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## **Phase I Study of Erlotinib, Bevacizumab, and Gemcitabine in Patients With Advanced Pancreatic Cancer**

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**Background:** Erlotinib is an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) active in combination with gemcitabine in patients with advanced pancreatic cancer (PC). The combination of gemcitabine and bevacizumab is also active in PC. A phase I study of gemcitabine, bevacizumab, and erlotinib in patients with unresectable locally advanced or metastatic PC is being conducted.

**Methods:** Two cohorts of six patients with advanced PC have been treated with erlotinib (150 mg/day orally [PO]), bevacizumab (5 mg/kg intravenously [IV], days 1 and 15, every 28 days), and gemcitabine administered as a 10 mg/m<sup>2</sup>/minute infusion at doses of either 850 mg/m<sup>2</sup> or 1,000 mg/m<sup>2</sup> on days 1 and 15. Treatment cycles are repeated every

28 days. Patients receive a maximum of six treatment cycles. Cohort 1: daily erlotinib 150 mg PO + bevacizumab 5 mg/kg IV days 1 and 15 + gemcitabine 850 mg/m<sup>2</sup> administered as 10 mg/m<sup>2</sup>/minute infusion days 1 and 15. Cohort 2: daily erlotinib 150 mg PO + bevacizumab 5 mg/kg IV days 1 and 15 + gemcitabine 1,000 mg/m<sup>2</sup> administered as 10 mg/m<sup>2</sup>/minute infusion days 1 and 15.

**Results:** Twelve patients have been included in this study (6 cohort 1 and 6 cohort 2) and are evaluable for toxicity. Eleven patients have completed the study and seven have received complete treatment per the study protocol. Patient characteristics include median patient age of 62.6 years (range, 38-71 years); male/female: 5/7 (42%/58%); stage III/IV: 3/9 (25%/75%); Karnofsky index 100%/80%: 2/10. Three of six patients in cohort 1 developed grade 3 asthenia (50%), two patients had grade 3 neutropenia (33.3%), and one patient had grade 3 leukopenia and grade 3 skin rash. In cohort 2, the most severe adverse events were one case of grade 4 gamma glutamyl transferase (GGT) elevation, one case of grade 3 skin rash, and one case of grade 3 asthenia. No severe hematologic toxicity in cohort 2 was reported. One patient in each cohort required dose reduction of erlotinib, both due to skin rash. Mild diarrhea was reported in 11 of 12 patients. No dose-limiting toxicities have been reported. All patients were evaluable for response: two patients had a partial response (both in cohort 1) and seven had disease stabilization (3 and 4 in cohorts 1 and 2, respectively). No complete responses were observed. The overall disease control rate was 75%.

**Conclusions:** The combination of gemcitabine, erlotinib, and bevacizumab is well tolerated. The maximum tolerated dose has not been reached. Encouraging clinical activity in advanced pancreatic cancer has been observed. This phase I trial is still ongoing. Toxicity data for all the patients will be presented.