

**Comparison of the pharmacokinetics of S-1,
an oral anticancer agent,
in Western and Japanese patients**

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S-1

- Oral anticancer combination
- Tegafur (FT)
 - parent drug of 5-fluorouracil (5-FU)
- Gimeracil (CDHP)
 - inhibits DPD
- Potassium oxonate (Oteracil)
 - inhibits OPRT

Objectives

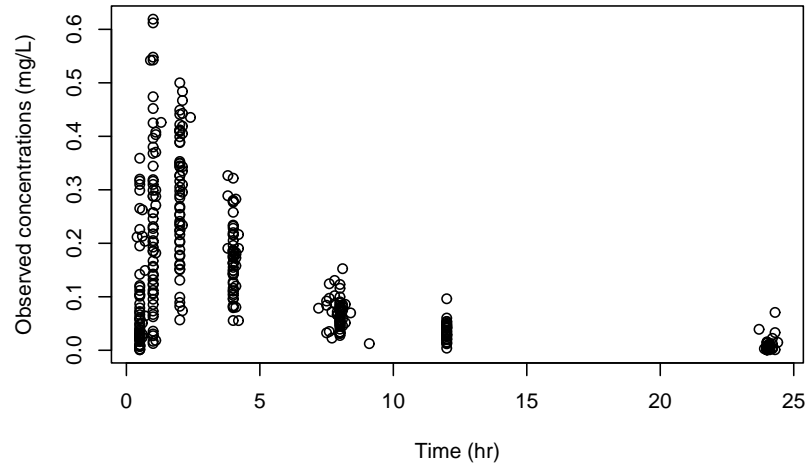
1. Analyse the pharmacokinetic data in Western patients
2. Compare with the results of a population analysis in Japanese patients

Data in Western patients

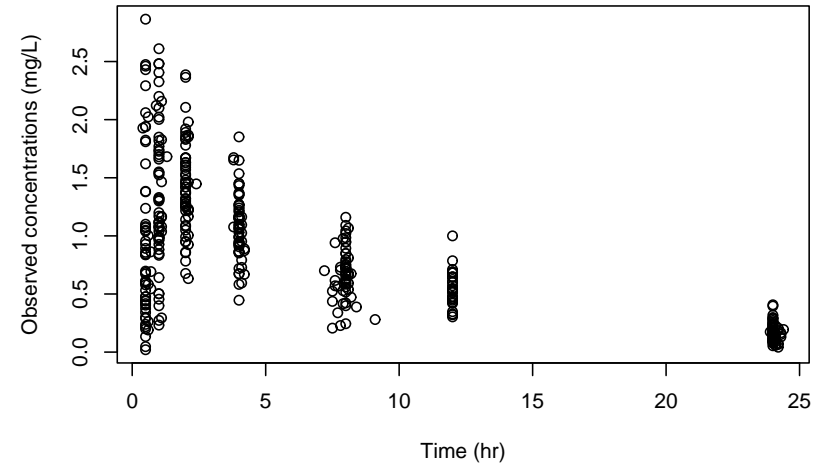
- Sixty European and American patients
 - phase I studies
- Single dose of S-1
 - oral administration
 - doses 25 to 45 mg/m²
- PK profile
 - 6 samples taken over 24 h after administration

