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Phase 2 study of intermittent pulse dacomitinib in patients with advanced non-small cell lung cancers

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ABSTRACT

Background: Dacomitinib is a second-generation, irreversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). Pre-clinical data suggest that intermittent pulsatile dosing of dacomitinib may result in inhibition of EGFR T790M.

Methods: We evaluated safety, pharmacokinetics and efficacy of intermittent pulsatile dacomitinib in both molecularly unselected patients and patients with lung cancers harboring EGFR T790M (Clinical Trial Registration Number NCT01858389).

Results: Thirty-eight patients were treated on study with pulse dacomitinib; sixteen with EGFR T790M in Cohort A and 22 who were not molecularly selected in Cohort B. One patient out of 16 patients in Cohort A had a partial response to study therapy (ORR 6.3%, 95% CI 0.2-30.2%). The median progression-free survival (PFS) in Cohort A was 2.3 months and median PFS in Cohort B was 1.6 months. The adverse event profile was similar to standard daily dose dacomitinib with the most frequent treatment-related toxicities occurring in > 20% of patients being diarrhea, rash, stomatitis, nausea, dry skin, paronychia, fatigue, and decreased appetite.

Conclusion: Intermittent pulsatile dacomitinib is safe and relatively well tolerated but is not effective in patients that harbor EGFR T790M or in unselected patients with non-small cell lung cancer.

1. Introduction

EGFR mutations in lung cancers confer response to EGFR tyrosine kinase inhibitors [1,2]. The first and second generation EGFR TKIs, erlotinib, gefitinib and afatinib, are approved as first-line treatment for patients with metastatic EGFR-mutant lung cancers [3–7]. Patients initially respond to these treatments, but then progress, on average 8–11 months after initiation of treatment. The most common mechanism of resistance to EGFR inhibitors is acquisition of a second site mutation, EGFR T790M [8]. A third generation EGFR inhibitor, osimertinib, has also recently been approved for patients with T790M mutation after failing on first or second generation EGFR inhibitors.

Abbreviations: NSCLC, non small-cell lung cancer; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; PFS, progression-free survival; ECOG, Eastern Cooperative Oncology Group; RECIST, Response Evaluation Criteria in Solid Tumors; ECG, electrocardiogram

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Dacomitinib is a second generation irreversible small molecular inhibitor of the HER family of tyrosine kinases including EGFR that has been extensively studied in non-small cell lung cancer (NSCLC). The maximum tolerated dose of dacomitinib was established to be 45 mg daily [9]. Dacomitinib was first assessed in molecularly unselected patients with previously treated advanced NSCLC. Despite promising results in earlier studies, the phase 3 confirmatory study did not show an improvement in outcomes in this population [10,11]. Dacomitinib was studied as first line treatment for clinically and molecularly selected patients [12]. In the subset of patients with EGFR-mutant lung cancers, dacomitinib was highly active with an overall response rate of 76% and an estimated median progression-free survival of 18.2 months. Severity and type of adverse of events was similar to other approved EGFR tyrosine kinase inhibitors. Results from the randomized phase 3 study comparing dacomitinib to gefitinib as first-line therapy for EGFR-mutant lung cancer, ARCHER 1050, were recently presented [13]. The median progression-free survival was 14.7 months compared to 9.2 months with gefitinib demonstrating dacomitinib's efficacy in patients with EGFR-mutant lung cancers.

At the time of this study initiation, there was promising early data for dacomitinib in both molecularly unselected patients after failure of previous treatment as well as in patients as first-line treatment for EGFR-mutant lung cancer. The rationale for intermittent pulsatile dosing was that pulsatile doses of dacomitinib would be able to inhibit EGFR T790M-positive cells while allowing the outgrowth of EGFR T790M-negative cells, as seen in preclinical studies allowing for control of EGFR T790M positive cells. [14]. Higher doses of continuous dosing dacomitinib are limited by excessive toxicity; intermittent pulsatile dosing may be more tolerable from a toxicity standpoint and could result in sufficiently high peak concentrations to control resistant, EGFR T790M-positive, subpopulations within a tumor. For these reasons, we initiated a phase 2 study of pulsatile intermittent dacomitinib in patients with advanced non-small cell lung cancer.

