Rilotumumab Exposure-Response Relationship in Patients With Advanced or Metastatic Gastric Cancer

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TRANSLATIONAL RELEVANCE

In gastric cancer, tumor MET expression is associated with tumor invasiveness, metastasis, and disease stage. Rilotumumab is an investigational, fully human, IgG2 monoclonal antibody that targets hepatocyte growth factor, the only known ligand for the MET receptor. In a randomized, placebo-controlled, phase 2 study, rilotumumab plus epirubicin, cisplatin, and capecitabine (ECX) compared with ECX alone showed trends toward improved survival in patients with gastric or gastroesophageal junction (GEJ) cancer, especially in patients with MET-positive tumors. In this study, we quantitatively characterized the longitudinal exposure-response (tumor growth [TG] and overall survival [OS]) relationship for rilotumumab. We found that rilotumumab plus ECX demonstrated concentration-dependent effects on TG and OS and the rilotumumab concentration-dependent effect on OS depended on MET expression in gastric/GEJ cancer patients. Further clinical testing of rilotumumab 15 mg/kg administered every 3 weeks in MET-positive gastric/GEJ cancer is warranted.
ABSTRACT

Purpose: Rilotumumab is an investigational, fully human monoclonal antibody to hepatocyte growth factor. In a randomized phase 2 study, trends toward improved survival were observed with rilotumumab (7.5 or 15 mg/kg) plus epirubicin, cisplatin, and capecitabine (ECX) versus placebo plus ECX in gastric/gastroesophageal junction (GEJ) cancer patients, especially in MET-positive patients. Here, we quantitatively characterized the longitudinal exposure-response (tumor growth [TG] and overall survival [OS]) relationship for rilotumumab.

Experimental Design: Rilotumumab concentrations, tumor sizes, and survival time from the phase 2 study were pooled to develop a longitudinal exposure versus TG model and parametric OS model that explored predictive/prognostic/treatment effects (MET expression, rilotumumab exposure, relative tumor size). Model evaluation included visual predictive checks, non-parametric bootstrap, and normalized prediction distribution errors. Simulations were undertaken to predict the relationship between rilotumumab dose and OS.

Results: Rilotumumab exhibited linear time-independent pharmacokinetics not affected by MET expression. The TG model adequately described tumor size across arms. A Weibull distribution best described OS. Rilotumumab exposure and change in tumor size from baseline at week 24 were predictive of OS. MET-positive patients showed shorter survival and responded better to rilotumumab than MET-negative patients. Simulations predicted a median (95% CI) HR of 0.38 (0.18, 0.60) in MET-positive patients treated with 15 mg/kg rilotumumab Q3W.

Conclusions: Rilotumumab plus ECX demonstrated concentration-dependent effects on OS, influenced by MET expression, and tumor size in gastric/GEJ cancer patients. These findings
support the phase 3 testing of rilotumumab 15 mg/kg every 3 weeks in MET-positive gastric/GEJ cancer (RILOMET-1; NCT01697072).
INTRODUCTION

Worldwide, gastric cancer is the second leading cause of cancer-related deaths, and its incidence and mortality are higher in developing countries (1). The 5-year survival rate for gastric cancer remains low at approximately 25% (2).

Hepatocyte growth factor (HGF) or scatter factor is the only known ligand for the MET proto-oncogene, a tyrosine kinase receptor activated upon HGF binding (3). Together, HGF/MET comprises a well-characterized ligand/receptor complex involved in multiple cellular functions, including proliferation and survival (3). The HGF/MET pathway is also necessary for tissue repair and regeneration (3). Abnormal signalling in this pathway has been directly implicated in tumor growth and progression in a wide variety of human cancer types, including gastric cancer, making this a promising pathway for developing new targeted anticancer therapies (4,5). Elevated levels of tumor MET have been associated with disease progression and poor prognosis in patients with gastric cancer (6-10).

Rilotumumab (AMG 102) is a fully human monoclonal antibody (IgG2) that binds to human HGF with high affinity (dissociation constant, $K_D = 6$ ng/mL) and neutralizes HGF (11). Rilotumumab inhibited tumor growth, induced tumor regression, increased apoptosis, and decreased cell proliferation in human xenograft models of cancer (12) and has demonstrated manageable toxicities in clinical studies (13-15). In humans, rilotumumab evidenced linear and time-independent pharmacokinetics (PK) up to 20 mg/kg administered intravenously (IV) every 2 weeks (Q2W) and 15 mg/kg every 3 weeks (Q3W) (16). Notably, rilotumumab clearance was not affected by baseline tumor HGF and MET levels, hepatic and renal functions, and drug-drug interactions.
interactions with other anticancer agents (16). In a placebo-controlled, randomized phase 2 study in patients with locally advanced or metastatic gastric or gastroesophageal junction (GEJ) cancer (ClinicalTrials.gov identifier: NCT00719550), 7.5 or 15 mg/kg rilotumumab administered Q3W in combination with epirubicin, cisplatin, and capecitabine (ECX) showed trends toward improved progression-free survival (PFS) and overall survival (OS), and a stronger rilotumumab effect was observed in a subset of patients with MET-positive tumor expression, as determined by an immunohistochemistry assay that used the MET4 monoclonal antibody (MET IHC pharmDx™ kit; Dako North America; Carpinteria, CA) (17).

