Figure S1. Visual predictive check of A.MARTIN phase II study ipatasertib concentration by doses. Black circles are observed concentrations. Solid red line represents the median observed concentration, and pink shaded area represents the 95% CI for the median predicted concentration. The observed 2.5[th] and 97.5[th] percentile concentrations are presented with dashed red lines, and the 95% CIs for the corresponding predicted percentiles are shown as purple shaded areas. CI, confidence intervals.
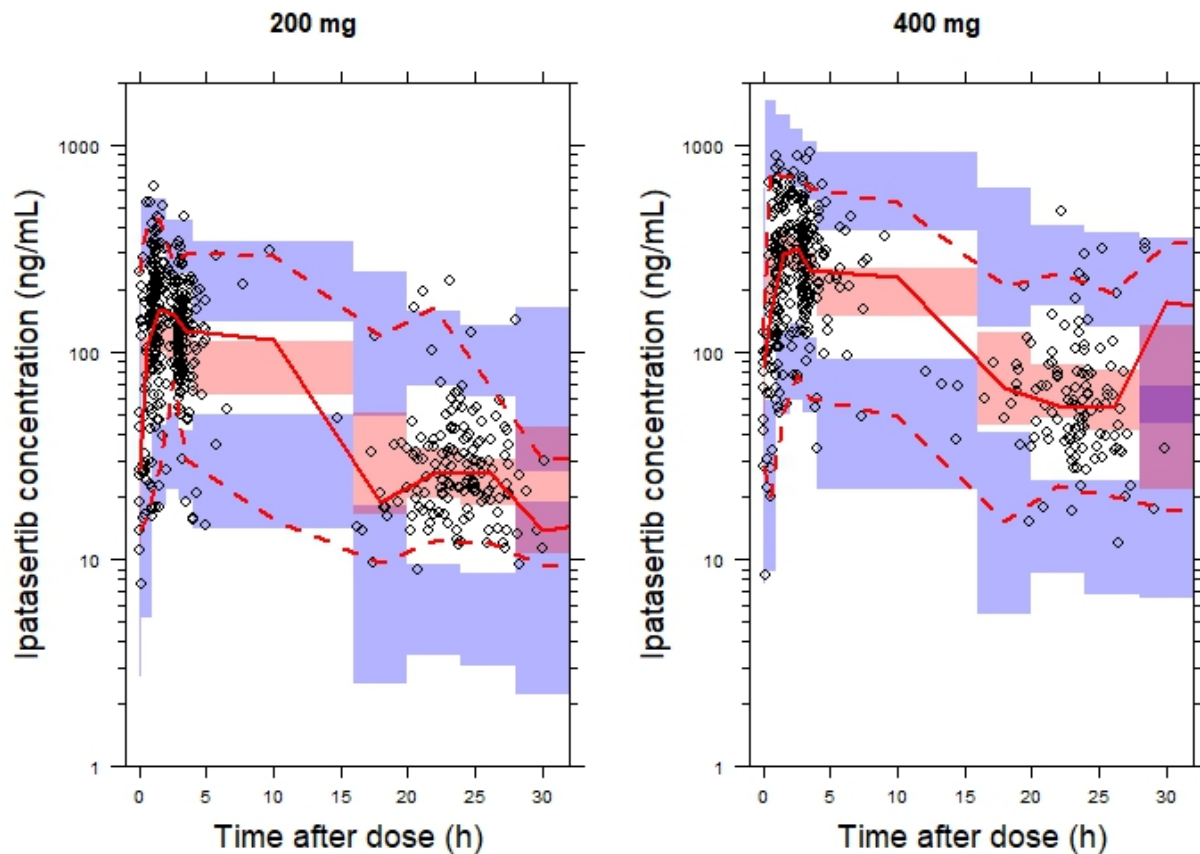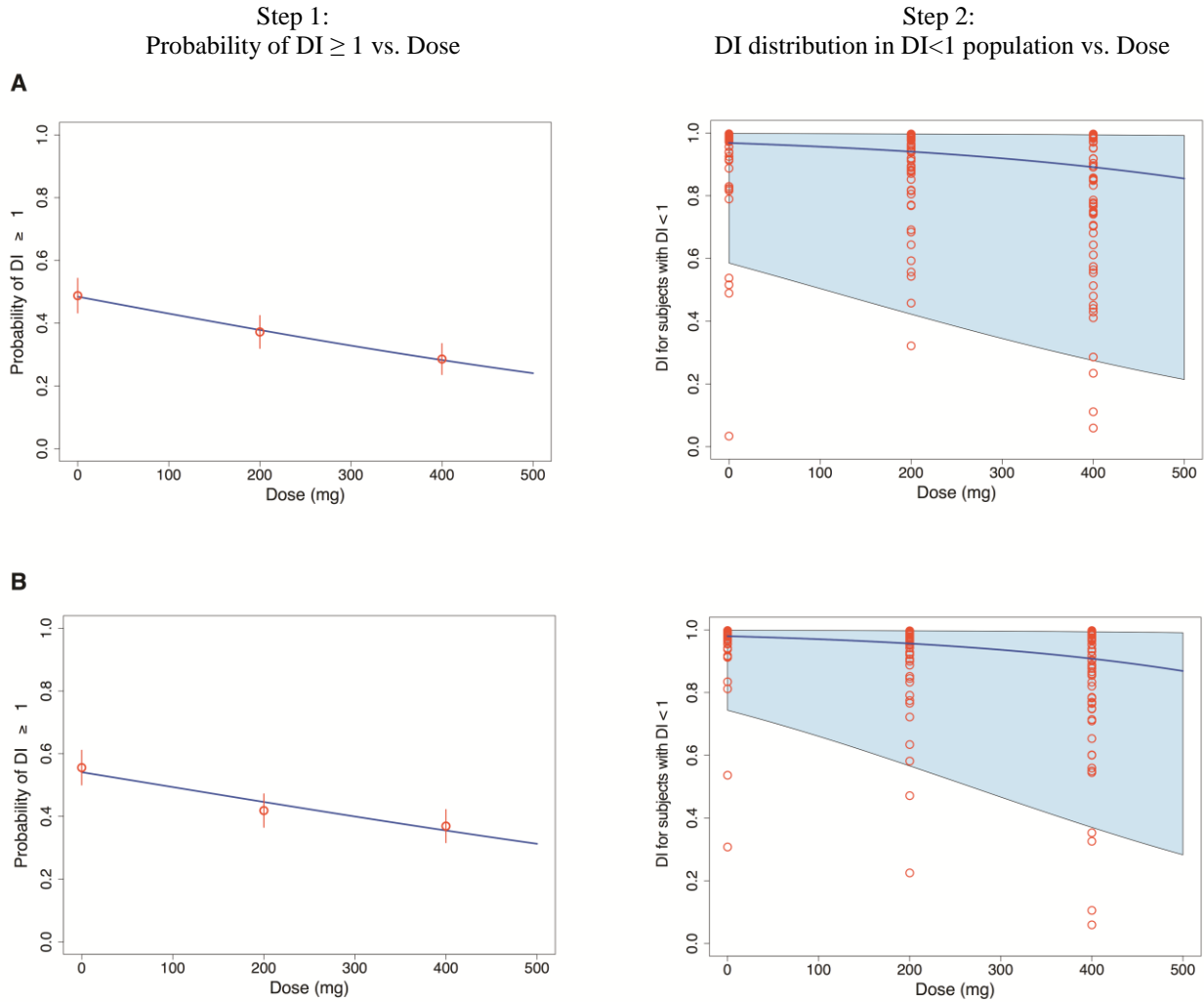
Figure S2. DI modeling results for rPFS (panel A), grade ≥ 2 diarrhea (panel B), grade ≥ 3 diarrhea (panel C), grade ≥ 2 rash (panel D), and grade ≥ 3 rash (panel E). Left panel plots show the probability of DI $\geqslant 1$ vs. dose, and right panel plots show the DI distribution in DI<1 population vs. dose. For left panel plots, red symbols and error bars are the observed mean and 90% CI, and blue line is the predicted regression line; For right panel plots, red symbols are the individual observations, and blue curves and shared bands are the predicted mean and 90% CI band. CI, confidence interval; DI, dose intensity; rPFS, radiographic progression-free survival.
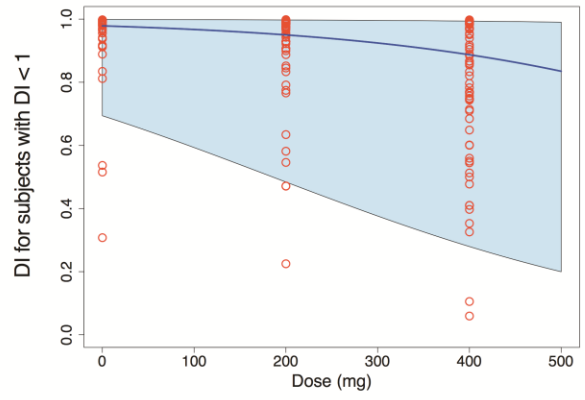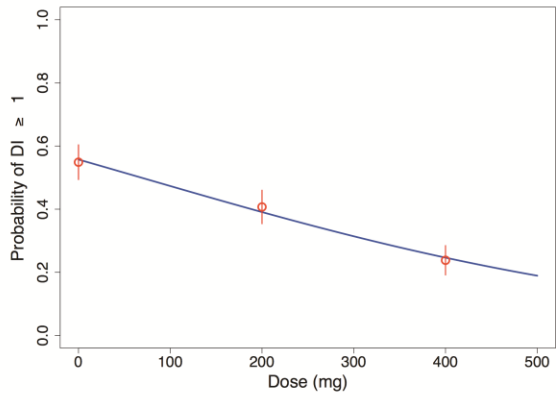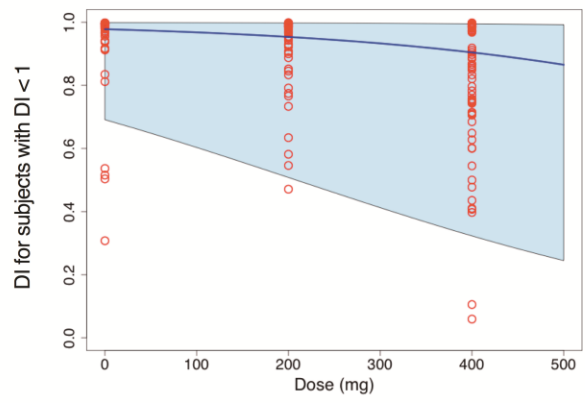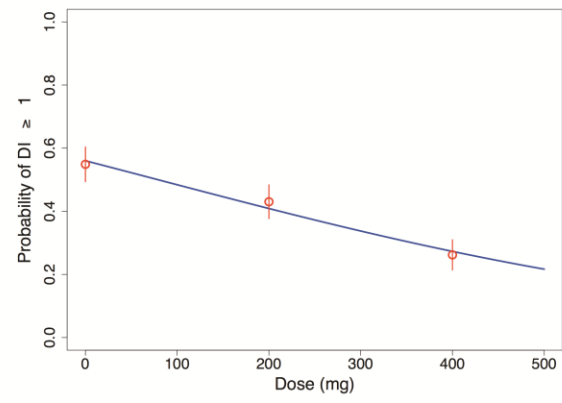