Observed concentrations

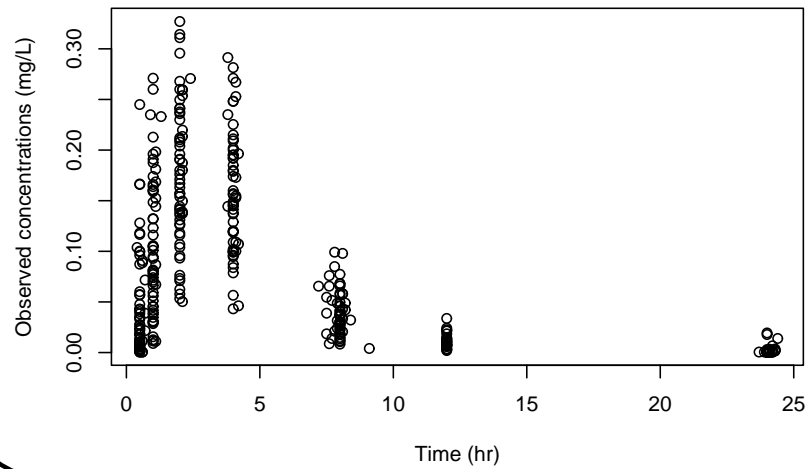
CDHP



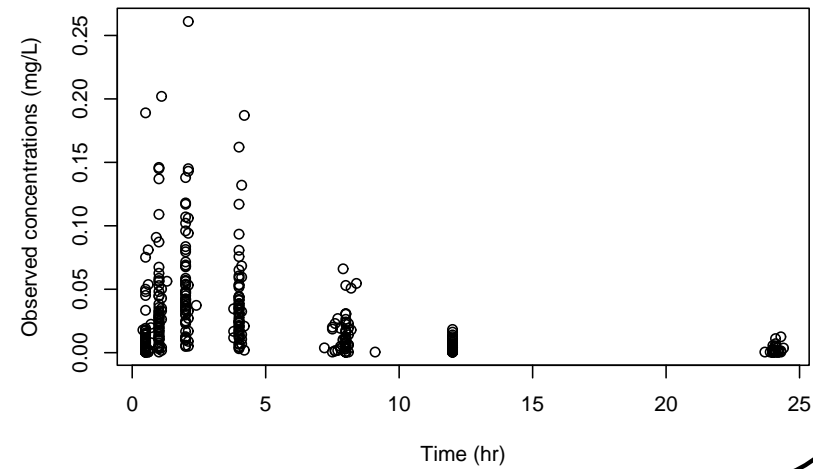
FT



5-FU



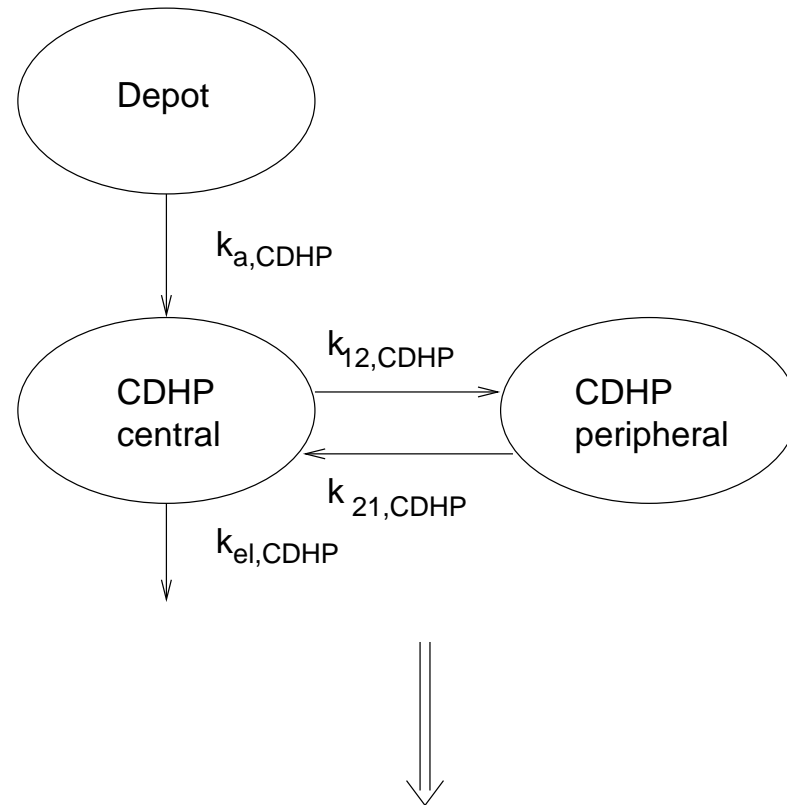
Oteracil



Model building

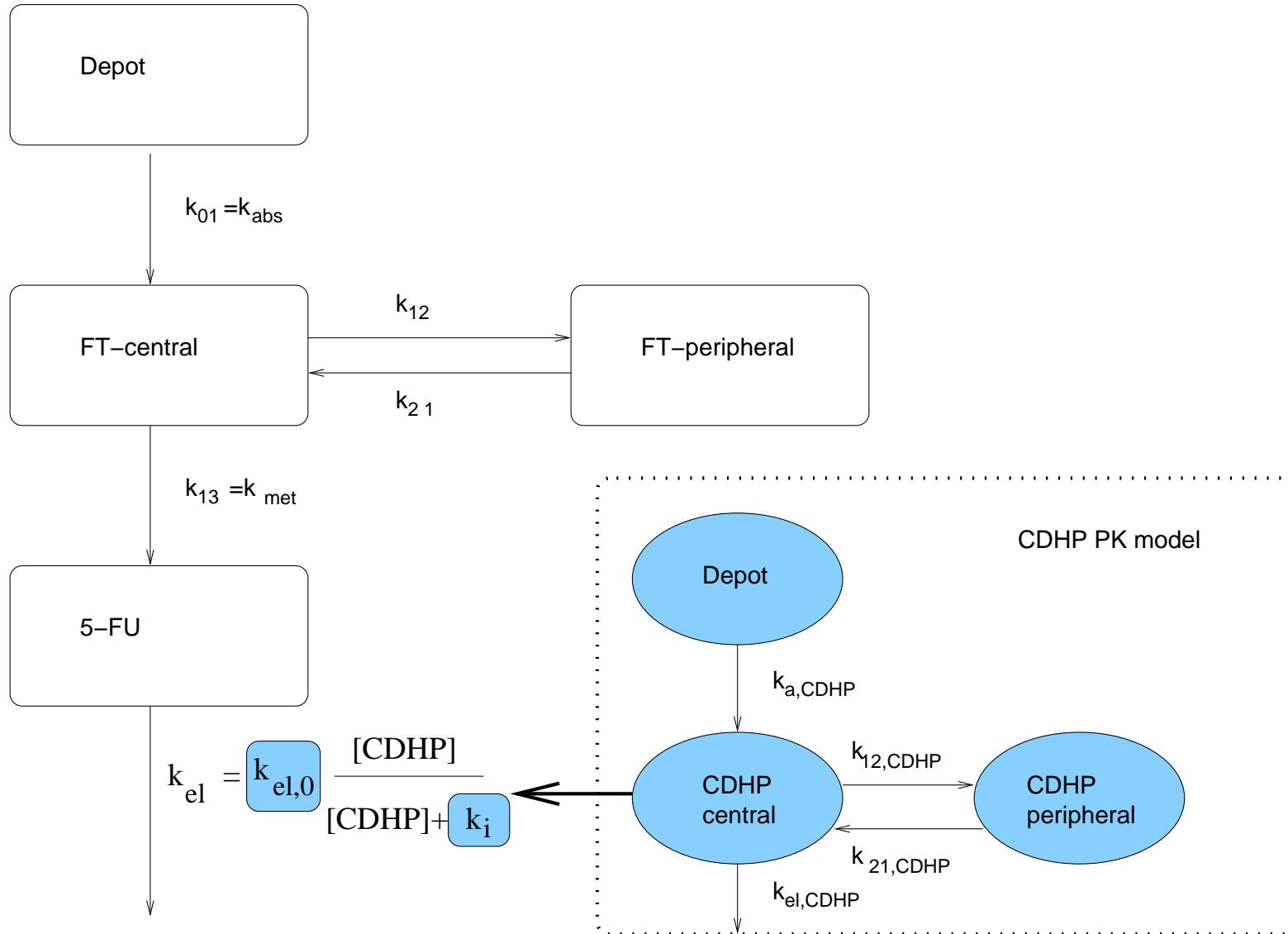
- Pharmacokinetic models
 - CDHP and oteracil analysed separately (independent PK)
 - joint analysis of FT and 5-FU using the individual parameters estimated for CDHP
- Statistical models