Drug-disease models are powerful tools to analyze early clinical data, optimize dosing schedule, and scale across patient populations and drug development phases (eg, phase 2 to phase 3) (18,19). In order to develop a drug-disease model for gastric/GEJ cancer and quantitatively establish the relationship among chemotherapy dosing, rilotumumab serum concentrations, and their anticancer effects, we developed a modeling framework that includes a longitudinal tumor growth (TG) and OS model. The TG model describes the inhibitory effect of ECX and ECX plus rilotumumab on tumor size and serves as an input for the OS model, which incorporates prognostic and predictive factors for patients with gastric/GEJ cancer. We used this approach to retrospectively evaluate patients from the phase 2 gastric/GEJ cancer study (17). Our objective was to predict the relationship between rilotumumab dose and OS and then predict the OS outcome of a study evaluating rilotumumab in combination with ECX versus ECX alone in MET-positive gastric/GEJ cancer (RILOMET-1; ClinicalTrials.gov identifier: NCT01697072).
PATIENTS AND METHODS

Clinical Data and Assessments

Rilotumumab serum concentrations, tumor size measurements, and OS data from a phase 2 clinical study in patients with locally advanced or metastatic gastric/GEJ cancer were used in this analysis. Briefly, eligible patients received ECX (epirubicin 50 mg/m\(^2\) IV on day 1, cisplatin 60 mg/m\(^2\) IV on day 1, and capecitabine 625 mg/m\(^2\) orally twice daily on days 1–21, respectively) and were randomized 1:1:1 to receive 7.5 mg/kg rilotumumab, 15 mg/kg rilotumumab, or placebo Q3W. In all cases, rilotumumab was administered as an IV infusion over 60 minutes for the first dose and 30 minutes for subsequent doses if it was well tolerated. Additional details of this clinical study have been reported elsewhere (17).

Serum samples for the measurement of rilotumumab concentrations were collected predose and postdose on day 1 of cycles 1, 3, 5, and 7 and at the safety follow-up visit. Rilotumumab concentrations were determined by an enzyme-linked immunosorbent assay using recombinant human HGF for the capture reagent and a biotinylated polyclonal rabbit anti-rilotumumab antibody for detection, as previously reported (14,20). Tumor size was assessed by computed tomography or magnetic resonance imaging at screening and every 6 weeks (±7 days) and was computed as the sum of the longest diameters of target lesions according to the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.0. OS time was determined as the time from randomization to death from any cause. For OS, patient follow up was censored at the date last known to be alive. Tumor MET expression was measured in archival tumor samples by immunohistochemistry as described elsewhere (17). Patients were divided into MET-positive
and MET-negative groups based on tumor MET membrane expression, per two definitions (≥25% or ≥50%) as previously described (17).

**Model Development**

The integrated model (Figure 1) was developed using the nonlinear mixed effects modeling (NONMEM) software Version 7.2.0 (ICON Development Solutions, Ellicott City, MD) with the Intel Fortran 11.1 compiler. Graphical data visualization, evaluation of NONMEM outputs, construction of goodness-of-fit plots, and graphical model comparisons were conducted using S-Plus Version 8.2 (TIBCO Software Inc., Palo Alto, CA).

*Pharmacokinetic Model.* Individual PK parameters were estimated from the observed rilotumumab serum concentrations and the population PK model that was previously developed (16), which was based on an open two-compartment disposition model. The inter-individual variability (IIV) in the model parameters was assumed to follow a log-normal distribution, and a proportional random error model was used to quantify the residual variability. The effect of tumor MET expression on PK parameters was formally explored using the statistical criteria, as previously described (21). Individual PK parameters were used to predict the individual rilotumumab serum concentrations over time, which in turn were used as an input function for the TG model following the sequential process, as described elsewhere (22).

*Tumor Growth Model.* In the absence of any treatment, the tumor size was assumed to grow exponentially at a first-order rate, $k_g$ (23). Treatment with ECX was assumed to simulate the first-order tumor-cell death rate, $k_d$. Since no PK data for ECX were available, a “kinetics of drug action” model was used to quantify the effect of ECX on $k_d$, which was driven by the first-
order rate constant, \( k_{PD} \). Furthermore, the effect of ECX on \( k_d \) was assumed to decrease over time, probably due to a resistance phenomenon, and was determined by a first-order process characterized by \( k_{res, ECX} \). The differential equations describing the time course of tumor size in patients treated with ECX were as follows:

\[
\frac{dTS}{dt} = k_g \cdot TS - k_d(t) \cdot TS \cdot ECX
\]

