Buparlisib and paclitaxel in patients with platinum-pretreated recurrent or metastatic squamous cell carcinoma of the head and neck (BERIL-1): a randomised, double-blind, placebo-controlled phase 2 trial

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Summary

Background Phosphatidylinositol 3-kinase (PI3K) pathway activation in squamous cell carcinoma of the head and neck contributes to treatment resistance and disease progression. Buparlisib, a pan-PI3K inhibitor, has shown preclinical antitumour activity and objective responses in patients with epithelial malignancies. We assessed whether the addition of buparlisib to paclitaxel improves clinical outcomes compared with paclitaxel and placebo in patients with recurrent or metastatic squamous cell carcinoma of the head and neck.

Methods In this multicentre, randomised, double-blind, placebo-controlled phase 2 study (BERIL-1), we recruited patients aged 18 years and older with histologically or cytologically confirmed recurrent and metastatic squamous cell carcinoma of the head and neck after disease progression on or after one previous platinum-based chemotherapy regimen in the metastatic setting. Eligible patients were enrolled from 58 centres across 18 countries and randomly assigned (1:1) to receive second-line oral buparlisib (100 mg once daily) or placebo, plus intravenous paclitaxel (80 mg/m² on days 1, 8, 15, and 22) in 28 day treatment cycles. Randomisation was done via a central patient screening and randomisation system with an interactive (voice and web) response system and stratification by number of previous lines of therapy in the recurrent and metastatic setting and study site. Patients and investigators (including local radiologists) were masked to treatment assignment from randomisation until the final overall survival analysis. The primary endpoint was progression-free survival by local investigator assessment per Response Evaluation Criteria In Solid Tumors (version 1.1) in all randomly assigned patients. Efficacy analyses were done on the intention-to-treat population, whereas safety was analysed in all patients who received at least one dose of study drug and had at least one post-baseline safety assessment according to the treatment they received. This trial is registered with ClinicalTrials.gov, number NCT01852292, and is ongoing but no longer enrolling patients.

Findings Between Nov 5, 2013, and May 5, 2015, 158 patients were enrolled and randomly assigned to receive either buparlisib plus paclitaxel (n=79) or placebo plus paclitaxel (n=79). Median progression-free survival was 4·6 months (95% CI 3·5–5·3) in the buparlisib group and 3·5 months (2·2–3·7) in the placebo group (hazard ratio 0·65 [95% CI 0·45–0·95], nominal one-sided p=0·011). Grade 3–4 adverse events were reported in 62 (82%) of 76 patients in the buparlisib group and 56 (72%) of 78 patients in the placebo group. The most common grade 3–4 adverse events (occurring in ≥10% of patients in the buparlisib group *vs* the placebo group) were hyperglycaemia (17 [22%] of 76 *vs* two [3%] of 78), anaemia (14 [18%] *vs* nine [12%]), neutropenia (13 [17%] *vs* four [5%]), and fatigue (six [8%] *vs* eight [10%]). Serious adverse events (regardless of relation to study treatment) were reported for 43 (57%) of 76 patients in the buparlisib group and 37 (47%) of 78 in the placebo group. On-treatment deaths occurred in 15 (20%) of 76 patients in the buparlisib group and 17 (22%) of 78 patients in the placebo group; most were caused by disease progression and none were judged to be related to study treatment.

Interpretation On the basis of the improved clinical efficacy with a manageable safety profile, the results of this randomised phase 2 study suggest that buparlisib in combination with paclitaxel could be an effective second-line treatment for patients with platinum-pretreated recurrent or metastatic squamous cell carcinoma of the head and neck. Further phase 3 studies are warranted to confirm this phase 2 finding.

Funding Novartis Pharmaceuticals Corporation.

Introduction

Squamous cell carcinoma of the head and neck is the fifth most frequent cancer and the sixth most common cause of cancer deaths globally.[1] Most patients with this type of cancer present with locally advanced disease, which might recur locally or as distant metastatic disease after treatment.[2] Platinum-based chemotherapy is the standard first-line treatment option, with paclitaxel as a

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed for reports of clinical trials published within the past 5 years using the terms "squamous cell carcinoma", "head and neck", and "metastatic". We reviewed abstracts to identify trials of platinum-pretreated disease and specifically any studies that investigated phosphatidylinositol 3-kinase (PI3K) inhibitors in this setting. Although many agents and treatment combinations have been evaluated in this setting, no present second-line therapy options for squamous cell carcinoma of the head and neck are based on phase 3 trial results. Of note, few studies that specifically investigated PI3K inhibitors in squamous cell carcinoma of the head and neck were identified, despite laboratory data suggesting a role for PI3K inhibition in squamous cell carcinoma of the head and neck.

Added value of this study

Our results show that use of buparlisib, a novel, oral pan-PI3K inhibitor, in combination with paclitaxel produced clinically meaningful improvements in progression-free survival, overall survival, and the proportion of patients with an overall response compared with paclitaxel alone in patients with platinum-pretreated recurrent or metastatic squamous cell carcinoma of the head and neck. To our knowledge, these results provide the first clinical data to show a role for PI3K inhibition specifically in squamous cell carcinoma of the head and neck. Of note, this study achieved a nearly three-times increase in the proportion of patients with an overall response with buparlisib compared with placebo. Additionally, to our knowledge, this study recorded the longest median overall survival reported so far in the second-line setting, which compares favourably with the overall survival reported with existing first-line standard-of-care treatment (ie, cetuximab, platinum, or fluorouracil triplet).

Implications of all the available evidence

On the basis of the improved clinical efficacy with a manageable safety profile, our findings suggest that buparlisib in combination with paclitaxel could become an important second-line treatment option for patients with recurrent or metastatic squamous cell carcinoma of the head and neck eligible for taxane therapy. Further phase 3 studies are warranted to confirm this phase 2 finding.

second-line option for platinum-pretreated metastatic disease.[3] However, the unsatisfactory prognosis of patients pretreated with platinum has prompted investigation of novel treatments with targeted agents or immunotherapy.[4]

The phosphatidylinositol 3-kinase (PI3K)–mTOR cell signalling pathway, which is often activated in patients with squamous cell carcinoma of the head and neck, whether they are chemotherapy-naive or chemotherapy-pretreated, has emerged as a potential mechanism of resistance to antineoplastic therapeutics.[3] Although the precise mechanisms underlying the development of treatment resistance towards paclitaxel are largely unknown, activation of the PI3K–mTOR pathway has been shown to confer resistance to paclitaxel[5] and an increase in protein kinase B (AKT) activity might be an early compensatory mechanism of resistance to chemotherapy.[6] Therefore, PI3K pathway activation is believed to have an important role in either primary or secondary paclitaxel resistance.[6] In preclinical models, concomitant inhibition of the PI3K pathway has been shown to enhance the efficacy of paclitaxel, compared with the administration of paclitaxel alone.[5] Buparlisib (BKM120) is an oral pan-PI3K inhibitor selective for all isoforms (α, β, γ, δ) of class I PI3K.[7] In xenograft models of squamous cell carcinoma of the head and neck, buparlisib treatment downregulated tumour PI3K–mTOR pathway signalling, reduced hypoxia, and remodelled tumour vasculature.[8] The combination of buparlisib plus paclitaxel has shown promising signs of clinical activity in a phase 1B study in patients with advanced solid tumours, including patients who had disease progression on taxane-based chemotherapy regimens.[9] Confirmed responses were recorded in several patients with tumours of squamous histology.[10]

On the basis of these initial findings, this phase 2 trial was designed to compare the efficacy and safety of buparlisib and placebo when combined with paclitaxel in patients with platinum-pretreated, recurrent or metastatic squamous cell carcinoma of the head and neck.

