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Original Research

A phase 1b study of afatinib in combination with standard-dose cetuximab in patients with advanced solid tumours

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Abstract This phase 1b, open-label trial assessed the combination of afatinib, an ErbB family blocker, with cetuximab, an epidermal growth factor receptor (EGFR) monoclonal antibody, in heavily pretreated patients with unselected/EGFR wild-type, advanced solid tumours.

In Part A, the maximum tolerated dose (MTD) of afatinib + cetuximab was evaluated using a 3 + 3 dose-escalation design; the starting dose was afatinib 30 mg/day plus cetuximab 250 mg/m^2/week (after cetuximab 400 mg/m^2 loading dose), escalating to afatinib 40 mg/day. Part B further evaluated safety and tolerability at the MTD and preliminary anti-

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tumour activity in three patient cohorts with squamous non–small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC) and other solid tumours.

Nine patients were treated in Part A; the MTD and recommended dose was determined as afatinib 40 mg/day plus cetuximab 250 mg/m^2/week. In Part B, 49 patients were treated at the recommended dose (12 with squamous NSCLC, 15 with HNSCC and 22 with other tumours). The most common treatment-related adverse events (AEs) across all 58 patients were diarrhoea (63.8%) and acneiform dermatitis (43.1%). Overall, the best confirmed response was stable disease (SD; 53.4%); mean duration of disease control was 4.5 months; median progression-free survival was 2.6 months. In Part B, 55.1% of patients had SD (squamous NSCLC, 75.0%; HNSCC, 66.7%; other tumours; 36.4%).

In conclusion, the recommended phase 2 dose was determined as afatinib 40 mg/day plus cetuximab 250 mg/m^2/week. AEs were predictable and manageable, and anti-tumour activity was observed in some patients, particularly in those with squamous NSCLC and HNSCC.

Clinical trial registration: ClinicalTrials.gov NCT02020577.

1. Introduction

Overexpression of the epidermal growth factor receptor (EGFR) occurs in many epithelial carcinomas, including non–small cell lung cancer (NSCLC) and head and neck squamous cell carcinoma (HNSCC) [1]. Although EGFR-directed monotherapy has demonstrated efficacy in advanced EGFR-driven cancer, its use remains controversial in unselected/wild-type EGFR tumours. A key strategy for improving outcomes is the use of combination regimens, including 'vertical EGFR inhibition' [2].

Afatinib is an irreversible ErbB family blocker that inhibits signalling from all ErbB family members (EGFR [ErbB1], HER2 [ErbB2], ErbB3 and ErbB4) [3]. Afatinib is approved for first-line treatment of *EGFR*-mutant NSCLC, based on significant progression-free survival (PFS) benefit versus chemotherapy in the phase 3 LUX-Lung 3 and LUX-Lung 6 studies [4,5]. Furthermore, in the recent phase 2b LUX-Lung 7 study, first-line afatinib demonstrated significantly improved PFS and time to treatment failure versus gefitinib [6]. Based on significant improvements in PFS and overall survival (OS) versus erlotinib in the phase 3 LUX-Lung 8 study [7], afatinib was also recently approved for patients with advanced squamous cell carcinoma (SCC) of the lung whose disease had progressed after platinum-based chemotherapy. In addition, afatinib has demonstrated efficacy as second-line treatment in patients with recurrent/metastatic (R/M) HNSCC [8] and is recommended in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Head and Neck Cancers, version 1.2018, as a category 2B therapy option for unresectable R/M HNSCC (non-nasopharyngeal) that has progressed on or after platinum-based chemotherapy [9].

Cetuximab is a chimeric, human-murine monoclonal antibody that binds to the extracellular domain of EGFR [10]. It is indicated for treatment of HNSCC in combination with radiation therapy for locally advanced disease, in combination with chemotherapy for R/M disease, or as monotherapy (US only) for R/M disease after failure on platinum-based chemotherapy [11]. Cetuximab is also indicated for metastatic colorectal cancer (EGFR-expressing and RAS wild-type) in combination with chemotherapy or as monotherapy (after failure on oxaliplatin- and irinotecan-based therapy) [11].

Early evidence suggested that afatinib plus cetuximab was a promising treatment combination. In a preclinical murine model, improved anti-tumour activity was observed with the combination, compared with either agent alone. This activity was associated with depleted tumour levels of both phosphorylated EGFR and total EGFR, reflecting the combined molecular activities of each agent [12]. These preclinical findings are supported by a recent phase 1b trial in patients with *EGFR* mutation-positive NSCLC and acquired resistance to erlotinib/gefitinib, in which combined EGFR blockade using afatinib and cetuximab demonstrated robust anti-tumour activity (regardless of T790M mutation status) and a manageable safety profile [13]. Based on these data, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for NSCLC, version 3.2018, state that afatinib plus cetuximab may be considered in patients with disease progression on EGFR tyrosine kinase inhibitor (TKI) therapy (category 2A evidence and consensus) [14]. Collectively, these data suggest that further investigations of this combination are warranted.

Here, we report a phase 1b dose-escalation study designed to assess afatinib in combination with standard weekly dose cetuximab in patients with unselected/EGFR wild-type, advanced solid tumours, including squamous NSCLC and HNSCC.