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A phase IB dose-escalation study of the safety and pharmacokinetics of pictilisib in combination with either paclitaxel and carboplatin (with or without bevacizumab) or pemetrexed and cisplatin (with or without bevacizumab) in patients with advanced non–small cell lung cancer

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Abstract ***Aim:*** The phosphatidylinositol 3-kinase (PI3K) pathway is a potential therapeutic target in non–small cell lung cancer (NSCLC). This study aimed to evaluate the pan-PI3K

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3-kinase;
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Metastatic NSCLC;
Front-line NSCLC;
First-line NSCLC

inhibitor pictilisib in combination with first-line treatment regimens that were the standard of care at the time of study, in patients with NSCLC.

Patients and methods: A 3 + 3 dose-escalation study was performed using a starting daily dose of 60 mg pictilisib on days 1–14 of a 21-day cycle. Depending on bevacizumab eligibility and NSCLC histology, patients also received either paclitaxel + carboplatin or pemetrexed + cisplatin, ± bevacizumab every 3 weeks. The primary objectives of the study were to assess safety and tolerability and to identify dose-limiting toxicities (DLTs), the maximum tolerated dose (MTD) and a recommended phase II dose (RP2D), for each combination.

Results: All 66 treated patients experienced at least one adverse event (AE). Grade ≥III AEs, serious AEs and deaths occurred in 57 (86.4%), 56 (84.8%) and 9 (13.6%) patients, respectively. Three patients reported DLTs across the four arms of the study. The MTD was not reached in any arm and the RP2D of pictilisib was determined to be 330 mg (capsules) or 340 mg (tablets) on a '14 days on, 7 days off' schedule. The best confirmed response was partial response in 29 (43.9%) patients and stable disease in 20 (30.9%) patients.

Conclusion: Combining pictilisib with various standard-of-care first-line treatment regimens is feasible from a safety perspective in patients with NSCLC, and encouraging preliminary anti-tumour activity was observed.

1. Introduction

As the most common cancer and the leading cause of cancer-related deaths worldwide, lung cancer accounted for 13.0% (1.82 million) of all new cancer cases and 19.4% (1.59 million) of cancer mortality in 2012 [1]. The majority of patients with lung cancer (85%) are diagnosed with non–small cell lung cancer (NSCLC) [2]. Platinum-containing chemotherapy is the standard of care for first-line treatment of patients with advanced NSCLC [3–5]. For patients with non-squamous NSCLC and no recent history of haemoptysis, chemotherapy may be administered in combination with bevacizumab [3–5]. Recently, the first programmed cell death-1 immune checkpoint inhibitor, pembrolizumab, was approved by the Food and Drug Administration for first-line treatment of patients with metastatic squamous and non-squamous NSCLC, whose tumours have high programmed death-ligand 1 expression and no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase genomic aberrations [6]. However, most patients with NSCLC eventually progress despite treatment, and 5-year survival remains poor, particularly for patients with stage IV disease (4.9%) [7]. Therefore, there is a significant unmet need for alternative effective treatments for these patients.

Genetic alterations in the phosphatidylinositol 3-kinase (PI3K) pathway are frequently observed in NSCLC [8], making PI3K a potential therapeutic target. These occur through mutation or amplification of the *PIK3CA* gene encoding the p110α catalytic subunit, loss of function of PTEN (through deletion, mutation or reduced expression), alterations in INPP4B and PHLPP phosphatases, mutations of PI3K regulatory subunits encoded by *PIK3R1* and *PIK3R3* or through activation of upstream receptor tyrosine kinases or crosstalk with the RAS pathway [8]. Pictilisib (GDC-0941) is a potent class I pan-PI3K inhibitor, with comparable activity against mutant and wild-type forms of the p110α subunit of class IA [9]. Pictilisib has demonstrated anti-tumour activity in xenograft models of human cancers [10] and has synergistic cytotoxicity in combination with platinum-based chemotherapies, EGFR inhibitors and mitogen-activated protein extracellular signal-regulated kinase inhibitors in NSCLC cell lines [11]. The single-agent maximum tolerated dose (MTD) for pictilisib from phase IA studies is 330 mg (capsule; equivalent to a 340-mg tablet) administered orally once daily, with maculopapular rash as a dose-limiting toxicity (DLT) [12].

This phase IB study was designed to evaluate the safety and pharmacokinetics (PK) of pictilisib in combination with first-line platinum-containing treatment regimens that were the standard of care at the time of study, in patients with NSCLC.

2. Patients and methods

2.1. Patients

Eligible patients were ≥18 years with advanced NSCLC (stage IIIB ineligible for chemoradiotherapy, stage IV or recurrent), who were chemotherapy-naïve or had received one line of chemotherapy, with an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1 and baseline diffusing capacity of the lungs for carbon monoxide (DL_{CO}) ≥50% of predicted, corrected for haemoglobin and alveolar volume. Adequate haematological and end organ function and evaluable or measurable disease (Response Evaluation

Criteria in Solid Tumors [RECIST], version 1.0) were also the inclusion criteria. Patients with known central nervous system (CNS) metastases were eligible if they had evaluable/measurable disease outside the CNS. Any radiotherapy for CNS metastases must have been completed at least 8 weeks before screening and any neurosurgical resection or brain biopsy must have been performed more than 3 months before day 1.