Methods

Study design and participants

BERIL-1 was an international, randomised, double-blind, placebo-controlled phase 2 trial done at 58 academic and tertiary referral centres across 18 countries (appendix p 1). Eligible patients were aged 18 years or older with histologically or cytologically confirmed recurrent or metastatic squamous cell carcinoma of the head and neck after disease progression on or after one previous platinum-based (carboplatin or cisplatin) chemotherapy regimen in the recurrent or second-line or more metastatic setting. Previous treatment with cetuximab (during radiotherapy, or as part of a first-line regimen including maintenance therapy, or as a single-agent second-line therapy) was allowed. Evaluation of disease progression before study inclusion was based on local investigator assessment. Measurable disease based on Response Evaluation Criteria In Solid Tumors (RECIST; version 1.1), availability of adequate archival or fresh tumour tissue for PI3K pathway-related biomarker analysis, and an Eastern Cooperative Oncology Group performance status of 0 or 1 were also required. Eligible

patients had to have adequate bone marrow and organ function as assessed by laboratory tests (for full details see appendix p 54,55). Patients' life expectancy was about 7 months based on available treatment options after failure of first-line platinum-based systemic therapy. At baseline, metastatic sites in each patient were derived from the case report form page of diagnosis and extent of cancer if available.

Patients previously treated with an AKT, mTOR, or PI3K pathway inhibitor; a taxane for metastatic disease; or more than one previous chemotherapy regimen for recurrent or metastatic squamous cell carcinoma of the head and neck (apart from adjuvant or neoadjuvant chemotherapy, or concomitant chemoradiotherapy) were excluded. Patients with previous or active major depression or another specified mood disorder; symptomatic CNS metastases; cardiac abnormality; or on active treatment with chronic corticosteroids or other immunosuppressants, strong inhibitors or inducers of cytochrome P450 3A4, drugs with a known risk of inducing torsades de pointes or QT prolongation, or a coumarin-based anticoagulant were also excluded (appendix p 55–58).

All patients provided written informed consent before enrolment. The study was done in accordance with guidelines for good clinical practice, following applicable local regulations, and with the ethical principles described in the Declaration of Helsinki, and approved by the appropriate ethics committee or institutional review board at each study centre. A steering committee supervised the conduct of the study according to the protocol, and an independent data monitoring committee did regular safety reviews.

Randomisation and masking

Enrolled patients were randomly assigned (1:1) to receive either buparlisib or placebo with paclitaxel with a central patient screening and randomisation system. Randomisation was stratified by the number of previous lines of therapy in the recurrent or metastatic setting (one *vs* two [this latter group comprised patients who received cetuximab as single-agent, second-line therapy]) and study site (North America *vs* rest of world). Randomisation was done with a block size of four within each strata. Interactive response technology (IRT) that included an interactive voice and web response system was used to gather screening information and allocate treatment. Investigators provided identifying information for each patient at enrolment to register them into the IRT system, and each patient was assigned a unique seven-digit patient number, which they retained throughout their participation in the study. Randomisation numbers were generated to ensure treatment assignment was unbiased and concealed from patients and investigators: a patient randomisation list was produced by the IRT provider using a validated system to automate the random assignment of patient numbers to randomisation numbers. Each randomisation number was linked to a treatment group and a unique medication number. A separate medication randomisation list was produced by Novartis Drug Supply Management (BSP Pharmaceuticals, Latino Scalo, Italy) with a validated system to automate the random assignment of medication numbers to medication packs containing each study treatment. Randomisation numbers were not communicated to investigators. Patients and investigators (including local radiologists) were unaware of the assigned treatments from time of randomisation until the final overall survival analysis. Premature unblinding of study drug assignment was only allowed in case of emergency. The identity of experimental treatments was concealed by use of buparlisib and placebo that were identical in packaging, labelling, appearance, and administration schedule.

Procedures

Patients received oral buparlisib or placebo (continuous dosing with 100 mg once daily starting on day 1) plus intravenous paclitaxel (80 mg/m² on days 1, 8, 15, and 22) in 28 day treatment cycles. Novartis Drug Supply Management provided buparlisib and matching placebo as 10 mg and 50 mg hard gelatin capsules as individual patient supply, packaged in bottles. Paclitaxel was prescribed by investigators and obtained as outlined in the investigator Clinical Trial Agreement.

Treatment continued until disease progression, unacceptable toxicity, death, or discontinuation for any other reason. Crossover from placebo to buparlisib at disease progression was not permitted. Protocol-specified reasons for treatment discontinuation were unacceptable adverse events, loss to follow-up, non-compliance with study treatment, physician or patient decision, pregnancy, progressive disease, protocol deviation, study termination, technical problems, or death. Dose adjustments were permitted if a patient was unable to tolerate the protocol-specified dose. Up to three levels of dose reduction of buparlisib and placebo were allowed: 80 mg/day continuously; 100 mg/day on five days of seven; and 80 mg/day on five days of seven, with no dose re-escalations permitted during any subsequent cycle. One level of dose reduction for intravenous paclitaxel was permitted to 65 mg/m². Dose interruptions of buparlisib or placebo were allowed in specific circumstances (appendix pp 63–72). Any study medication that was interrupted for more than 4 weeks consecutively could not be reintroduced. Patients who discontinued one of the study drugs for any reason besides disease progression were allowed to continue the other study drug at the investigator's discretion.

Tumour assessments were done locally (at the radiological facilities of the participating sites) with CT or MRI at screening, 4 weeks after randomisation, and then every 6 weeks until radiological progression. Imaging data used for tumour assessments were also collected centrally

and subjected to retrospective review by a blinded independent central radiology committee. Laboratory evaluations were done locally at screening and at the end of treatment, as well as during each treatment cycle as follows: haematology (days 1, 8, 15, and 22); biochemistry, coagulation, creatinine clearance, pregnancy test (day 1), fasting plasma glucose (cycle 1, day 15; days 1 and 15 of subsequent cycles), fasting C-peptide (cycle 1, day 15; day 1 of subsequent cycles), glycosylated haemoglobin (every three cycles starting cycle 3, day 1). Visit windows of give or take 3 days were permitted (except at cycle 1, day 1). Screening laboratory assessments done within 7 days of first dosing did not need to be repeated at cycle 1, day 1.

All patients were followed up for survival every 3 months, irrespective of treatment discontinuation (except if the patient withdrew consent, refused survival follow-up, or was lost to follow-up). Safety was monitored throughout the study by physical examination, laboratory evaluations, vital signs, bodyweight, performance status evaluation, electrocardiogram, cardiac imaging, patient self-rated questionnaires, and adverse event collection (graded according to CTCAE version 4.03). Health-related quality of life was also monitored throughout the study with the patient-rated European Organisation for Research and Treatment of Cancer core quality of life questionnaire (EORTC QLQ-C30 version 3.0) and its head and neck-specific module (EORTC QLQ-HN35).

Prespecified exploratory molecular assessments were done on archival tumour samples and circulating tumour DNA (ctDNA) samples isolated from blood obtained at screening. Samples of sufficient volume and quality were analysed by sponsor-designated laboratories (Genoptix Inc, Carlsbad, CA, USA) with validated analytical methods. Tumour analyses included *PIK3CA* mutation (by PCR or next-generation sequencing) or loss of phosphatase and tensin homologue (PTEN) expression (by immunohistochemistry), human papillomavirus (HPV) status by immunohistochemistry or in-situ hybridisation, and next-generation sequencing with a targeted 44-gene panel that included *TP53*. Analyses of ctDNA included next-generation sequencing with a targeted 542-gene panel that included *TP53* and HPV viral probes, with mutational load calculated as the number of non-synonymous mutations detected per patient.

After treatment discontinuation, all patients continued to be followed up for safety evaluations for 30 days after the last dose of study treatment. Patients who discontinued because of disease progression had their progression documented according to RECIST version 1.1. All other patients continued tumour assessments every 6 weeks until the start of new anti-cancer therapy, disease progression, death, loss to follow-up, or withdrawal of consent. Additionally, all new anticancer therapies given after the final dose of the study treatment were recorded until disease progression, death, loss to follow-up, or withdrawal of consent. All patients were followed up for survival status every 3 months or earlier if needed, irrespective of reason for treatment discontinuation (except withdrawal of consent or loss to follow-up).

