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EVALUATION OF MET-PATHWAY BIOMARKERS IN A PHASE 2 STUDY OF RILOTUMUMAB PLUS EPIRUBICIN, CISPLATIN, AND CAPECITABINE IN GASTRIC/ESOPHAGOGASTRIC JUNCTION CANCER

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Abstract

Introduction Rilotumumab (AMG 102) is an investigational, fully human, monoclonal antibody to hepatocyte growth factor (HGF)/scatter factor, the ligand of the MET receptor. HGF/MET signaling promotes the proliferation, migration, and survival of tumor cells. A double-blind, placebo-controlled, phase 2 study randomized 121 patients with locally advanced or metastatic gastric or esophagogastric junction (EGJ) cancer 1:1:1 to 15 mg/kg rilotumumab + ECX (Arm A, n = 40), 7.5 mg/kg rilotumumab + ECX (Arm B, n = 42), or placebo + ECX (Arm C, n = 39). Overall survival (OS) (median months, 11.1 vs 8.9; HR = 0.73) and progression-free survival (PFS) (median months, 5.6 vs 4.2; HR = 0.64) were improved with the addition of rilotumumab to ECX (Arms A + B) compared with ECX alone. High tumor MET levels have been associated with poor prognosis in gastric cancer. The aim of this biomarker analysis was to explore MET-pathway biomarkers to identify patients who may benefit from rilotumumab.

Methods MET protein levels and gene copy numbers were measured in archival tumor samples by immunohistochemistry and fluorescence in situ hybridization, respectively. High and low MET subgroups were analyzed by several predefined strategies. Total HGF and soluble MET (sMET) protein in plasma were measured by ELISA and MSD assays, respectively. Treatment and biomarker effects on OS and PFS were analyzed by Cox proportional hazard models and Kaplan-Meier estimates.

Results Tumor samples were evaluable for MET protein from 62 patients in Arms A + B and 28 patients in Arm C. In the chemotherapy only arm (Arm C), patients with MET^{High} tumors (> 50% tumor cells positive) had poorer OS (HR = 3.22, 95% CI: 1.08-9.63) than patients with MET^{Low} tumors. The addition of rilotumumab to ECX improved OS in patients with MET^{High} tumors compared with ECX alone (median months, 11.1 [80% CI: 9.2-13.3] vs 5.7 [80% CI: 4.5-10.4]; HR = 0.29, 95% CI: 0.11-0.76, p = 0.012). Of note, patients with MET^{Low} tumors (≤ 50% tumor cells positive) had a trend toward unfavorable OS with the addition of rilotumumab to ECX compared with ECX alone (HR = 1.84, 95% CI: 0.78-4.34). Similar trends were seen with PFS. Predefined dichotomization schemes for tumor MET gene copy number and baseline plasma levels of total HGF or sMET did not correlate with OS or PFS.

Conclusion Rilotumumab demonstrated a stronger treatment effect in the MET^{High} population compared with the overall population. High MET expression by immunohistochemistry may predict clinical benefit for the addition of rilotumumab to ECX in patients with gastric/EGJ cancer. A phase 3 trial is planned to test the efficacy and safety of rilotumumab in patients with high MET-expressing tumors.