Key exclusion criteria were type 1 or type 2 diabetes (glycosylated haemoglobin ≥7%, fasting glucose ≥7.49 mmol/L and/or requiring regular medication), any adjuvant or neoadjuvant anti-cancer regimen for NSCLC within 4 weeks or >1 previous anti-cancer regimen for advanced NSCLC. Additional key exclusion criteria for patients in the bevacizumab arms included inadequately controlled hypertension, prior history of hypertensive crisis or encephalopathy, myocardial infarction or unstable angina, stroke or transient ischaemic attacks, vascular disease and haemoptysis. Patients with squamous cell NSCLC were not eligible for bevacizumab and pemetrexed combinations.

2.2. Study design

This was a non-randomised, open-label, multicentre, phase IB dose-escalation study to assess the safety, tolerability and PK of pictilisib administered with paclitaxel and carboplatin with or without bevacizumab in patients with NSCLC or pemetrexed and cisplatin with and without bevacizumab in patients with non-squamous NSCLC (Fig. 1).

Paclitaxel (200 mg/m^2), carboplatin (6 mg/mL·min), pemetrexed (500 mg/m^2), cisplatin (75 mg/m^2) and bevacizumab (15 mg/kg) were administered intravenously every 3 weeks. Pictilisib was administered orally once daily on days 1–14 of each 21-day cycle. Patients received paclitaxel + carboplatin ± bevacizumab or pemetrexed + cisplatin ± bevacizumab on day 1 of each 21-day cycle for up to six cycles, except for cycle 1. During cycle 1, pictilisib was administered as a single agent on day 1 of a 22-day cycle followed by chemotherapy on day 2. Patients could continue with pictilisib maintenance therapy (squamous NSCLC) or pictilisib and pemetrexed (non-squamous NSCLC), with or without bevacizumab, beyond six cycles if they had no disease progression or intolerable toxicity.

A dose-escalation stage using a 3 + 3 design was performed for each arm to determine the MTD. A starting dose of 60-mg pictilisib on a '14 day in phase IA studies on a continuous once-daily schedule (330-mg capsule) [12], was used in cohort 1. Pictilisib was administered by capsule or tablet according to availability. Due to the slightly higher bioavailability of the capsule (Roche/Genentech data on file) the 340-mg tablet is equivalent to the 330-mg capsule. Cohort 4 received a dose of 250 mg (capsule) or 260 mg (tablet), while cohort 5 and the expansion cohort received 330 mg (capsule) or 340 mg (tablet).

The MTD of the combination was defined as the highest dose at which fewer than two of six evaluable patients had a DLT during cycle 1. DLTs were defined as study drug–related toxicities occurring during the 22-day assessment window in cycle 1 and included: grade ≥III non-haematological, non-hepatic organ toxicity (excluding nausea, vomiting or diarrhoea that resolved to grade ≤I within 3 days, hypertension for patients treated with bevacizumab or hyperglycaemia within 3 days of steroid premedication for paclitaxel or pemetrexed); grade ≥IV thrombocytopenia lasting >7 days or associated with clinically significant bleeding; grade ≥IV neutropenia lasting >7 days; grade ≥IV febrile neutropenia; grade ≥III total bilirubin or hepatic transaminases (alanine aminotransferase or aspartate aminotransferase) (for patients with grade I hepatic

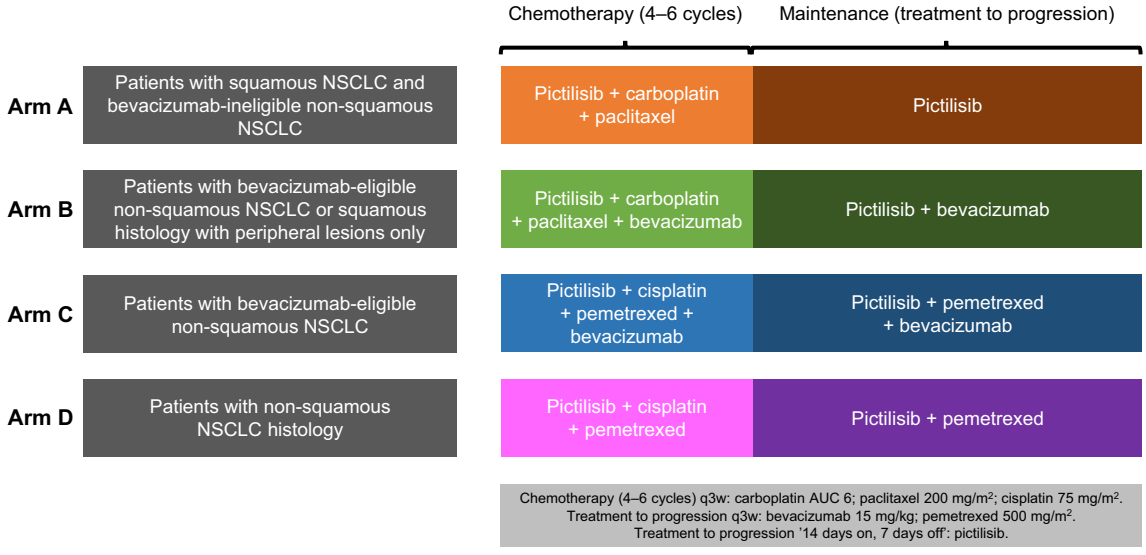

Fig. 1. Study design. AUC, area under the plasma-concentration time curve; NSCLC, non–small cell lung cancer; q3w, every 3 weeks.