Outcomes

The primary endpoint was progression-free survival per local investigator assessment based on RECIST. Progression-free survival was defined as time from randomisation until the first documented tumour progression or death from any cause (the date of progression was the earliest time when any RECIST progression event [ie, radiological progression or death] was noted with no more than one previous missing assessment). The key secondary endpoint was overall survival, defined as time from randomisation to date of death due to any cause. Other secondary endpoints were: safety (based on the frequency of adverse events and number of abnormal laboratory values that were outside predetermined ranges); the proportion of patients who achieved an overall response (those with a best overall response of complete response or partial response, based on local radiological assessment per RECIST); time to response (time from randomisation to first documented response [complete response or partial response]); the proportion of patients with disease control (patients with a best overall response of complete response, partial response, or stable disease, based on local radiological assessment per RECIST); duration of response (defined as elapsed time between first documented response and after first documented progression or death due to underlying cancer, which was defined only for the responder subset [ie, patients with a confirmed complete response or partial response based on investigator assessment]); pharmacokinetics (based on preliminary pharmacokinetic assessment of buparlisib exposure when administered in combination with paclitaxel in this population); and quality of life (based on global health status or quality of life scale and pain score of the EORTC QLQ-C30 questionnaire and EORTC QLQ-HN35). Prespecified exploratory endpoints included analyses of potential biomarkers of response, including PI3K pathway activation, HPV status, and frequently changed genes or signalling pathways.

Statistical analysis

The primary endpoint of progression-free survival as per local investigator review was assessed based on a prespecified Bayesian double criteria requiring an estimated hazard ratio (HR) of 0·67 or lower and a posterior probability criteria (HR <1) of more than 97·5% (equivalent to a two-sided 95% CI of <1). A minimum of 114 progression-free survival events were required, so that the probability to meet the prespecified progression-free survival criteria would be 1·2% if the true HR was 1·00, and about 50% if the true HR was 0·67. Similarly, the efficacy criteria for overall survival were defined based on a prespecified Bayesian double criteria

requiring an estimated HR of 0·77 or lower and a posterior probability criteria (HR <1) of more than 90% (equivalent to a two-sided 80% CI of <1). A minimum of 112 deaths were required for overall survival analysis, so that the probability to meet the prespecified overall survival criteria would be 9·3% if the true HR was 1·00. We needed to enrol an estimated 150 patients (75 per group) to observe the required number of events.

HRs were estimated with a stratified Cox proportional hazard model, incorporating the stratification factors defined at randomisation. The HR as a measure of treatment effect was derived from a stratified unadjusted Cox proportional hazards model, which included only the treatment group variable as a covariate. No substantial departure from proportional hazards assumptions was observed with respect to this variable. Additional sensitivity analyses were done, including repetition of the primary progression-free survival analysis excluding patients with any protocol deviations that were likely to affect the primary endpoint, and with the stratification variables as per the electronic case report form instead of IRT to assess the effect of any mis-stratification. A multivariate Cox proportional hazard analysis adjusting for risk factors was also done to assess the robustness of the estimated treatment effect adjusted for the baseline differences. The Kaplan-Meier method was used to summarise progression-free survival, overall survival, and duration of response endpoints; one-sided retrospective tests for significance were done for progression-free survival and overall survival, and were not adjusted for multiplicity. The proportion of patients with an overall response was summarised with 95% CIs based on the Clopper–Pearson method. Sensitivity analyses of progression-free survival, the proportion of patients with an overall response, and duration of response were done on central radiology assessments.

Efficacy analyses were done on the full analysis set (all randomised patients) according to the intention-to-treat principle. Missing adequate tumour assessments were defined as tumour assessments not done or those with overall lesion response as "unknown". In the primary progression-free survival analysis, events occurring after two or more missing assessments were censored at the final adequate tumour assessment. Additional reasons for progression-free survival censoring were: ongoing without event, loss to follow-up, consent withdrawal, and new cancer therapy added. Reasons for overall survival censoring were survival and loss to follow-up. All safety analyses were done on the safety set (all patients who received at least one dose of study treatment, either paclitaxel or buparlisib, and had at least one post-baseline safety assessment) according to study treatment received on day 1. A per-protocol set was defined as a subset of the full analysis set excluding patients with protocol deviations that might have affected the primary endpoint, and was used to assess the primary endpoint as a sensitivity analysis. There were no planned interim efficacy analyses. All statistical analyses were done and figures generated with SAS, version 9.4.

This trial is registered with ClinicalTrials.gov, number NCT01852292. The full study protocol is available in the appendix (p 25).

Role of the funding source

This study was designed, conducted, and analysed by the funder in conjunction with investigators and the study steering committee. The funder provided study drugs and participated in regulatory and ethics approval, safety monitoring, data collection, and statistical analyses. PA, AC, MC, SH, and ST had access to the raw data. All authors had full access to study data for interpretation and analysis. The funder provided financial support for medical editorial assistance in the writing of this report. No authors were paid to write this report, and all authors had responsibility for the decision to submit for publication. The corresponding author had full access to all the data and had final responsibility to submit for publication.

Results

Between Nov 5, 2013, and May 5, 2015, 242 patients were enrolled in the study and assessed for eligibility for randomisation. Eligible patients were randomly assigned at 58 centres across 18 countries; 37 centres each had fewer than five patients enrolled and randomly assigned to treatment groups (appendix p 1). After 84 patients were excluded for various reasons (figure 1), a total of 158 patients were randomly assigned to receive either buparlisib and paclitaxel (n=79) or placebo and paclitaxel (n=79).

Baseline characteristics of randomised patients were well balanced between the treatment groups (table 1). The median patient age was 58·5 years (IQR 53·0–65·0) and most patients were men (133 [84%] of 158) and white (112 [71%]). The most common primary cancer sites were the oral cavity (46 [29%] of 158 patients), oropharynx (45 [29%]), hypopharynx (29 [18%]), and larynx (25 [16%]). Based on tumour tissue analysis, 115 (73%) of 158 patients had HPV-negative disease and 18 (11%) had PI3K pathway-activated tumours. Of the 28 (18%) patients with HPV-positive status, 18 presented with the oropharynx as the primary cancer site, four with the hypopharynx, three with the oral cavity, two with the larynx, and one with the nasopharynx. All 158 patients had received previous antineoplastic therapy: 91 (58%) had undergone previous surgery; 128 (81%) radiotherapy, 59 (37%) chemotherapy in the adjuvant or neoadjuvant setting; and 153 (97%) chemotherapy in the recurrent or metastatic setting, excluding those with protocol deviations. Previous EGFR inhibitor treatment in the recurrent or metastatic setting was reported for 41 (52%) of 79 patients in the buparlisib group and 30 (38%) of 79 patients in the placebo group.

