## SUPPLEMENTARY MATERIAL

### Final NONMEM code

```
$SUBROUTINE ADVAN5 TRANS1
$MODEL     COMP=(PARENT,DEFDOSE,DEFOBS) COMP=(MET1) COMP=(PERIP)
        COMP=(TRANSIT1)
$PK
;;; VCPSEX-DEFINITION START
IF(SEX.EQ.0.0000E+00) VCPSEX = 1  ; Most common
IF(SEX.EQ.1.0000E+00) VCPSEX = ( 1 + THETA(22))
;;; VCPSEX-DEFINITION END


;;; VCPMFG-DEFINITION START
IF(MFG.EQ.1.0000E+00) VCPMFG = 1  ; Most common
IF(MFG.EQ.0.0000E+00) VCPMFG = ( 1 + THETA(21))
;;; VCPMFG-DEFINITION END


;;; VCPBSA-DEFINITION START
  VCPBSA = ((BSA/1.71)**THETA(20))
;;; VCPBSA-DEFINITION END

;;; VCP-RELATION START
VCPCOV=VCPBSA*VCPMFG*VCPSEX
;;; VCP-RELATION END


;;; FR2MFG-DEFINITION START
IF(MFG.EQ.1.0000E+00) FR2MFG = 1  ; Most common
IF(MFG.EQ.0.0000E+00) FR2MFG = ( 1 + THETA(19))
;;; FR2MFG-DEFINITION END

;;; FR2-RELATION START
FR2COV=FR2MFG
;;; FR2-RELATION END


;;; CLPTRTOXA-DEFINITION START
IF(TRTOXA.EQ.0.0000E+00) CLPTRTOXA = 1  ; Most common
IF(TRTOXA.EQ.1.0000E+00) CLPTRTOXA = ( 1 + THETA(18))
;;; CLPTRTOXA-DEFINITION END


;;; CLPSEX-DEFINITION START
IF(SEX.EQ.0.0000E+00) CLPSEX = 1  ; Most common
IF(SEX.EQ.1.0000E+00) CLPSEX = ( 1 + THETA(17))
;;; CLPSEX-DEFINITION END


;;; CLPMFG-DEFINITION START
```

```
IF(MFG.EQ.1.0000E+00) CLPMFG = 1  ; Most common
IF(MFG.EQ.0.0000E+00) CLPMFG = ( 1 + THETA(16))
;;; CLPMFG-DEFINITION END


;;; CLPASIAN-DEFINITION START
IF(ASIAN.EQ.0.0000E+00) CLPASIAN = 1  ; Most common
IF(ASIAN.EQ.1.0000E+00) CLPASIAN = ( 1 + THETA(15))
;;; CLPASIAN-DEFINITION END

;;; CLP-RELATION START
CLPCOV=CLPASIAN*CLPMFG*CLPSEX*CLPTRTOXA
;;; CLP-RELATION END


;;; CLMTRTOXA-DEFINITION START
IF(TRTOXA.EQ.0.0000E+00) CLMTRTOXA = 1  ; Most common
IF(TRTOXA.EQ.1.0000E+00) CLMTRTOXA = ( 1 + THETA(14))
;;; CLMTRTOXA-DEFINITION END


;;; CLMSEX-DEFINITION START
IF(SEX.EQ.0.0000E+00) CLMSEX = 1  ; Most common
IF(SEX.EQ.1.0000E+00) CLMSEX = ( 1 + THETA(13))
;;; CLMSEX-DEFINITION END


;;; CLMCRCL-DEFINITION START
IF(CRCL.EQ.-99) THEN
  CLMCRCL = 1
ELSE
  CLMCRCL = ((CRCL/85.04)**THETA(12))
ENDIF
;;; CLMCRCL-DEFINITION END


;;; CLMBIL-DEFINITION START
IF(BIL.EQ.-99) THEN
  CLMBIL = 1
ELSE
  CLMBIL = ((BIL/0.41)**THETA(11))
ENDIF
;;; CLMBIL-DEFINITION END

;;; CLM-RELATION START
CLMCOV=CLMBIL*CLMCRCL*CLMSEX*CLMTRTOXA
;;; CLM-RELATION END



; PARENT CENTRAL
```

```
TVCLP = THETA(1)

TVCLP = CLPCOV*TVCLP
CLP = TVCLP * EXP(ETA(4)) ; total CL for irinotecan

TVVCP = THETA(2)

TVVCP = VCPCOV*TVVCP
VCP = TVVCP * EXP(ETA(6)) ; central volume for irinotecan
;*****
KT = CLP/VCP  ; total elimination rate for irinotecan

; PARENT PERIPHERAL
TVQP = THETA(3)
QP = TVQP

TVV3P = THETA(4)
V3P = TVV3P
;*****
K13 = QP/VCP ; rate from central to peripheral for irinotecan
K31 = QP/V3P ; rate from peripheral to central for irinotecan

; METABOLITE

TVFR1 = THETA(5)
TVFR2 = THETA(6)

TVFR2 = FR2COV*TVFR2
FR1 = TVFR1 * EXP(ETA(5))
FR2 = TVFR2 * EXP(ETA(3))
FM1 = FR1 / (1+FR1+FR2) ; fraction of parent metabolized via 1st order process
FM2 = FR2 / (1+FR1+FR2) ; fraction of parent metabolized via transit
;*****
K12 = FM1*KT ; fraction of total CL to SN-38 (1st order)
K14 = FM2*KT ; fraction of total CL to SN-38 (transit)
K10 = (1-FM1-FM2)*KT ; fraction of total CL not transformed to SN-38

TVKFM = THETA(7)
KFM = TVKFM * EXP(ETA(2)) ; rate of transformation out of transit
;*****
K42 = KFM

TVCLM = THETA(8)

TVCLM = CLMCOV*TVCLM
CLM = TVCLM * EXP(ETA(1)) ; SN-38 clearance

VCM = VCP ; SN-38 central compartment volume
;*****
K20 = CLM/VCM ; rate of elimination of SN-38
```

```
;Scaling parameters
S1 = VCP
S2 = VCP/1000
S3 = V3P
S4 = 1

;*****************************************************************************
******************************

$ERROR

IPRDP = A(1)/S1
IPRDM = A(2)/S2

DEL = 0.0000001

RHO = THETA(23)
WP = THETA(9)*IPRDP
WM = THETA(10)*IPRDM

IF(CMT.EQ.1) THEN
    ;Parent
    IPRED = IPRDP
    IRES  = DV-IPRED
    ;W     = SQRT((THETA(9)*IPRED)**2 + THETA(10)**2)
    IWRES = IRES/(WP + DEL)
    Y     = IPRED + WP*EPS(1)
ELSE
    ;Metabolite
    IPRED = IPRDM
    IRES  = DV-IPRED
    ;W     = SQRT((THETA(11)*IPRED)**2 + THETA(12)**2)
    IWRES = IRES/(WM + DEL)
    Y     = IPRED + WM*EPS(1)*RHO + WM*EPS(2)*SQRT(1-RHO**2)
ENDIF
```

**Population PK model development, base model**

Inter-individual variability was modeled assuming a log-normal distribution for patient-level random effects:

$$\theta_{in} = \theta_{TV_n} \cdot \exp(\eta_{in})$$
$$\eta_1 \cdots \eta_m \sim MVN(0, \Omega)$$

where $\theta_{TVn}$ is the population typical value for the nth pharmacokinetic (PK) parameter (e.g. elimination clearance) and $\eta_{in}$ is the random inter-individual effect on the nth parameter for patient i. Random effects ($\eta_1 \ldots \eta_m$) were assumed to be normally distributed with zero mean and estimated variance $\omega^2$ included in the OMEGA (Ω) matrix.

Residual unexplained variability was tested as additive, proportional, or combined (additive + proportional) on the dependent variable; the equation below describes the combination of additive and proportional residual variability:

$$Cp_{ij} = \hat{C}p_{ij} \cdot (1 + \varepsilon_{1,ij}) + \epsilon_{2,ij}$$

where $\varepsilon_1$ and $\varepsilon_2$ are normally distributed with zero mean and variance $\sigma_1^2$ and $\sigma_2^2$, respectively, included in the SIGMA (∑) matrix. In this expression, $Cp_{ij}$ is the observation in individual i at sampling time j, $\hat{C}p_{ij}$ is the typical individual prediction at sampling time j, $\varepsilon_{1,ij}$ is a proportional residual error term, and $\varepsilon_{2,ij}$ is an additive residual error term.

**Population PK model development, inclusion of covariates**

Continuous covariates were included in the population PK model as power functions, whereas categorical covariates were implemented as factors:

$$\theta_{TV,i} = \theta_{TV,Pop} \cdot \left(\frac{x_{Cont,i}}{median(x_{Cont,i})}\right)^{\theta_1} \cdot (1 + x_{Cat,i} \cdot \theta_2)$$

where $\theta_{TV,i}$ is the typical parameter for patient i, defined as a function of the population typical value ($\theta_{TV,Pop}$) and the individual contributions from continuous ($x_{Cont}$) and categorical ($x_{Cat}$ , with values 0 and 1) covariates. $\theta_1$ and $\theta_2$ represent the respective covariate coefficients.

**Population PK model development, model evaluation**

Statistical shrinkage of the Empirical Bayes Estimates (EBEs) for all variability components of the model was evaluated, as described previously.[1] The shrinkage magnitude for a structural parameter P (h-shrinkage) was calculated as follows:

$$shp = 1 - \frac{SD(\eta_{EBE,P})}{\omega p}$$

where $SD(\eta_{EBE,P})$ is the standard deviation of the individual EBEs for parameter P and ωp is the model estimate of the standard deviation associated with parameter P. If no shrinkage is present in parameter P, the ratio between $SD(\eta_{EBE,P})$ and ωp is unity and shp becomes zero. Shrinkage values of ≤30% are considered to indicate good individual estimates of a parameter of interest, while larger shrinkage values indicate that the individual Bayesian estimates "shrunk" towards the population mean values.