transaminase at baseline as a result of metastases, hepatic transaminase >7.5 × the upper limit of normal was considered a DLT) and grade ≥II DL_{CO} with a decrease of ≥20% from baseline. Patients not evaluable for DLTs were replaced, including those who withdrew from treatment before completing the first cycle for reasons other than a DLT, who missed ≥4 days of pictilisib treatment for reasons other than a DLT or who did not receive the full dose of their chemotherapy regimen for reasons other than a DLT.

Following identification of the MTD of pictilisib plus the various chemotherapy combinations, a cohort-expansion stage with a planned additional six to nine patients was performed for three arms to evaluate the safety, tolerability, PK and anti-tumour activity of pictilisib with different combination chemotherapies. The pictilisib + carboplatin + paclitaxel arm (Fig. 1, Arm A) was not included in the expansion part.

The study was conducted in accordance with the guidelines for Good Clinical Practice. Institutional Review Board/Ethics Committee approval was obtained for the protocol, patient recruitment material, informed consent forms, any information given to the patient and relevant supporting information. The study was registered on ClinicalTrials.gov (NCT00974584) and the European Clinical Trials Database (EudraCT; number 2009-010780-16).

2.3. End-points

The primary objectives for the study were the evaluation of safety and tolerability, the identification of DLTs and estimation of the MTD and the identification of a recommended phase II dose (RP2D) for pictilisib administered with the different first-line treatment regimens for advanced NSCLC. Secondary objectives included evaluation of the PK and anti-tumour activity of pictilisib in combination with chemotherapy.

2.4. Assessments

Adverse events (AEs) were graded according to the National Cancer Institute - Common Terminology Criteria for Adverse Events, version 3.0 [13]. Tumour assessments were performed at baseline and at the end of cycles 2, 4, 6 and 9, then every third cycle thereafter or as clinically indicated, and disease status was categorised per RECIST, version 1.0. Blood samples were taken for pictilisib PK evaluations during cycle 1 before and after dosing on day 1, before dosing on day 9 and at study completion. Additional samples were taken on days 2 and 3 for PK evaluations of all study drugs. Plasma concentrations of pictilisib, bevacizumab and chemotherapy drugs (including paclitaxel and its cytochrome P450 2C8 [CYP2C8]–formed metabolite, 6 α-hydroxypaclitaxel [6α-OH-paclitaxel]) were determined using validated liquid chromatography - tandem mass spectrometry methods and PK parameters were estimated using non-compartmental analysis (WinNonlin 6.4; Pharsight, Mountain View, CA).

2.5. Statistical methods

Descriptive statistics were used for the safety population before study discontinuation. Summaries are presented by study arm and dose level. Data cut-off was 20th May 2015.

3. Results

3.1. Patients

A total of 50 patients were treated across all arms in the dose-escalation stage, with an additional 16 patients across three arms in the cohort-expansion stage. The first patient was enrolled on 15th October 2009 and the last patient on 28th January 2014. The median age of all treated patients was 59 years (range: 34–80 years) and 53% were male (Table 1). The majority of patients (65.2%) had an ECOG performance status of 1, and 63.6% had received no prior systemic therapy (Table 1). The number of patients included in each cohort is shown in Fig. 2.

3.2. Safety

The median duration of pictilisib exposure across all arms was 126 days (range 14–959 days) and the median

Table 1
Patient demographics and baseline characteristics.

Characteristic, *n* (%)	*N* = 66
Median age, years (range)	59.0 (34–80)
Age category	
18–40 years	4 (6.1)
41–64 years	46 (69.7)
≥65 years	16 (24.2)
Gender	
Male	35 (53.0)
Female	31 (47.0)
Ethnicity	
Not Hispanic or Latino	64 (97.0)
Not available	2 (3.0)
Race	
American Indian or Alaska Native	1 (1.5)
Black or African American	3 (4.5)
White	58 (87.9)
Not available	4 (6.1)
Smoking status	
Never	7 (10.6)
Previous	45 (68.2)
Current	14 (21.2)
ECOG performance status	
0	23 (34.8)
1	43 (65.2)
Prior systemic therapy	
≥1 prior systemic therapy	24 (36.4)
No prior systemic therapy	42 (63.6)

ECOG, Eastern Cooperative Oncology Group.