At the cutoff date for overall survival analysis (March 30, 2016), 148 (94%) of 158 patients had

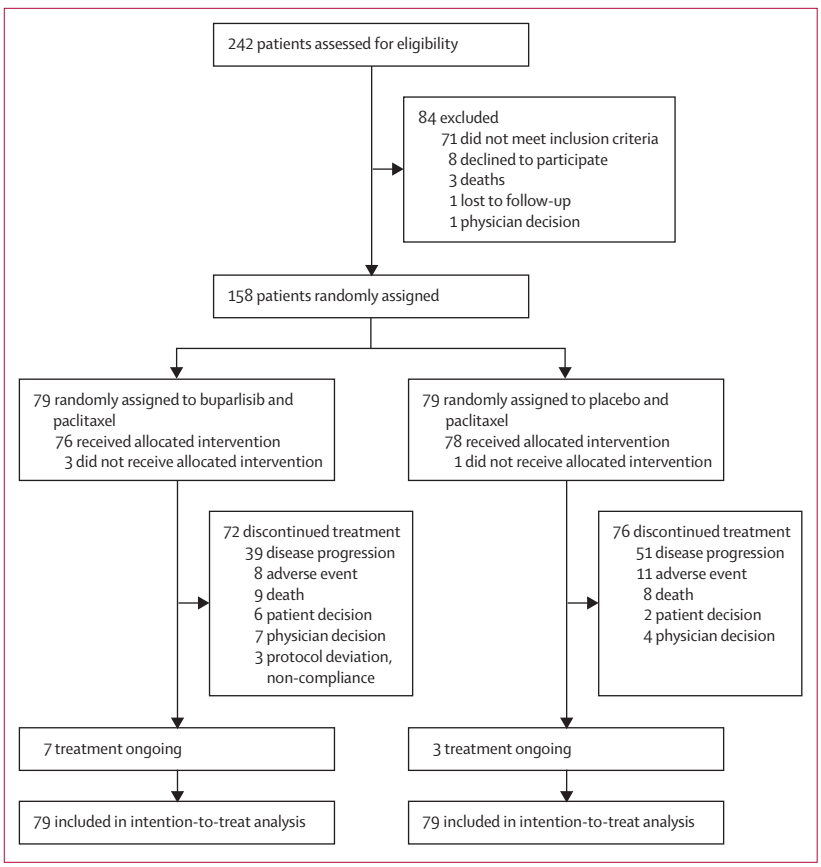

Figure 1: **Trial profile**

discontinued treatment (figure 1; appendix, p 3). The median duration of follow-up was 18·1 months (IQR 14·4–22·2). A similar proportion of patients received additional antineoplastic therapy after treatment discontinuation in the buparlisib group (22 [28%] of 79 patients) and the placebo group (25 [32%] of 79 patients), including various immunomodulatory agents.

The primary analysis was done at the data cutoff of Aug 31, 2015, at which time a total of 115 progression-free survival events were reported: 51 in the buparlisib group and 64 in the placebo group. The study met the primary endpoint of progression-free survival based on the prespecified criteria (HR 0·65 [95% CI 0·45–0·95]; posterior probability [HR <1] 98·9%; one-sided p=0·011), with a median progression-free survival of 4·6 months (95% CI 3·5–5·3) in the buparlisib group and 3·5 months (95% CI 2·2–3·7) in the placebo group (figure 2A). In the buparlisib group, 8 (10%) of 79 patients were censored after the median progression-free survival was reached (one [1%] had a new cancer therapy, six [8%] were ongoing without a progression-free survival event, and one [1%] withdrew consent) and 20 (25%) were censored before the median (five [6%] no longer had adequate assessment available, six [8%] had a new cancer therapy, seven [9%] were ongoing without an event, and two [3%] withdrew consent). In the placebo group, ten (13%) of 79 patients were censored after median progression free survival (one [1%] had a new cancer therapy and nine [11%] were ongoing without an event) and five (6%) were censored before the median (two [3%] no longer had adequate assessment available, two [3%] had a new cancer therapy, and one [1%] withdrew consent).

At the final overall survival cutoff (March 30, 2016), a total of 113 deaths were reported: 53 in the buparlisib group and 60 in the placebo group. The key secondary endpoint of overall survival was also met based on the prespecified criteria (HR 0·72 [95% CI 0·49–1·04]; posterior probability [HR <1] 95·9%; one-sided p=0·041; 80% CI 0·56–0·92), with a median overall survival of 10·4 months (95% CI 7·3–12·8) in the buparlisib group and 6·5 months (95% CI 5·3–8·8) in the placebo group (figure 2B). In the buparlisib group, 19 (24%) of 79 patients were censored after the median overall survival was reached (of whom 18 [23%] were alive and 1 [1%] was lost to follow-up) and seven (9%) were censored before the median overall survival (two [3%] were alive and five [6%] were lost to follow-up). In the placebo group, 14 (18%) of 79 patients were censored after median overall survival was reached because they were alive, and five (6%) were censored before the median because they were lost to follow-up.

The proportion of patients who achieved an overall response was higher in the buparlisib group (31 [39%] of 79 patients [95% CI 28·4–50·9]) than in the placebo group (11 [14%] of 79 [7·2–23·5]; p=0·00031; table 2). Similarly, calculated from the local radiological assessment, the proportion of patients with tumour shrinkage was higher in the buparlisib group (57 [80%] of 71 patients) than in the placebo group (41 [55%] of 74 patients; appendix, p 8). However, the proportion of patients who had disease control was similar between treatment groups, and the median duration of overall response in the buparlisib group was shorter than in the placebo group (table 2). Time to 10% deterioration on key patient quality of life and symptom subscales as measured by EORTC QLQ-C30 and EORTC QLQ-HN35 did not differ substantially between treatment groups (figure 3).

The median time to overall response among responding patients was similar; 1·02 months (0·8–9·2) in the buparlisib group compared with 0·99 months (0·8–5·1) in the placebo group.

The per-protocol study set included 145 patients (excluding the three patients discontinued due to protocol deviations and 13 additional patients with protocol deviations). The results of the progression-free survival sensitivity analysis in the per-protocol set were consistent with those of the primary analysis (HR 0·63 [95% CI 0·42–0·93]). The results of the progression-free survival analysis based on stratification factors in the electronic case report form were consistent with the results of the primary analysis based on stratification factors from the IRT (HR 0·64 [95% CI 0·43–0·93]).

	Buparlisib and paclitaxel (n=79)	Placebo and paclitaxel (n=79)
Age (years)	59·0 (53·0–65·0)	58·0 (53·0–65·0)
Sex		
Men	65 (82%)	68 (86%)
Women	14 (18%)	11 (14%)
Race		
White	57 (72%)	55 (70%)
Asian	22 (28%)	23 (29%)
Unknown	0	1 (1%)
Smoking history		
Never	19 (24%)	15 (19%)
Current	11 (14%)	17 (22%)
Former	49 (62%)	47 (60%)
ECOG performance status		
0	31 (39%)	25 (32%)
1	48 (61%)	53 (67%)
Unknown	0	1 (1%)
Site of primary cancer		
Hypopharynx	13 (16%)	16 (20%)
Larynx	10 (13%)	15 (19%)
Nasopharynx	2 (3%)	2 (3%)
Oral cavity	23 (29%)	23 (29%)
Oropharynx	26 (33%)	19 (24%)
Other	4 (5%)	4 (5%)
Unknown	1 (1%)	0
Any metastatic site*	59 (75%)	62 (79%)
Previous antineoplastic therapy		
Surgery	53 (67%)	38 (48%)
Radiotherapy	65 (82%)	63 (80%)
Chemotherapy (adjuvant/ neoadjuvant setting)	34 (43%)	25 (32%)
Previous lines of therapy (any setting)		
≥1	79 (100%)	79 (100%)
≥2	44 (56%)	42 (53%)
≥3	9 (11%)	7 (9%)
No previous lines of therapy for recurrent or metastatic squamous cell carcinoma of the head and neck†	5 (6%)	0
(Continued from previous column)		
One previous line of therapy for recurrent or metastatic squamous cell carcinoma of the head and neck	71 (90%)	77 (98%)
Chemotherapy	33 (42%)	48 (61%)
Chemotherapy and EGFR inhibitor	38 (48%)	29 (37%)
Two previous lines of therapy for recurrent or metastatic squamous cell carcinoma of the head and neck	3 (4%)	2 (2%)
First-line chemotherapy and second-line EGFR inhibitor	0	1 (1%)
First-line chemotherapy and EGFR inhibitor and second-line EGFR inhibitor	3 (4%)	0
Other	0	1 (1%)
HPV status‡		
HPV negative	53 (67%)	62 (79%)
HPV positive	17 (22%)	11 (14%)
Unknown or missing	9 (11%)	6 (8%)
Tumour PI3K pathway activation§	8 (10%)	10 (13%)
PIK3CA mutation¶	7/61 (11%)	9/69 (13%)
Loss of PTEN expression¶	1/77 (1%)	1/79 (1%)

ECOG=Eastern Cooperative Oncology Group. HPV=human papillomavirus. PI3K=phosphatidylinositol 3-kinase. PTEN=phosphatase and tensin homologue. *Metastatic sites included the adrenal gland, bone, brain, liver, lung, lymph nodes, skin, soft tissue, spleen, and other. †These patients had protocol deviations. ‡HPV status ascertained in archival tumour tissue with immunohistochemistry or in-situ hybridisation. §PI3K pathway activation defined as *PIK3CA* mutation or loss of PTEN expression. ¶Based on the number of patients with non-missing somatic mutation status.