Equation 1

where \( TS(t=0) = TS_0 \), \( k_d(t) = k_d \cdot e^{-k_{res, ECX} \cdot t} \) and

\[
\frac{dECX}{dt} = -k_{PD} \cdot ECX
\]

Equation 2

In these equations, \( TS \) represented the tumor size at time \( t \), and \( TS_0 \) was the estimated baseline tumor size. The addition of rilotumumab resulted in an inhibitory effect on \( k_g \), which depended on the rilotumumab serum concentration and was set to 0 in the placebo group. The maximum \( k_g \) inhibition was assumed to be 100%, and the rilotumumab concentration that provided half maximal \( k_g \) inhibition, \( EC_{50} \), was estimated directly from the tumor size data. Rilotumumab resistance effects were similarly incorporated into the model to describe the increase in tumor size apparent in some patients receiving ECX and rilotumumab and were determined by the first-order rate constant, \( k_{res, R} \). Consequently, Equation 1 was modified to Equation 3 in order to describe the combined effect of ECX and rilotumumab:

\[
\frac{dTS}{dt} = k_g \cdot TS \cdot \left( 1 - \frac{C}{EC_{50} + C} \cdot e^{-k_{res, R} \cdot t} \right) - k_d(t) \cdot TS \cdot ECX
\]

Equation 3
IIV in $k_g$, $k_{ds}$, $k_{res,ECX}$ was described by an exponential error model, while IIV in $TS_0$ was modeled through a semiparametric logit transformation (24). A proportional random error model was used to describe the residual variability associated with the tumor size measurements. The effect of tumor MET expression on TG model parameters was also formally tested as a covariate.

**OS Model.** A parametric OS model was developed to describe the survival time (T) distribution. Normal, lognormal, Weibull, logistic, log-logistic, exponential, or Gompertz probability density functions were evaluated, and the likelihood ratio test was used to select the best probability density functions to describe the OS data. In addition, improvement of the model by the inclusion of MET expression as a prognostic and/or predictive factor and treatment-related factors (steady-state rilotumumab exposure and predicted reduction in tumor size at varying study weeks [ie, 6, 12, 18, 24, or 30]) on absolute baseline hazard was evaluated.

**Model Selection and Evaluation**

The improvement of the fit obtained for each nested model was assessed by the likelihood ratio test. The precision and the correlation in parameter estimates and the examination of diagnostic plots and visual predictive checks (VPCs) were also used to evaluate each candidate model (25,26). In addition, the shrinkage, reduction in the IIV and residual variability, and normalized prediction distribution errors (NPDEs) in the PK and TG models were also assessed (27). Additionally, non-parametric bootstrap of the TG and OS models was also performed as internal validation (28).

**Model-Based Simulations**
Model-based Monte Carlo simulations were conducted to explore the effect of the rilotumumab Q3W dose (7.5, 10, 15, 20 mg/kg) on the OS hazard ratio of a virtual study with the same characteristics as a phase 3 trial in patients with advanced MET-positive (≥25% membrane staining) gastric/GEJ cancer (NCT01697072). In this virtual study, 450 patients were randomized 1:1 to ECX alone or rilotumumab plus ECX, as previously described (32). The virtual study was replicated 1000 times per each dose level evaluated using the PK, tumor size and parametric OS model previously described. The rate of patient enrollment was simulated to mimic the observed patient enrollment in the phase 2 study. The simulations accounted for censored data by using a dropout model, which was based on an exponential hazard for the first 200 days after enrollment, followed by a Weibull hazard until the end of study. The dropout model was necessary to account for the differential dropout observed in the phase 2 study, which is likely to similarly occur during the phase 3 study. The virtual trials were stopped once the target number of events (n = 316) was reached. Virtual patients who dropped out or were alive at the time of study termination were considered as censored. The OS for each study arm and replicate as well as the hazard ratio of each virtual trial replicate were computed and then summarized across replicates.
RESULTS

Pharmacokinetic Model

A total of 390 serum concentrations from 88 patients with gastric/GEJ cancer were used to describe the time course of rilotumumab using an open two-compartment disposition model with nonspecific distribution to a peripheral compartment and linear elimination from the central compartment. The typical values (IIV, %) for linear clearance ($CL$), 0.216 L/day/70 kg (37.5%), and central volume ($V_c$), 3.74 L (20.7%), were consistent with those previously published (16), and the IIVs were associated with shrinkages lower than 0.2. Tumor MET expression did not significantly affect rilotumumab exposure ($P > 0.05$), regardless of the cutoff used, which is consistent with previous analyses (16). The goodness-of-fit plots showed concentrations randomly distributed around the identity line, indicating the absence of systematic bias in parameter estimation and the adequacy of the model to describe the observed concentration (Supplementary Figure S1). The NPDE mean, 0.032 (95% confidence interval [CI]: −0.041, 0.088), and SD, 1.02 (95% CI: 0.97, 1.06), indicated an adequate accuracy and precision of the population model since the NPDE mean and SD were not significantly different from 0 and 1, respectively. Additionally, the VPC evidenced an acceptable predictive ability of the model to describe the time course of rilotumumab serum concentrations (Figure 2, top row). Model-based simulations showed that average trough steady-state concentrations of rilotumumab after 7.5 and 15 mg/kg Q3W dosing schedules were 15- and 30-fold higher, respectively, than the rilotumumab-HGF $K_D$ (16), 6 ng/mL, suggesting that rilotumumab would not exhibit target-mediated disposition.
Tumor Growth Model