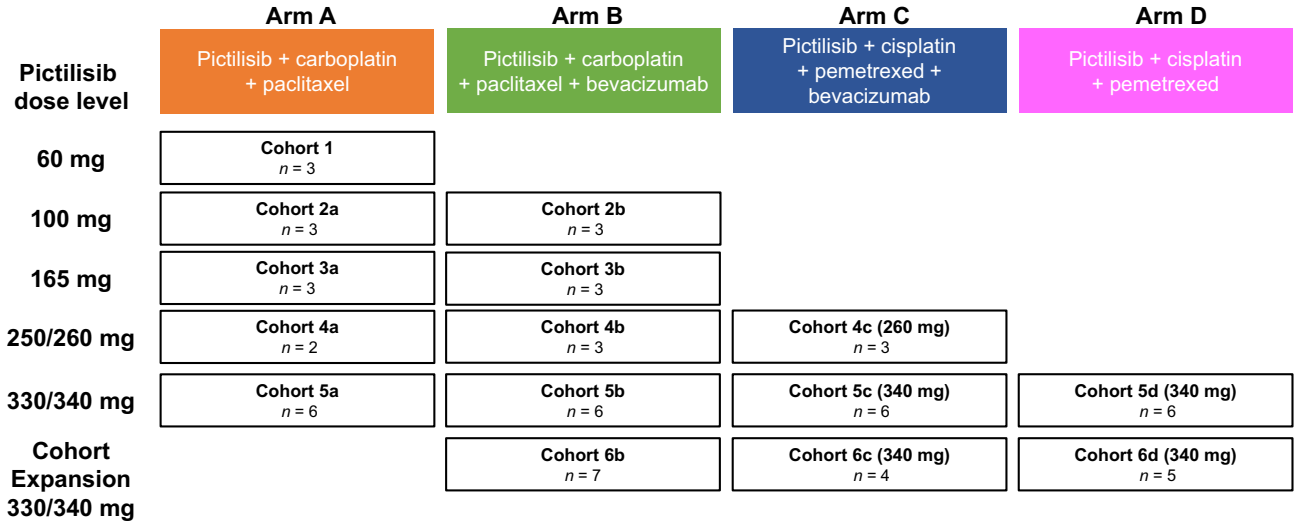

Fig. 2. Dosing cohorts and dose levels. *n* refers to patients evaluable for dose-limiting toxicities. One patient assigned to cohort 2a and two to cohort 5c, were replaced due to missing doses or non-compliance. The combination of 250-mg pictilisib with carboplatin and paclitaxel was considered tolerable for dose escalation based on data from cohorts 4a and 4b.

number of pictilisib treatments administered was 79.5 (range 8–618).

All patients experienced at least one AE (Table 2), most commonly nausea (68.2%), vomiting, fatigue and decreased appetite (54.5% each) and diarrhoea (48.5%) (Table 3). Grade ≥III AEs occurred in 57 (86.4%) patients (Table 2). The most common grade ≥III AEs were neutropenia (27.3%), dyspnoea (15.2%) and anaemia and dehydration (12.1% each) (Table 4). Serious AEs were reported in 56 (84.8%) patients (Table 2), the most common of which were dehydration (10.6%), lung infection and febrile neutropenia (7.6% each), dyspnoea (6.1%) and increased blood creatinine (6.0%). There were nine deaths (13.6%) on the study (Table 2), seven from disease progression and one each from cardiorespiratory arrest and cardiac failure (cohorts 5a and 5d, respectively). No deaths were considered related to study treatment.

Pictilisib treatment was discontinued in 22 (33.3%) patients due to AEs (Table 2), most commonly due to fatigue ($n = 4$ p), nausea ($n = 2$) and myalgia ($n = 2$). All patients had withdrawn from the study at the time of data cut-off. Withdrawal was attributed to disease progression in 32 (48.5%) patients, patient or physician decision in 18 (27.2%) patients, AEs in 11 (16.7%) patients and death (not preceded by AEs or disease progression) in five (7.6%) patients.

DLTs occurred in three patients during the study. Grade III rash occurred in two patients who were treated with 330-mg pictilisib + paclitaxel + carboplatin + bevacizumab (from cohort 5b and the cohort-expansion stage, 6b) and grade III nausea in one patient treated with 340-mg pictilisib + pemetrexed + cisplatin + bevacizumab (from cohort 5c). The MTD of pictilisib in combination with paclitaxel + carboplatin ± bevacizumab or pemetrexed + cisplatin ± bevacizumab was not reached. The maximum administered dose (MAD) of 330 mg (capsules) or 340 mg (tablets) taken on a '14 days on, 7 days off' schedule was selected as the RP2D of pictilisib in combination with the different regimens assessed in this study.

3.3. Pharmacokinetics

Pictilisib is an *in vitro* inhibitor of CYP2C8-mediated paclitaxel 6α hydroxylation [14], and therefore could alter the CYP2C8-mediated metabolism of paclitaxel when used in the clinical setting. However, the exposure ratio of 6α-OH-paclitaxel to paclitaxel observed in patients across all pictilisib dose levels was stable over time (Fig. 3) and consistent with published data for paclitaxel alone [15], suggesting that the PK of paclitaxel is independent of the administered pictilisib dose. Similarly, no differences in the PK of pictilisib, carboplatin, bevacizumab, pemetrexed, cisplatin or paclitaxel were observed in the combination regimens compared with historical single-agent data (data not shown).

