Original Study

Preliminary Safety, Pharmacokinetics, and Efficacy of Regorafenib, Cisplatin, and Pemetrexed in Patients With Advanced Nonsquamous Non–Small-Cell Lung Cancers

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Abstract

Regorafenib is an oral multitargeted kinase inhibitor with potent antiangiogenic activity. In this phase I trial we evaluated the safety, pharmacokinetics, and efficacy of regorafenib with cisplatin and pemetrexed for patients with advanced nonsquamous non–small-cell lung cancers (nsNSCLCs). Nine patients enrolled before premature termination of the study. Five of 9 (56%) patients had a partial response and the median progression-free survival was 7 months (range, 1.5-15.1 months). Regorafenib had acceptable tolerability and minor pharmacokinetic interactions in combination with standard doses of cisplatin and pemetrexed in patients with advanced nsNSCLCs.

Background: The combination of bevacizumab, an antiangiogenesis agent, with cytotoxic chemotherapy improves survival in patients with advanced nonsquamous non–small-cell lung cancers (nsNSCLCs). Regorafenib is an oral multitargeted kinase inhibitor with potent antiangiogenic activity that is approved for patients with advanced colorectal cancer and gastrointestinal stromal tumors. In this phase I trial we evaluated the safety, pharmacokinetics (PK), and efficacy of regorafenib with cisplatin and pemetrexed for patients with advanced nsNSCLCs. **Patients and Methods:** Chemotherapy-naive patients with advanced nsNSCLCs were treated with regorafenib 60 mg/d continuously and cisplatin 75 mg/m^2 with pemetrexed 500 mg/m^2 once every 21 days for up to 6 cycles. Thereafter, regorafenib with or without pemetrexed could be continued as maintenance. **Results:** Nine patients enrolled before premature termination of the study because of slow recruitment and a change in the development strategy of regorafenib by the study sponsor. Five patients experienced at least 1 treatment-related Grade 3 adverse event. No Grade 4 or 5 toxicity occurred. Five of 9 (56%) patients had a partial response and the median progression-free survival was 7 months (range, 1.5-15.1 months). Minor PK interactions between regorafenib and chemotherapy were observed. **Conclusion:** Regorafenib had acceptable tolerability and minor PK interactions in combination with standard doses of cisplatin and pemetrexed in patients with advanced nsNSCLCs. Encouraging activity was appreciated in chemotherapy-naive patients with advanced nsNSCLCs. However, the small number of patients treated limits conclusions that can be drawn from these results.

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Introduction

Lung cancer continues to be the leading cause of cancer-related mortality in the United States and worldwide.[1] Most patients are diagnosed with advanced disease, for which platinum-based doublet chemotherapy remains the standard first-line therapy.[2] The median survival of patients with advanced nonsquamous non–small-cell lungs cancers (nsNSCLCs) treated with platinum-based doublet chemotherapy is approximately 10 months, with improvement to 12 months with the combination of the antiangiogenesis agent, bevacizumab.[3]

Regorafenib (BAY 73-4506; Bayer Pharma AG, Berlin, Germany) is a small molecule multikinase inhibitor with potent activity against multiple drivers of angiogenesis including vascular endothelial growth factor receptors (VEGFR-1, -2, -3), tie-2, fibroblast growth factor receptor-1 (FGFR-1), platelet derived growth factor receptor (PDGFR), and other oncogenic kinases such as RAF, Kit, and RET.[4] Regorafenib (160 mg/d for 21 of 28 days) was recently approved for monotherapy use in patients with refractory, advanced colorectal cancers[5] and gastrointestinal stromal tumors.[6] In patients with advanced nsNSCLCs, regorafenib was previously evaluated as a single agent in a continuous dose regimen in the expansion cohort of a dose-escalation phase I study.[7] Of 23 patients who were treated, 7 (30.4%) experienced a treatment-related adverse event requiring reduction, interruption, or discontinuation of treatment; no Grade 4 or 5 toxicities were observed. In 18 patients who were evaluable for efficacy, 13 (73%) had stable disease for $\geq$ 6 weeks and 4 (22%) had stable disease for $\geq$ 12 weeks. One patient had progression-free survival of nearly 40 weeks and a tumor reduction of $>$ 30% in 2 nonconsecutive measurements.