In total, 504 tumor size measurements from 120 patients were available to develop the TG model. Eleven patients (two in the 7.5 mg/kg group, five in the 15 mg/kg group, and four in the placebo group) only had available tumor size data at screening and were excluded from the analysis. The TG model was suitable to describe the time course of the tumor size in patients with gastric/GEJ cancer following IV administration of 7.5 and 15 mg/kg rilotumumab in combination with ECX or ECX alone. The final model parameter estimates and their relative standard error (RSE) are presented in Table 1. If left untreated, the gastric/GEJ tumor was assumed to grow exponentially, and approximately 16 months were needed to double its size. The half-life associated with the effect of ECX administration, which provides an assessment of the duration of ECX effect, was estimated and fixed to 331 hours (approximately 2 weeks) based on data from patients receiving placebo plus ECX. In the absence of ECX resistance, Q3W dosing of ECX resulted in 50% average tumor shrinkage in approximately 2 months. However, the effect of ECX on $k_d$ was reduced by 50% every 1.4 months. A linear function was sufficient in describing the ECX effect on the stimulation of $k_d$ and attempts made to characterize the ECX effect as an $E_{max}$ or log-linear model failed as the parameters could not be reliably estimated, probably because all patients received the same dosing regimen, and the maximum ECX effect was not achieved.

The typical value of rilotumumab $EC_{50}$ was estimated to be 6.71 μg/mL. The mean (SD) rilotumumab trough levels at steady state ($C_{minss}$) were 72.7 (34.7) μg/mL and 171 (80) μg/mL following the 7.5 and 15 mg/kg doses, respectively. At these concentrations, the mean (SD)
inhibition of $k_g$ was 90.1% (3.8%) and 95.5% (1.9%), respectively, which is consistent with the observation that the change in tumor size was similar at the two rilotumumab doses (Figure 2, middle row). The estimated resistance effects suggested the rilotumumab inhibitory effect would decrease by 50% every 20.5 months. Taken together, based on the TG model, after 12 weeks (corresponding to a median PFS of 4.2 months in the ECX arm of the phase 2 study) of treatment with ECX plus placebo, 7.5, or 15 mg/kg rilotumumab, 50% of patients were projected to have at least 29.4%, 41.8%, or 44.7% reduction in tumor size from baseline, respectively.

MET expression was not statistically associated with any parameter of the TG model, regardless of the cutoff value of MET used. Therefore, positive (or negative) tumor MET expression does not appear to be associated with the rate of tumor growth or the effect of treatment with ECX or ECX plus rilotumumab on tumor dynamics. Both fixed and random effects were estimated with acceptable precision (Table 1), except $EC_{50}$ (RSE 227%) and $k_{res,R}$ (RSE 72%), which was probably due to the fact that the two rilotumumab dose levels evaluated were well above the $EC_{50}$, and the maximum follow-up time was 25.5 months, which is comparable to the half-life associated with the rilotumumab resistance effect. However, the goodness-of-fit plots showed that observations were randomly distributed around the identity line, indicating the absence of systematic bias in parameter estimation and the adequacy of the model to describe the observed tumor size data (Supplementary Figure S2). The VPC (Figure 2, middle row) indicated adequate predictive ability of the TG model to describe tumor size dynamics following treatment with ECX or ECX and rilotumumab.

**Overall Survival Model**
The maximal OS follow-up time was 765 days (~25.5 months), and several MET-positive patients displayed survival times greater than 18 months. Based on the likelihood ratio test, the Weibull model was the best probability density function to parametrically describe the OS data (Table 2). Tumor MET expression was found to be associated with the scale parameter ($\lambda$) of the Weibull model ($P = 0.003$). A 71.6% increase in $\lambda$ was observed in patients with MET-positive status ($\geq 25\%$ membrane staining) relative to patients with MET-negative status, indicating that positive MET expression was a negative prognostic factor for OS as was expected given the observation that median OS in the ECX arm was longer in MET-negative patients (17). Furthermore the predicted tumor size at 6 months was found to be a significant predictive factor of OS ($P = 0.009$) and was better than the predicted tumor size at earlier or later time points. On average, an 18% reduction of the hazard was achieved after 25% reduction in tumor size at 6 months.