 - exponential interindividual variability: $\theta_i = \theta_0 e^{\eta_i}$
 - additive error model: $C_p(t) = f(t, \theta) + \varepsilon$
 - constant variance for FT
 - combined additive and proportional variance for the other compounds
 - BQL measurements set to LOQ/2
- Population parameters estimated using NONMEM

PK model for CDHP



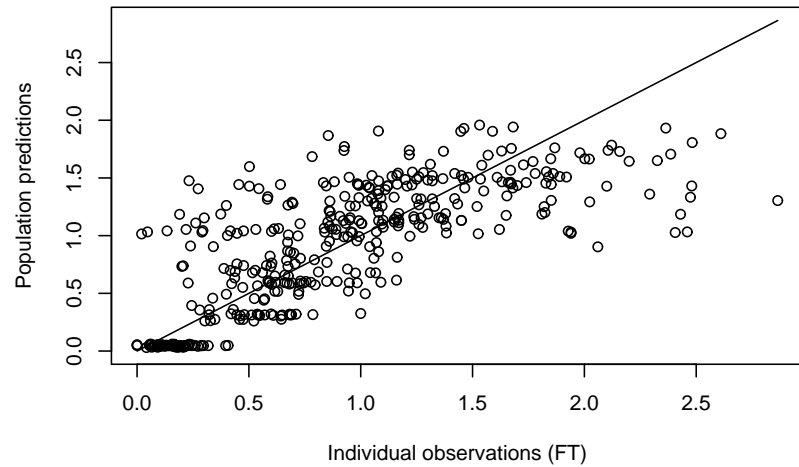
- Empirical Bayes estimates of individual parameters
- Simulation of the individual concentration time-profiles