3.4. Anti-tumour activity

The best confirmed response at any time across the four arms of the study was partial response in 29 (43.9%) patients and stable disease in 20 (30.9%) patients. Table 5 shows the best confirmed response, time to response and duration of response by treatment arm. Time to response ranged from 39 days for patients treated with pictilisib + cisplatin + pemetrexed to 86 days for patients treated with pictilisib + carboplatin + paclitaxel + bevacizumab (Table 5). Median duration of response ranged from 6.6 months in the pictilisib + cisplatin + pemetrexed + bevacizumab arm to 9.0 months in the pictilisib + carboplatin + paclitaxel + bevacizumab arm

Table 2
Overview of safety from all arms and cohorts.

Patients, n (%)	Pictilisib + carboplatin + paclitaxel					Pictilisib + carboplatin + paclitaxel + bevacizumab				Pictilisib + cisplatin + pemetrexed + bevacizumab		Pictilisib + cisplatin + pemetrexed	All patients $N = 66$
Pictilisib dose[a]	60 mg ($n = 3$)	100 mg ($n = 3$)	165 mg ($n = 4$)	250 mg ($n = 2$)	330 mg ($n = 6$)	100 mg ($n = 3$)	165 mg ($n = 3$)	250 mg ($n = 3$)	330 mg ($n = 15$)	260 mg ($n = 3$)	340 mg ($n = 10$)	340 mg ($n = 11$)	
Any AE	3 (100.0)	3 (100.0)	4 (100.0)	2 (100.0)	6 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)	15 (100.0)	3 (100.0)	10 (100.0)	11 (100.0)	66 (100.0)
Grade III–IV AEs	1 (33.3)	2 (66.7)	3 (75.0)	2 (100.0)	5 (83.4)	3 (100.0)	3 (100.0)	0	12 (80.0)	2 (66.7)	7 (70.0)	8 (72.7)	48 (72.7)
SAEs	1 (33.3)	3 (100.0)	3 (75.0)	2 (100.0)	6 (100.0)	2 (66.7)	1 (33.3)	3 (100.0)	14 (93.3)	2 (66.7)	9 (90.0)	10 (90.9)	56 (84.8)
Deaths[b]	1 (33.3)	1 (33.3)	1 (25.0)	0	1 (16.7)	0	0	1 (33.3)	2 (13.3)	0	0	2 (18.2)	9 (13.6)
Study withdrawal due to AEs	0	0	1 (25.0)	0	0	0	0	2 (66.7)	5 (33.3)	1 (33.3)	2 (20.0)	0	11 (16.7)
Pictilisib withdrawals due to AEs[c]	1 (33.3)	0	1 (25.0)	0	1 (16.7)	0	1 (33.3)	2 (66.7)	7 (46.7)	1 (33.3)	3 (30.0)	5 (45.5)	22 (33.3)
Carboplatin withdrawals due to AEs	0	0	0	0	2 (33.3)	0	1 (33.3)	0	6 (40.0)	–	–	–	9 (21.4)
Paclitaxel withdrawals due to AEs	0	0	0	0	2 (33.3)	0	0	0	5 (33.3)	–	–	–	7 (16.7)
Bevacizumab withdrawals due to AEs	–	–	–	–	–	0	2 (66.7)	2 (66.7)	7 (46.7)	1 (33.3)	4 (40.0)	–	16 (43.2)
Cisplatin withdrawals due to AEs	–	–	–	–	–	–	–	–	–	1 (33.3)	3 (30.0)	4 (36.4)	8 (33.3)
Pemetrexed withdrawals due to AEs	–	–	–	–	–	–	–	–	–	2 (66.7)	3 (30.0)	3 (27.3)	8 (33.3)

AE, adverse event; MAD, maximum administered dose; SAE, serious adverse event.

[a] Dose-escalation and cohort-expansion stages are combined at the MAD in each arm.

[b] The nine reported deaths were due to disease progression ($n = 7$) and AEs (cardio-respiratory arrest and cardiac failure; $n = 2$).

[c] The most common AEs leading to pictilisib discontinuation were fatigue ($n = 4$ patients), nausea ($n = 2$) and myalgia ($n = 2$). The following AEs leading to pictilisib discontinuation occurred in one patient each: cardiac failure, cardio-respiratory arrest, vomiting, oedema, pyrexia, anaphylactic shock, lung infection, sepsis, increased blood creatine, neck pain, non–small cell lung cancer, headache, acute kidney injury, dyspnoea, hypoxia, pulmonary embolism, exfoliative dermatitis, rash, hypertension and superior vena cava syndrome.

Table 3
All-grade AEs occurring in ≥30% overall of all patients by preferred term for each cohort.

