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Research Article

Exposure–Response and Tumor Growth Inhibition Analyses of the Monovalent Anti-c-MET Antibody Onartuzumab (MetMAb) in the Second- and Third-Line Non-Small Cell Lung Cancer

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Abstract. The phase III trial comparing onartuzumab + erlotinib *vs.* erlotinib in the second- and third-line non-small cell lung cancer (NSCLC) did not meet its primary endpoint of overall survival (OS). The objective was to assess whether doses higher than the phase III dose (15 mg/kg) might yield better efficacy without compromising the safety profile. Data were from 636 patients from the phase II and III NSCLC studies. Tumor growth inhibition (TGI) models were fit to longitudinal tumor size data to estimate individual TGI metrics including time to tumor re-growth (TTG). Cox regression models were developed for time-to-event endpoints (progression-free survival (PFS), OS, and TTG) to investigate relationships with baseline prognostic factors and onartuzumab exposure. Incidence of adverse events was modeled by logistic regression. In the final models, higher onartuzumab exposure was associated with longer PFS, but not with longer OS. Longer OS was associated with higher baseline albumin, longer TTG, smaller number of metastatic sites, female gender, lower ECOG score, and younger age. TTG was the only TGI metric retained in the final OS model. Onartuzumab exposure was not significantly associated with TTG after adjusting for prognostic factors. Higher Cmin was associated with increased incidence of infusion reactions and peripheral edema. Higher onartuzumab exposure was not significantly associated with improved OS after adjusting for prognostic factors and TTG, and there was a trend of unknown clinical significance toward increased incidence of infusion reactions and peripheral edema. These results did not support testing higher onartuzumab doses.

KEY WORDS: Cox regression; exposure–response; NSCLC; onartuzumab; survival model; time to tumor re-growth; tumor growth inhibition.

INTRODUCTION

c-MET is a receptor tyrosine kinase and plays a key role in a variety of cellular processes including motility, morphogenesis, proliferation, and survival and invasion and may also contribute to angiogenesis (1). Clinically, the c-MET pathway has been strongly linked to oncogenic potential. First, activating kinase domain mutations have been described in a variety of cancers, with particularly high levels observed in renal papillary carcinoma patients (2,3). Second, high levels of tumoral expression of c-MET and/or its ligand hepatocyte growth factor (HGF) have been correlated with worse prognosis in several tumor types, including non-small cell lung cancer (NSCLC), breast cancer, ovarian cancer, cervical cancer, gastric cancer, transitional bladder carcinoma, glioblastoma, head and neck cancers, and multiple myeloma (4–13). Collectively, these provide compelling evidence that therapeutics abrogating c-MET activation warrant clinical evaluation.

Onartuzumab (MetMAb) is a recombinant humanized monoclonal monovalent anti-c-MET antibody that binds the extracellular domain of c-MET, blocking HGF ligand binding, and inhibiting subsequent receptor activation. In a randomized placebo-controlled phase II study in recurrent NSCLC (OAM4558g, ClinicalTrials.gov Identifier: NCT00854308), onartuzumab plus erlotinib significantly improved progression-free survival (PFS) and overall survival (OS) as compared to erlotinib plus placebo in MET-positive (MET

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immunohistochemistry diagnostic positive) patients (14). However, in a double-blind randomized placebo-controlled phase III study in recurrent NSCLC (OAM4971g, ClinicalTrials.gov Identifier: NCT01456325), onartuzumab plus erlotinib did not significantly improve PFS or OS as compared to erlotinib plus placebo in MET-positive patients (15).

The onartuzumab dose used in the phase III study, 15 mg/kg administered once every 3 weeks (Q3W), was supported by cumulative preclinical and clinical experience. Simulations based on a population pharmacokinetic (PK) model derived from phase I study OAM4224g and phase II study OAM4558g suggested that onartuzumab 15 mg/kg Q3W would achieve a target tumoristatic trough concentration of 15 μg/mL, which was derived from xenograft studies (16). However, OAM4224g showed that onartuzumab was tolerable up to 30 mg/kg (17), opening up the possibility of dose intensification.