Structural model

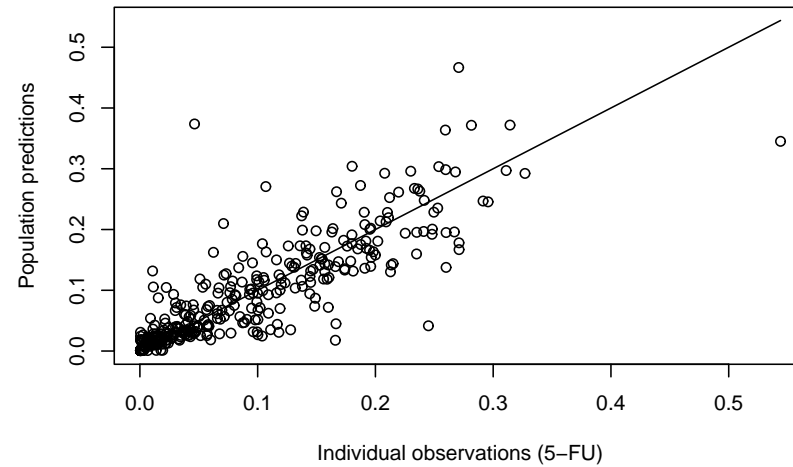


Graphical diagnostics for FT and 5-FU

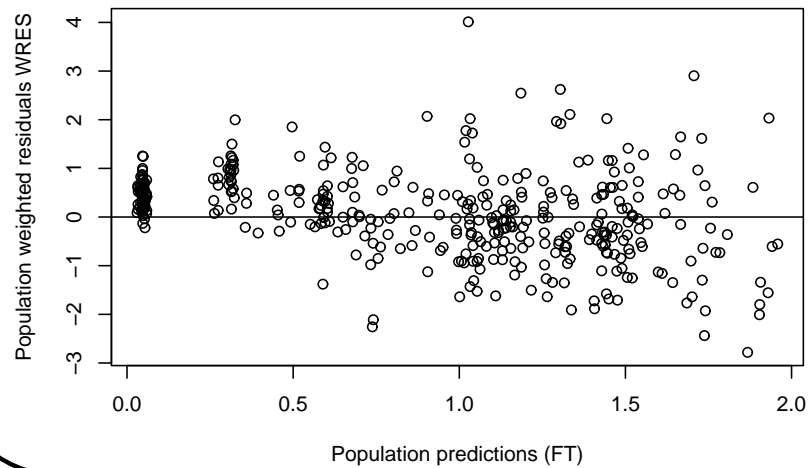
PRED vs DV, FT



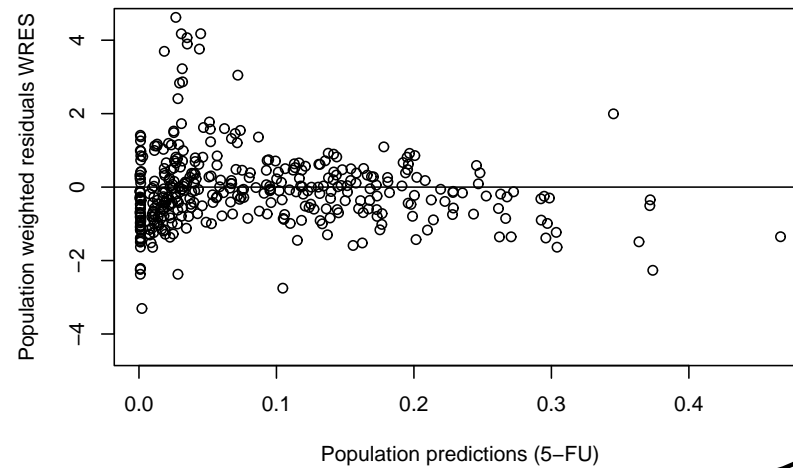
5-FU



WRES vs PRED, FT



5-FU



Parameter estimates

Parameter	Population mean (% SE)	CV (% SE)
$k_{0,1}$ (hr^{-1})	1.4 (25%)	103 (39%)
$k_{1,3}$ (hr^{-1})	0.18 (13%)	26 (38%)
$k_{el,0}$ (hr^{-1})	12.7 (19%)	(-)
$V_{d,FT}$ (L)	16.0*BSA (10%)	27 (44%)
$V_{d,5-FU}$ (L)	11.5*BSA (17%)	16 (38%)
k_i ($\mu\text{g.mL}^{-1}$)	women: 0.037 (16%)	(-)
	men: 0.042 (17%)	(-)
σ_{FT} ($\mu\text{g.mL}^{-1}$)	0.25 (17%)	(-)
σ_{5-FU} (CV%)	41% (7%)	(-)