***Table 1*: Baseline characteristics**

The results of the retrospective, blinded central review showed a consistent treatment effect compared with local investigator assessment in terms of progression-free survival (median progression-free survival 3·8 months [95% CI 2·8–5·2] in the buparlisib group *vs* 2·3 months [1·9–3·7] in the placebo group; HR 0·54 [95% CI 0·37–0·79]) and the proportion of patients with an overall response (20 [25%] of 79 patients in the buparlisib group *vs* 12 [15%] of 79 in the placebo group). According to central review, 61 (77%) of 79 patients in the buparlisib group and 64 (81%) of 79 patients in the control group were judged to have measurable disease at baseline. Of these patients, 20 (33%) of 61 patients achieved an overall response in the buparlisib group versus 12 (19%) of 64 in the placebo group. Compared with placebo, buparlisib showed some treatment benefit in terms of progression-free survival in primary cancer in the hypopharynx (data not shown), the proportion of patients with an overall response (data not shown), and overall survival (figure 4) across some negative clinical prognostic factors (specifically, HPV-negative status in archival tissue, primary cancer in the hypopharynx, and patients whose previous best overall response to therapy had been progressive disease). Notably, patients with HPV-positive status and oropharynx primary tumours did not derive a benefit from buparlisib versus placebo (figure 4). A prespecified multivariate analysis done after adjustments for risk factors also showed consistent results with buparlisib compared with placebo for progression-free survival (HR 0·61 [95% CI 0·40–0·94]), overall survival (HR 0·75; 95% CI 0·50–1·12) and the proportion of patients who achieved an overall response (odds ratio 3·3 [95% CI 1·3–8·8]).

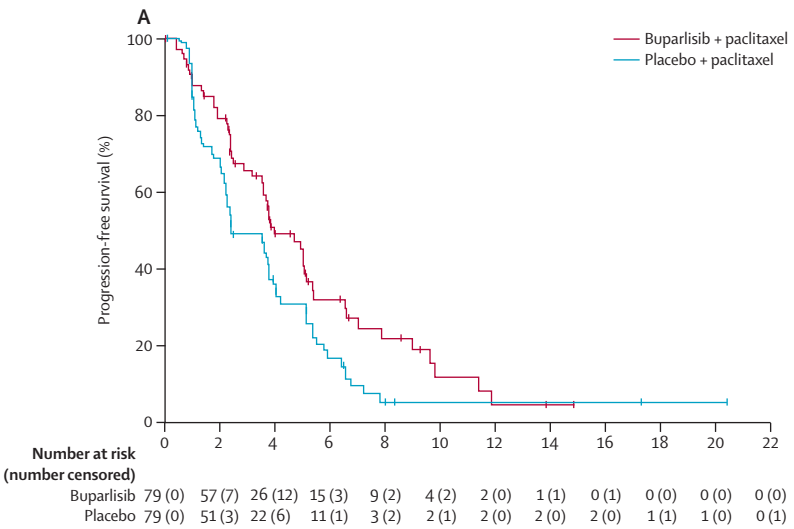

***Figure 2*: Progression-free and overall survival**
Shown are the Kaplan-Meier plots of patient progression-free survival (A) and overall survival (B) by treatment group for the full analysis set. Nominal p values are presented with no adjustment for multiple testing. HR=hazard ratio. PFS=progression-free survival.

	Buparlisib and paclitaxel (n=79)	Placebo and paclitaxel (n=79)
Complete response	3 (4%)	1 (1%)
Partial response	28 (35%)	10 (13%)
Stable disease	26 (33%)	44 (56%)
Progressive disease	10 (13%)	19 (24%)
Unknown	11 (14%)	5 (6%)
Not assessed*	1 (1%)	0
Overall response†	31 (39%; 28·4–50·9)	11 (14%; 7·2–23·5)
Median duration of overall response (months)	4·5 (3·1–6·7)	7·1 (2·8–NE)
Disease control‡	57 (72%; 60·9–81·7)	55 (70%; 58·2–79·5)

Data are n (%), n (%; 95% CI), or median (95% CI). NE=not evaluable. *One patient did not have a baseline or post-baseline assessment. †Complete response and partial response. ‡Complete response, partial response, or stable disease.

***Table 2*: Best overall response to therapy**

The results of a prespecified exploratory analysis to establish the potential influence of tumour characteristics on treatment effect (overall survival and the proportion of patients achieving an overall response) are shown in appendix p 9. A statistically significant benefit for buparlisib versus placebo on overall survival and overall response outcomes was maintained in patients with HPV-negative status (according to archival tissue or ctDNA), *TP53* mutations in archival tissue, and those with a low mutational load (<13 variants) on ctDNA. However, no significant difference between the treatment groups in terms of overall survival or overall responses was shown for the following tumour characteristics: HPV-positive status, *TP53* mutations in ctDNA, non-altered *TP53* (in archival tissue or ctDNA), and high mutational load (≥13 variants; appendix p 9).

A total of 154 patients were assessed for safety (76 in the buparlisib group and 78 in the placebo group); the remaining three patients in the buparlisib group and one patient in the placebo arm were randomly assigned to a treatment group but did not receive study treatment. In the buparlisib group versus the placebo group, median exposure to study drug was 2·9 months (IQR 1·5–5·1) versus 2·5 months (1·2–4·5), and median exposure to paclitaxel was 3·4 months (IQR 1·9–5·2) versus 2·3 months (1·1–4·1). At least one dose reduction was required for 29 (38%) of 76 patients given buparlisib and 13 (17%) of 78 patients who received placebo, and at least one dose interruption was required for 47 (62%) patients given buparlisib and 29 (37%) patients given placebo. Dose reductions and interruptions for paclitaxel were more frequent in the buparlisib group (31 [41%] and 54 [71%] patients, respectively) than in the placebo group (17 [22%] and 43 [55%] patients, respectively). Most dose reductions and interruptions were due to adverse events (appendix p 4).

The most frequent adverse events (irrespective of relation to study treatment) are summarised in table 3 (grade 1–2 events reported in ≥10% patients in either group and grade 3–4 events reported in ≥2% patients in either group). A full table of all adverse events is included in the appendix, pp 5–7. Grade 3–4 adverse events were reported in 62 (82%) of 76 patients in the buparlisib group and 56 (72%) of 78 patients in the placebo group. The most common grade 3–4 adverse events were hyperglycaemia (17 [22%] of 76 patients in the buparlisib group *vs* two [3%] of 78 patients in the placebo group), anaemia (14 [18%] *vs* nine [12%]), neutropenia (13 [17%] *vs* four [5%]), and fatigue (six [8%] *vs* eight [10%]). Treatment discontinuation because of adverse events occurred at a similar frequency with buparlisib (eight [10%] of

79 patients [10%]) and placebo (11 [14%] of 79 patients; appendix p 3). Serious adverse events (irrespective of relation study treatment) were reported for 43 (57%) of 76 patients in the buparlisib group and 37 (47%) of 78 patients in the placebo group, with rare reports of suicidal ideation (two patients in the buparlisib group and one in the placebo group). 15 (20%) on-treatment deaths were reported in the buparlisib group and 17 (22%) reported in the placebo group, with disease progression the most frequent cause of death (nine [12%] patients in the buparlisib group *vs* 11 [14%] in the placebo group). Other on-treatment deaths were caused by: infections (two [3%] patients *vs* one [1%] patient); cardiac disorders (one [1%] *vs* two [3%]); respiratory disorders (one [1%] *vs* two [3%]); cachexia (one [1%] *vs* none); general physical health deterioration (one [1%] *vs* none); post-procedural complications (none *vs* one [1%]). No on-treatment deaths were suspected to be study treatment-related.