In order to facilitate the interpretation of the phase III outcomes and assess whether further dose intensification might yield better efficacy without compromising the safety profile, exposure–response analyses were conducted. However, exposure–response models may be confounded by disease severity and prognostic factors that may be observed (*e.g.*, albumin, ECOG score, number of metastatic sites) or unobserved (*e.g.*, inflammatory status). Confounding is related to the fact that disease severity and health status may impact both OS and PK (18,19), especially for monoclonal antibodies. One way to address the confounding issue is to incorporate an explanatory variable, such as TGI metrics as illustrated in the causal pathway in Fig. 1 (18) to make inferences about OS.

The objectives of these analyses were to (1) assess the relationship between onartuzumab exposure and efficacy as well as safety and (2) estimate TGI metrics and assess onartuzumab exposure–TGI and TGI–efficacy relationships (18).

METHODS

Patients and Exposure Metrics

Onartuzumab PK, efficacy, and safety data were obtained from OAM4558g (14) and OAM4971g (15). The clinically relevant covariates tested included those related to demographics, laboratory tests, concomitant medications, and pathophysiological factors (Table I). Onartuzumab serum concentrations were determined at Genentech Inc. by a validated sandwich enzyme-linked immunosorbent assay described previously that was designed to measure free onartuzumab (16). The lower limit of quantification (LLOQ) was 0.2 μg/mL.

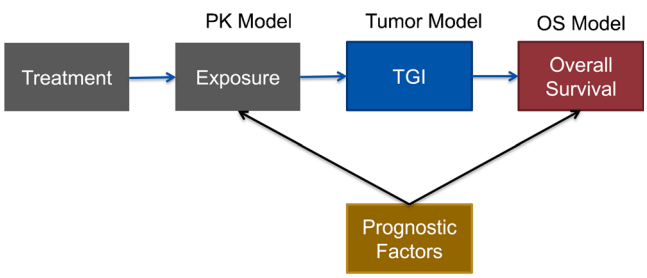

Fig. 1. Causal pathway to the elicitation of treatment effect. *TGI* tumor growth inhibition. TGI metrics includes the growth rate constant (KG) (24), the time to tumor re-growth (TTG) (25), and tumor size ratio to baseline (25)

Erlotinib was administered at the approved daily oral dose of 150 mg. Onartuzumab was administered at 15 mg/kg via intravenous infusion once every 3 weeks. Per study protocol, patients in the erlotinib arm were allowed to cross over to the onartuzumab + erlotinib arm after disease progression. A population PK model of onartuzumab (two-compartment model with linear elimination) has been previously established (16) based on data from phase I and II studies. The estimates for clearance (CL), central volume of distribution (V1), and terminal half-life were 0.439 L/day, 2.77 L, and 13.4 days, respectively. Onartuzumab CL increased with creatinine CL. Onartuzumab V1 increased with body weight and was higher in males. Onartuzumab peripheral volume of distribution increased with body weight. Exposure of onartuzumab or erlotinib was not associated with MET diagnostic status (degree of tissue MET expression). No pharmacokinetic drug–drug interaction was observed between onartuzumab and erlotinib.

Non-linear mixed effects modeling was performed with NONMEM (version 7.3; ICON Development Solutions, Ellicott City, Maryland, USA) (20) using the FOCE method of estimation with interaction, Perl-speaks-NONMEM (version 3.5.3; Uppsala University, Uppsala, Sweden) (21), and R 3.0.1 (22). Serum concentration data were fit to the previously published population PK model (16) to obtain individual empirical Bayesian estimates of PK parameters (*post hoc* step using NONMEM (20)), which were subsequently used to derive the individual onartuzumab exposure (trough (Cmin) and peak (Cmax) concentration and area under the concentration time curve (AUC)) during the first dosing interval and at steady state (fifth dosing interval). AUC was calculated using the trapezoidal method. Patients in the erlotinib single-agent arm were assumed to have an onartuzumab exposure of zero. Exposure was tested both as continuous variable and categorical variable (quartiles and tertiles).