Comparison of Western and Japanese patients

- Use the Western analysis to predict the Japanese data
 - prediction discrepancies
 - prediction intervals
- Compare the population estimates in the two separate analyses

Population PK analysis in Japanese patients

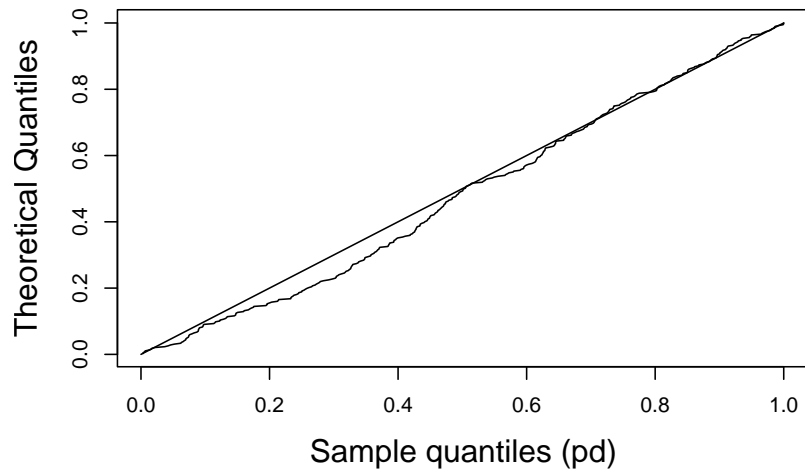
- Data
 - 46 patients from phase I with rich data
 - 53 patients from phase II with sparse data
 - Japanese patients older and thinner than Western patients
 - same distribution of cancer types
- Results
 - same structural models
 - different covariates selected

Comparison using the Western results

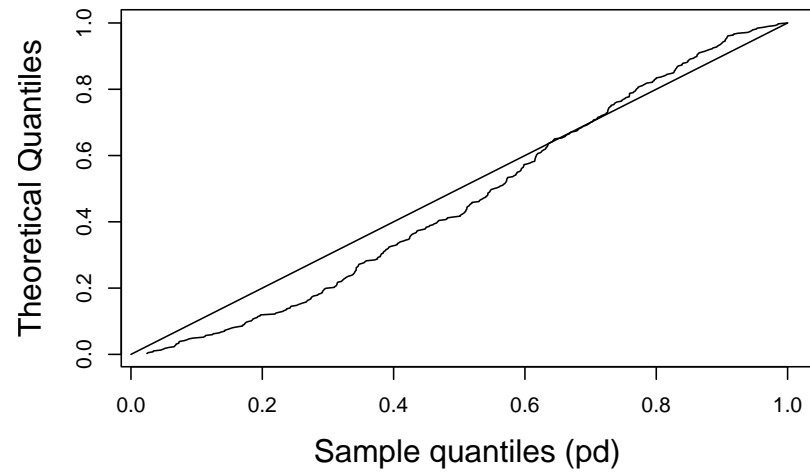
- Prediction discrepancies (*Mentré and Escolano, PAGE 2000*)
 - pd_i : percentile of the observation in the predictive distribution
 - given the model and parameter estimates
 - $pd_i \sim \mathcal{U}[0,1]$ (Kolmogorov-Smirnov test)
- Prediction intervals
 - simulate individual parameters and predict concentration-time profiles
 - 5-95% interval of the simulated concentrations
 - coverage frequency: percentage of observations within the interval

Prediction discrepancies in Western patients

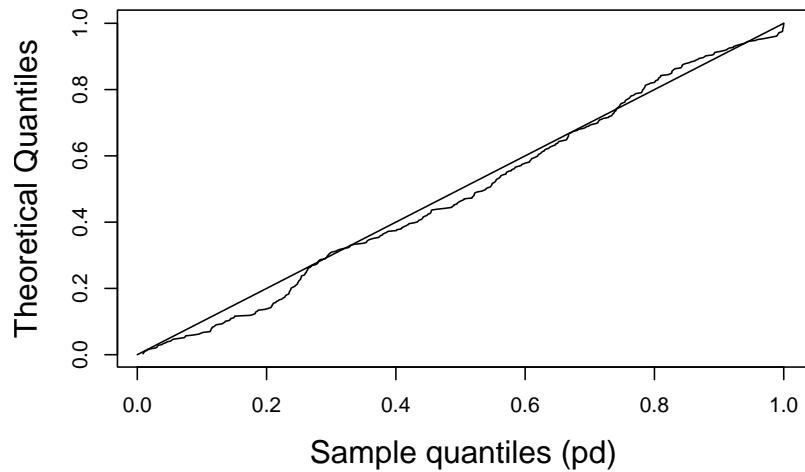
CDHP (NS)



