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Original Research

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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Phosphatidylinositol 3-kinase;

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 inhibitor pictilisib in combination with first-line treatment regimens that were the standard

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Front-line NSCLC;
First-line NSCLC

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