**Reference**

1. Karlsson, M.O. & Savic, R.M. Diagnosing model diagnostics. *Clin Pharmacol Ther* **82**, 17–20 (2007).

**Figure S1** Dose-normalized total irinotecan (**a**) and SN-38 (**b**) plasma concentration–time profiles by study. Data are presented on a semi-log scale. Clinicaltrials.gov identifiers for the studies shown are: PEP0203, NCT02884128; PEP0206, NCT00813072; PIST-CRC-01, NCT00940758; CITS, NCT01770353; NAPOLI-1, NCT01494506; 1L PDAC, NCT02551991. CPT-11, irinotecan

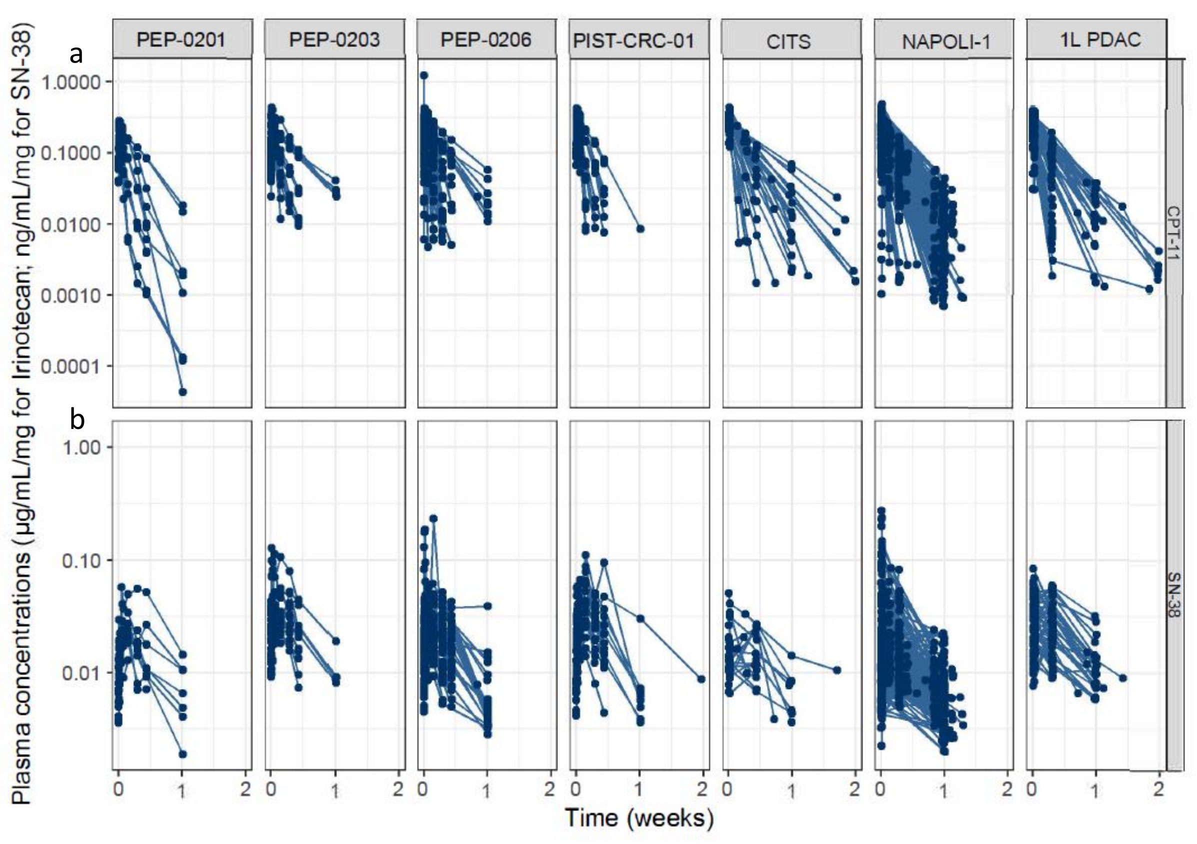


**Figure S2** VPCs for total irinotecan and SN-38 concentrations over time. Raw data are presented on a semi-log scale, split by LLOQ values in the first row and the probability of LOQ in the second row. The observed median (green bold line) and 2.5th and 97.5th observed percentiles (green dashed lines) are compared with the 95% confidence intervals (shaded area) for the median (gray area) and the 2.5th and 97.5th percentiles of the simulated (*n* = 1000) data (blue area) and with the simulated median (red semi-dashed line) and 2.5th and 97.5th simulated percentiles (red dotted line). LLOQ, lower limit of quantification; LOQ, limit of quantification; VPC, visual predictive check

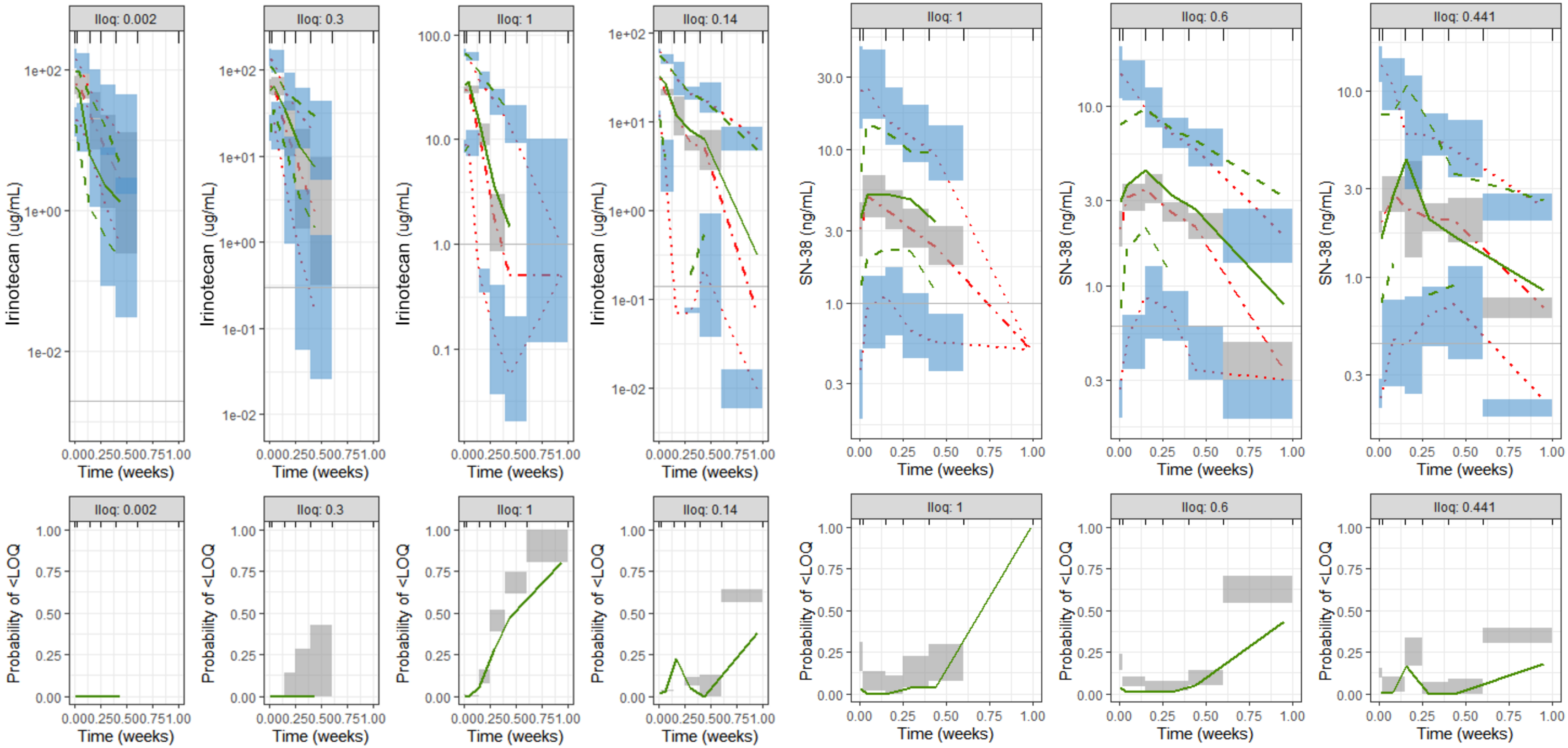


**Figure S3** Goodness-of-fit plots for irinotecan and SN-38, including individual model-predicted concentration versus observed concentration in log scale (**a**), as raw data (**b**), conditional weighted residuals versus population model predictions (**c**), and conditional weighted residuals versus time (**d**), CWRES, conditional weighted residuals; DV, dependent variable; IPRED, individual predicted; PRED, predicted

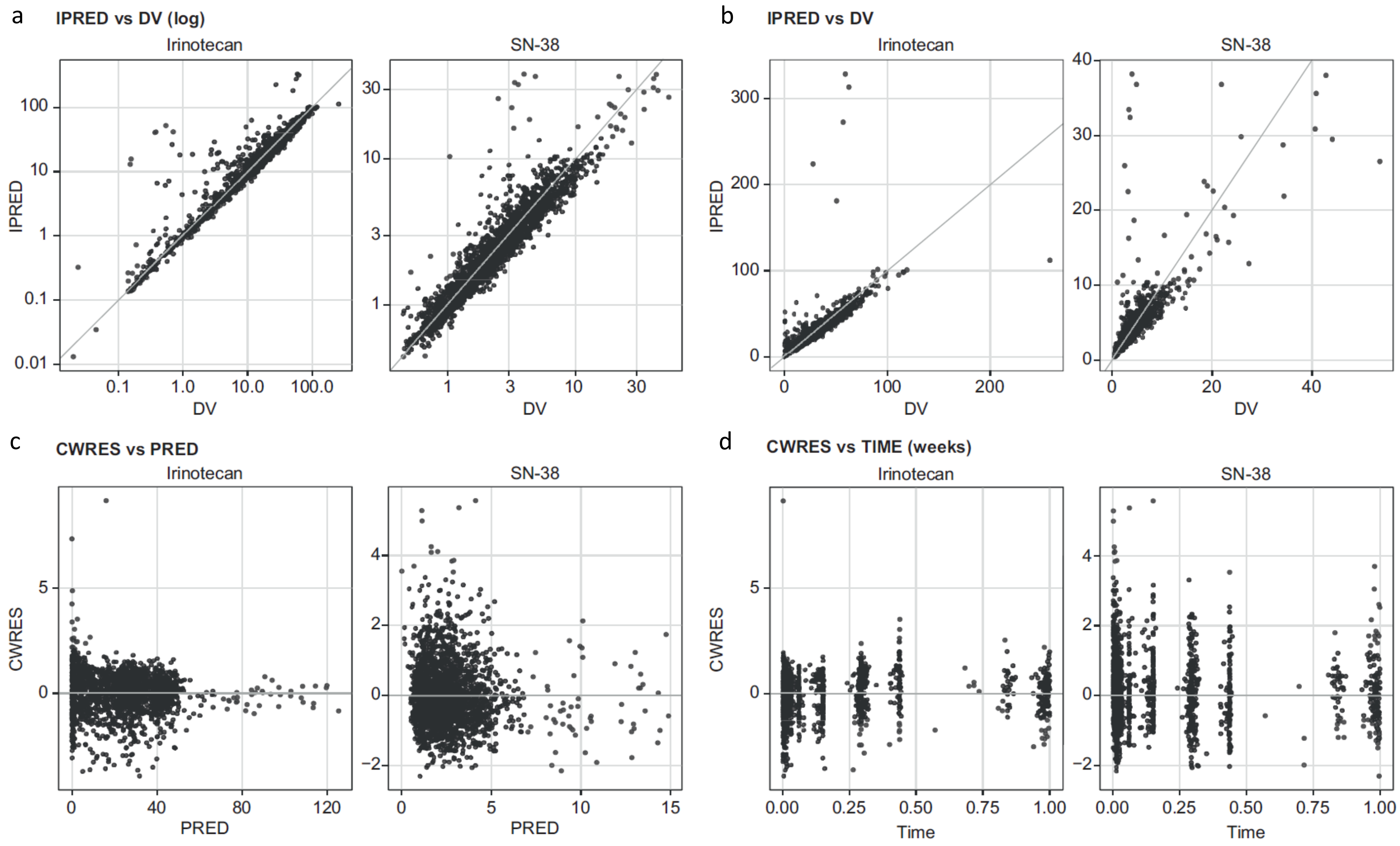


**Figure S4** pcVPCs for total irinotecan (**a**) and SN-38 (**b**) concentrations over time. Raw data are presented. The observed median (green bold line) and 2.5th and 97.5th observed percentiles (green dashed lines) are compared with the 95% confidence intervals (shaded area) for the median (gray area) and the 2.5th and 97.5th percentiles of the simulated (*n* = 1000) data (blue area). Simulated median (red semi-dashed line) and 2.5th and 97.5th simulated percentiles (red dotted line) are overlaid.