We performed this phase I trial (NCT01187615) to evaluate the safety, pharmacokinetics (PK), and preliminary activity of daily regorafenib administered with standard first-line cisplatin and pemetrexed chemotherapy for patients with advanced nsNSCLCs. After enrollment of 9 patients, the trial was prematurely terminated because of slow recruitment and a change in developmental strategy by the sponsor, partly because of the slow enrollment. The results of these 9 patients are presented herein.

Patients and Methods

Patients

The patients had pathologically confirmed stage IIIB or IV nsNSCLCs and had not previously received systemic therapy for advanced-stage disease. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and adequate hematologic and organ function. Excluded patients were those with poor baseline hearing, brain metastases, history of seizures, radiographic evidence of major blood vessel involvement, history of arterial or venous thrombosis within the previous 6 months, major surgical procedures within the previous 4 weeks, or a history of hemoptysis within the previous 3 months (defined as $\geq$ 1 teaspoon of blood).

Study Design

This was a multicenter, open-label, phase I study. The primary objectives were to characterize the safety profile, examine potential PK interactions, and define the maximum tolerated dose of regorafenib in combination with cisplatin and pemetrexed. The secondary end points included evaluation of the objective response rate to study treatment according to the National Cancer Institute Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1. The study was intended to have 2 parts. In part B, regorafenib was administered continuously (ie, days 1-21 of each cycle). In part A, regorafenib was to be administered in a sequential dosing with a 7-day washout period before the next dose of chemotherapy (ie, days 2-14 of each cycle, followed by a 7-day break). Ultimately, patients were only enrolled in part B of the study and no patients were assigned to part A before termination of the study. The study was approved by the institutional review boards of participating institutions and all patients signed informed consent.

Dosing and Administration

Regorafenib 60 mg daily was administered continuously from day 1 to day 21 of each 21 day cycle, except for in cycle 1 when regorafenib dosing started on day 2 to assess the PK of pemetrexed and cisplatin without concomitant regorafenib dosing. Alternative dosing schedules (eg, 14 days on, 7 days off) and dose escalation of regorafenib were planned but did not occur because of premature termination of the study.

Pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 were administered on day 1 of each cycle for up to 6 cycles, along with standard premedications and vitamin supplementation. After cycle 6, regorafenib as a single agent or in combination with pemetrexed was continued at the discretion of the investigator. Patients were allowed to continue treatment until disease progression, defined according to RECIST version 1.1.

Statistical Analyses

Safety. Safety analysis was preplanned; toxicity was monitored and graded using National Cancer Institute Common Terminology Criteria for adverse events version 3.0. The dose-limiting toxicity (DLT) evaluation period was the first 21 days of treatment. Toxicity was considered a DLT only if it was believed to be related to regorafenib alone or the combination treatment if it was worse than expected from cytotoxic chemotherapy alone.

Pharmacokinetics. Plasma concentrations of regorafenib (BAY 73-4506) and its active metabolites, M-2 (BAY 75-7495), and M-5 (BAY 81-8752),[8] were determined at Bayer Pharma AG in Wuppertal, Germany after protein precipitation with acetonitrile/ammonium acetate buffer containing the internal standards followed by separation using high-pressure liquid chromatography and tandem mass spectrometric detection (LC-MS/MS). Pemetrexed concentrations in plasma were determined at NorthEast Bioanalytical Labs (Hamden, CT). Pemetrexed was determined in plasma after addition of an internal standard, protein precipitation with methanol (0.1% acetic acid) followed by separation using high-pressure LC-MS/MS. Analyses of plasma samples for platinum were conducted at Nuvisan GmbH, Neu-Ulm, Germany. Platinum (from cisplatin) was determined in plasma (total) and plasma ultrafiltrate (unbound) after addition of an internal standard (lutetium) by ionization in an argon plasma and separation using inductively coupled plasma and mass spectrometric detection.