SUPPLEMENTARY MATERIALS

Exposure-response analysis of overall survival for tremelimumab in unresectable malignant mesothelioma: the confounding effect of disease status

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METHODS

Step 1 - Base population PK model development

The base model consists of the structural model (describing the mean profile within the treated population) and the stochastic model (comprising unexplained inter-individual variability in PK and residual error). Based on prior modeling of tremelimumab (1,2), the chosen base structural PK model was a two-compartment linear model.

When supported by the data, model parameters were described as multivariate log-normal distributions:

$$P_i = P_{avg} \bullet \exp(\eta_{P,i})$$

where P_i is the value of a parameter P for the i^{th} individual, P_{avg} is the population average of the parameter, and $\eta_{P,i}$ is a realization of a normally distributed random variable with a mean of zero and a variance of Ω_P^2 (i.e., $\eta_{P,i} \sim N(0,\Omega_P^2)$).

A proportional error model was used to describe the residual unexplained, random variability:

$$C(t)_{ij} = \hat{C}(t)_{ij} \bullet (1+\varepsilon_{pij})$$

where $C(t)_{ij}$ is the j^{th} observed concentration of individual i; $\hat{C}(t)_{ij}$ is the j^{th} model predicted value (plasma concentration) for individual i; t is the time; and ε_{pij} is a normally distributed residual random error, with mean of 0 and variances of σ^2.

Model selection was based on successful minimization and completion of the covariance step in NONMEM, and diagnostics used included assessment of standard goodness-of-fit plots, reductions in NONMEM objective function value (OFV) for hierarchical models for model selection, and parameter plausibility and imprecision. The method used for estimating the parameters of the mixed-effects model was the first-order conditional estimation with ε and η interaction (FOCE INTER) (3–5).

Step 2: Exposure–Efficacy (OS) Analysis and confounding analysis

AUC_{ss} was the preferred exposure metric as opposed to CL to conduct the exposure-efficacy analysis as it accounts for the higher dose administered in heavier patients than cachexic patients given that tremelimumab was given in a per-Kg basis and the potential confounding role of catabolism of any exposure-response in cancer. A sensitivity analysis was performed by repeating the Kaplan-Meier empirical evaluation split by quartiles of exposure with observed concentration measurements after end of infusion at the first cycle of treatment ($C_{max,1}$), instead of predicted AUC_{ss}.

Step 3: Covariate analysis to confirm potential PK predictors

PK parameter–covariate relationships were first examined graphically and correlation between covariates was investigated. Only covariates that showed a trend by graphical exploration were then evaluated within the nonlinear mixed-effects modelling framework to quantify their potential impact on tremelimumab PK. This way, statistical tests of covariate-parameter relationships suggested by the graphical analysis were assessed with the likelihood ratio test (LRT). The LRT is based on the property that the difference of the NONMEM objective function values (OFV) of two hierarchical models (-2 log-likelihood) is asymptotically χ^2 distributed. Covariate effects found statistically significant ($p<0.05$) were then evaluated for clinical relevance, defined *a priori* as a change of 30% in PK parameter compared to a typical patient at the extremes of the distribution for a continuous covariate (taken as the 10^{th} and 90^{th} percentiles) or at each subcategory of interest for a categorical covariate.

SUPPLEMENTARY REFERENCES

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