There was a direct effect of rilotumumab $C_{minss}$ on OS hazard ($P = 0.002$). The effect was quantified with a step function, parameterized as a sigmoid $E_{max}$ function with a fixed high Hill-factor, where the estimated maximum reduction of the OS hazard was 65% and the rilotumumab $C_{minss}$ providing half-maximal reduction ($EC_{50}$) was 71.5 and 202 $\mu$g/mL for a MET-positive and MET-negative patient, respectively. Based on the limited number of MET-positive patients in the 7.5 ($n = 16$) and 15 mg/kg ($n = 11$) dose groups, positive MET expression was also found to have a predictive effect on rilotumumab treatment outcome on OS and was significantly associated with the $EC_{50/C_{minss}}$ ($P = 0.0008$). The analysis was repeated using an alternative definition of MET positivity ($\geq 50\%$ membrane staining), and results were similar (data not shown). The equations for the OS model are presented below.
\[
hazard = \lambda \cdot MET_{\lambda} \cdot \rho \cdot (\lambda \cdot MET_{\lambda} \cdot t)^{(\rho-1)} \cdot (1 + R) \cdot (1 - (Slope \cdot RTS_{Wk24})]
\]

\[
MET_{\lambda} = \begin{cases} 
1 & \text{if } MET \text{ is negative} \\
1 + MET \text{ effect on } \lambda & \text{if } MET \text{ is positive} \\
1 + 0.5 \cdot MET \text{ effect on } \lambda & \text{if } MET \text{ is missing}
\end{cases}
\]

\[
R = \frac{E_{\max} \cdot C_{\min ss}^{hill}}{(EC50C_{\min ss} \cdot MET_{C_{\min ss}})^{hill} + C_{\min ss}^{hill}}
\]

\[
MET_{C_{\min ss}} = \begin{cases} 
1 & \text{if } MET \text{ is negative} \\
1 + MET \text{ effect on } EC50_{C_{\min ss}} & \text{if } MET \text{ is positive} \\
1 + 0.5 \cdot MET \text{ effect on } EC50_{C_{\min ss}} & \text{if } MET \text{ is missing}
\end{cases}
\]

where \(\lambda\) and \(\rho\) are the scale and shape parameters, respectively, of the Weibull distribution; \(MET_{\lambda}\) is the effect of MET-positive status (≥25% membrane staining) on \(\lambda\); \(R\) is the effect of rilotumumab treatment on the hazard; \(E_{\max}\) is the maximum effect of rilotumumab treatment on the hazard; \(C_{\min ss}\) is the steady-state trough concentration of rilotumumab; \(EC50C_{\min ss}\) is the rilotumumab concentration providing 50% of the maximum effect of rilotumumab treatment; \(MET_{C_{\min ss}}\) is the effect of MET-positive status on \(EC50C_{\min ss}\) and \(hill\) is the Hill-factor for the sigmoid \(E_{\max}\) function. All OS model parameters were well estimated, and the VPC (Figures 2 [bottom row] and 3) indicated adequate predictive ability of the OS model, especially when stratifying by rilotumumab exposure and MET expression.

**Clinical Trial Simulations**
Simulations based on a phase 3 study design corresponded with the results observed in the phase 2 study and demonstrated the efficacy of rilotumumab plus ECX compared with ECX alone in MET-positive patients. The predicted median OS (95% CI) for ECX alone was 7.6 (5.6, 10.0) months, which is similar to the median OS observed for the MET-positive ECX group in the phase 2 study. The predicted median OS (95% CI) for ECX plus rilotumumab at doses of 7.5, 10, 15, and 20 mg/kg Q3W was 11.9 (9.4, 15.7), 13.9 (10.6, 19.5), 15.7 (11.9, 23.9) and 16.3 (12.1, 25.3), respectively. Corresponding to the increasing median OS by dose, the HR (95% CI) was 0.54 (0.35, 0.76), 0.45 (0.27, 0.65), 0.38 (0.18, 0.60) and 0.36 (0.16, 0.56) for the rilotumumab doses of 7.5, 10, 15, and 20 mg/kg, respectively (Figure 4).
DISCUSSION

The Critical Path Initiative of the United States Food and Drug Administration calls for leveraging existing knowledge from clinical data through the use of quantitative modeling to improve the drug development process, including anticancer drugs (29). In this context, TG models that account for the effect of disease characteristics (e.g., tumor growth rate) and drug effects (e.g., drug potency) and/or exposure (e.g., AUC, Cmin) can predict the OS outcomes in several solid tumors, such as colorectal (30), breast (31), non-small cell lung (32), and thyroid (33) cancer. We aimed to characterize the relationship between ECX/rilotumumab exposures, their TG inhibition effect and their subsequent impact on OS in patients with gastric/GEJ cancer in order to develop a drug-disease model that allows exploration of different scenarios of potential future clinical trials. Additionally, we investigated the role of tumor MET expression, steady-state rilotumumab exposure, and relative change in tumor size as potential prognostic and/or predictive factors of OS in patients with gastric/GEJ cancer who were treated with rilotumumab plus ECX or ECX alone.

