

INTRODUCTION

Onartuzumab (ONT) is a recombinant humanized monoclonal monovalent anti-c-MET antibody that binds the extracellular domain of c-MET, blocks HGF binding, and inhibits activation.

In randomized placebo-controlled phase II Non-Small Cell Lung Cancer (NSCLC) study OAM4558g, ONT plus erlotinib significantly improved progression-free survival (PFS) and overall survival (OS) as compared to erlotinib plus placebo in MET immunohistochemistry diagnostic positive (MET-positive) patients [1].

The phase III trial OAM4971g comparing ONT plus erlotinib vs erlotinib in MET-positive patients with 2nd and 3rd line NSCLC did not meet the primary endpoint of OS.

The objective of this evaluation was to assess whether a higher ONT dose may yield better efficacy without significantly changing the safety profile.

METHODS

Patients and Exposure Data

Data from 636 patients from the phase II study OAM4558g and phase III study OAM4971g were pooled.

PK data were fit to a published population PK model [2] to obtain individual empirical Bayesian estimates of PK parameters.

Exposure-Response and Longitudinal Tumor Size Modeling

A bi-exponential model [3] and a simplified tumor growth inhibition (TGI) model [4] were fit to longitudinal tumor size data to estimate individual growth rate constant (KG) [3], the time to tumor re-growth (TTG) [4], and tumor size ratio to baseline at week 8 [4].

OS and TTG were explored and compared between patient subgroups with different ONT exposure using Kaplan-Meier analysis and log rank test.

Multivariate models were developed using Cox regression analysis. A “full” model was built with all significant covariates from a Cox univariate analysis (p<0.05 per the log-likelihood ratio test). A backward stepwise elimination was carried out using a cut-off of p<0.01.

Exposure-Safety Analysis

The proportions of safety endpoints and 95% confidence intervals were computed for intervals of ONT exposure (e.g., quartiles or tertiles).

The correlation between each safety endpoint and ONT exposure subgroups was tested using logistic regression and the Wald test.

Multivariate logistic regression models were developed for safety endpoints that showed a statistically significant (p<0.05) correlation with ONT exposure metrics.

Candidate covariates and exposure metrics were tested in a univariate and multivariate manner with the significance level of p<0.05.

Software

Modeling was performed with NONMEM (version 7.3; ICON Development Solutions, Ellicott City, Maryland, USA) using the FOCE method of estimation with interaction, Perl-speaks-NONMEM (version 3.5.3; Uppsala University, Uppsala, Sweden) and R 3.0.1.

RESULTS and DISCUSSION

- Baseline patient characteristics evaluated as covariates are summarized in Table 1.

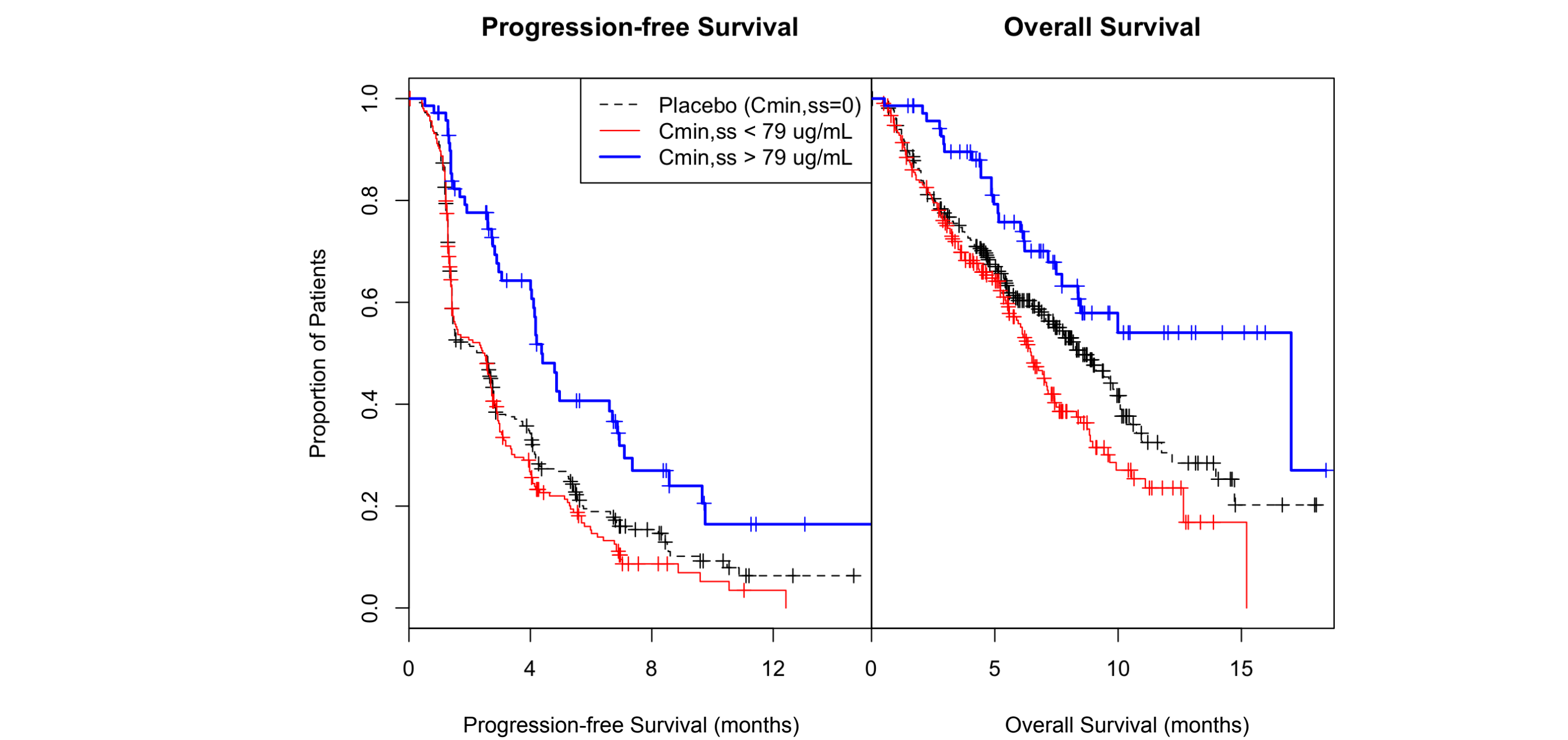
Table 1. Patient characteristics by treatment