Discussion

The results of this randomised phase 2 study show that the addition of buparlisib to paclitaxel therapy for patients with platinum-pretreated recurrent or metastatic squamous cell carcinoma of the head and neck produces clinically meaningful improvement in progression-free survival, overall survival, and the proportion of patients with an overall response, with a manageable safety profile. To our knowledge, this study achieved the longest median overall survival (10·4 months) reported in this second-line setting, which compares favourably with the 10·1 month overall survival recorded with the existing first-line standard-of-care treatment (cetuximab, platinum, and fluorouracil triplet).[11] Although the pre-specified criteria for overall survival benefit with the addition of buparlisib to paclitaxel were met at the time of the final overall survival analysis, the retrospective nominal one-sided p value for overall survival was greater than 0·025 and therefore did not achieve statistical significance. However, this result should be interpreted with caution because the study was not powered for statistical significance of overall survival. There was also a nearly three-times increase in the proportion of patients with an overall response with buparlisib (39%) versus placebo (14%); the proportion of patients who achieved an overall response with buparlisib is the highest reported so far in this setting. Although the median duration of response was shorter in the buparlisib group versus the placebo group, duration of response was measured solely on the subset of responders within each group and not the intention-to-treat population, and the potential effect of the imbalance in responder numbers between the two treatment groups limits any conclusions that can be drawn from these results.

Extension of treatment efficacy in recurrent or metastatic squamous cell carcinoma of the head and neck has proven challenging. Clinical trials in the first-line setting have assessed various systemic therapies (including platinum chemotherapy doublets; platinum monotherapy; and cetuximab, platinum, and fluorouracil triplet therapy), showing improvements in the proportion of patients achieving an overall response; however, median overall survival remains shorter than 1 year.[3] Existing treatment options used in clinical practice as second-line therapy (including methotrexate, docetaxel, paclitaxel, and cetuximab) are not supported by phase 3 trial results.[2,3] Many agents and combinations have been assessed in this setting, including taxanes, methotrexate, receptor tyrosine kinase inhibitors, and immunotherapies. For example, in a comparison of second-line afatinib (a receptor tyrosine kinase inhibitor) versus methotrexate, median progression-free survival

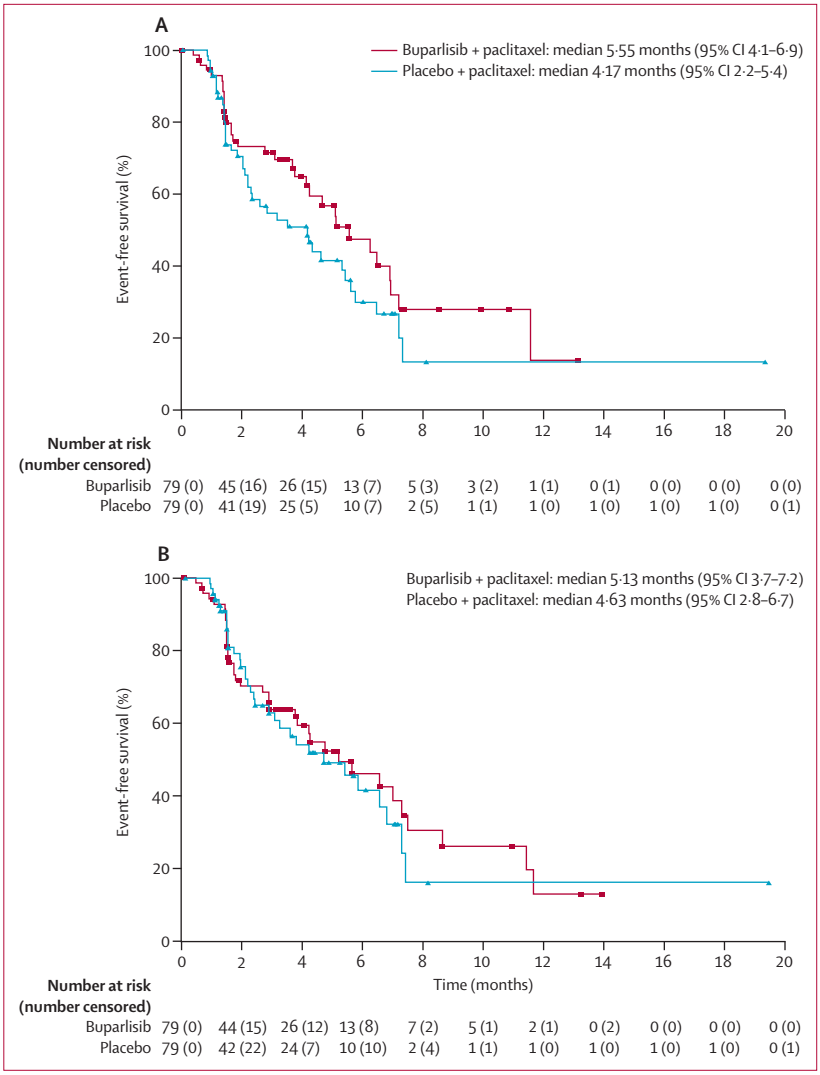

***Figure 3*: Time to deterioration of EORTC QLQ-HN35 head and neck symptoms subscale scores**
Kaplan–Meier symptoms subscale scores for speech problems (A) and swallowing (B) by at least 10%, by treatment group in the full analysis set. Blocks correspond to censoring times. EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer core quality of life questionnaire. EORTC QLQ-HN35=EORTC QLQ head and neck-specific module.