Longitudinal Tumor Size Modeling

Longitudinal tumor size, defined as the sum of the longest diameters of target lesions according to the RECIST criterion (23), was analyzed. Patients with at least two tumor size measurements were defined as evaluable. Two TGI models (Supplementary Material) previously proposed were fit to data from evaluable patients using NONMEM: a bi-exponential model (24) and a simplified TGI (sTGI) model (25). Shrinkage in parameter estimates was estimated (26). The fits of models were compared using the log-likelihood ratio test as well as standard goodness of fit plots. These models were not subjected to any simulation-based assessment since they were not meant to be used for simulation but only to estimate individual TGI metrics to be tested in the survival model. Three individual TGI metrics were calculated using individual *post hoc* TGI parameter estimates: the growth rate constant (KG) (24), the TTG (25), and tumor size ratio to baseline at week 8 (25).

Table I. Patient Characteristics by Treatment

	Onartuzumab arm	Placebo arm
Total number of patients	319	317
Study (OAM4558g:OAM4971g)[a]	69:250	68:249
Age (year)	63 [24~83]	63 [27~84]
Gender (female:male)[a]	140:179	136:181
Body weight (kg)	69.1 [41.9~119.8]	70.1 [32.8~141]
Asian patients[b]	11.6%	12.0%
ECOG score (0:1:2)[a]	115:196:8	99:214:3
Stage (IIIB:IV)[a]	82:237	78:239
Non-squamous:squamous[a]	283:36	281:36
Albumin (g/L)	39 [25~49]	39 [24~49]
Total protein (g/L)	70 [0.072~96]	69 [6.9~94]
Baseline tumor burden (mm)	47.5 [1~245]	48 [1~324]
Number of metastatic sites	3 [1~8]	2.5 [1~9]
More than one metastatic site[b]	75.5%	81%
Liver metastasis present[b]	20.7%	20.2%
Smoking history (current:previous:never)[a]	50:209:59	57:208:50
EGFR mutation (yes:no:missing)[a]	43:232:44	41:237:39
KRAS mutation (yes:no:missing)[a]	36:80:203	27:101:199
MET mutation (yes:no:missing)[a]	270:31:18	271:31:15
Time since diagnosis (months)	11.8 [0.46~90.7]	12.4 [1.87~97.3]
Estimate of TTG (weeks)	1.445 [−44.62~68.50]	1.357 [−36.68~70.49]
Tumor size ratio to baseline at week 8	1.010 [0.199~3.458]	1.010 [0.144~1.879]
Estimate of KG (per week)	0.0083 [0.0043~0.1558]	0.0083 [0.0028~0.0803]

Patients in the onartuzumab arm receive both erlotinib and onartuzumab. Patients in the placebo arm received erlotinib alone. The numbers displayed represent the median (range) except for the number of patients is displayed (superscript letter a) and the percentage of patients is displayed (superscript letter b)
ECOG score Eastern Cooperative Oncology Group performance score, *EGFR* epidermal growth factor receptor, *KG* growth rate constant, *KRAS* Kirsten rat sarcoma viral oncogene homolog, *MET* hepatocyte growth factor receptor, *TTG* time to tumor re-growth

Exposure–Response Analysis of Efficacy Endpoints

Time-to-event variables (PFS, OS, and TTG) were explored and compared between patient subgroups with different onartuzumab exposure using Kaplan–Meier analysis and log-rank test. Multivariate models were developed using Cox regression analysis to associate time-to-event variables with onartuzumab exposure, clinically relevant covariates, and TGI metrics (when applicable). A "full" model was built by including all significant covariates from the Cox univariate analysis ($p < 0.05$ as per the log-likelihood ratio test where the difference in −2*log-likelihood (score) between the alternative models follows a χ^2 distribution). If several exposure or TGI metrics were significant from the univariate analysis, only the most significant one was included in the full model. Then, a backward stepwise elimination was carried out. At each elimination step, the relative influence of each remaining covariate on the model was re-evaluated one by one by deleting it from the reduced model using a cutoff of $p < 0.01$. The model was built only based on the patient subset with complete information without imputation. The PFS model was developed without inclusion of TGI metrics as covariates in MET-positive patients because tumor response was already considered and included in the overall clinical assessment of PFS.