	ONT 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:Mssing) ^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 a) the number of patients is displayed, and b) the percentage of patients is displayed. 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.

- An exposure- response analysis of MET–positive patients in OAM4558g and OAM4971g suggested longer PFS and OS for patients whose ONT steady--state trough concentration is above the upper quartile (Figure 1). However, exposure-response relationship with these clinical endpoints may be confounded by unobserved prognostic (Px) factors (Figure 2).

Figure 1. Kaplan-Meier plot comparing time-to-event endpoints by ONT exposure in MET-positive patients.



- After TGI metrics were included while building the OS model, ONT exposure was no longer significant. The final OS model indicated that longer OS is associated with higher albumin, longer TTG, fewer metastatic sites, female gender, ECOG performance score equal to 0, and higher age. On the other hand, ONT exposure was not significantly associated with TTG after adjusting for baseline Px factors. Longer TTG is associated with the presence of EGFR mutation and higher albumin.

Figure 2. Causal pathway to the elicitation of treatment effect

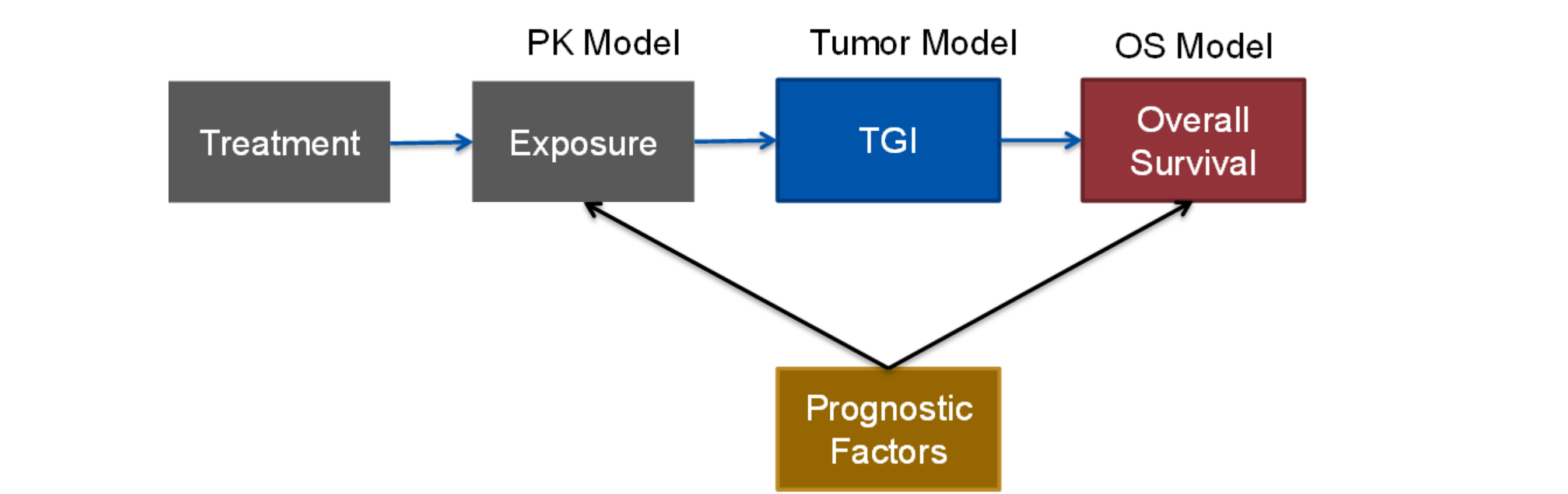
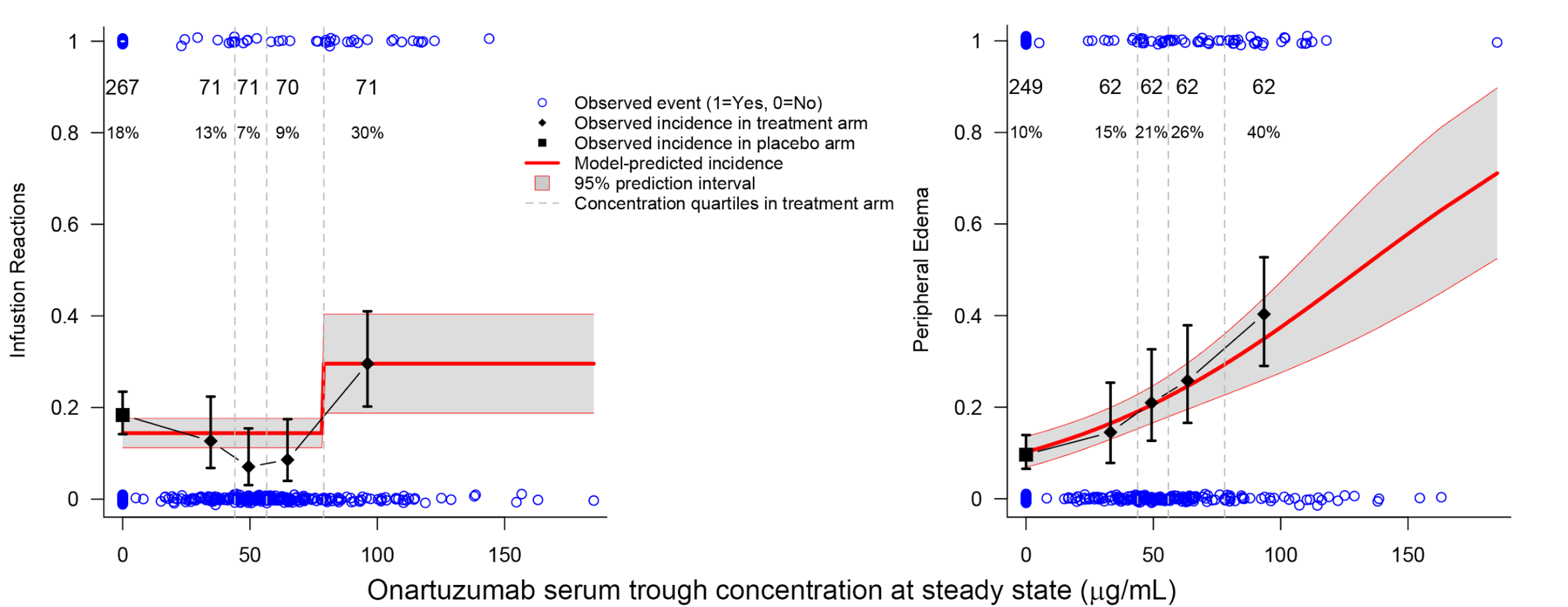


Table 2. Parameter estimates of final models for efficacy endpoints in MET-positive patients

Parameter	Estimate	RSE	z	p value
<i>Final OS model ^a</i>				
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
<i>Final TTG Model ^b</i>				
EGFR mutation positive	-0.802	16.9	-5.91	<0.0001
Baseline albumin (g/L)	-0.0287	35.9	-2.78	0.0054

- Higher ONT exposure is associated with increased incidence of infusion reactions and peripheral edema. However, the clinical significance of this exposure-safety relationship has not been determined.

Figure 3. Exposure-safety relationship for infusion reactions and peripheral edema.



CONCLUSIONS

- Higher ONT exposure is not significantly associated with improved OS after adjusting for Px factor and TTG, but there was a trend of unknown clinical significance toward increased incidence of infusion reactions and peripheral edema.
- These results do not support testing a higher ONT dose in this population.

REFERENCES

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