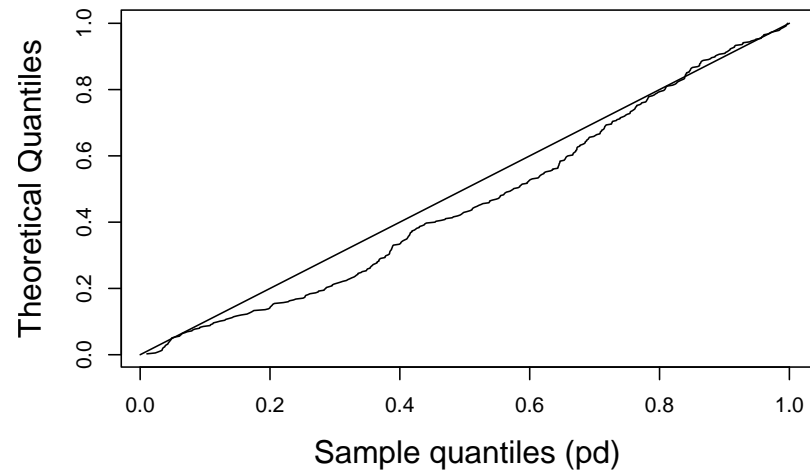
FT (p<0.05)



5-FU (NS)

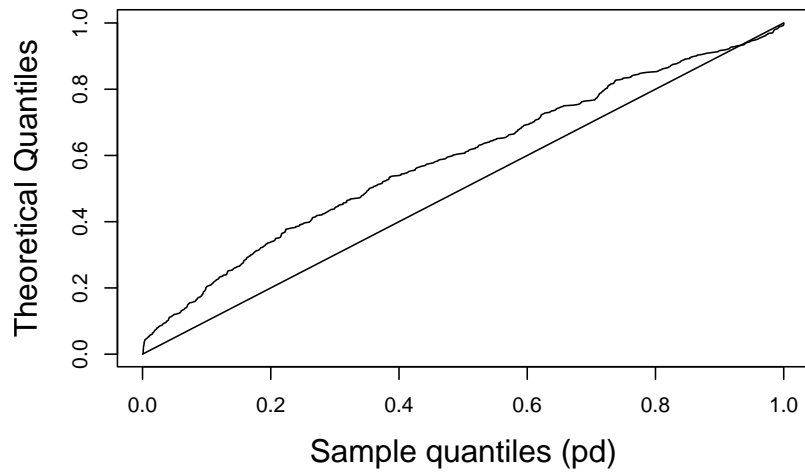


Oteracil (NS)