Exposure–Response Analysis of Safety Endpoints

The safety endpoints (adverse events) were characterized by frequency (yes/no). The proportions of frequency and 95% confidence intervals were computed for intervals of onartuzumab exposure with an equivalent number of individuals (*e.g.*, quartiles or tertiles). The correlation between each safety endpoint and onartuzumab exposure subgroups was tested using logistic regression and the Wald test. Multivariate logistic regression models were developed only for the safety endpoints that showed a statistically significant ($p < 0.05$) correlation with any onartuzumab exposure metrics. All candidate covariates and exposure metrics were tested in a univariate and multivariate manner with the significance level of $p < 0.05$. The model was built only based on the patient subset with complete information without imputation.

RESULTS

Patients and Exposure Metrics

Data from a total of 636 patients were collected. Baseline patient characteristics evaluated as covariates are summarized in Table I. Both MET-positive and MET-negative patients were enrolled in OAM4558g, while only MET-positive patients were enrolled in OAM4971g. In OAM4558g, 27 patients (13 MET-positive, 12 MET-negative, and 2 unknown MET status) in the placebo arm received onartuzumab at some point (crossover patients) and thus were excluded from the analysis. Exposure data were unavailable in three patients who received onartuzumab, leaving 606 patients included in the analysis (550 MET-positive). PK parameter estimates

based on the PK data from OAM4558g and OAM4971g were consistent with those previously reported (16).

Longitudinal Tumor Size Modeling

Two TGI models were fit to the longitudinal tumor size data. A total of 584 patients were evaluable for TGI modeling. Parameter estimates and goodness-of-fit plots for these two TGI models were summarized in Supplementary Tables 1 and 2 and Supplementary Figures 1 and 2. Both models provided adequate fit to the data with a slightly better fit by the bi-exponential model. The KG, TTG, and tumor size ratio to baseline at week 8 were derived.

Exposure–Response Analysis for Survival

The highest quartile of onartuzumab steady-state Cmin (Cmin,ss) was associated with a longer PFS (median 4.37 months) than the other three quartiles (median 2.50 months) and the placebo arm (median 2.50 months) (Fig. 2) (Supplementary Tables 3 and 4). Univariate Cox regression analysis for OS (Table II) showed a strong association between OS and TTG ($p < 0.0001$). The association between OS and tumor size ratio or log (KG) was statistically significant ($p < 0.0001$), but not as strong as TTG. The final OS model (Table III) was obtained by multivariate backward stepwise elimination. In this model, none of the exposure metrics was significant ($p > 0.05$) whether they were considered a continuous variable or a categorical variable with the upper quartile as threshold.

Correlation Between Time to Tumor Re-growth and Onartuzumab Exposure

As illustrated in Fig. 1, one possible reason why onartuzumab exposure was eliminated from the final OS model could be due to the potential association between longer TTG and higher onartuzumab exposure. Therefore, this was subsequently examined by univariate and multivariate Cox regression analysis linking TTG with baseline prognostic factors and onartuzumab exposure.

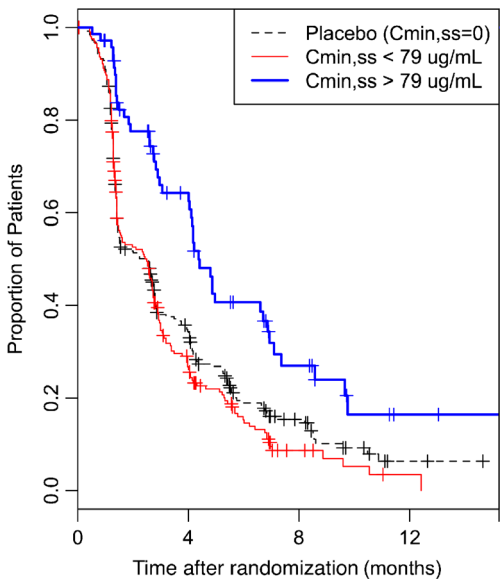

Fig. 2. Kaplan–Meier plot comparing progression-free survival by onartuzumab exposure. *Cmin,ss* onartuzumab steady-state trough serum concentration with an upper quartile threshold of 79 μg/mL