Rilotumumab exhibited linear and time-independent PK, which was adequately described by a two-compartment disposition model over a dose range of 0.5–20 mg/kg (16). Following Q3W administration, steady state was reached at 4 months with a two-fold accumulation factor. The estimated systemic CL and Vc were comparable with endogenous IgGs, as reported in a previous population PK analysis (16). Consistent with previous results, our findings confirmed that no covariates, including tumor MET expression or the administration of ECX, affected
rilotumumab PK other than body weight, suggesting weight-based dosing is appropriate for rilotumumab (16).

Consistent with the literature, the TG inhibition model suggests that on average 16 months are needed to double the gastric/GEJ tumor size with significant variability in the doubling time (±13 months) (34). However, any estimate of untreated tumor growth is complicated by the lack of information on tumor growth and death in the absence of treatment since all patients received ECX, and the estimate of tumor growth is based on data from patients who are resistant or develop resistance to treatment. The gastric/GEJ tumor doubling time is slightly higher than the time for colorectal tumors, 8 to 12 months (30), but lower than the 40 months needed in breast tumors (31). These findings clearly reflect the differences in disease progression due to the primary tumor origin. The effect of ECX in killing tumor cells indicated that the time to reduce tumor size by half from baseline was approximately 2 months, and it took 1.5 months on average to develop resistance to ECX treatment. The dynamic for the resistance phenomena has been previously determined for other anticancer drugs (31). Thus, in breast cancer, the half-lives of the resistance phenomenon for capecitabine and docetaxel were determined to be 3.25 and 4 months, respectively (31).

TG models assume that cytotoxic drugs affect tumor-cell death rate because of their intrinsic mechanism of action. However, rilotumumab has an effect on the tumor growth process as HGF/MET is necessary for tumorigenesis and results in activation and production of proteins needed for cell cycle progression and cell proliferation (3,4). This specific mechanism of action of rilotumumab compared with ECX is illustrated by the relatively long time to develop tumor resistance (20.5 and 1.5 months for rilotumumab and ECX, respectively). Additionally, as ECX
was the major contributor to tumor reduction and with limited further tumor reduction due to saturation of tumor growth inhibition at the rilotumumab doses tested (~30% decrease from baseline for ECX alone versus ~40% for ECX plus 7.5 or 15 mg/kg rilotumumab), it was difficult to further discern any apoptotic effect of rilotumumab, as previously reported (12), or the relationship between MET-expression and rilotumumab-related TG model parameters.

The joint effect of ECX and rilotumumab on tumor reduction further contributes to the decrease of the OS hazard. The change in tumor size from baseline at week 6 or 8 has been proposed to capture the treatment effect and predict survival in several tumor types (30-33). However, it has been postulated that these times might not fully capture the treatment effect, particularly for the new targeted therapies. In fact, in the present analysis, the tumor size reduction at 24 weeks was the best OS predictive factor among the tumor sizes at other time points. However, the inclusion of predicted reduction in tumor size at 24 weeks in the model is problematic, as the majority of patients were not dosed with rilotumumab for 24 weeks nor was the tumor size assessed at 24 weeks. Thus, while reduction in tumor size at week 24 was most predictive, it may not be feasible to observe in patients. Additionally, the influence of tumor size on OS was based on a predicted rather than observed tumor assessment. Higher rilotumumab concentrations ($C_{\text{minss}} > 71.5 \mu g/mL$) had an additional predictive value of the OS hazard in MET-positive patients. The effect of MET expression on $EC_{50C\text{minss}}$, with approximately a three-fold higher $EC_{50C\text{minss}}$ in MET-negative patients, suggests that patients with positive MET expression are more sensitive or responsive to rilotumumab treatment than patients with negative MET expression, as previously observed (17). Interestingly, tumor MET expression appeared to be both prognostic and predictive of OS in patients with gastric/GEJ cancer who were treated
with rilotumumab. MET expression in tumor tissues, therefore, becomes direct evidence for the
degree of involvement of the HGF/MET pathway in the tumor development for a particular
patient. Similarly, the rilotumumab treatment effect appeared to be limited in patients whose
gastric/GEJ cancer development may not highly depend on HGF/MET signalling for
tumorigenesis. As patients were not screened for or stratified by tumor MET expression in the
clinical trial, the predictive and prognostic effects of MET expression on overall survival is
based on a limited number of patients with positive MET expression (n=13 treated with ECX
alone, and n=33 treated with ECX + rilotumumab). Thus, while there is a significant effect of
tumor MET expression within this small sample of gastric cancer patients, results from
additional patients are needed to confirm this relationship.