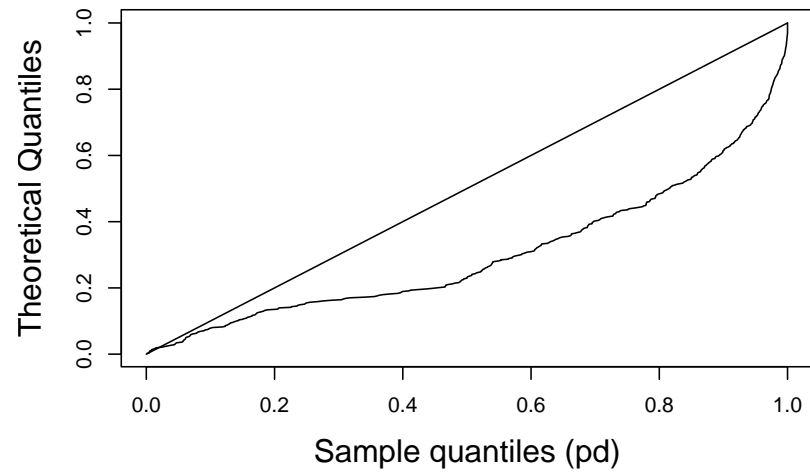


Prediction discrepancies in Japanese patients

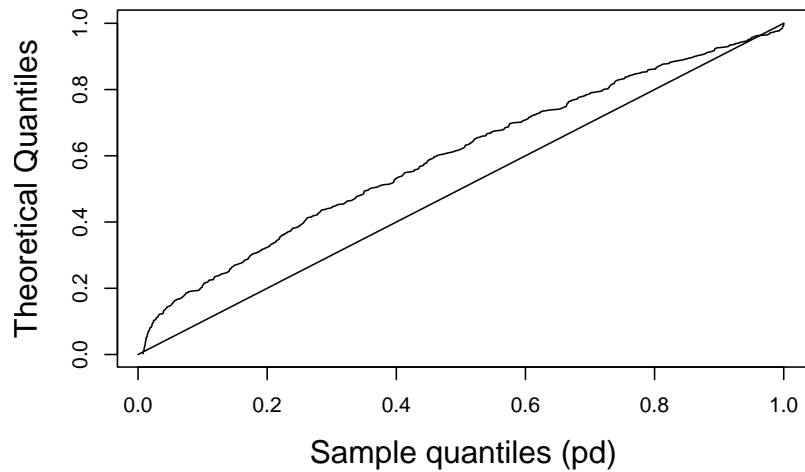
CDHP ($p < 0.05$)



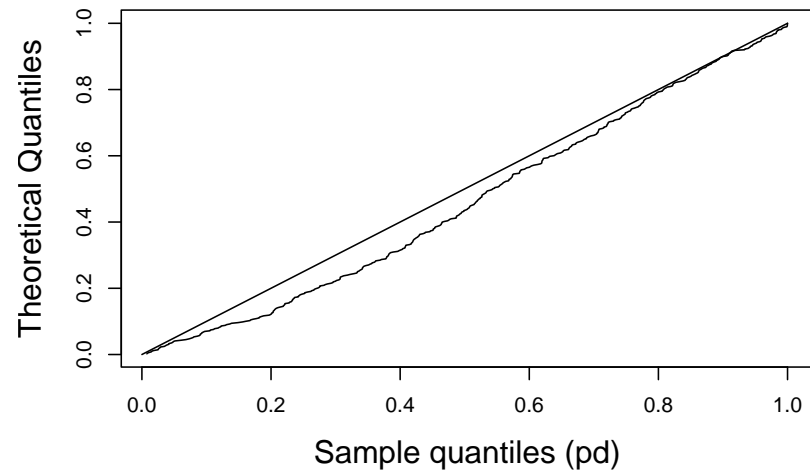
FT ($p < 0.05$)



5-FU ($p < 0.05$)

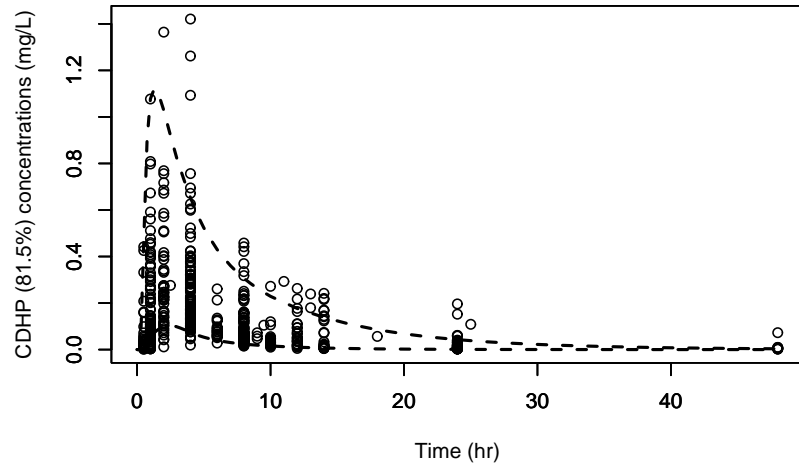


Oteracil (NS)

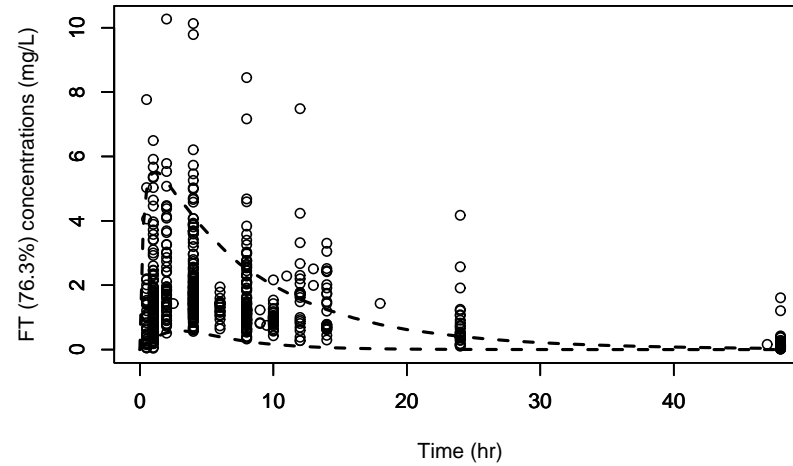


5-95% prediction intervals from Western analysis with observations in Japanese patients

