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A Phase II, Open-Label Study of Ramucirumab in Combination with Paclitaxel and Carboplatin as First-Line Therapy in Patients with Stage IIIB/IV Non–Small-Cell Lung Cancer

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Introduction: The objective of this study was to determine whether the addition of ramucirumab to first-line paclitaxel–carboplatin chemotherapy in patients with advanced non–small-cell lung cancer (NSCLC) resulted in a 6-month progression-free survival (PFS) rate that compares favorably with the historic rate for bevacizumab combined with paclitaxel–carboplatin in this patient population.

Methods: In this phase II, single-arm, open-label, multicenter study, 40 patients with advanced NSCLC received ramucirumab (10 mg/kg intravenous [IV]) followed by paclitaxel (200 mg/m^2 IV) and carboplatin area under the curve = 6 on day 1 every 21 days as first-line therapy. Therapy continued for up to six cycles. Patients not experiencing withdrawal criteria may have continued ramucirumab monotherapy every 3 weeks. The primary endpoint was PFS at 6 months, with 80% power to detect a 6-month PFS rate of at least 55%.

Results: The 6-month PFS rate was 59.0% and the objective response rate was 55.0%. The most common treatment-related adverse events were fatigue, peripheral neuropathy, nausea, epistaxis, and myalgia. Single-nucleotide polymorphism (SNP) rs2981582 on the *FGFR-2* gene had significant associations with improved overall survival, PFS, and best overall response (p values without multiplicity adjustment were 0.0059, 0.0429, and 0.0392, respectively).

Conclusion: Ramucirumab in combination with paclitaxel–carboplatin resulted in a 6-month PFS rate and safety profile that compared favorably with the historical control. In addition, no deaths were associated with this treatment. Furthermore, we describe an association of SNP on *FGFR-2* gene with survival and response. These findings warrant further clinical investigation in patients with NSCLC.

Key Words: Angiogenesis, Lung cancer, Ramucirumab, Paclitaxel, Carboplatin.

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Angiogenesis, the formation of new capillaries and blood vessels, is a tightly controlled, multistep process that is a component of normal human physiology, including development of the embryonic vasculature, wound healing, and tissue repair. Pathologic angiogenesis contributes to tumor growth and metastasis, and other human diseases such as diabetic retinopathy, rheumatoid arthritis, and psoriasis.[1–3] The importance of vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor-2 (VEGFR-2) in angiogenesis and tumor growth has been demonstrated in a variety of animal models, in which disabling the function of the VEGF/VEGFR-2 pathway inhibited new blood vessel formation and tumor growth.[4–7]

VEGF and VEGFR-2 are overexpressed in the majority of human cancers, including carcinomas of the gastrointestinal

tract, pancreas, breast, cervix, bladder, ovary, uterus, endometrium, kidney, and lung.[6] VEGFR-2 expression and tumor microvessel density have been associated with poor prognosis, advanced disease, increased risk of metastasis and recurrence, and lower progression-free survival (PFS) in multiple types of cancers, including non–small-cell lung cancer (NSCLC).[2,6,7]

Therapeutic agents that interfere with the function of VEGF and its receptors may be efficacious antitumor therapy. Antitumor effects have been demonstrated by disabling the function of the VEGFR-2 signaling pathway using anti-VEGF antibodies and small molecule VEGFR-2 tyrosine kinase inhibitors (TKIs) in a variety of animal models.

The addition of antiangiogenic therapy (anti-VEGF: bevacizumab) to cytotoxic chemotherapy in treatment-naïve patients with advanced NSCLC in Eastern Cooperative Oncology Group (ECOG) Study Trial-E4599 was shown to improve survival.[8]

Ramucirumab is a human immunoglobulin G, subclass 1 monoclonal antibody that specifically binds to the extracellular domain of VEGFR-2 with high affinity.[9] This antibody blocks the binding of the VEGF ligand to VEGFR-2, inhibits VEGF-stimulated activation of both VEGFR-2 and p44/p42 MAP kinases, and neutralizes VEGF-induced endothelial cells' proliferation and migration.[9]

Two completed phase I studies of ramucirumab have evaluated pharmacokinetics and demonstrated safety and tolerability at clinically relevant doses, with preliminary evidence of clinical efficacy.[10,11] In these studies, 62 patients with advanced cancer received ramucirumab either weekly, every other week, or every third week at doses ranging from 2 to 20 mg/kg. Objective antitumor activity and antiangiogenic effects were observed over a wide range of dose levels, suggesting that ramucirumab may have a favorable therapeutic index in treating malignancies amenable to VEGFR-2 inhibition. Furthermore, ramucirumab has been approved by the US Food and Drug Administration in gastric cancer following progression on initial chemotherapy based on the positive results of a phase III study.[12]

This phase II trial was conducted to assess whether the addition of ramucirumab to combination therapy with paclitaxel and carboplatin results in favorable PFS in patients with advanced NSCLC compared with historical controls.