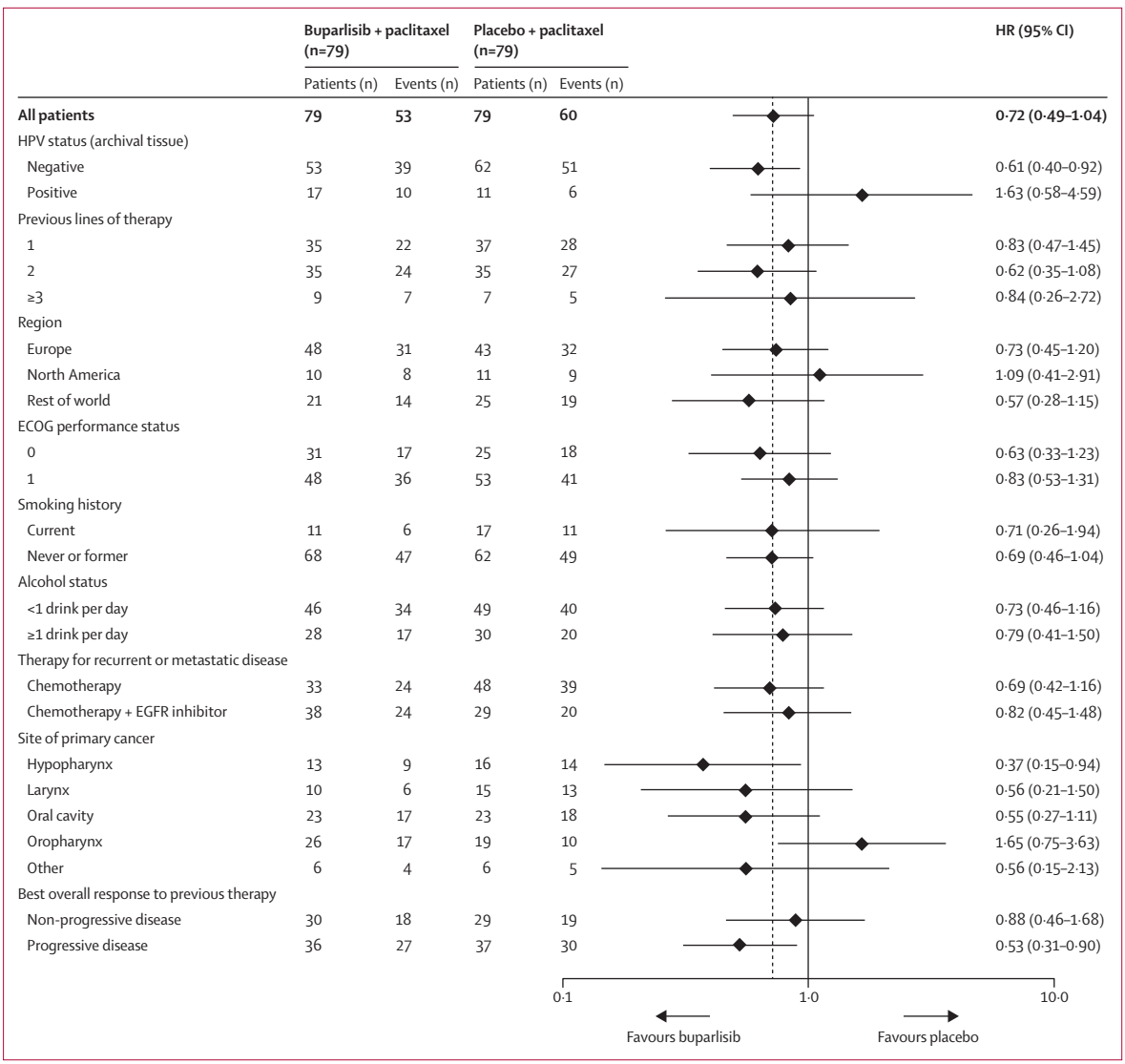

***Figure 4*: Overall survival according to prognostic factors**

Forest plot of HRs (95% CIs) for overall survival with buparlisib plus paclitaxel *vs* placebo plus paclitaxel according to clinical prognostic factors of squamous cell carcinoma of the head and neck. The vertical dashed line represents the overall survival HR between the two groups for all patients overall. ECOG=Eastern Cooperative Oncology Group. HPV=human papillomavirus. HR=hazard ratios.

was 2·6 months versus 1·7 months and overall survival was 6·8 months versus 6·0 months.[12] Clinical evaluations are ongoing, but none so far have yielded progression-free survival outcomes or proportions of patients with an overall response equal to the present results achieved with buparlisib plus paclitaxel combination therapy.

Immune checkpoint inhibitors that facilitate activation of an antitumour immune response are also being assessed in squamous cell carcinoma of the head and neck.[4] In CheckMate-141,[13] median overall survival was 7·5 months (95% CI 5·5–9·1) for patients treated with nivolumab versus 5·1 months (95% CI 4·0–6·0) for those assigned a therapy of the investigator's choice. Treatment with pembrolizumab in a phase 1 KEYNOTE 012 trial expansion cohort[14] led to a proportion of people with a confirmed and unconfirmed overall response of 18% (95% CI 11·1–27·2), with 18 of 99 patients with a partial response, and disease control of roughly 50%. By contrast, in the present trial, treatment with buparlisib plus paclitaxel led to an overall response in 39% of patients and disease control in 72%.

Prespecified exploratory analyses indicated that clinical benefit was maintained across some patient subgroups. Of note, despite the poor prognosis and limited life expectancy associated with HPV-negative status,[15–17] our results suggest that this subgroup might derive benefit from the combination of buparlisib and paclitaxel therapy. However, clinical activity in these patients might be

linked to the strong association in squamous cell carcinoma of the head and neck between HPV-negative status and other poor-prognosis factors such as *TP53* alterations or a non-oropharynx primary tumour.[18–20] Additionally, the basis for limited efficacy in the buparlisib group versus placebo group in patients with HPV-positive squamous cell carcinoma of the head and neck and oropharynx primary tumours, which are typically associated with better disease outcomes than patients with HPV-negative disease and non-oropharynx primary tumours, requires further investigation. However, given the small sample sizes of these subgroups, caution is advised in the interpretation of these results with respect to specific treatment effects. Notably, in the patients treated with buparlisib, those with HPV-positive squamous cell carcinoma of the head and neck had better outcomes than did those with HPV-negative status with respect to progression-free and overall survival.

Patients showed good tolerance of buparlisib plus paclitaxel, with similar or less toxicity than reported with other PI3K inhibitors and buparlisib monotherapy in squamous cell carcinoma of the head and neck.[21–23] The proportions of patients discontinuing treatment because of adverse events were similar in the buparlisib and placebo groups, suggesting that buparlisib did not substantially increase paclitaxel toxicity. The frequency of hyperglycaemia was higher with buparlisib versus placebo, suggesting effective PI3K pharmacodynamic inhibition.[24] Known adverse events associated with buparlisib, including hyperglycaemia and gastrointestinal adverse events (eg, stomatitis, diarrhoea, nausea, and vomiting),[22,23] were managed with established strategies of dose reduction and treatment of symptoms with appropriate concomitant medications.

Although the combination of another treatment with chemotherapy might be expected to reduce patient quality of life, the addition of buparlisib to paclitaxel was not associated with such deterioration, and quality of life indicators were generally stable and similar between the groups. Exposure to treatment and discontinuations due to adverse events were similar in the buparlisib and placebo groups, which might help to explain the similarity in quality of life scores between the groups. However, absence of differentiation between patients with local recurrence versus distant metastasis and psychological factors probably also affected quality of life findings. Additionally, EORTC QLQ-C30 assessment might have not had specificity in this population because this assessment was not head and neck specific. These aspects will require further investigation.

Buparlisib-induced PI3K inhibition in combination with paclitaxel was effective despite the limited PI3K pathway alteration identified, potentially because PI3K signalling in squamous cell carcinoma of the head and neck is often activated through independent mechanisms, such as EGFR overexpression upstream of PI3K.[18] Molecular alterations of the PI3K pathway might therefore

	Buparlisib and paclitaxel (n=76)			Placebo and paclitaxel (n=78)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Hyperglycaemia	31 (41%)	17 (22%)	0	25 (32%)	2 (3%)	0
Anaemia	17 (22%)	14 (18%)	0	24 (31%)	9 (12%)	0
Fatigue	25 (33%)	6 (8%)	0	9 (12%)	8 (10%)	0
Diarrhoea	28 (37%)	1 (1%)	0	12 (15%)	1 (1%)	0
Neutropenia	12 (16%)	12 (16%)	1 (1%)	5 (6%)	3 (4%)	1 (1%)
Alopecia	24 (32%)	0	0	15 (19%)	0	0
Stomatitis	17 (22%)	7 (9%)	0	9 (12%)	1 (1%)	0
Decreased appetite	18 (24%)	5 (7%)	0	11 (14%)	4 (5%)	0
Asthenia	15 (20%)	6 (8%)	0	14 (18%)	3 (4%)	0
Nausea	18 (24%)	2 (3%)	0	13 (17%)	0	0
Vomiting	17 (22)	3 (4%)	0	11 (14%)	0	0
Decreased bodyweight	19 (25%)	0	0	7 (9%)	2 (3%)	0
Cough	16 (21%)	0	0	18 (23%)	0	0
Constipation	14 (18%)	0	0	8 (10%)	0	0
Headache	13 (17%)	1 (1%)	0	6 (8%)	0	0
Rash	12 (16%)	2 (3%)	0	11 (14%)	0	0
Anxiety	13 (17%)	0	0	9 (12%)	0	0
Depression	11 (15%)	2 (3%)	0	7 (9%)	0	0
Pyrexia	12 (16%)	0	0	17 (22%)	1 (1%)	0
Dyspnoea	7 (9%)	2 (3%)	1 (1%)	9 (12%)	5 (6%)	0
Insomnia	10 (13%)	0	0	6 (8%)	0	0
Dry skin	8 (11%)	0	0	2 (3%)	0	0
Leucopenia	3 (4%)	3 (4%)	2 (3%)	9 (12%)	3 (4%)	1 (1%)
Paraesthesia	7 (9%)	1 (1%)	0	8 (10%)	1 (1%)	0
Peripheral neuropathy	6 (8%)	0	0	14 (18%)	4 (5%)	0
Peripheral oedema	5 (7%)	0	0	9 (12%)	0	0
Hyperkalaemia	2 (3%)	0	0	8 (10%)	0	0
Dysphagia	6 (8%)	5 (7%)	0	5 (6%)	3 (4%)	0
Hypertension	6 (8%)	4 (5%)	0	3 (4%)	3 (4%)	0
γ-glutamyltransferase increased	6 (8%)	2 (3%)	0	3 (4%)	4 (5%)	0
Pneumonia	4 (5%)	3 (4%)	1 (1%)	4 (5%)	6 (8%)	0
Hypokalaemia	2 (3%)	4 (5%)	1 (1%)	2 (3%)	1 (1%)	2 (3%)
White blood cell count decreased	5 (7%)	2 (3%)	0	0	1 (1%)	1 (1%)
Aspartate aminotransferase increased	4 (5%)	2 (3%)	0	7 (9%)	0	0
Neck pain	4 (5%)	2 (3%)	0	7 (9%)	0	0
Neutrophil count decreased	3 (4%)	0	3 (4%)	2 (3%)	2 (3%)	0
Hyponatraemia	1 (1%)	3 (4%)	1 (1%)	2 (3%)	4 (5%)	0
Oropharyngeal pain	4 (5%)	1 (1%)	0	4 (5%)	2 (3%)	0
Respiratory tract infection	3 (4%)	2 (3%)	0	2 (3%)	0	0
Tumour haemorrhage	2 (3%)	3 (4%)	0	2 (3%)	2 (3%)	2 (3%)
Hypoaesthesia	2 (3%)	2 (3%)	0	0	0	0
Hypotension	3 (4%)	1 (1%)	0	1 (1%)	3 (4%)	0
Oral pain	2 (3%)	2 (3%)	0	1 (1%)	0	0
Bronchitis	2 (3%)	1 (1%)	0	2 (3%)	2 (3%)	0

