPV-unrelated HNSCC. Biomarker studies will be important to predict subsets of patients more likely to benefit from this treatment strategy. Further investigation of selective CDK4/6 inhibition as a therapeutic strategy in HPV-unrelated HNSCC is warranted.

Contributors

All authors contributed to data collection, data interpretation, and writing of the manuscript. KT, NNS, JL, and DA designed the figures and did data analysis. JL and DA also contributed through study design and literature searches.

Declaration of interests

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