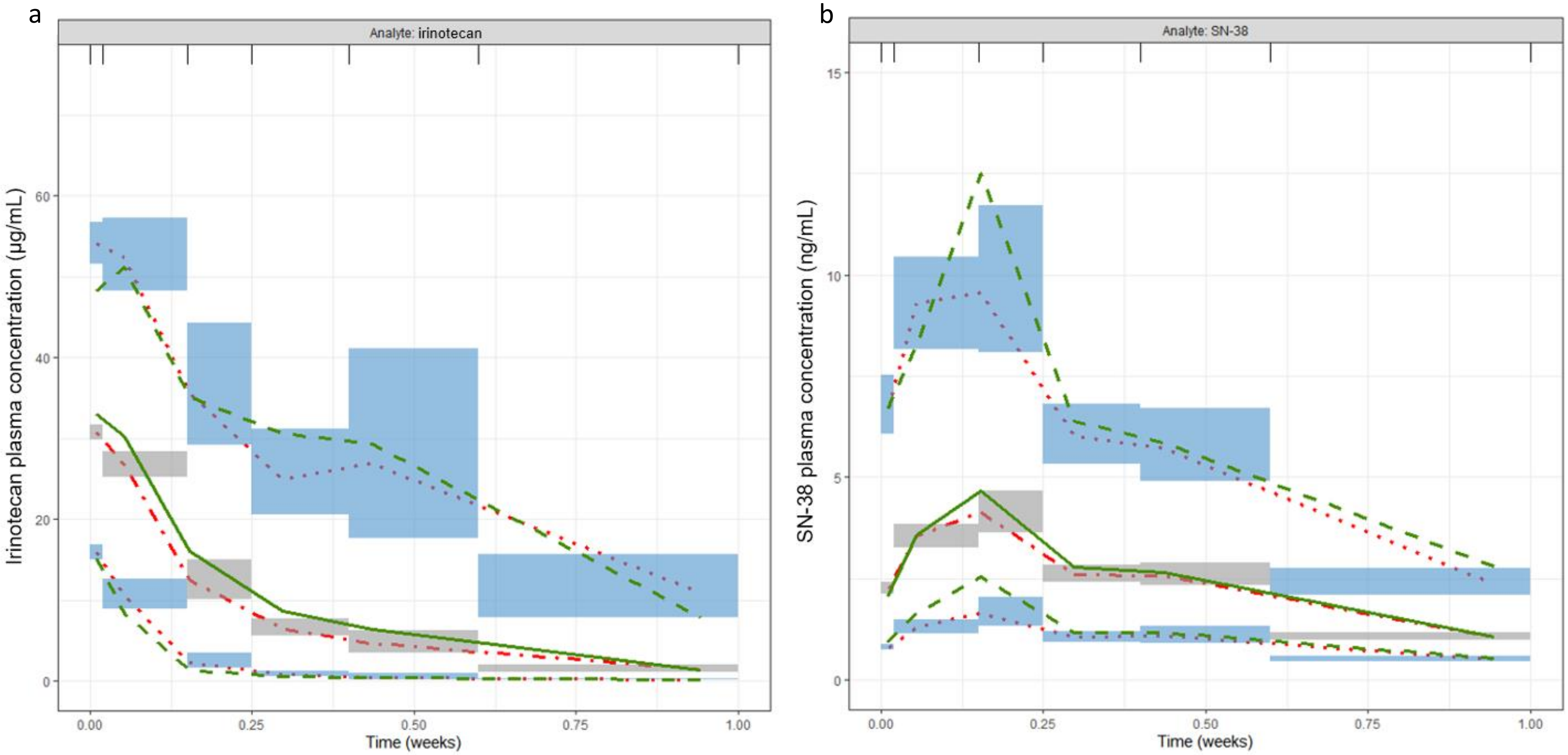
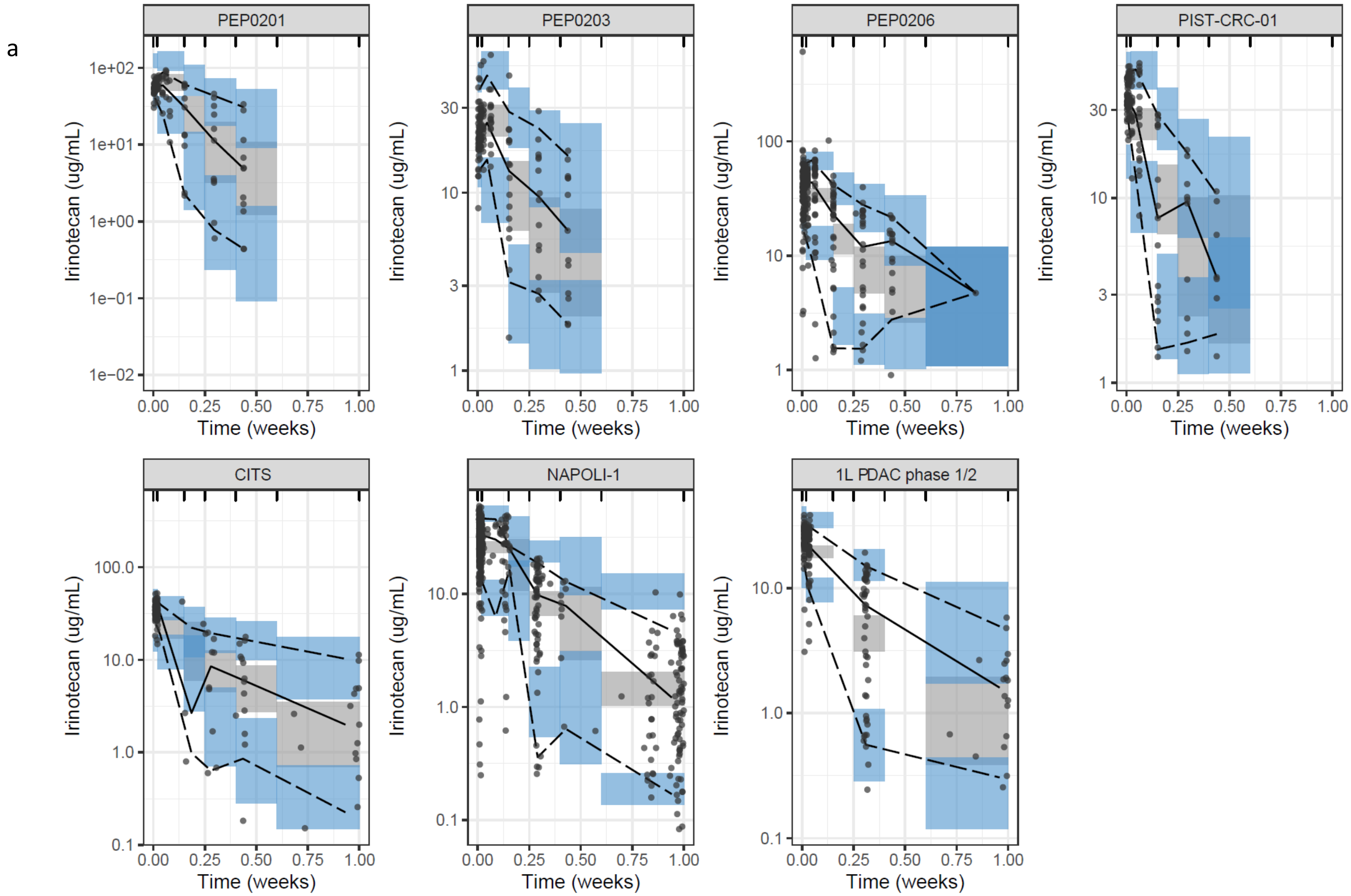


**Figure S5** pcVPCs for total irinotecan (**a**) and SN-38 (**b**) concentrations over time. Raw data are presented by study. The median (bold line) and 2.5th and 97.5th percentiles (dashed lines) are compared with the 95% confidence intervals (shaded area) for the median (gray area) and the 2.5th and 97.5th percentiles of the simulated (*n* = 1000) data (blue area).