Patients, n (%)	Pictilisib + carboplatin + paclitaxel					Pictilisib + carboplatin + paclitaxel + bevacizumab				Pictilisib + cisplatin + pemetrexed + bevacizumab		Pictilisib + cisplatin + pemetrexed	All patients[b] $N = 66$
Pictilisib dose[a]	60 mg ($n = 3$)	100 mg ($n = 3$)	165 mg ($n = 4$)	250 mg ($n = 2$)	330 mg ($n = 6$)	100 mg ($n = 3$)	165 mg ($n = 3$)	250 mg ($n = 3$)	330 mg ($n = 15$)	260 mg ($n = 3$)	340 mg ($n = 10$)	340 mg ($n = 11$)	
Nausea	2 (66.7)	3 (100.0)	2 (50.0)	1 (50.0)	3 (50.0)	3 (100.0)	1 (33.3)	2 (66.7)	7 (46.7)	3 (100.0)	9 (90.0)	9 (81.8)	45 (68.2)
Vomiting	2 (66.7)	1 (33.3)	1 (25.0)	0	2 (33.3)	1 (33.3)	0	2 (66.7)	9 (60.0)	2 (66.70)	8 (80.0)	8 (72.7)	36 (54.5)
Fatigue	1 (33.3)	1 (33.3)	1 (25.0)	1 (50.0)	4 (66.7)	1 (33.3)	1 (33.3)	2 (66.7)	7 (46.7)	2 (66.7)	8 (80.0)	7 (63.3)	36 (54.5)
Decreased appetite	2 (66.7)	2 (66.7)	1 (25.0)	0	4 (66.7)	2 (66.7)	1 (33.3)	1 (33.3)	12 (80.0)	2 (66.7)	6 (60.0)	3 (27.3)	36 (54.5)
Diarrhoea	2 (66.7)	2 (66.7)	1 (25.0)	2 (100.0)	3 (50.0)	1 (33.3)	3 (100.0)	2 (66.7)	7 (46.7)	1 (33.3)	7 (70.0)	1 (9.1)	32 (48.5)
Dyspnoea	1 (33.3)	1 (33.3)	2 (50.0)	2 (100.0)	1 (16.7)	1 (33.3)	1 (33.3)	3 (100.0)	7 (46.7)	0	4 (40.0)	6 (54.5)	29 (43.9)
Alopecia	2 (66.7)	3 (100.0)	2 (50.0)	2 (100.0)	2 (33.3)	3 (100.0)	2 (66.70)	2 (66.7)	6 (40.0)	0	4 (40.0)	1 (9.1)	29 (43.9)
Constipation	2 (66.7)	2 (66.7)	1 (25.0)	0	4 (66.7)	3 (100.0)	0	0	6 (40.0)	0	6 (60.0)	4 (36.4)	28 (42.4)
Neutropenia	2 (66.7)	1 (33.3)	4 (100.0)	1 (50.0)	3 (50.0)	2 (66.7)	3 (100.0)	1 (33.3)	7 (46.7)	0	3 (30.0)	0	27 (40.9)
Asthenia	2 (66.7)	1 (33.3)	2 (50.0)	1 (50.0)	4 (66.7)	2 (66.7)	2 (66.7)	1 (33.3)	4 (26.7)	1 (33.3)	5 (50.0)	1 (9.1)	26 (39.4)
Rash	0	2 (66.7)	1 (25.0)	2 (100.0)	3 (50.0)	1 (33.3)	0	2 (66.7)	10 (66.7)	1 (33.3)	2 (20.0)	1 (9.1)	25 (37.9)
Cough	2 (66.7)	2 (66.7)	1 (25.0)	2 (100.0)	1 (16.7)	1 (33.3)	0	1 (33.3)	6 (40.0)	1 (33.3)	4 (40.0)	2 (18.2)	23 (34.8)
Epistaxis	1 (33.3)	1 (33.3)	2 (50.0)	0	2 (33.3)	1 (33.3)	2 (66.7)	2 (66.7)	2 (13.3)	1 (33.3)	4 (40.0)	2 (18.2)	20 (30.3)
Dry skin	1 (33.3)	1 (33.3)	1 (25.00)	1 (50.0)	3 (50.0)	2 (66.7)	1 (33.3)	1 (33.3)	4 (26.7)	0	3 (30.0)	2 (18.2)	20 (30.3)

AE, adverse event.

[a] Dose-escalation and cohort-expansion stages are combined at the maximum administered dose in each arm.

[b] In addition to the listed AEs, 'peripheral sensory neuropathy' and 'neuropathy, peripheral' were reported separately as AEs by 16 (24.2%) patients and 14 (21.2%) of patients, respectively.

Table 4
Grade ≥III AEs occurring in ≥10% overall of all patients by preferred term for each cohort.

Patients, n (%)	Pictilisib + carboplatin + paclitaxel					Pictilisib + carboplatin + paclitaxel + bevacizumab				Pictilisib + cisplatin + pemetrexed	Pictilisib + cisplatin + pemetrexed + bevacizumab		All patients[b] $N = 66$
Pictilisib dose[a]	60 mg ($n = 3$)	100 mg ($n = 3$)	165 mg ($n = 4$)	250 mg ($n = 2$)	330 mg ($n = 6$)	100 mg ($n = 3$)	165 mg ($n = 3$)	250 mg ($n = 3$)	330 mg ($n = 15$)	260 mg ($n = 3$)	340 mg ($n = 10$)	340 mg ($n = 11$)	
Neutropenia	1 (33.3)	1 (33.3)	3 (75.0)	1 (50.0)	3 (50.0)	2 (66.7)	3 (100.0)	0	4 (26.7)	0	0	0	18 (27.3)
Dyspnoea	0	0	1 (25.0)	0	1 (16.7)	1 (33.3)	0	1 (33.3)	2 (13.3)	0	1 (10.0)	3 (27.3)	10 (15.2)
Anaemia	0	0	2 (50.0)	0	1 (16.7)	0	0	0	1 (6.7)	0	1 (10.0)	3 (27.3)	8 (12.1)
Dehydration	0	0	0	0	0	0	0	0	1 (6.7)	0	2 (20.0)	5 (45.5)	8 (12.1)