Step 1:
Probability of DI ≥ 1 vs. Dose

Step 2:
DI distribution in DI<1 population vs. Dose

C

Left panel: Probability of DI ≥ 1 vs Dose (mg)
Right panel: DI for subjects with DI < 1 vs Dose (mg)

D

Left panel: Probability of DI ≥ 1 vs Dose (mg)
Right panel: DI for subjects with DI < 1 vs Dose (mg)

E

Left panel: Probability of DI ≥ 1 vs Dose (mg)
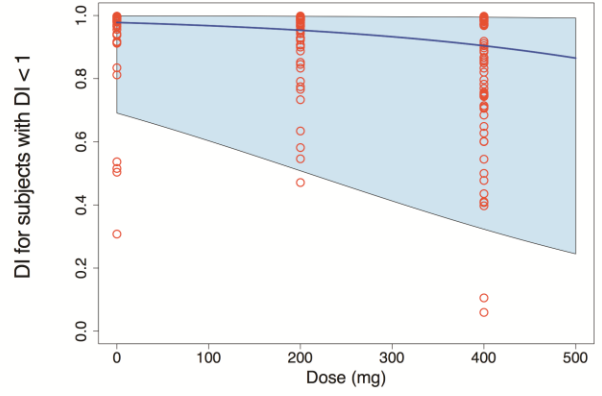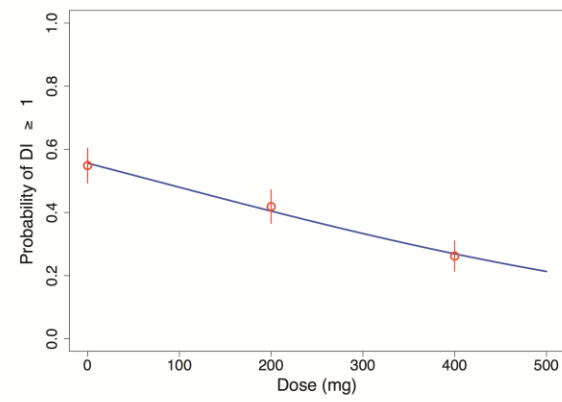Right panel: DI for subjects with DI < 1 vs Dose (mg)