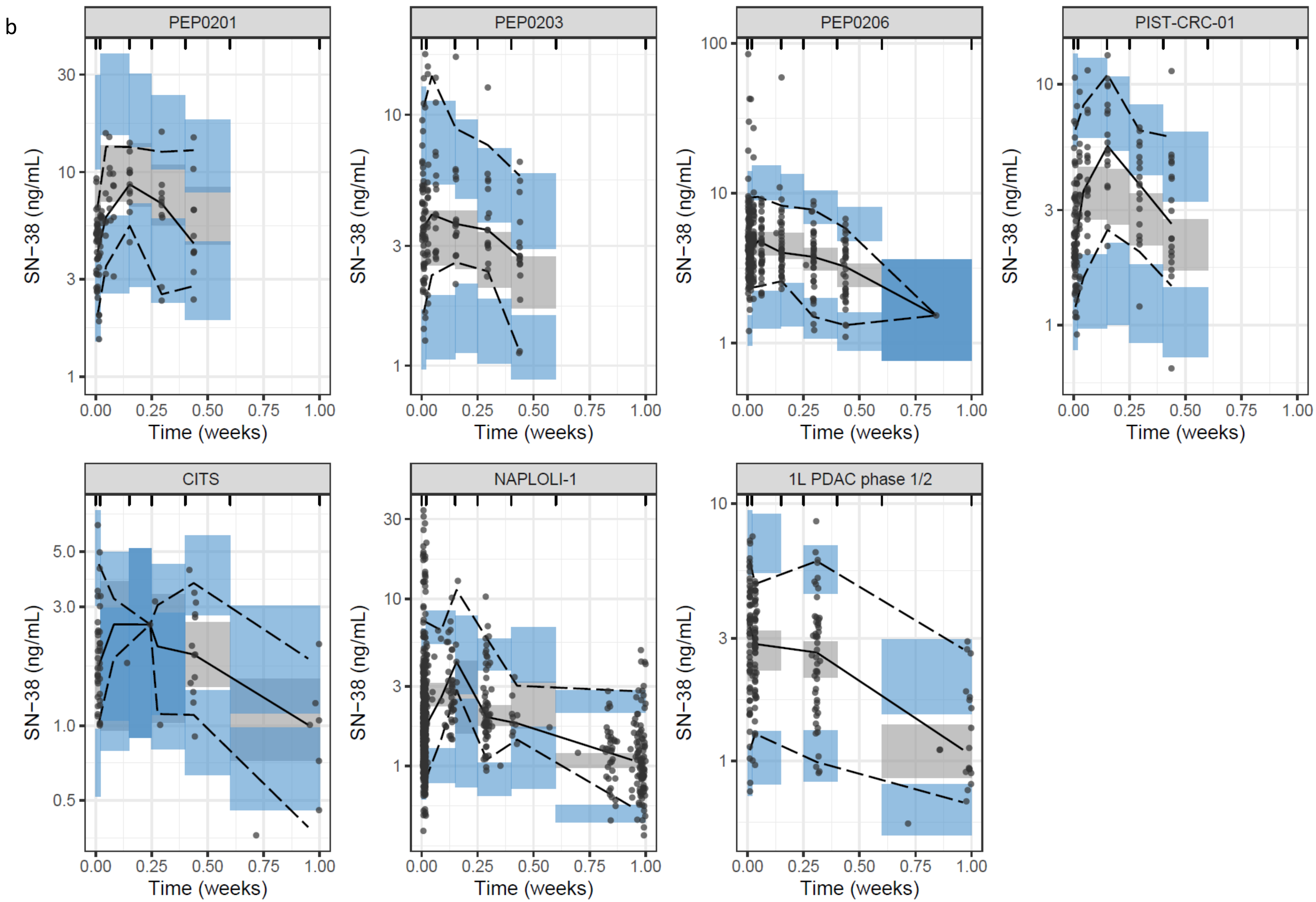

b
PEP0201
PEP0203
PEP0206
PIST-CRC-01
CITS
NAPLOLI-1
1L PDAC phase 1/2
SN−38 (ng/mL)
Time (weeks)
0.00
0.25
0.50
0.75
1.00
100
30
10
5.0
3.0
3
1.0
1
0.5

**Figure S6** Probability of developing grade ≥3 diarrhea as a function of $C_{avg}$ at first event **(left panel)** and $C_{avg,ss}$ for total irinotecan (**right panel**) after administration of liposomal irinotecan. $C_{avg}$, average plasma concentration; $C_{avg,ss}$, average plasma concentration at steady state; CI, confidence interval

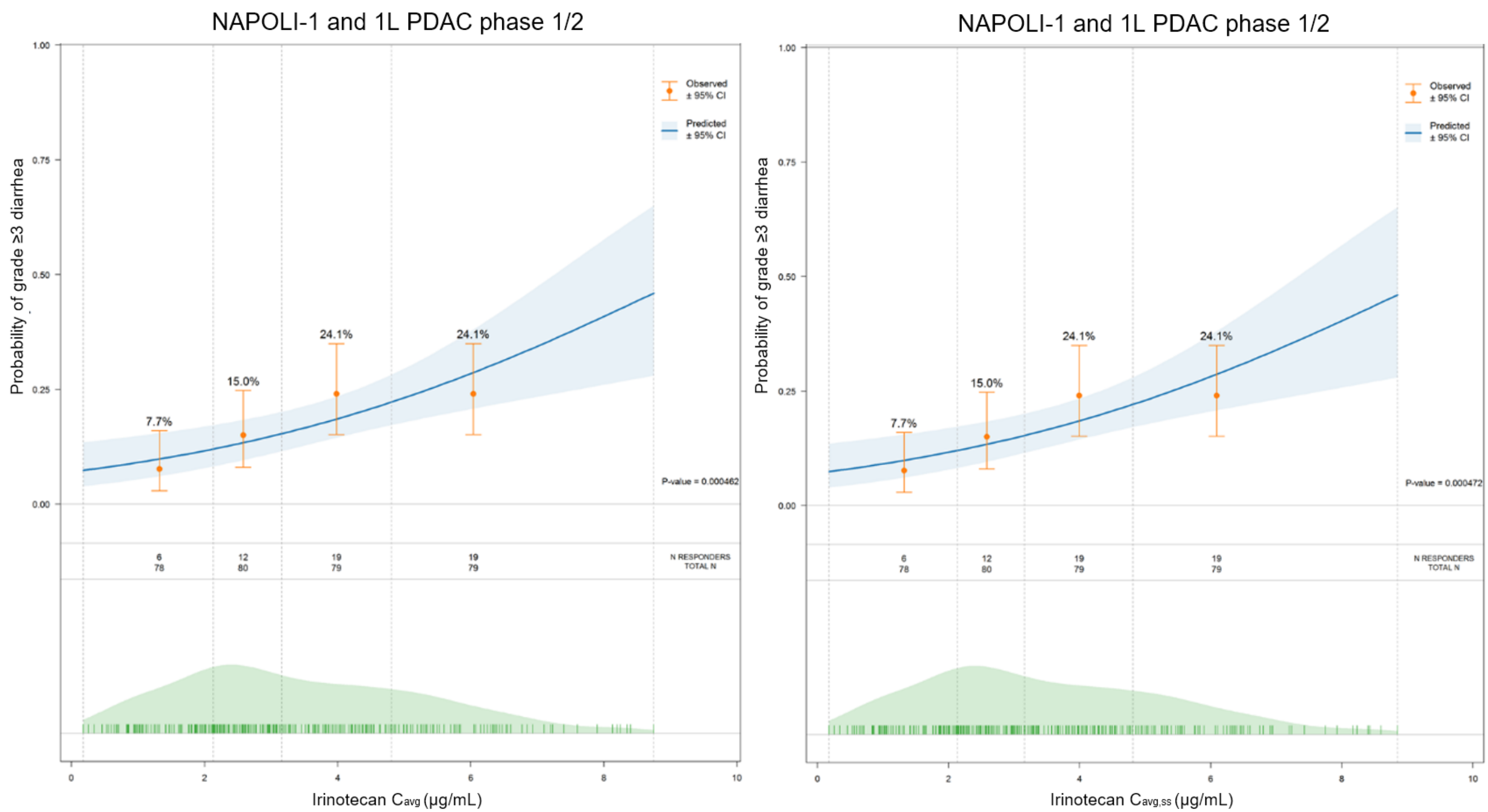


**Figure S7** Probability of developing grade ≥3 diarrhea as a function of $C_{avg}$ at first event **(left panel)** and $C_{avg,ss}$ for SN-38 (**right panel**) after administration of liposomal irinotecan. $C_{avg}$, average plasma concentration; $C_{avg,ss}$, average plasma concentration at steady state; CI, confidence interval

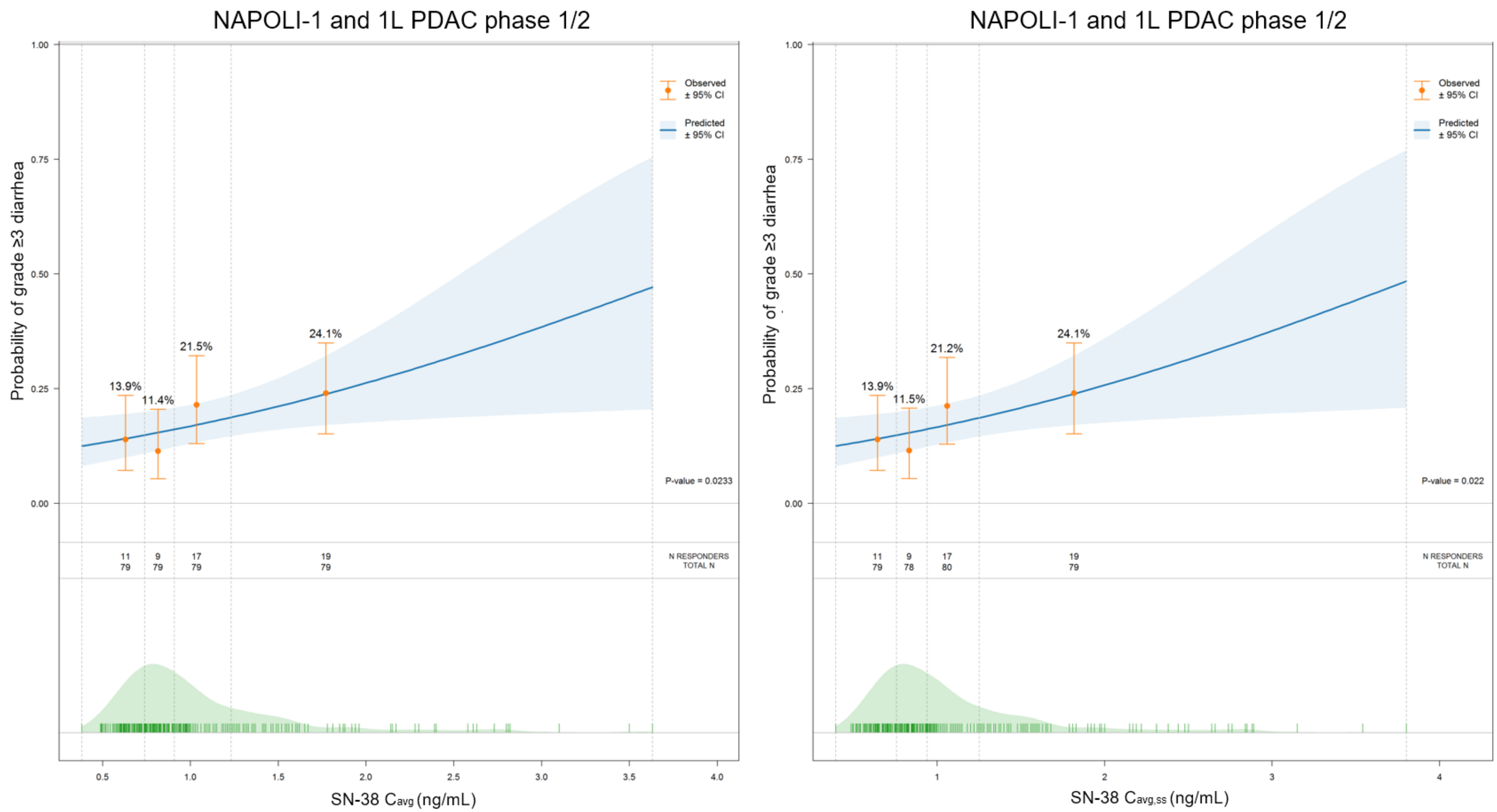


**Figure S8** Probability of developing grade ≥3 diarrhea as a function of $C_{avg,ss}$ (**left panel**) and log-transformed $C_{avg,ss}$ for total irinotecan (**right panel**) after administration of liposomal irinotecan. $C_{avg,ss}$, average plasma concentration at steady state; CI, confidence interval