AE, adverse event.
[a] Dose-escalation and cohort-expansion stages are combined at the maximum administered dose in each arm.
[b] In addition to the listed grade ≥III AEs, grade ≥III febrile neutropenia and fatigue were reported by six (9.1%) patients each.

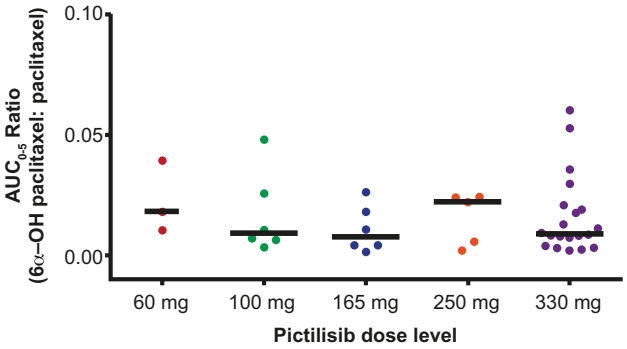

Fig. 3. – Observed 6α-OH paclitaxel: paclitaxel AUC ratio by pictilisib dose. The observed ratio of the cytochrome P450 2C8 metabolite, 6α-OH paclitaxel, to parent paclitaxel after the second daily dose of pictilisib at 60 mg, 100 mg, 165 mg, 250 mg and 330 mg. Black lines represent the median ratio for each dose level; dots represent individual subject ratios. AUC_{0-5}, area under the plasma-concentration time curve in the first 5 hours following administration.

(Table 5). Median duration of response had not been reached for patients treated with pictilisib + cisplatin + pemetrexed at the time of the data cut-off (Table 5). Target lesion percentage change from baseline and time on study for each patient by treatment arm are shown in Fig. 4.

4. Discussion

This phase IB study was designed to evaluate the safety and PK of pictilisib with different first-line platinum-containing chemotherapy regimens that were the standard of care at the time of the study, in patients with NSCLC. It was a part of a larger clinical development programme undertaken to evaluate pictilisib in combination with chemotherapy, hormone therapy and targeted anti-cancer therapies across several indications.

The MAD and RP2D of pictilisib when administered with chemotherapy in patients with advanced NSCLC was 330 mg (capsules) or 340 mg (tablets) administered once daily on days 1–14 of a 21-day cycle. Combining pictilisib at this dose with various chemotherapy regimens, with or without biological therapy, demonstrated an acceptable safety profile, and the AEs observed in the study were consistent with those seen in other studies with pictilisib alone [12] and/or are commonly seen with the chemotherapy regimens used.

The response rate of 44% was sufficiently encouraging to move forward with the phase II FIGARO study (NCT01493843). However, preliminary data from FIGARO failed to show statistically significant improvements in progression-free survival (PFS) and overall survival when pictilisib was combined with carboplatin + paclitaxel with and without bevacizumab in patients with non-squamous and squamous NSCLC, respectively [16,17].

Table 5
Anti-tumour activity.

	Pictilisib + carboplatin + paclitaxel (n = 18)	Pictilisib + carboplatin + paclitaxel + bevacizumab (n = 24)	Pictilisib + cisplatin + pemetrexed + bevacizumab (n = 13)	Pictilisib + cisplatin + pemetrexed (n = 11)
Best confirmed response, n (%)				
n	18	24	13	11
Partial response	9 (50.0)	9 (37.5)	9 (69.2)	2 (18.2)
Stable disease	3 (16.7)	9 (37.5)	3 (23.1)	5 (45.5)
Progressive disease − radiographic	5 (27.8)	1 (4.2)	0	2 (18.2)
NE	1 (5.6)	5 (20.8)	1 (7.7)	2 (18.2)
Time to objective response, days				
n	9	9	9	2
Median (range)	42.0 (34–83)	86.0 (34–532)	43.0 (36–84)	39.0 (39–39)
Duration of objective response, months				
n	9	9	9	2
Median (range)[a]	7.3 (1.2$^+$–8.6)	9.0 (2.9–24.1$^+$)	6.6 (1.4$^+$–12.0)	NE (1.7$^+$–3.0$^+$)

NE, not evaluable.
[a] Values with a + symbol are censored values.