(Table 3 continues on next page)

	Buparlisib and paclitaxel (n=76)			Placebo and paclitaxel (n=78)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
(Continued from previous page)						
General physical health deterioration	0	2 (3%)	1 (1%)	0	0	0
Hypophosphataemia	1 (1%)	2 (3%)	0	3 (4%)	2 (3%)	0
Lung infection	1 (1%)	2 (3%)	0	1 (1%)	0	0
Non-cardiac chest pain	2 (3%)	1 (1%)	0	3 (4%)	3 (4%)	0
Septic shock	0	2 (3%)	1 (1%)	0	1 (1%)	0
Cachexia	1 (1%)	1 (1%)	0	0	1 (1%)	2 (3%)
Hypermagnesaemia	0	2 (3%)	0	0	0	0
Irritability	0	2 (3%)	0	0	1 (1%)	0
Lymphopenia	0	2 (3%)	0	2 (3%)	1 (1%)	0
Sepsis	0	2 (3%)	0	0	0	2 (3%)
Pneumothorax	0	1 (1%)	0	0	2 (3%)	0
Respiratory failure	0	0	1 (1%)	0	0	2 (3%)
Syncope	0	1 (1%)	0	0	4 (5%)	0
Mouth haemorrhage	0	0	0	0	2 (3%)	0

Grade 1–2 adverse events reported in 10% or more of patients in either treatment group and grade 3–4 events occurring in 2% or more of patients in either group are listed. A full table of all adverse events is in appendix pp 5–7. On-treatment deaths occurred in 15 (20%) of 76 patients in the buparlisib group and 17 (22%) of 78 patients in the placebo group, caused by: disease progression (nine [12%] patients *vs* 11 [14%] patients); infections (two [3%] *vs* one [1%]); cardiac disorders (one [1%] *vs* two [3%]); respiratory disorders (one [1%] *vs* two [3%]); cachexia (one [1%] *vs* none); general physical health deterioration (one [1%] *vs* none); and post-procedural complications (none *vs* one [1%]).

***Table 3*: Adverse events, irrespective of relation to study treatment**

not be a requisite for sensitivity to PI3K inhibition in this cancer type. Additionally, pan-PI3K inhibition might exert its effects via the downstream pathway.

Based on ctDNA analyses, patients with squamous cell carcinoma of the head and neck and a low mutational load might also derive benefit from the combination of buparlisib and paclitaxel therapy. Although an absence of association between mutational load and HPV status was previously reported,[25] a lower involvement of the immune system in tumours with low mutational load or HPV-negative status,[26,27] together with the potential ability of buparlisib to prime the immune system,[28] might explain the improved outcome observed in some patient subgroups. By contrast, an increased benefit from immunotherapies has been reported in patients with a high mutational load.[29,30]

The findings of our study should be interpreted in the context of the study design. Specifically, this randomised controlled phase 2 study had a lower patient recruitment rate than a similar phase 3 study,[13] and several sites enrolled only a small number of patients (fewer than five patients randomly allocated, mainly due to difficulties in accruing patients for this second-line chemotherapy-based study). Despite its recognition as a prognostic factor in squamous cell carcinoma of the head and neck, HPV status was not used as a stratification factor for efficacy analyses because its prognostic importance in patients receiving second-line treatment has yet to be determined. Additionally, baseline data for whether patients progressed on versus after platinum-based chemotherapy in the metastatic setting were not collected. There might have been some heterogeneity between the two treatment groups due to the many sites that participated in the study, especially with respect to the potential effects of post-protocol therapy on overall survival. Some baseline imbalances were noted based on the case report form data, such as previous exposure to EGFR inhibitor treatment, although multivariate analysis controlling for baseline factors showed a consistent treatment effect across demographic and clinical subgroups, including in patients who received previous chemotherapy only and those who received previous chemotherapy plus EGFR inhibitor treatment.

Overall, the results of this study showed that buparlisib plus paclitaxel could be an effective treatment for patients with platinum-pretreated recurrent or metastatic squamous cell carcinoma of the head and neck, with those having poor prognostic features such as a primary tumour in the hypopharynx, disease progression on previous therapy, and HPV-negative status potentially deriving the greatest benefit. Further phase 3 studies are warranted to confirm this phase 2 finding.

Contributors

PA, AC, SF, and ST designed the study. SF, LL, and DS were members of the steering committee that oversaw the conduct of the study. DS, LL, RM, ER, S-HL, AK, AD, SO, LAK, J-CL, RN, LT, S-BK, JE, AA, SK, and CB contributed substantially to patient recruitment and data collection. AC was the trial statistician. PA, AC, MC, SH, and ST contributed to data analysis and PA, AC, MC, SF, SH, LL, DS, and ST and contributed to data interpretation. MC was responsible for biomarker data generation, analysis, and interpretation. All authors contributed to the drafting and revision of the report, and had final review and approval of the submitted version.

Declaration of interests

AA, SF, DS, and LT received grants or honoraria from Novartis Pharmaceuticals Corporation during the conduct of the study. CB, S-BK, LL, SO, and DS received grants or advisory fees from Novartis Pharmaceuticals Corporation outside of this study. CB received advisory fees from Merck, Bayer, Roche, and Celgene. SF received advisory fees from Merck Serono, Celgene, and Bayer. S-BK received a grant from Sanofi-Aventis. LL received grants or advisory fees from Eisai, Bristol-Myers Squibb, MSD, Merck Serono, Boehringer Ingelheim, Debiopharm, Sobi, AstraZeneca, Bayer, and Roche. RM received advisory fees from Merck, MSD, and Innate Pharma. LT received grants or advisory fees from MSD, Boehringer Ingelheim, and AstraZeneca. PA, AC, MC, SH, and ST are employees of Novartis Pharmaceuticals Corporation. AC also owns stock in Novartis Pharmaceuticals Corporation. ER, S-HL, AK, AD, LAK, J-CL, RN, JE, and SK declare no competing interests.

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