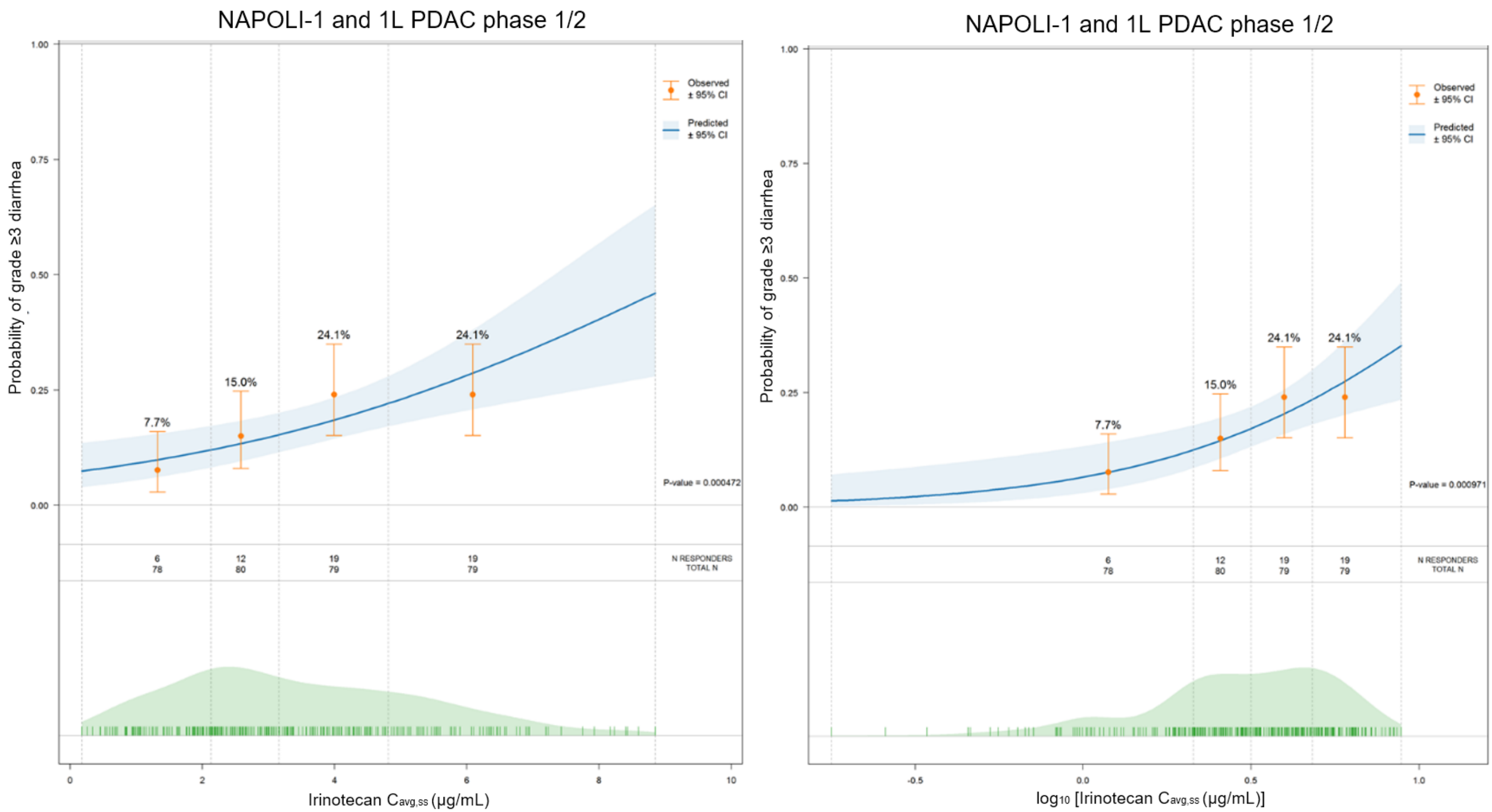


**Figure S9** Probability of developing grade ≥3 diarrhea as a function of $C_{max,ss}$ (**left panel**) and log-transformed $C_{max,ss}$ for total irinotecan (**right panel**) after administration of liposomal irinotecan. $C_{max,ss}$, maximum plasma concentration at steady state; CI, confidence interval

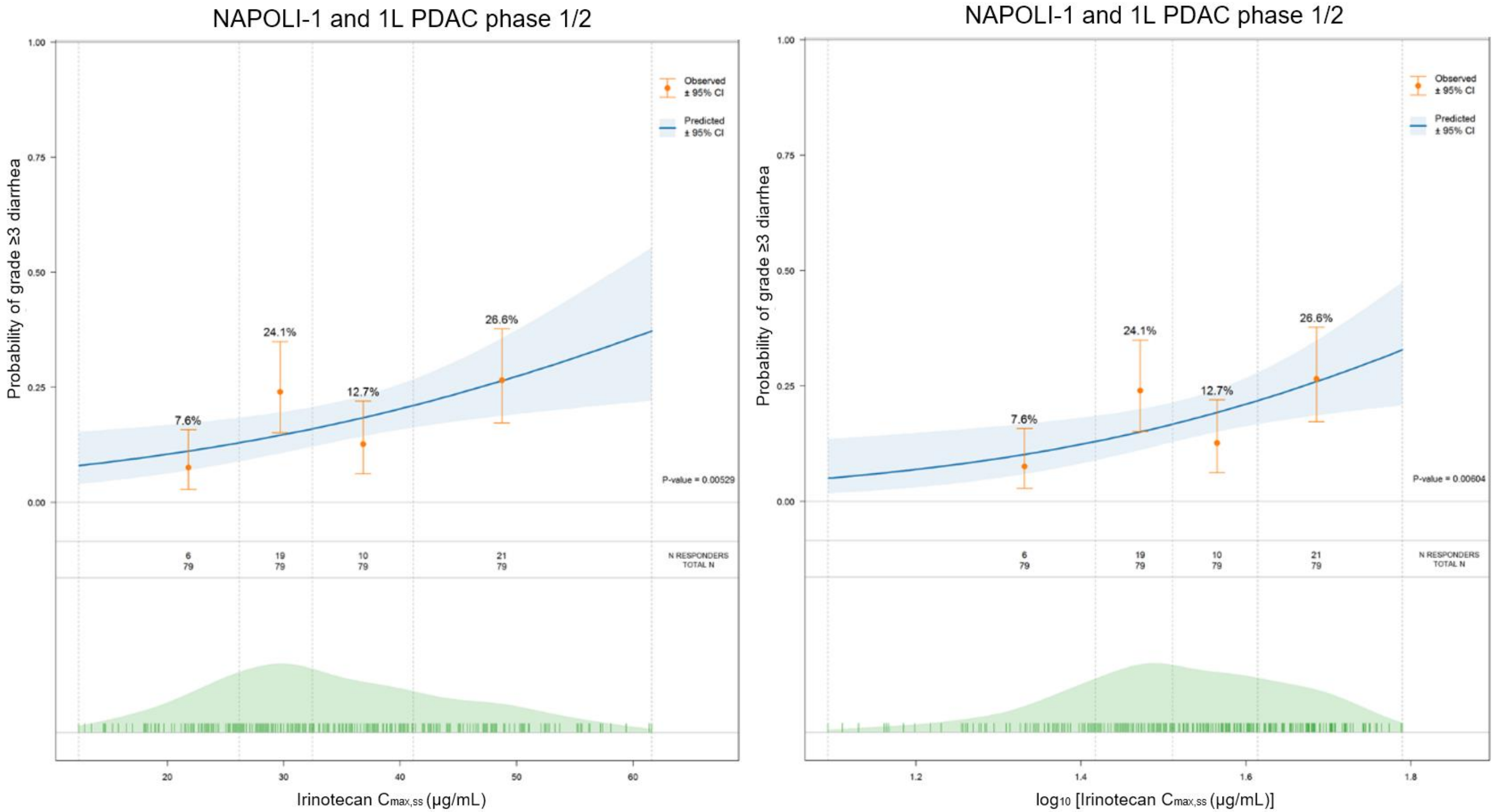


**Figure S10** Probability of developing grade ≥3 diarrhea as a function of $C_{avg,ss}$ (**left panel**) and log-transformed $C_{avg,ss}$ for SN-38 (**right panel**) after administration of liposomal irinotecan. $C_{avg,ss}$, average plasma concentration at steady state; CI, confidence interval