Table II. Univariate Cox Regression Analysis for Overall Survival

Covariate	Score	*p* value	Number	Sign
Albumin (g/L)	26.8	<0.0001	506	–
Number of metastatic sites	21.4	<0.0001	587	+
Estimate of TTG (weeks)	20.5	<0.0001	582	–
Baseline tumor burden (mm)	16.4	<0.0001	582	+
More than one metastatic site	14.9	<0.0001	587	+
ECOG score >0	14	<0.0001	606	+
TR to baseline at week 8	12.4	<0.0001	582	+
EGFR mutation positive	11.4	<0.0001	606	–
log (KG)	9.9	<0.0001	582	+
Gender = male	7.5	0.0001	606	+
Current smoker	7.2	0.0001	606	+
Cmin,ss >77 μg/mL	6.2	0.0005	606	–
Liver metastasis present	4.9	0.0017	606	+
Time since diagnosis (month)	4.6	0.0024	584	–
Asian ethnicity	3.2	0.012	606	–
Age (year)	2.2	0.0352	606	–
Onartuzumab treatment	0.5	0.3093	606	+
OAM4558g study	0.1	0.6789	606	–
MET mutation positive	0.1	0.7426	600	–

Covariates are ordered by the level of significance (score). Covariates tested included all baseline covariates, onartuzumab exposure, and TGI (tumor growth inhibition) metrics. *p* value is calculated using the likelihood ratio test. Score means the difference in −2*log-likelihood between the alternative models following a χ^2 distribution. Sign is the death hazard increases (+) or decreases (−) with the increased value of the covariate with a positive sign indicating bad prognosis

Abbreviations: Cmin,ss steady-state trough onartuzumab serum concentration with an upper quartile threshold of 77 μg/mL, *ECOG score* Eastern Cooperative Oncology Group performance score, *EGFR* epidermal growth factor receptor, *KG* growth rate constant, *N* number of patients with available information of the specific covariate, *TR* tumor size ratio to baseline, *TTG* time to tumor re-growth

The univariate Cox regression analysis for TTG is summarized in Supplementary Table 5. EGFR mutation status and baseline albumin were selected to remain in the final TTG model as independent predictors for TTG (Table III). In the final TTG model, the presence of EGFR mutation and higher albumin was associated with longer TTG. None of the onartuzumab exposure metrics was significant in the final TTG model. There was no interaction between onartuzumab Cmin,ss and MET diagnostic status.

Exposure–Response of Safety Endpoints

Seven adverse events were evaluated: infusion reactions, allergic reactions, venous thromboembolism, arterial thromboembolism, interstitial lung disease, gastrointestinal perforations, and peripheral edema. Peripheral edema data were unavailable in OAM4558g. Exploratory logistic regression showed that only infusion reactions and peripheral edema were statistically significantly associated with onartuzumab exposure (Fig. 3). The final logistic regression (Table III) was obtained by multivariate logistic regression. Among all

Table III. Parameter Estimates of Final Models for Efficacy and Safety Endpoints

Parameter	Estimate	RSE	*z*	*p* value
Final OS model [a]				
Baseline albumin (g/L)	−0.09545	15.1	−6.61	<0.0001
Estimate of TTG (weeks)	−0.02413	17.4	−5.73	<0.0001
Number of metastatic sites	0.22365	19.5	5.13	<0.0001
Gender = male	0.5510	25.1	3.98	<0.0001
ECOG score >0	0.4450	33.9	2.95	0.0032
Age (year)	−0.01891	35.2	−2.84	0.0045
Final TTG model [b]				
EGFR mutation positive	−0.802	16.9	−5.91	<0.0001
Baseline albumin (g/L)	−0.0287	35.9	−2.78	0.0054
Infusion reactions[c]				
(Intercept)	−1.78	7.30	−13.7	<0.0001
Cmin,ss >79 μg/mL	0.915	31.8	3.14	0.0017
Peripheral Edema[c]				
(Intercept)	−2.17	8.39	−11.9	<0.0001
Cmin,ss (μg/mL)	0.0166	18.6	5.37	<0.0001

p value: Wald test (χ^2). *z*: Wald statistic
Abbreviations: Cmin,ss steady-state trough onartuzumab serum concentration with an upper quartile threshold of 79 μg/ml, *ECOG score* Eastern Cooperative Oncology Group performance score, *EGFR* epidermal growth factor receptor, *OS* overall survival. *RSE* relative standard error (%) indicating the precision of parameter estimation, *TTG* time to tumor re-growth
[a] Developed using multivariate Cox regression models to associate OS with all baseline covariates, onartuzumab exposure, and tumor growth inhibition metrics
[b] Developed using multivariate Cox regression models to associate TTG with all baseline covariates and onartuzumab exposure
[c] Developed using multivariate logistic regression models to associate the incidence of adverse events with all baseline covariates and onartuzumab exposure