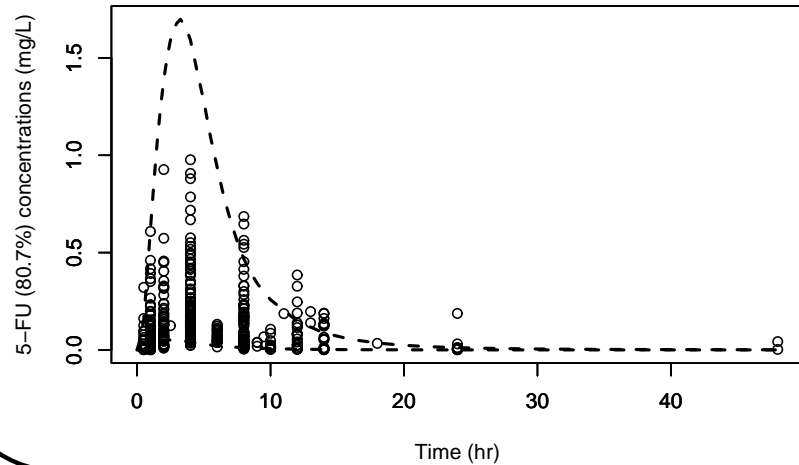
CDHP (81.5%)



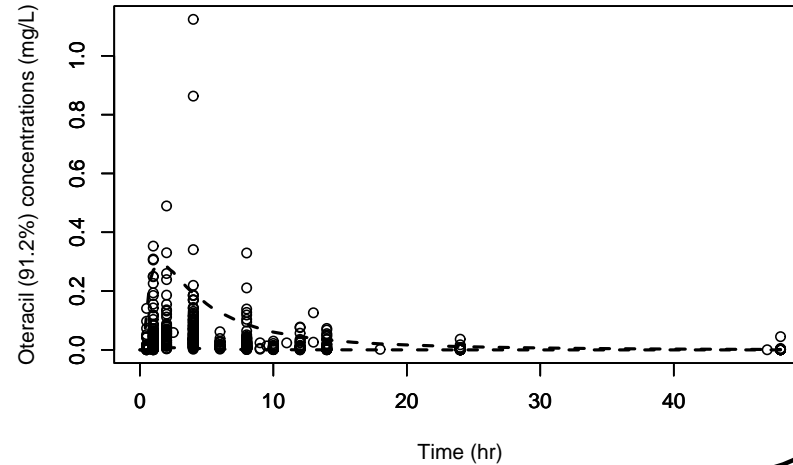
FT (76.3%)



5-FU (80.7%)



Oteracil (91.2%)



Mean population parameters

	Parameter	Western	Japanese
CDHP	k_{abs} (hr^{-1})	1.2 (83%)	1.2 (114%)
	CL ($\text{L}\cdot\text{hr}^{-1}$)	6.2*BSA (34%)	10.9 (41%)
	V_d (L)	18.8*BSA (20%)	51.4 (29%)
FT	k_{abs} (hr^{-1})	1.4 (103%)	0.9 (98%)
	CL ($\text{L}\cdot\text{hr}^{-1}$)	2.9*BSA (31%)	1.2*BSA (40%)
	V_d (L)	16.0*BSA (27%)	13.8*BSA (19%)
5-FU	CL_0 ($\text{L}\cdot\text{hr}^{-1}$)	146*BSA (16%)	170*BSA (22%)
	V_d (L)	11.5*BSA (16%)	9.4*BSA (22%)
	k_i ($\text{mg}\cdot\text{L}^{-1}$)	0.04 (-)	0.03 (-)

Conclusion

- Main differences between the two populations
 - FT: faster metabolism for western patients
 - CDHP: lower volume of distribution
- Clinical impact on treatment probably limited
- Methods to compare the two populations
 - methods based on validation approaches
 - tests on population parameters
 - avoids a new global analysis of all data