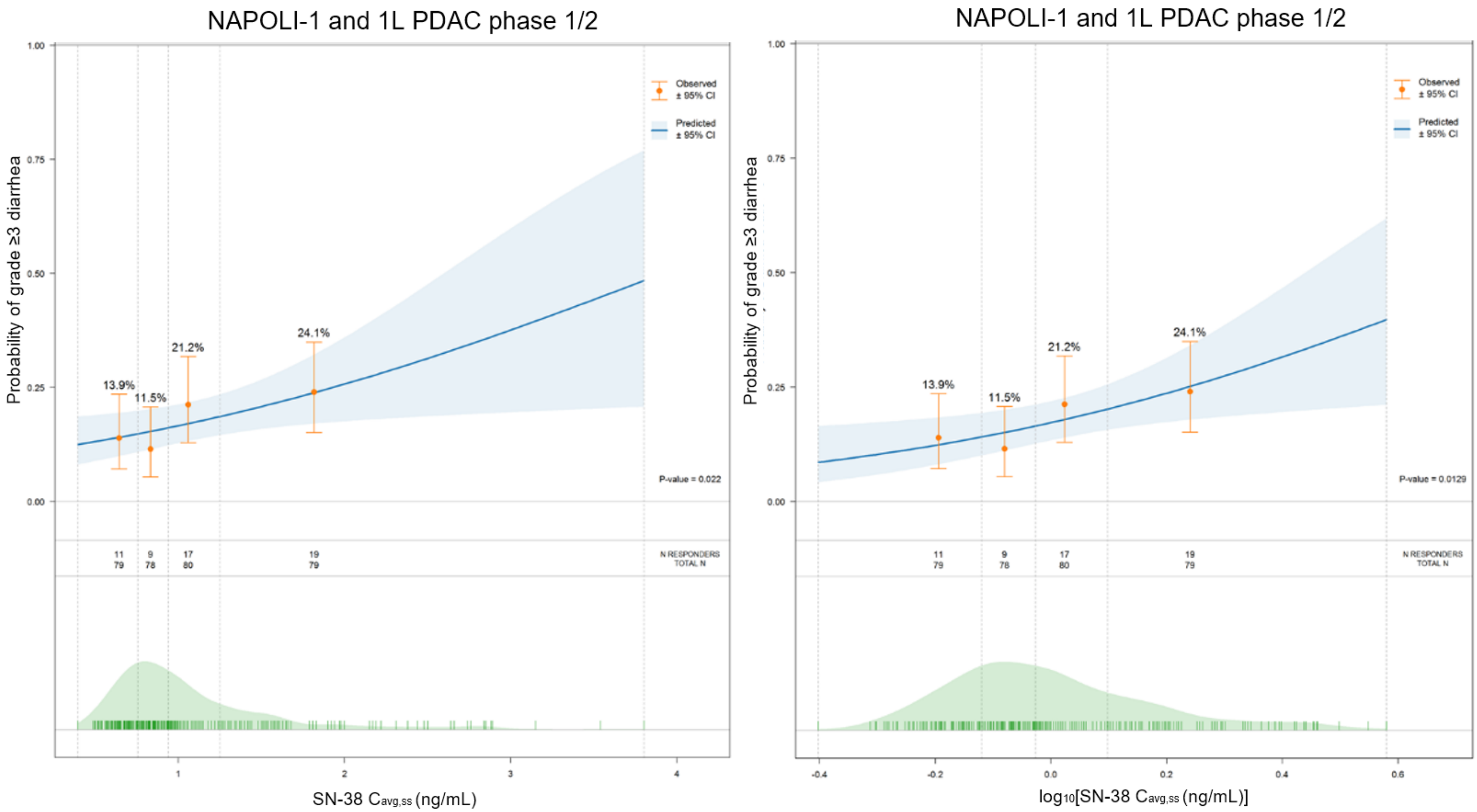


**Figure S11** Probability of developing grade ≥3 diarrhea as a function of $C_{max,ss}$ (**left panel**) and log-transformed $C_{max,ss}$ for SN38 (**right panel**) after administration of liposomal irinotecan. $C_{max,ss}$, maximum plasma concentration at steady state; CI, confidence interval

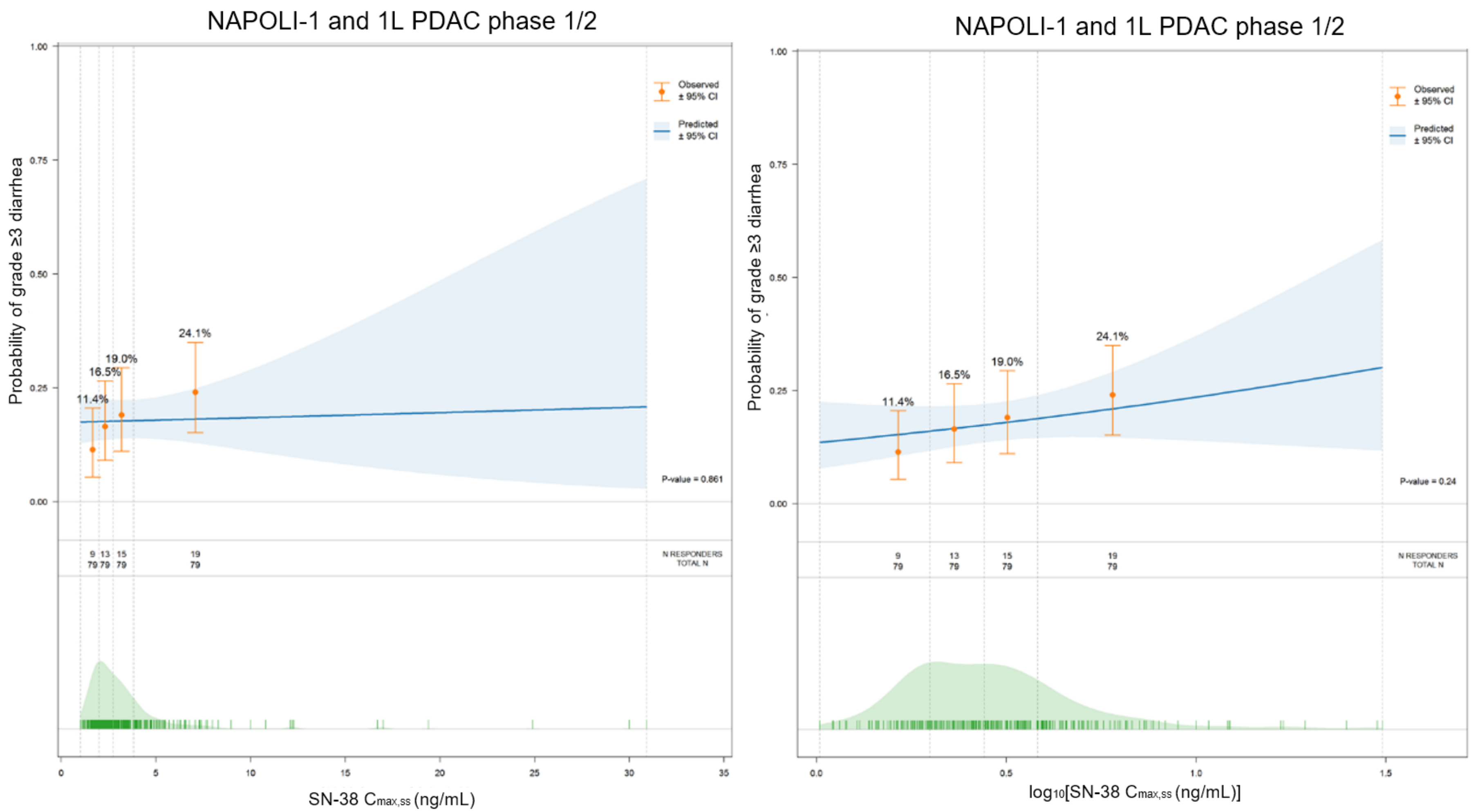


**Figure S12** Probability of developing grade ≥3 neutropenia as a function of $C_{avg,ss}$ (**left panel**) and log-transformed $C_{avg,ss}$ for total irinotecan (**right panel**) after administration of liposomal irinotecan. $C_{avg,ss}$, average plasma concentration at steady state; CI, confidence interval

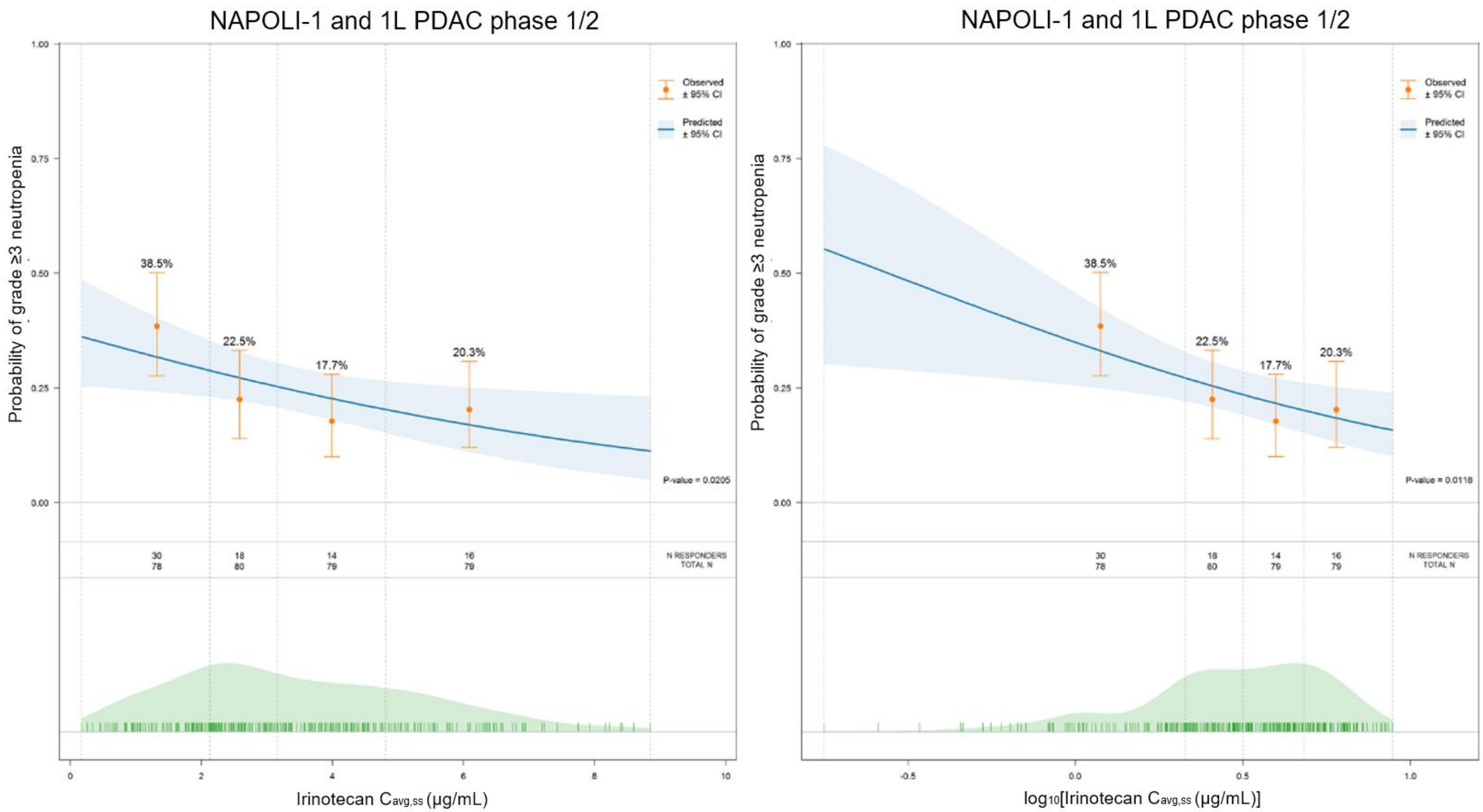


**Figure S13** Probability of developing grade ≥3 neutropenia as a function of $C_{max,ss}$ (**left panel**) and log-transformed $C_{max,ss}$ for total irinotecan (**right panel**) after administration of liposomal irinotecan. $C_{max,ss}$, maximum plasma concentration at steady state; CI, confidence interval