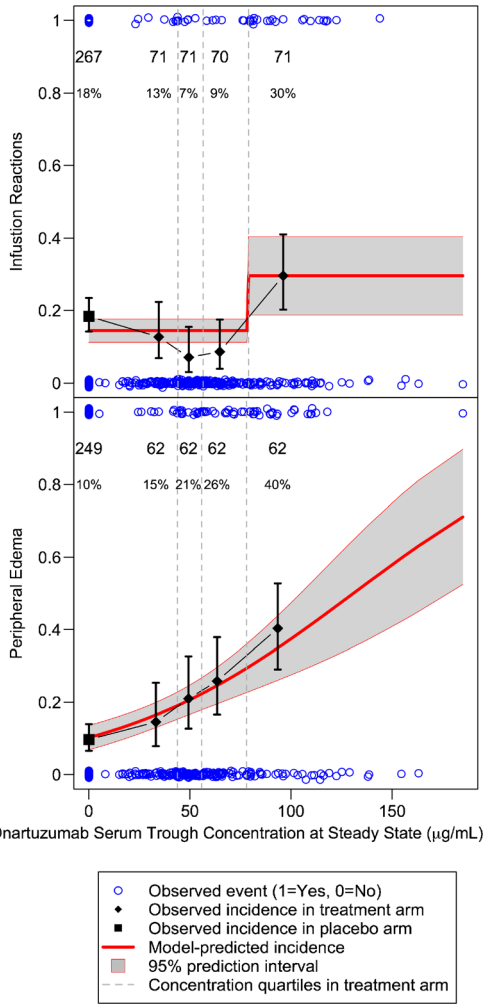

Fig. 3. Exposure–safety relationship for infusion reactions and peripheral edema. The model-predicted incidence with 95% prediction interval was generated by the final logistic regression model. Onartuzumab concentration was assumed to be zero in the placebo arm. Observed incidence was calculated with *error bar* in the placebo arm and in each concentration quartile in the treatment arm. The number displayed above each observed incidence was the corresponding number of patients and calculated incidence

baseline prognostic factors and onartuzumab exposure metrics tested, only onartuzumab Cmin,ss in the highest quartile was associated with increased incidence of infusion reactions, and only increased onartuzumab Cmin,ss was associated with increased incidence of peripheral edema.

DISCUSSION

The phase III trial OAM4971g comparing onartuzumab plus erlotinib *vs.* erlotinib in MET-positive patients with the second- and third-line NSCLC did not meet the primary endpoint of OS. This analysis was performed to assess whether higher onartuzumab doses might yield better efficacy without compromising the safety profile. Our analysis demonstrated that higher onartuzumab PK exposure was not associated with improved OS after accounting for baseline prognostic factors and TGI metrics, but there was a trend of unknown clinical significance toward increased incidence of infusion reactions and peripheral edema. These results did not support testing of a higher onartuzumab dose in this population.

Exploratory analysis suggested that patients with the onartuzumab steady-state trough concentration (Cmin,ss) above the highest quartile tended to have a longer OS than patients with Cmin,ss in the lowest three quartiles, who had similar or even slightly lower OS as compared to patients receiving erlotinib alone. In the final multivariate model after adjusting for baseline prognostic factors and TGI metrics, higher Cmin,ss was no longer significantly associated with longer OS.

Exposure–response models may be confounded by observed and unobserved prognostic and disease risk factors (18,19). Prognostic factors may impact both OS and PK exposure (Fig. 1), especially for antibody drugs. Patients with the characteristics related to poor prognosis (*e.g.*, low albumin and high ECOG score) have demonstrated faster clearance and thus lower exposure for large molecule drugs (27). This may be adjusted for by using multivariate models incorporating baseline prognostic factors, such as the Cox regression employed in this analysis. The resulting multivariate models may be used to simulate the expected response under unstudied doses (28). However, such simulations may lead to biased inferences if the confounding is not fully

adjusted for. One way to address the confounding issue is to incorporate an explanatory variable, such as TGI metrics, as illustrated in the causal pathway (18) in Fig. 1. A good example has been established using data for trastuzumab in HER2-positive gastric cancer (29). The multivariate OS model accounts for both baseline prognostic factors and treatment effect on TGI. Assuming that the drug effect is mediated via TGI, the direct exposure−OS link should be removed when TGI enters the OS model, which has been the case in this analysis. If the exposure–OS link is valid, valid inferences can be made assuming exposure impacts TGI and TGI impacts OS. However, there was no exposure–TGI link in this analysis, demonstrating that a valid exposure–OS link does not exist.