PATIENTS AND METHODS

Eligibility Criteria

Patients greater than or equal to 18 years with ECOG performance status (PS) of 0 to 1 and histologically or cytologically confirmed, measurable, stage IIIB or IV NSCLC were eligible. American Joint Committee on Cancer (AJCC) sixth edition was used for staging derivation. Eligibility criteria included adequate hepatic, renal, hematologic, and coagulation function. Patients with untreated central nervous system metastases were excluded. Other exclusion criteria included prior systemic chemotherapy for stage IIIB/IV NSCLC, prior systemic chemotherapy or radiation therapy for stage I–IIIA NSCLC less than 1 year before the first dose of study medication, prior bevacizumab therapy, evidence of major blood vessel invasion or encasement by cancer, uncontrolled thrombotic or hemorrhagic disorders, serious nonhealing wounds, or grade 3 to 4 gastrointestinal bleeding within 3 months before study entry.

Study Design

This was a phase II, single-arm, multicenter, open-label study of combination therapy of ramucirumab with paclitaxel and carboplatin in patients with advanced NSCLC conducted at eight centers in the United States. The primary objective of the study was to evaluate the 6-month PFS rate. Secondary objectives included PFS, overall survival (OS), objective response rate (ORR), safety/tolerability, and the pharmacokinetic profile of ramucirumab, in addition to an exploratory analysis of potential biomarkers in tumor tissue and their potential association with clinical outcomes.

Each center's institutional review board or ethics committee approved the protocol. This study was conducted in accordance with good clinical practices and International Conference on Harmonisation (ICH) guidelines as implemented in the European Union and Japanese guidelines, and any other regional/national requirements for clinical trials, as applicable. Patients provided written informed consent before undergoing study procedures or receiving study treatment.

Treatment and Dose Adjustments

Patients received ramucirumab 10 mg/kg via IV infusion over 1 hour on day 1 of each 21-day cycle (i.e., every 3 weeks). Study combination treatment continued for up to six cycles (each cycle consisting of 1 infusion of each medication on day 1 of a 3-week period), or until there was evidence of disease progression or intolerable toxicity. In the absence of any withdrawal criteria, patients completing combination therapy could continue to receive ramucirumab monotherapy every 3 weeks, provided there was ongoing evidence of clinical benefit.

Patients received paclitaxel 200 mg/m^2 via IV infusion over 3 hours on day 1 following the ramucirumab infusion. Before each infusion of paclitaxel, patients were premedicated with an oral steroid (such as dexamethasone 20 mg administered 6 and 12 hours before paclitaxel [or IV equivalent]), an antihistamine (H1 antagonist), and an antiemetic (such as cimetidine [300 mg IV]). Patients received carboplatin on day 1 after paclitaxel as an IV infusion over 30 minutes. The target area under the curve (AUC) for carboplatin treatment was AUC = 6, unless the dose was modified. The creatinine clearance used to calculate the carboplatin dose was estimated based on serum creatinine, using the modified Calvert formula. Antiemetics (a 5-HT3 receptor antagonist or equivalent) were given in conjunction with carboplatin and therapy; corticosteroids were given prophylactically before carboplatin administration and continued for 72 hours.

Doses were modified for ramucirumab-related infusion reactions, hypertension, thrombotic events, and proteinuria; paclitaxel hypersensitivity reactions; and carboplatin treatment-related events. In addition, doses of paclitaxel and/or carboplatin were reduced (by 20–25%) or held in the presence of certain hematologic and nonhematologic toxicities. If a second episode of certain events occurred or if the event resolved, chemotherapy was readministered at a reduced dose (30–50%). If the dose of chemotherapy was reduced, subsequent dose increases were not permitted. Events causing ramucirumab discontinuation were occurrence of greater than