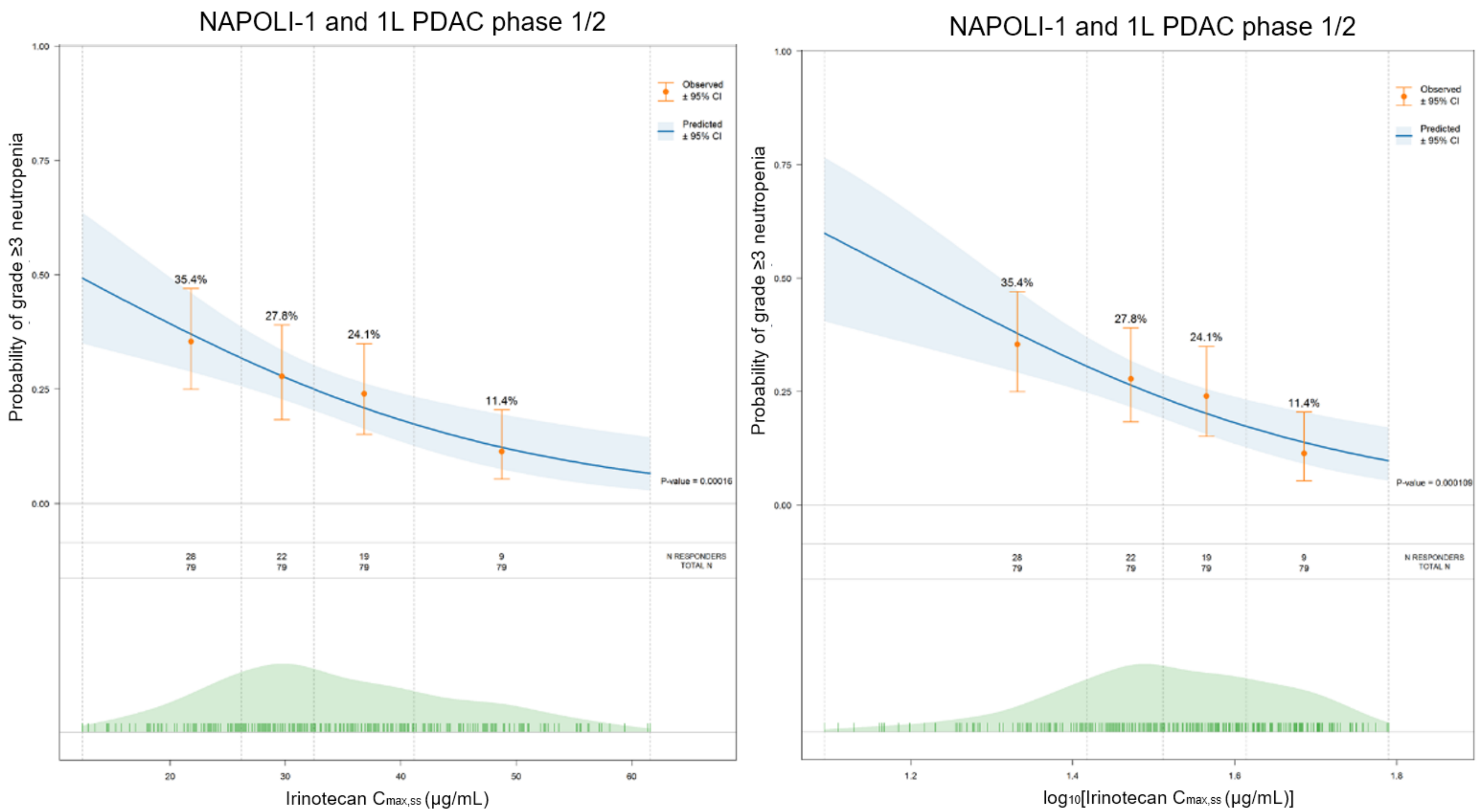


**Figure S14** Probability of developing grade ≥3 neutropenia as a function of $C_{avg,ss}$ (**left panel**) and log-transformed $C_{avg,ss}$ for SN38 (**right panel**) after administration of liposomal irinotecan. $C_{avg,ss}$, average plasma concentration at steady state; CI, confidence interval

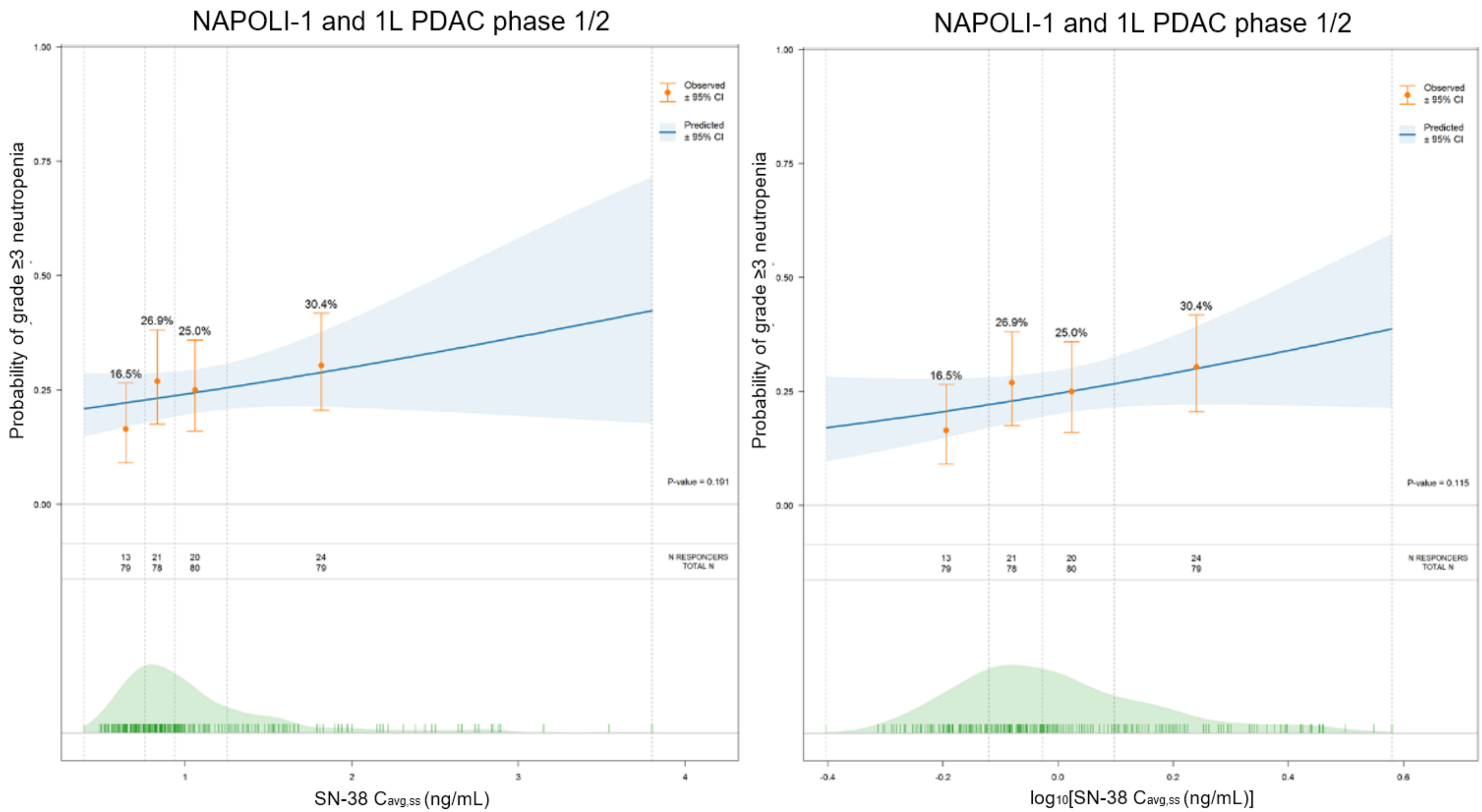


**Figure S15** Probability of developing grade ≥3 neutropenia as a function of $C_{max,ss}$ (**left panel**) and log-transformed $C_{max,ss}$ for SN38 (**right panel**) after administration of liposomal irinotecan. $C_{max,ss}$, maximum plasma concentration at steady state; CI, confidence interval