2. Methods

2.1. Study design

This was a global, multicenter, open-label phase 2 study of oral intermittent dacomitinib in patients with advanced NSCLC. Two cohorts were concurrently enrolled. Cohort A included patients whose tumor had evidence of EGFR T790M. Cohort B included T790M-negative tumors that were otherwise molecularly unselected. The primary endpoint of the study was best overall response per Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 for patients in Cohort A. Secondary endpoints included characterizing the effects of dacomitinib and its metabolite concentration on the QT interval for both cohorts, additional efficacy measures including disease control rate and duration of response for Cohort A, PFS and progression free survival rate at four months for both Cohort A and Cohort B, as well as assessment of the safety and tolerability of intermittent pulse dacomitinib. All patients signed an informed consent form approved by an institutional review board.

2.2. Patient population

Patients aged $>$ 18 years with evidence of histologically confirmed advanced NSCLC were eligible to enroll. Cohort A patients (EGFR T790M-positive) could have received any number of prior chemotherapy regimens and could have received prior reversible EGFR directed therapy. If patients were treated with prior EGFR TKI therapy, they must have demonstrated progression and could not have had any intervening treatment between progression on prior EGFR treatment and study enrollment. Patients in Cohort B (molecularly unselected) could have had 0–1 lines of systemic cytotoxic therapy, and could have received prior reversible EGFR-directed therapy. All patients must have had a performance status of 0–2 on the Eastern Cooperative Oncology Group (ECOG) scale, presence of measurable disease and adequate renal and liver function. All therapy including systemic treatment, radiation and surgery must have been completed at least 2 weeks prior to enrollment with the exception of erlotinib or gefitinib which required a washout of 3 days. Patients with evidence of mixed histology with elements of small cell or carcinoid were excluded. Patients with known leptomeningeal metastases or symptomatic brain metastases were excluded; patients with treated brain metastases that were neurologically stable and off corticosteroids for at least 2 weeks prior to study start were eligible.

2.3. Treatment

Treatment began with a lead in cycle (Cycle 0) during which patients received dacomitinib 45 mg without food every 12 h (q12 h) for six doses. Cycle 1 began the following week with patients taking dacomitinib 60 mg q12 h for six doses and cycles were repeated every two weeks. Intra-patient dose escalation beyond 60 mg was considered for patients in Cohort A provided they did not have significant toxicity after two cycles on the same dose and was done in 15 mg intervals following sponsor approval. Dose interruptions followed by dose reductions, in 15 mg intervals to a decreased dose of 30 mg occurred in response to toxicity. Dose reductions below 30 mg required sponsor approval. Patients maintained medication diaries to track treatment compliance. Treatment was discontinued for progression of disease, unacceptable side effects, non-compliance or withdrawal of informed consent.

At baseline, patients underwent review of interval medical history and physical examination, electrocardiogram (ECG), laboratory assessments and disease evaluation using CT or MRI. Women of reproductive potential underwent a pregnancy test prior to study initiation. During the lead-in cycle, time-matched ECG evaluations were done on Day 1 (prior to first dose) and Day 4 (following 6th dose). Pharmacokinetic (PK) samples were collected around the ECG evaluations on Day 4 at pre-dose, 2, 4, 6, 8 and 10 h post-dose. During Cycle 1 and any cycle where the dacomitinib dose was escalated, patients had an adverse event assessment and physical examination including vitals, ECG, laboratory assessments and a pre-dose pharmacokinetic blood sample drawn on Days 1 and 4. All other cycles required an adverse event assessment and physical examination including vitals, ECG and laboratory assessments. Tumor assessments were done at baseline and every 6 weeks for the first 3 assessments and then every 8 weeks thereafter.

2.4. Statistical analysis

2.4.1. The Fleming single stage design was used for Cohort A to test the null hypothesis

ORR was $<$ $=$ 1% at a significance level of 0.05. A minimum of 15 patients was required to be enrolled in Cohort A providing 80% power when true ORR was 19%. The exact test was conducted to test the null hypothesis.

The analysis of effect on QTc interval was based on a non-inferiority hypothesis testing framework. A minimum of 31 dacomitinib-treated patients, evaluable for QTc, were needed for a non-inferiority margin of 20 msec, assuming 90% power, an overall 1-sided significance level of 0.05. A random effect model was used to estimate the mean change in QTc from baseline at each post-baseline nominal time point. The intent-to-treat population included all patients enrolled and this was the population assessed for efficacy and baseline characteristics. Safety, pharmacokinetics and ECGs were assessed in all patients dosed with dacomitinib. The overall response rate was estimated with a corresponding 95% confidence interval using a method based on the binomial distribution. Time-to-event endpoints were estimated using the Kaplan-Meier method. Dacomitinib concentration–time data and ECG data were summarized using descriptive statistics.