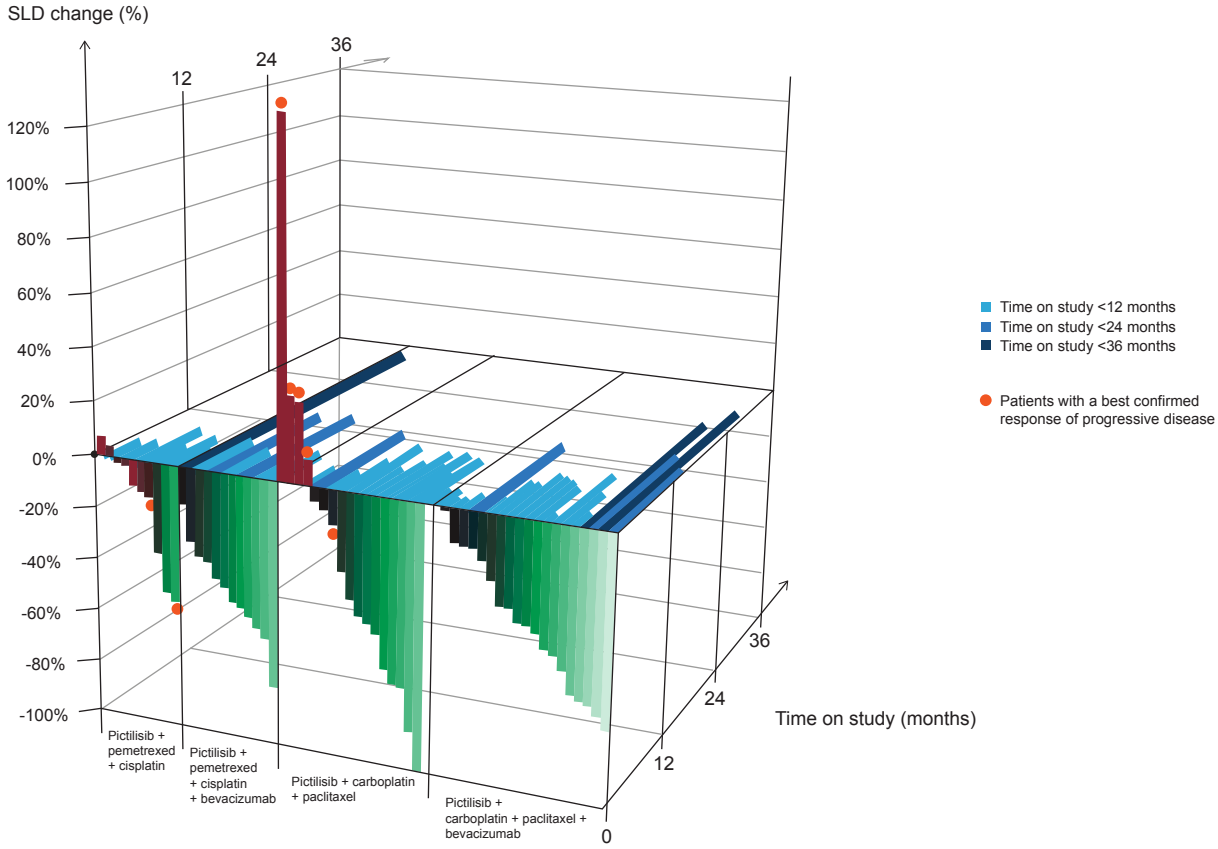

Fig. 4. Target lesion percentage change from baseline versus time on study. RECIST, Response Evaluation Criteria in Solid Tumours; SLD, sum of the longest diameter.

Pictilisib in combination with paclitaxel or fulvestrant also showed no significant PFS benefit in patients with hormone receptor–positive breast cancer in two recent studies (PEGGY [NCT01740336] and FERGI [NCT01437566]). In PEGGY and FERGI, the lack of efficacy may have been a result of limited and/or variable exposure to pictilisib from dose modifications and discontinuations due to the toxicity of the combination regimens [18,19]. Current strategies that try to improve the therapeutic index of PI3K inhibitors include the

investigation of isoform-selective inhibitors that may demonstrate greater activity than pan-PI3K inhibitors with potentially more favourable long-term safety profiles [20–22], or to select patients with known PI3K-activating mutations.

In conclusion, pictilisib can be safely combined with different first-line chemotherapy regimens in patients with NSCLC. However, the anti-tumour activity observed in this study did not translate to improved PFS in the randomised phase II FIGARO study.

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Conflict of interest statement

J.C.S received consultancy fees from AstraZeneca, Astex, Clovis, GlaxoSmithkline, Gammamabs, Lilly, MSD, Mission Therapeutics, Merus, Pfizer, Pharmamar, Pierre Fabre, Roche-Genentech, Sanofi, Servier, Symphogen and Takeda. C.F received consultancy fees from Roche. Merck, Bayer, Bristol-Myers Squibb, Merck Serono, AstraZeneca/MedImmune, Amgen and Chugai. B.B received research grants from Amgen. D.P was a member of the Advisory Boards for AstraZeneca, Boehringer, Roche, Bristol-Myers Squibb, MSD and Pfizer. H.G received research grants from Lilly, Roche, Bristol-Myers Squibb; consultancy fees from AstraZeneca, GlaxoSmithKline, Lilly, MSD. Pfizer and Roche/Genentech. G.S, J.S, J.W, J.Z, K.M, W.L. were employees of F. Hoffman–La Roche Ltd. The remaining authors had no conflicts to disclose.

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