Clinical trial simulations based on a meta-analysis of studies in patients with locally advanced and/or metastatic adenocarcinoma pancreatic cancer receiving gemcitabine (GEM) alone or in combination.

Dana Nickens1, Meg Bennetts2, Holger Thurm3, Carla Hernandez4, Sima Ahadieh5, Michael Amantea1

Pharmacometrics, Pfizer, 1La Jolla, USA; 2Sandwich, UK; 3Groton, USA; 4Global Clinical Lead, Oncology; 4Information & Library Sciences, Pfizer, La Jolla, USA;

Objectives: To develop a model to: (1) describe median overall survival (mOS) in trials with locally advanced and/or metastatic adenocarcinoma pancreatic cancer treated with GEM alone and in combination; (2) to simulate predictive distributions based on Von Hoff 20131 and assess the probability of the results in a future study; and 3) to compare predictions based on mOS and overall survival hazard ratios (OS-HR).

Methods: A systematic review of randomized clinical trials with GEM alone or in combination was conducted. A linear mixed-effects model was fit to log-transformed mOS data, with an intercept reflecting GEM treatment alone, a between-trial random effect (ηi ~ N(0, τ2)) and residual error term (εij ~ N(0, σ2/Nij), i = study, j = treatment arm). Potential confounding or prognostic factors were tested as covariates. Drug-class combinations were simulated to produce model-based prediction distributions. The R® software was used.

Results: Data consisted of 83 arms (40 studies;4813 patients) and first-line treatment across 21 drug-classes. The final model (abbreviated) is shown below: \( \text{LN(mOS}_{ij}) = \text{intercept} + \theta_1 \cdot \text{platinum}_{ij} + \theta_2 \cdot \text{taxane}_{ij} + \theta_3 \cdot \text{igf1r.inhibitor}_{ij} + \ldots + \theta_n \cdot \text{immunomodulator}_{ij} + \text{asian.study}_{i} + \eta_i + \epsilon_{ij} \) where drug-class and asian.study are indicators (0 or 1). Estimated mOS values for each drug class are shown below:

Simulations showed that the model predicts the Von Hoff study well and results related to drug classes for mOS and OS-HR were comparable.

Conclusions: This meta-analysis is useful: (1) as a repository for data exploration of current randomized trials; (2) in characterizing typical endpoints for designing randomized clinical trials; (3) to guide a default product profile for pancreatic cancer therapies and; (4) for informing decisions during the drug development process.