In this analysis, TGI metrics were estimated based on longitudinal tumor size data (18). The estimate of time to tumor re-growth (TTG) was a strong predictor for OS as observed in previous studies using similar methodologies (18). TTG remained a strong predictor of OS after adjustment for baseline prognostic factors. In the univariate analysis for TTG, patients with the onartuzumab Cmin,ss above the highest quartile tended to have longer TTG. However, the main covariate effects were EGFR mutation status and baseline albumin with EGFR-mutated patients with higher albumin having a trend to have longer TTG. It is well known that EGFR-mutated patients respond better to erlotinib treatment than other patients, and patients with higher albumin are healthier and usually show better clinical outcomes than patients with lower albumin. Onartuzumab exposure was no longer significant after adjusting for EGFR mutation status and albumin, suggesting that onartuzumab treatment had no discernable effect on TGI and that the exposure–OS relationship observed in the exploratory analysis was mainly due to disease prognostic.

The exposure–response analysis was performed for all seven selected adverse events without distinguishing onartuzumab-related or erlotinib-related adverse events. Statistically significant relations between onartuzumab Cmin,ss and infusion reactions and peripheral edema were observed. In the multivariate analyses, no baseline prognostic factors entered the model and onartuzumab exposure was the only predictor. For infusion reactions, the incidence appeared to be increased in patients with the onartuzumab Cmin,ss above the highest quartile. In addition, the incidence was notably higher in OAM4558g than in OAM4971g, likely due to the higher onartuzumab concentrations in OAM4558g. Onartuzumab Cmin,ss in 34% of patients in OAM4558g but only 24% in OAM4971g were above the highest quartile threshold of 79 μg/mL. However, this result should be interpreted with caution because an infusion reaction might be caused by infusion that lasted longer than was prespecified in the protocol, especially when a higher dose was given. Unfortunately, this could not be further evaluated due to the lack of information on the exact time when the infusion reaction occurred. In contrast, the incidence of peripheral edema appeared to be associated with onartuzumab exposure that was evaluated as either a continuous or categorical variable, and all onartuzumab exposure metrics were statistically significant. The clinical significance of the exposure–response relationships for infusion reactions and peripheral edema was unclear.

There are several limitations in this analysis. First, only one dose level (15 mg/kg) was evaluated in the phase II and phase III studies, which may limit the range of exposure. However, onartuzumab Cmin,ss ranged from 5.2 to 185 μg/mL in the pooled data, with a coefficient of variation (CV) of 46%. This may provide an adequately wide range of exposure to be tested in the model. Second, there was some shrinkage in parameter and individual estimates of the TGI metrics (Supplementary Tables 1 and 2). Shrinkage might decrease the predictive power of these metrics. However, all the metrics were still strong predictors of OS indicating that the shrinkage was not a major problem.

In conclusion, in patients with second- and third-line NSCLC, higher onartuzumab PK exposure was not associated with improved OS after accounting for baseline prognostic factors and TGI metrics, but there was a trend of unknown clinical significance toward increased incidence of infusion reactions and peripheral edema. Collectively, these results did not suggest that dose intensification would improve clinical outcomes and thus did not support further clinical investigation of a higher onartuzumab dose in this population.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest Kelong Han, Jin Jin, Helen Winter, and Mark Stroh receive salary from Genentech and hold stocks in Roche Pharmaceuticals. In addition, Jin Jin also holds stock in Eli Lilly. Fredrik Jonsson, Pascal Chanu, and René Bruno received salary from Pharsight Consulting Services at the time of work.

Authors' Contributions All authors have contributed substantially to the conception and design of the analysis and drafting or revising the paper as well as giving final approval for submission.

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