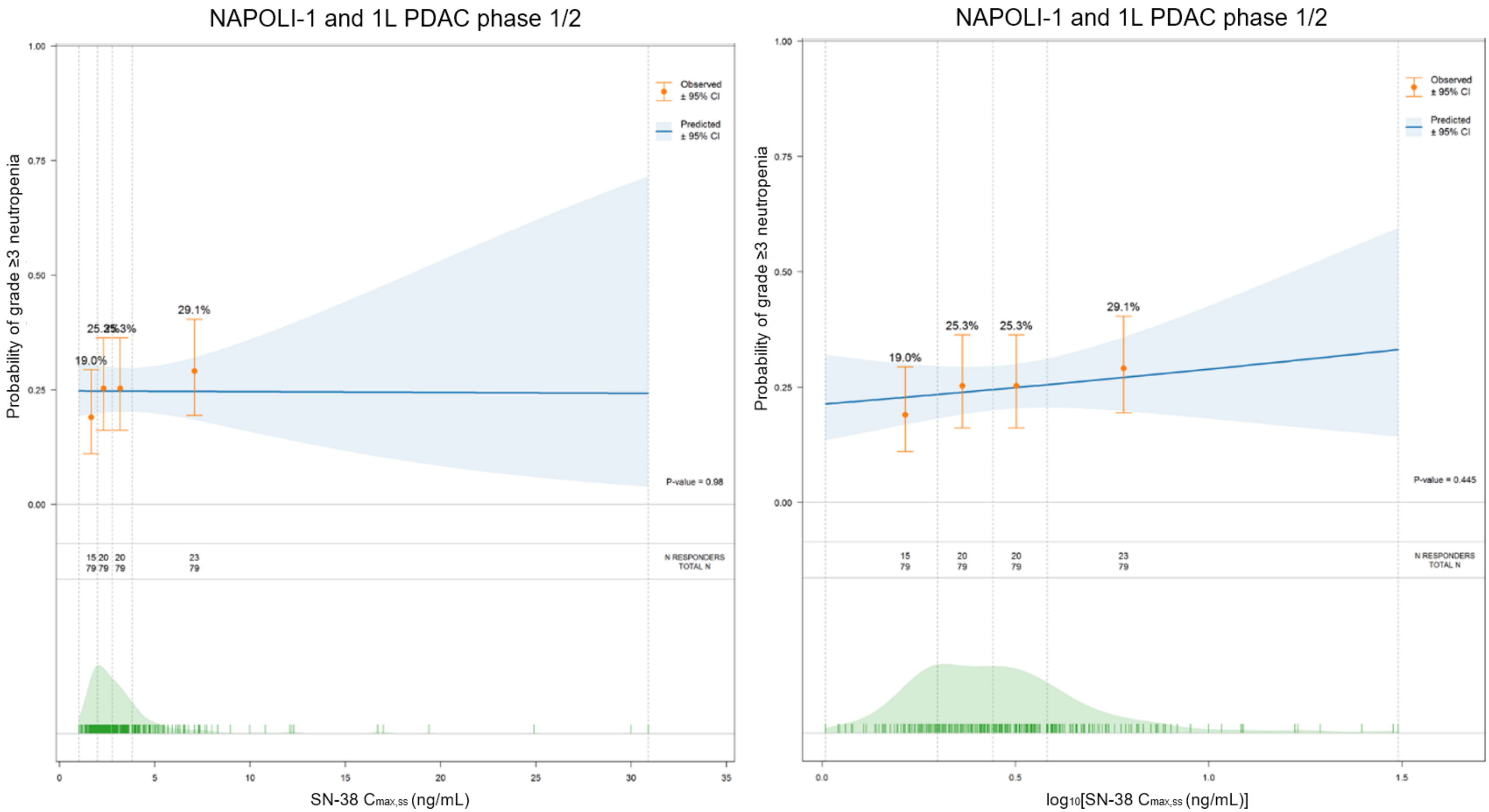


**Table S1** Continuous and categorical covariates (*N* = 440 patients)

| Continuous covariate | Mean (SD) | Median (range) |
|---|---|---|
| Age, years | 61 (11) | 62 (28–87) |
| Albumin, g/dL | 3.9 (0.47) | 4 (2.1–5.1) |
| ALT, IU/L | 31 (23) | 24 (4–202) |
| Bilirubin, mg/dL | 0.51 (0.26) | 0.41 (0.12–2.11) |
| BSA, $m^2$ | 1.73 (0.22) | 1.71 (1.29–2.48) |
| CrCl (mL/min) | 88 (30) | 85 (27–177) |
| **Categorical covariate** | **Proportion of patients, %** | |
| Asian | | |
| Yes | 35.2 | |
| No | 64.8 | |
| Gender | | |
| Male | 51.4 | |
| Female | 48.6 | |
| Liver metastasis | | |
| Yes | 43.2 | |
| No | 26.8 | |
| Missing | 30 | |
| Manufacturing site | | |
| Old | 18.6 | |
| Actual | 81.4 | |
| Co-administration with 5FU/LV | | |
| Yes | 42.7 | |
| No | 57.3 | |
| Co-administration with oxaliplatin | | |
| Yes | 12.7 | |
| No | 87.3 | |
| UGT1A1*28 homozygous 7/7 | | |
| Yes | 6.1 | |
| No | 93.9 | |

5FU/LV, 5-fluorouracil/leucovorin; ALT, alanine aminotransferase; BSA, body surface area; CrCl, creatinine clearance; SD, standard deviation

**Table S2** Comparison of the effect of the M1 and M3 methods on parameters generated using the base model

| Parameter | Base model (M1 method) estimate, RSE% | Base model (M3 method) estimate, RSE% | Wald test statistics |
|---|---|---|---|
| [CLP] | 18.6 (4.3) | 24.1 (8) | 2.63 (S) |
| [VCP] | 3.71 (1.60) | 3.57 (1216) | 0.003 (NS) |
| [QP] | 1.48 (29.4) | 1.1 (2473) | 0.014 (NS) |
| [V3P] | 0.453 (21.9) | 0.325 (7631) | 0.005 (NS) |
| [FR1] | 0.195 (23.7) | 0.477 (51.6) | 1.12 (NS) |
| [FR2] | 0.841 (24.9) | 2.8 (55) | 1.26 (NS) |
| [KFM] | 2.13 (4.70) | 2.42 (16.4) | 0.71 (NS) |
| [CLM] | 18100 (11.4) | 26400 (1856) | 0.017 (NS) |
| [PR_P] | 0.25 (6%) | 0.269 (38.7) | – |
| [PR_M] | 0.283 (5%) | 0.304 (17.7) | – |
| [IIV_CLM] | 0.203 (9.9) | 0.212 (49.5) | – |
| [IIV_KFM] | 0.122 (31.1) | 0.115 (52.20) | – |
| [IIV_CLP] | 0.554 (9.7) | 0.77 (60.3) | – |
| [IIV_FR1] | 0.722 (13.20) | 2.47 (2.4) | – |
| [IIV_FR2] | 0.185 (46.9) | 0.957 (9) | – |
| [IIV_VCP] | 0.0735 (26.1) | 0.0668 (0.5) | – |

CLM, SN-38 clearance; CLP, total irinotecan clearance; FR1, fraction of irinotecan metabolized by first-order process; FR2, fraction of irinotecan metabolized via transit; IIV, inter-individual variation; KFM, rate of transformation after delay; PR M, proportional residual error for SN-38; PR P, proportional residual error for total irinotecan; QP, inter-compartmental clearance for total irinotecan; RSE, residual standard error; V3P, irinotecan peripheral volume; VCP, irinotecan central volume of distribution

**Table S3** Estimated population PK parameters from the final model and performance of the PK model (bootstrap results)

| Parameter | Estimate | RSE, % | Bootstrap results, median (95% CI) |
|---|---|---|---|
| **Irinotecan total clearance, L/week** | 17.9 | 5.14 | 17.8 (16.3, 19.7) |
| Asian race[a] | 1.204 | 44.6 | 0.192 (0.0423, 0.377) |
| Manufacturing site[a] | 1.515 | 27.9 | 0.547 (0.275, 0.82) |
| Gender[a] | 0.799 | 23.5 | −0.199 (−0.292, −0.106) |
| Oxaliplatin administration[a] | 1.339 | 28.1 | 0.345 (0.166, 0.547) |
| **Irinotecan central volume, L** | 4.09 | 2.23 | 4.07 (3.92, 4.26) |
| Body surface area[b] | $(BSA/1.71)^{0.573}$ | 17.9 | 0.587 (0.383, 0.786) |
| Manufacturing site[a] | 0.872 | 29.4 | −0.117 (−0.19, −0.0576) |
| Gender[a] | 0.886 | 22.9 | −0.116 (−0.167, −0.066) |
| **Fraction of delayed irinotecan total rate of elimination** | 0.629 | 23.4 | 0.625 (0.399, 1.02) |
| Manufacturing site[a] | 1.376 | 41 | 0.379 (0.124, 0.677) |
| **Fraction of direct irinotecan total rate of elimination** | 0.152 | 22.4 | 0.15 (0.095, 0.248) |
| **Irinotecan inter-compartmental clearance, L/week** | 1.35 | 28.6 | 1.28 (0.681, 2.22) |
| **Irinotecan peripheral volume, L** | 0.421 | 22.6 | 0.405 (0.177, 0.628) |
| **SN-38 total clearance, L/week** | 19 800 | 12.8 | 19 700 (15 000, 24 900) |
| Bilirubin[b] | $(BIL/0.41)^{-0.266}$ | 17.5 | −0.234 (−0.326, −0.15) |
| Creatinine clearance[b] | $(CrCL/85.04)^{0.25}$ | 28.7 | 0.235 (0.0821, 0.368) |
| Gender[a] | 0.802 | 20.3 | −0.198 (−0.278, −0.121) |
| Oxaliplatin administration[a] | 0.656 | 14.1 | −0.346 (−0.432, −0.235) |
| Rate of transformation after delay, 1/week | 2 | 5.1 | 2.01 (1.81, 2.19) |
| Between-patient variability | | | |
| Irinotecan total clearance | 0.545 (CV, 85.2%) | 11 | 0.532 (0.428, 0.647) |
| Irinotecan central volume | 0.066 (CV, 26.1%) | 27.5 | 0.0577 (0.036, 0.0938) |
| Fraction of delayed irinotecan total rate of elimination | 0.188 (CV, 45.4%) | 26.4 | 0.19 (0.09, 0.286) |
| Fraction of direct irinotecan total rate of elimination | 0.928 (CV, 124%) | 10.9 | 0.916 (0.737, 1.12) |

| Parameter | Estimate | RSE, % | Bootstrap results, median (95% CI) |
|---|---|---|---|
| SN-38 total clearance | 0.126 (CV, 36.6%) | 13.6 | 0.123 (0.0892, 0.155) |
| Rate of transformation after delay | 0.135 (CV, 38%) | 29.1 | 0.133 (0.0576, 0.216) |
| Covariance (correlation) between irinotecan total clearance and fraction of direct transformation | −0.558 (−0.785) | 12 | −0.55 (−0.681, −0.434) |
| Covariance (correlation) between irinotecan total clearance and central volume | 0.117 (0.617) | 17.8 | 0.109 (0.0758, 0.154) |
| Covariance (correlation) between irinotecan central volume and fraction of direct transformation | −0.103 (−0.416) | 24.4 | −0.0952 (−0.147, −0.052) |
| Residual error | | | |
| Proportional error on irinotecan | 0.243 (CV, 24.3%) | 6.25 | 0.24 (0.215, 0.27) |
| Proportional error on SN-38 | 0.291 (CV, 29.1%) | 5.23 | 0.289 (0.26, 0.317) |
| Correlation between irinotecan and SN-38 errors | 0.323 | 26.4 | 0.279 (0.149, 0.399) |

BIL, bilirubin; BSA, body surface area; CI, confidence interval; CrCL, creatinine clearance; CV, coefficient of variation; PK, pharmacokinetic; RSE, relative standard error

[a]Categorical covariates

[b]Continuous covariates:

$$irinotecan\ total\ clearance, i = 17.9 \times 1.204^{ASIAN} \times 1.515^{Manufacturing\ site} \times 0.799^{Gender} \times 1.339^{Oxaliplatin\ coadministration}$$

$$irinotecan\ central\ volume, i = 4.09 \times \left(\frac{BSA, i}{1.71}^{0.573}\right) \times 0.872^{Manufacturing\ site} \times 0.886^{Gender}$$

$$fraction\ of\ delayed\ irinotecan\ total\ rate\ of\ elimination, i = 0.629 \times 1.376^{Manufacturing\ site}$$

$$fraction\ of\ direct\ irinotecan\ total\ rate\ of\ elimination, i = 0.152$$

$$irinotecan\ intercompartmental\ clearance, i = 1.35$$

$$irinotecan\ peripheral\ volume, i = 0.421$$

$$SN-38\ total\ clearance, i = 19\ 800 \times \left(\frac{BIL, i}{0.41}^{-0.266}\right) \times \left(\frac{CrCL, i}{85.04}^{0.25}\right) \times 0.802^{Gender} \times 0.656^{Oxaliplatin\ coadministration}$$