ORIGINAL ARTICLE

Combined Pan-HER and ALK/ROS1/MET Inhibition with Dacomitinib and Crizotinib in Advanced Non–Small Cell Lung Cancer: Results of a Phase I Study

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ABSTRACT

Introduction: This phase I study investigated the activity of the irreversible pan-human epidermal growth factor receptor inhibitor dacomitinib in combination with the mesenchymal-epithelial transition factor/anaplastic lymphoma kinase/ROS proto-oncogene 1, receptor tyrosine kinase inhibitor crizotinib in advanced non–small cell lung cancer.

Methods: Patients with progression after at least one line of chemotherapy or targeted therapy received dacomitinib once daily and crizotinib once daily or twice daily, with doses escalated until intolerable toxicity; the expansion cohorts received the maximum tolerated dose of the combination. The primary objective was to define the recommended phase II dose; secondary objectives included assessment of safety and activity of the combination in epidermal growth factor receptor inhibitor-resistant patients and correlation with tumor biomarkers.

Results: Seventy patients were treated in the dose-escalation (n = 33) and expansion phases (n = 37), with the maximum tolerated dose defined as dacomitinib, 30 mg once daily, plus crizotinib, 200 mg twice daily. Grade 3 or 4 treatment-related adverse events were reported in 43% of patients: the most common were diarrhea (16%), rash (7%), and fatigue (6%). There were 16 deaths; none were considered treatment related. One patient (1%) had a partial response; 46% had stable disease. Most of the tumor samples analyzed had activating epidermal growth factor receptor gene (*EGFR*) mutations (18 of 20 [90%]); 50% (10 of 20) had a concurrent resistance mutation. Only one sample showed MMNG HOS Transforming gene (*MET*) amplification (the patient had progressive disease), whereas 59% (13 of 22) and 47% (14 of 30) had high levels of expression of epidermal growth factor receptor and mesenchymal-epithelial transition factor on the basis of H-scores, respectively. There was no apparent association between biomarker expression and antitumor activity.

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Conclusion: The combination of dacomitinib and crizotinib showed limited antitumor activity in patients with advanced non–small cell lung cancer and was associated with substantial toxicity.

Keywords: Non–small cell; Dacomitinib; Crizotinib; EGFR TKI resistance; Biomarkers

Introduction

In non–small cell lung cancer (NSCLC), the presence of specific activating mutations in the epidermal growth factor receptor gene *(EGFR)* is predictive of benefit from treatment with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs).[1–5] Sensitizing mutations have been reported to occur in 8% to 17% of non-Asian patients,[1,6,7] with frequencies of 30% reported in Asian patients.[1] For patients with advanced *EGFR*-mutant lung cancer, EGFR TKIs are the standard of care,[8] offering marked improvements in clinical outcomes compared with standard chemotherapy.[9] Development of resistance to EGFR TKIs, however, is inevitable,[10] most frequently through the acquisition of a T790M mutation in EGFR (responsible for an estimated 50% to 60% of cases[11]). Upregulation or activation of other receptor tyrosine kinases (RTKs) such as mesenchymal-epithelial transition factor (MET) through gene amplification has also been observed, with earlier reports putting the frequency of MMNG HOS Transforming gene (*MET)* amplification at 15% to 22%[12–15] and more recent analyses reporting frequencies of 5%.[16,17] Both *EGFR* mutations and *MET* amplification have been detected in the same tumor and individually in independent tumors from the same individual,[12,13,18] suggesting that heterogeneity may play an important role in resistance.

Dacomitinib and crizotinib are active against *EGFR*-mutated and *MET*-activated tumors, respectively.[19–25] Dacomitinib is a highly selective irreversible second-generation inhibitor of the human epidermal growth factor receptor (HER) family of RTKs—including EGFR (HER1)—and was effective in preclinical models that showed resistance to the first-generation EGFR TKIs gefitinib or erlotinib, including those expressing the T790M resistance mutation.[19,20] In the clinic, dacomitinib has demonstrated efficacy in a phase II trial in EGFR TKI–naive patients with advanced NSCLC who were selected on the basis of clinical or molecular criteria.[26] In phase III trials, dacomitinib has not demonstrated superiority over placebo or erlotinib in unselected patients who were previously treated with chemotherapy.[27,28] Crizotinib, an inhibitor of MET, anaplastic lymphoma kinase, and ROS proto-oncogene 1 (ROS1), was first approved by the U.S. Food and Drug Administration in 2011 for the treatment of advanced anaplastic lymphoma kinase gene (*ALK*)-positive NSCLC.[29] A fast and durable response with crizotinib was achieved in a patient with *MET* amplification but negative for *ALK*.[21] Several other case reports have also shown a response to crizotinib in patients with tumors bearing *MET* amplification and/or *MET* mutations.[22–24,30] In a cohort of 14 patients with NSCLC and *MET* amplification treated with crizotinib, five were shown to have objective responses (ORs).[25]

In vitro studies and an in vivo study using a transgenic mouse lung tumor model expressing *EGFR*-mutant Del19-T790M or L858R-T790M, each with concurrent MET overexpression, have shown synergistic effects between MET and EGFR inhibition when combined.[31–33] A second study also demonstrated synergy of crizotinib and newer-generation EGFR TKIs in mouse tumor models, although toxicity was an issue when crizotinib was combined with afatinib at higher doses.[34] These data suggested that patients in whom resistance to EGFR TKIs has developed through *MET* amplification or upregulation may benefit from combined inhibition of MET and EGFR.

This report describes the results of a phase I study of the combination of dacomitinib and crizotinib in patients with NSCLC after failure of at least one prior chemotherapy regimen or EGFR TKI (ClinicalTrials.gov identifier: NCT01121575). The study consisted of two phases: a dose-escalation phase and an expansion phase.

Patients and Methods

Patient Population

The study enrolled adults aged 18 years or older with histologically proven locally advanced or metastatic NSCLC after failure of prior chemotherapy or targeted therapy (dose-escalation phase) or acquired resistance to erlotinib or gefitinib (expansion phase). Acquired resistance was defined as progression after an initial response (complete or partial response [PR]) or stable disease (SD) for at least 6 months while receiving single-agent erlotinib or gefitinib. Other key eligibility criteria were an Eastern Cooperative Oncology Group performance status of 0 to 2, adequate organ function, and at least one measurable or evaluable lesion. Exclusion criteria included participation in other studies or lung cancer treatment within 2 weeks of the study's start, interstitial fibrosis or lung disease, brain metastases unless neurologically stable, cardiac abnormalities or uncontrolled hypertension, and prior malignancy (other than NSCLC) within the past 3 years. Each patient gave written informed consent to their participation in the study.