Figure S3. Exposure-AE logistic regression modeling results for grade ≥ 2 diarrhea (panel A), grade ≥ 3 diarrhea (panel B), grade ≥ 2 rash (panel C), and grade ≥ 3 rash (panel D). Symbols and error bars represent mean observations and associated 95% CI of the mean, respectively, for placebo patients (triangle) and for treated patients stratified by quartiles of ipatasertib exposure $AUC_{ss,event}$ (circles). Gray curves and associated shaded area represent the mean model predictions and associated 95% CI of the prediction, respectively. AEs, adverse events; CI, confidence interval.
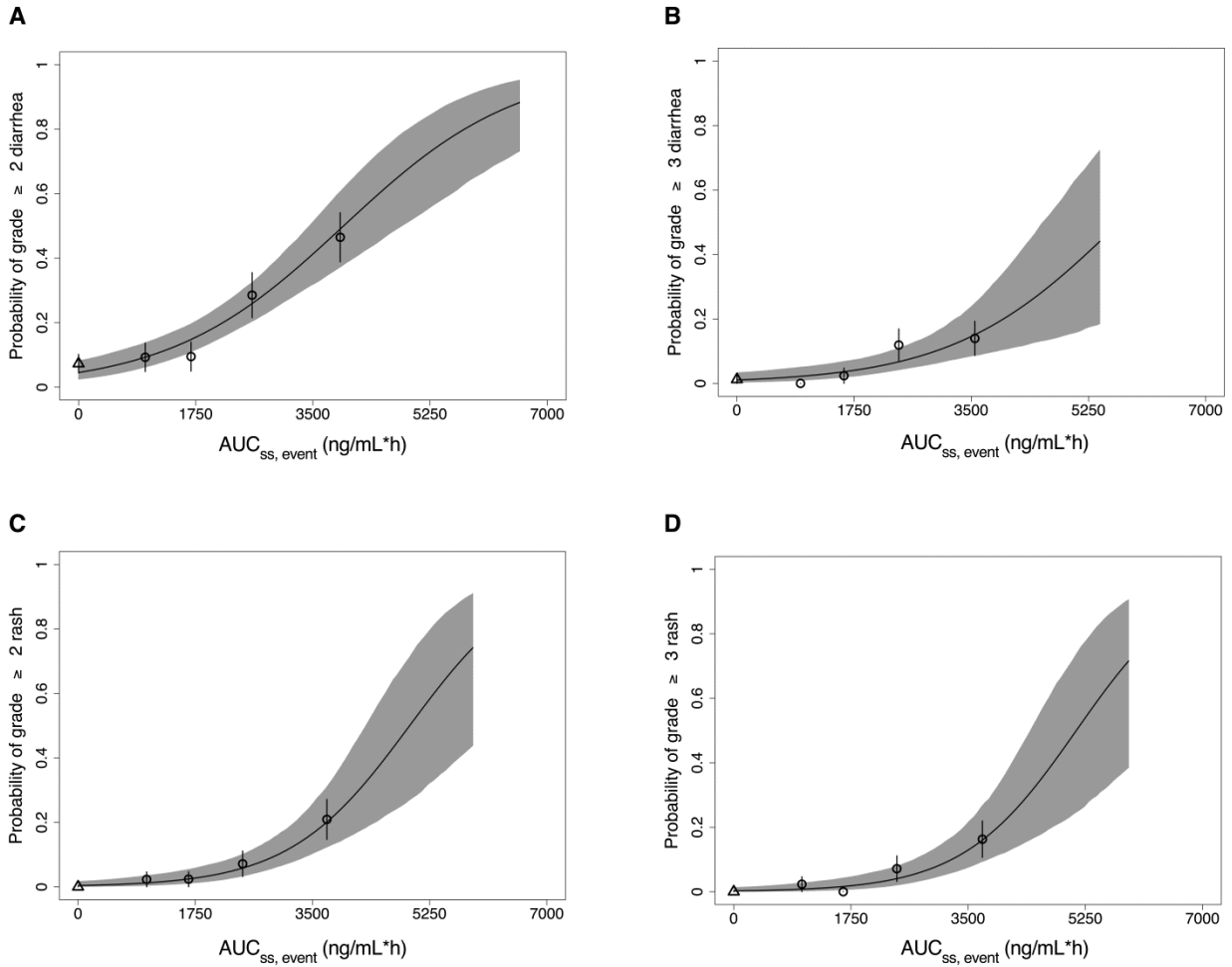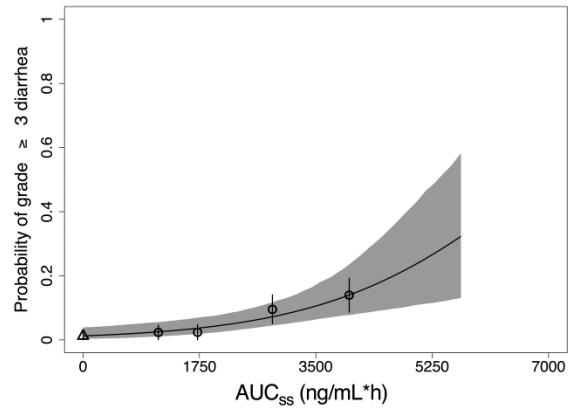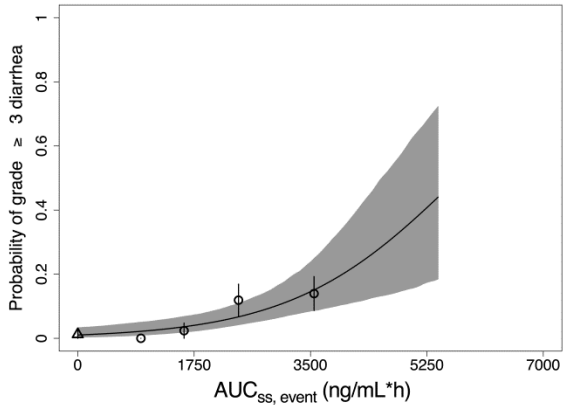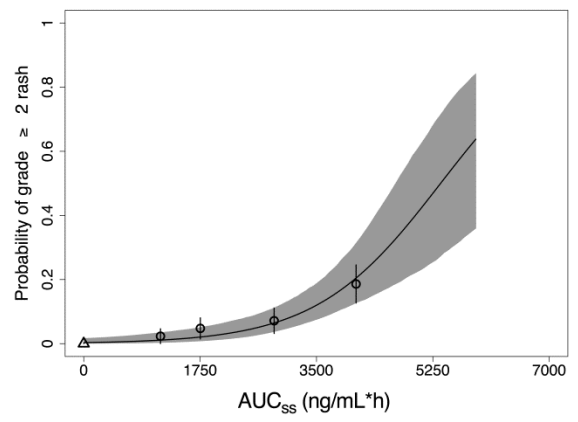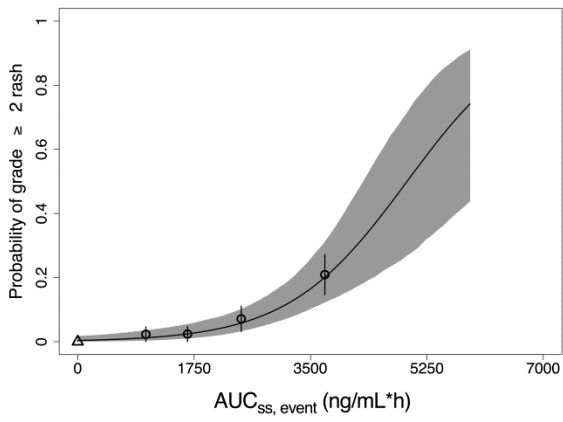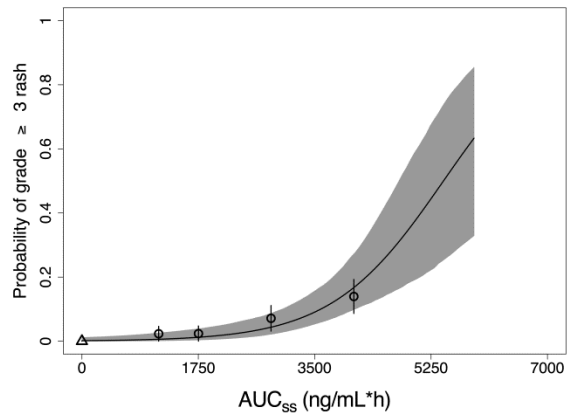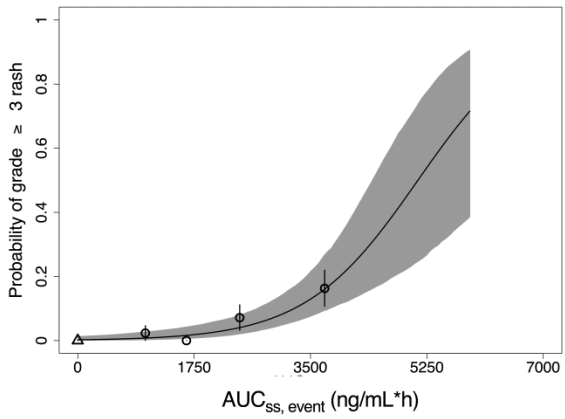
Figure S4. Comparision between E-R modeling with (AUC$_{ss,event}$ as exposure metric, left panels) and without (AUC$_{ss}$ as exposure metric, right panels) considering dose modification. Panels A, B, and C are the logistic regression modeling results, and panels D, E, F, and G are the dose-response projection results. Projections in left panel plots were from the E-R models (AUC$_{ss,event}$ as exposure metric) coupled with their corresponding DI models, while projections in right