Model-based clinical trial simulations have demonstrated utility in predicting the
outcome of phase 3 studies for some oncology programs on the basis of phase 2 results
(18,23,35). Incorporating the effects of MET expression, TG inhibition, and rilotumumab
treatment within the OS parametric model to conduct clinical trial simulations illustrated the
increasing OS projected with rilotumumab doses and supported the selection of 15 mg/kg
rilotumumab Q3W, as it is projected to have a 30% or 18% lower HR compared to doses of 7.5
or 10 mg/kg, respectively, and to have only a 5% difference compared to a dose of 20 mg/kg.
Furthermore, the probability of success of a phase 3 trial using rilotumumab 15 mg/kg Q3W is
>90% at the pre-specified sample size, with the same patient population and MET positivity
observed in the phase 2 study. This new technology should be applied at the end of phase 2
studies in order to optimize the phase 3 study design, maximize its probability of success, and
ultimately, decrease the attrition rate of the oncology development program and streamline the clinical development of efficacious and safe new oncology therapeutics.

However, as it is often the case at the end of phase 2 development for novel therapeutics in cancer patients, there is limited information for both model development and evaluation. In this analysis, a single phase 2 clinical study in gastric cancer patients was used to develop and evaluate the OS model. Additionally, key components of the OS model (i.e., rilotumumab steady state exposure, predicted tumor size at week 24, and MET status) were not available for all subjects in the phase 2 study, thus, the OS model incorporates a subset of the phase 2 population which may not adequately represent the overall gastric cancer population which will enrol in the phase 3 study. Differences in the study characteristics, specifically, inclusion/exclusion criteria, prior treatment, changes in co-medications or standard of care, between the phase 2 and phase 3 studies may also impact the validity of the model based predictions for the outcome of the phase 3 study. Thus, evaluation of the model against and updating with data from subsequent trials with rilotumumab in gastric cancer patients is needed to confirm its validity.

In summary, the current PK and pharmacodynamic assessment revealed that rilotumumab exhibited linear time-independent PK not affected by tumor MET expression. Rilotumumab demonstrated concentration-dependent effects in reducing tumor size and prolonging OS in patients with gastric/GEJ cancer treated with ECX. The rilotumumab concentration-dependent effect on OS was associated with tumor MET expression, and longer survival is expected in patients who have positive MET expression and sufficiently high rilotumumab exposure. Model-based clinical trial simulations supported the selection of 15 mg/kg Q3W for a phase 3 study.
(RIOMET-1) compared to alternative doses. Consequently, the rilotumumab 15 mg/kg Q3W dose is warranted for further clinical testing in patients with MET-positive gastric/GEJ cancer and further study of rilotumumab in gastric cancer patients is needed to confirm the relationships identified in the survival model.
Acknowledgments

The authors wish to thank the patients, investigators, and the medical, nursing, and laboratory staff who participated in the rilotumumab clinical trials. The authors wish to thank Mark Ma and Teresa Wong of Amgen Inc. for support with the analytical assay development and sample analysis; Andrew Chow and Tom Sun of Amgen Inc. for the support and the insightful comments provided during the completion of this analysis; and Jenilyn Virrey of Amgen Inc. for editorial and formatting support.
REFERENCES


Table 1. Tumor Growth Model Parameter Estimates.

<table>
<thead>
<tr>
<th>Model Parameters</th>
<th>Typical Value (RSE)</th>
<th>Bootstrap Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (mm)(^a)</td>
<td>96.5 (9.51)</td>
<td>96.4 (79.2, 115)</td>
</tr>
<tr>
<td>(k_g) (yr(^{-1}))</td>
<td>0.531 (41.7)</td>
<td>0.534 (0.0397, 1.11)</td>
</tr>
<tr>
<td>(EC_{50}) (µg/mL)</td>
<td>6.71 (227)</td>
<td>6.41 (0, 21.3)</td>
</tr>
<tr>
<td>(k_{res,R}) (yr(^{-1}))</td>
<td>0.406 (72.4)</td>
<td>0.427 (0, 1.67)</td>
</tr>
<tr>
<td>(k_d) (yr(^{-1}).mg(^{-1}))</td>
<td>0.0527 (17.9)</td>
<td>0.0584 (0.0367, 0.0929)</td>
</tr>
<tr>
<td>(k_{PD}) (yr(^{-1}))</td>
<td>18.3 (fixed)</td>
<td>NA</td>
</tr>
<tr>
<td>(k_{res,ECX}) (yr(^{-1}))</td>
<td>5.89 (22.8)</td>
<td>7.20 (3.88, 16.2)</td>
</tr>
<tr>
<td>(\eta_{Baseline})</td>
<td>0.344(^a) (9.51)</td>
<td>0.439 (0.145, 0.99)(^a)</td>
</tr>
</tbody>
</table>

**Logit transformation of \(\eta_{Baseline}\)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Typical Value (RSE)</th>
<th>Bootstrap Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skewness parameter</td>
<td>0.665 (20.6)</td>
<td>0.657 (0.527, 0.797)</td>
</tr>
<tr>
<td>Width parameter</td>
<td>6.72 (76.9)</td>
<td>6.74 (4.31, 11.1)</td>
</tr>
<tr>
<td>(\eta_{kd})</td>
<td>88 (17.9)</td>
<td>85.7 (44.6, 122)</td>
</tr>
<tr>
<td>(\eta_{kres,ECX})</td>
<td>50.3 (22.8)</td>
<td>70.8 (0.59, 156)</td>
</tr>
<tr>
<td>(\eta_{kg})</td>
<td>118 (41.7)</td>
<td>139 (1.17, 248)</td>
</tr>
</tbody>
</table>

**Residual Variability (%CV)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Typical Value (RSE)</th>
<th>Bootstrap Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>17.4 (1.45)</td>
<td>16.9 (10.1, 24.2)</td>
</tr>
</tbody>
</table>

\(^a\)RSE value is for the logit-transformed value.