panel plots were from the E-R models (AUC$_{ss}$ as exposure metric) alone. In panels A, B, and C, symbols and error bars represent mean observation and associated 95% CI of the mean, respectively, for placebo patients (triangle) and for treated patients stratified by quartiles of ipatasertib exposure AUC$_{ss,event}$ (circles). Curves and associated shaded area represent the mean model predictions and associated 95% CI of the mean prediction, respectively. In panels D, E, F, and G, black squares and error bars are the observed median and 90% CI. Gray curves and shaded area are the model-predicted median and 90% CI. AEs, adverse events; AUC, area under the curve; CI, confidence interval; DI, dose intensity; E-R, exposure-response; HR, hazard ratio; rPFS, radiographic progression-free survival.
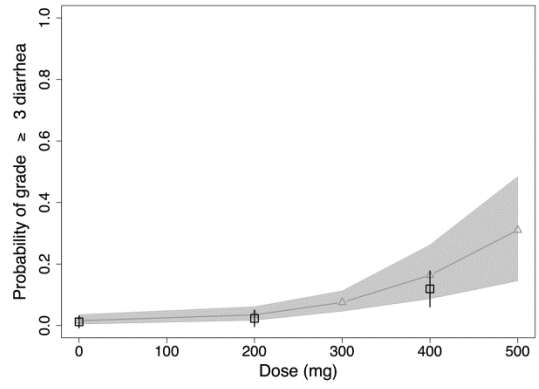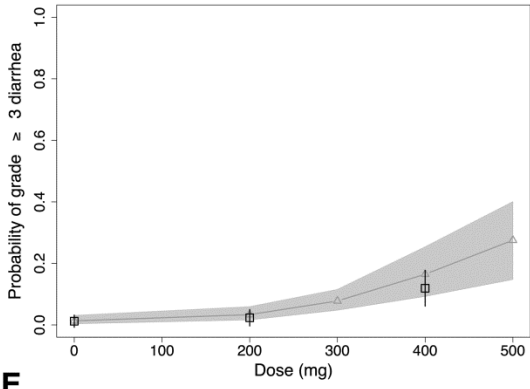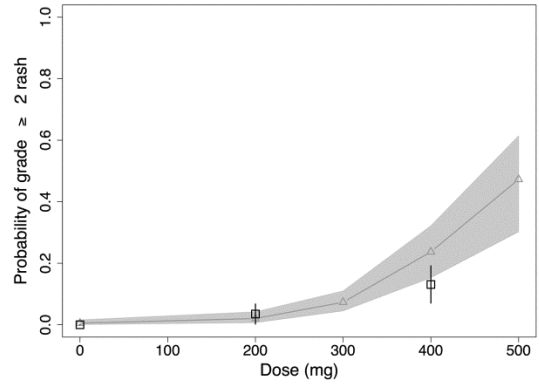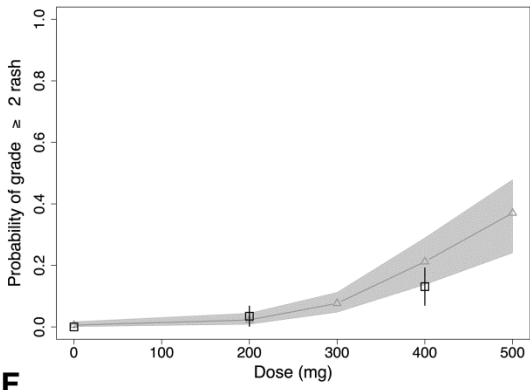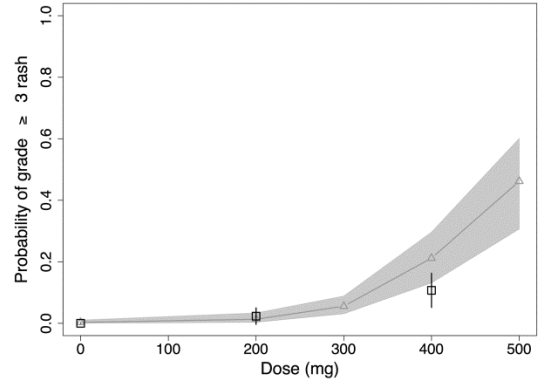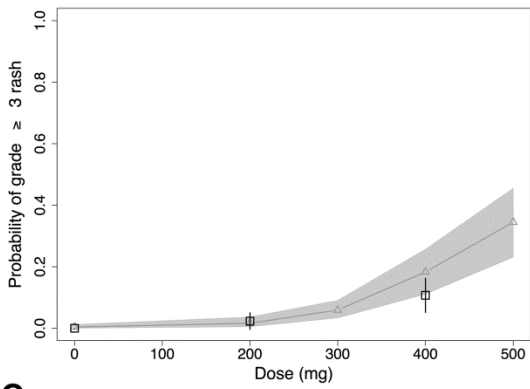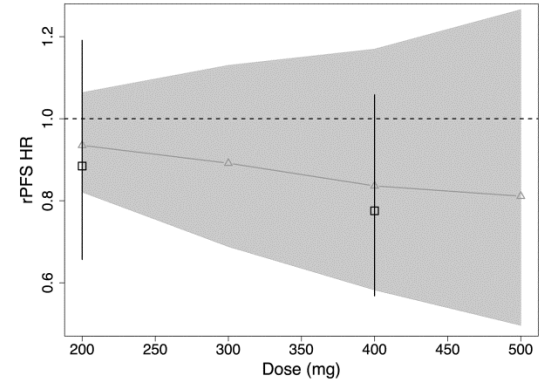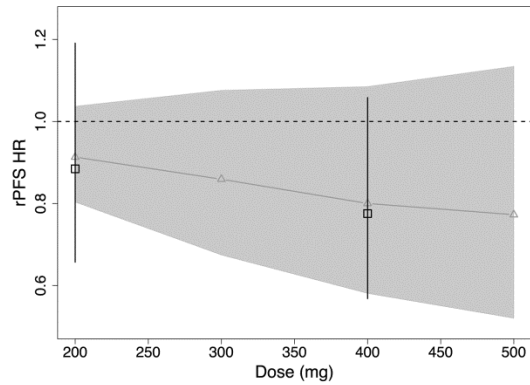
A

B

C

D

E

F

G

Figure S5. CUI distribution and probabilities of reaching product profiles vs. dose for scenario #1 (panel A), scenario #3 (panel B), and scenario #4 (panel C). CUI, clinical utility index; PP, product profiles.