\(^b\)Results expressed as coefficient of variation, %. (RSE: relative standard error of the \(\omega^2\), %).

NA: not applicable.
Table 2. Survival Model Parameter Estimates.

<table>
<thead>
<tr>
<th>Model Parameters</th>
<th>Estimate Value (RSE)</th>
<th>Bootstrap Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \lambda ) (d(^{-1}))(^{a})</td>
<td>0.00295 (12.6)</td>
<td>0.00292 (0.00223, 0.00380)</td>
</tr>
<tr>
<td>( \lambda ) (d(^{-1}))(^{b})</td>
<td>0.00412</td>
<td>0.00420 (0.00320, 0.00522)</td>
</tr>
<tr>
<td>MET effect on ( \lambda )</td>
<td>0.396 (54.6)</td>
<td>0.419 (0.00473, 1.00)</td>
</tr>
<tr>
<td>( \rho ) (d(^{-1}))</td>
<td>1.65 (8.85)</td>
<td>1.71 (1.43, 2.02)</td>
</tr>
<tr>
<td>Slope (effect of ( \Delta T_{\text{SWeek 24}} ))</td>
<td>-0.730 (30)</td>
<td>-0.760 (-0.997, -0.181)</td>
</tr>
<tr>
<td>( E_{\text{max}} )</td>
<td>-0.646 (15.8)</td>
<td>-0.696 (-0.830, -0.462)</td>
</tr>
<tr>
<td>( EC_{50C_{\text{minss}}} ) (( \mu )g/mL)(^{a})</td>
<td>202 (2.91)</td>
<td>204 (190, 250)</td>
</tr>
<tr>
<td>( EC_{50C_{\text{minss}}} ) (( \mu )g/mL)(^{c})</td>
<td>71.5</td>
<td>71.5 (60.3, 107)</td>
</tr>
<tr>
<td>MET effect on ( EC_{50C_{\text{minss}}} ) (^{a})</td>
<td>-0.646 (2.31)</td>
<td>-0.652 (-0.742, -0.467)</td>
</tr>
<tr>
<td>Hill</td>
<td>50 (fixed)</td>
<td>NA</td>
</tr>
</tbody>
</table>

\(^{a}\)Value for patients with MET-negative expression

\(^{b}\)Value for patients with MET-positive expression and was derived using \( \lambda \) for MET-negative patients and the effect of MET-expression on \( \lambda \): \( \lambda_{\text{MET-positive}} = \lambda_{\text{MET-negative}} \times (1 + \text{MET effect on } \lambda) \)

\(^{c}\)Value for patients with MET-positive expression and was derived using \( EC_{50C_{\text{minss}}} \) for MET-negative patients and the effect of MET-expression on \( EC_{50C_{\text{minss}}} \): \( EC_{50C_{\text{minss,MET-positive}}} = EC_{50C_{\text{minss,MET-negative}}} \times (1 + \text{MET effect on } EC_{50C_{\text{minss}}}) \)

NA: not applicable.
FIGURE LEGENDS

**Figure 1.** Schematics of Tumor Growth and Overall Survival Models.

**Figure 2.** Visual Predictive Check on Pharmacokinetics, Tumor Size, and Overall Survival – Time Profiles by Cohort. For the top and middle rows, the open circles represent observations, the solid line represents the predicted median exposure, and the shaded area represents the 95% prediction interval. For the bottom row, the solid line represents the proportion of patients surviving over time stratified by treatment arm, and the shaded area represents the 95% prediction interval of the projected overall survival simulated.

**Figure 3.** Visual Predictive Check on Overall Survival by Treatment Stratified by MET-positive and MET-negative or $C_{\text{minss}} (> \text{or} \leq 71.5 \mu\text{g/mL})$. For each panel, the solid line represents the proportion of patients surviving over time stratified by treatment arm (ECX, ECX plus 7.5 mg/kg rilotumumab, or ECX plus 15 mg/kg rilotumumab).

**Figure 4.** Hazard Ratio Versus Dose in MET-Positive Patients. The open circles represent the median hazard ratios observed across replicates, and the vertical segments represent the 95% CI of the hazard ratios across replicates.
Figure 1
Figure 3
Figure 4
Rilotumumab Exposure-Response Relationship in Patients With Advanced or Metastatic Gastric Cancer

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