

Supplemental files

Table S1 Summary of dosing regimens for patients recruited to the study.

Dosing Regimen	Dose Reduction	Number of Patients
500 mg/m ² /day x 2	6-12 months–75% dose; <6 months–66% dose	3
1 g/m ² /day	7-≤12 months–75% dose; ≤ 6 months–66% dose	11
4 g/m ² /course		4
50 mg/kg/day		2
5 mg/kg/day x 5		2
10 mg/kg/day x 5		3

Table S2 Patient toxicities reported following administration of cyclophosphamide (only toxicities of grade 3 or above were recorded) (*n*=25).

Toxicity	Number of patients (%)		
	Grade 3	Grade 4	Grade 3/4
Neutrophil	4 (16)	8 (32)	12 (48)
Haemoglobin	12 (48)	0 (0)	12 (48)
White Blood Cell	6 (24)	4 (16)	10 (40)
Fever	0 (0)	4 (16)	4 (16)
Diarrhoea	0 (0)	2 (8)	2 (8)
Infection	0 (0)	4 (16)	4 (16)
Platelets	3 (12)	0 (0)	3 (12)
Stomatitis	0 (0)	1 (4)	1 (4)
Central Neurotoxicity	1 (4)	0 (0)	1 (4)
Peripheral Neurotoxicity	1 (4)	0 (0)	1 (4)
SGOT/SGPT	0 (0)	1 (4)	1 (4)
Other	1 (4)	0 (0)	1 (4)

Toxicity was assessed by the National Cancer Institute Common Toxicity Criteria (CTC), version 2.0

Table S3 Pharmacokinetic parameter final estimates

Parameter	Estimate	CI 95%	IIV (CV%)	η -Shrinkage
Clearance (L/min)	0.0225	[0.0197–0.0252]	46	15%
Volume 1 (L)	4.6	[4.3–4.9]	20	17%
Q (L/min)	0.128	[0.113–0.142]	56	52%
Volume 2 (L)	1.72	[1.66–1.79]	15	99%
Residual error				ϵ-shrinkage
Residual error ϵ -shrinkage				32.73%

CI 95%: confidence interval 95%; IIV: inter-individual variability

Figure S1 Diagnostic plots from the population pharmacokinetic model showing (A) individual predicted concentrations vs. observed concentrations, (B) population predicted concentrations vs. observed concentrations, (C) time vs. weighted residuals and (D) population predicted concentrations vs. weighted residuals. Panel E) shows the visual predictive check (VPC) for the final model.

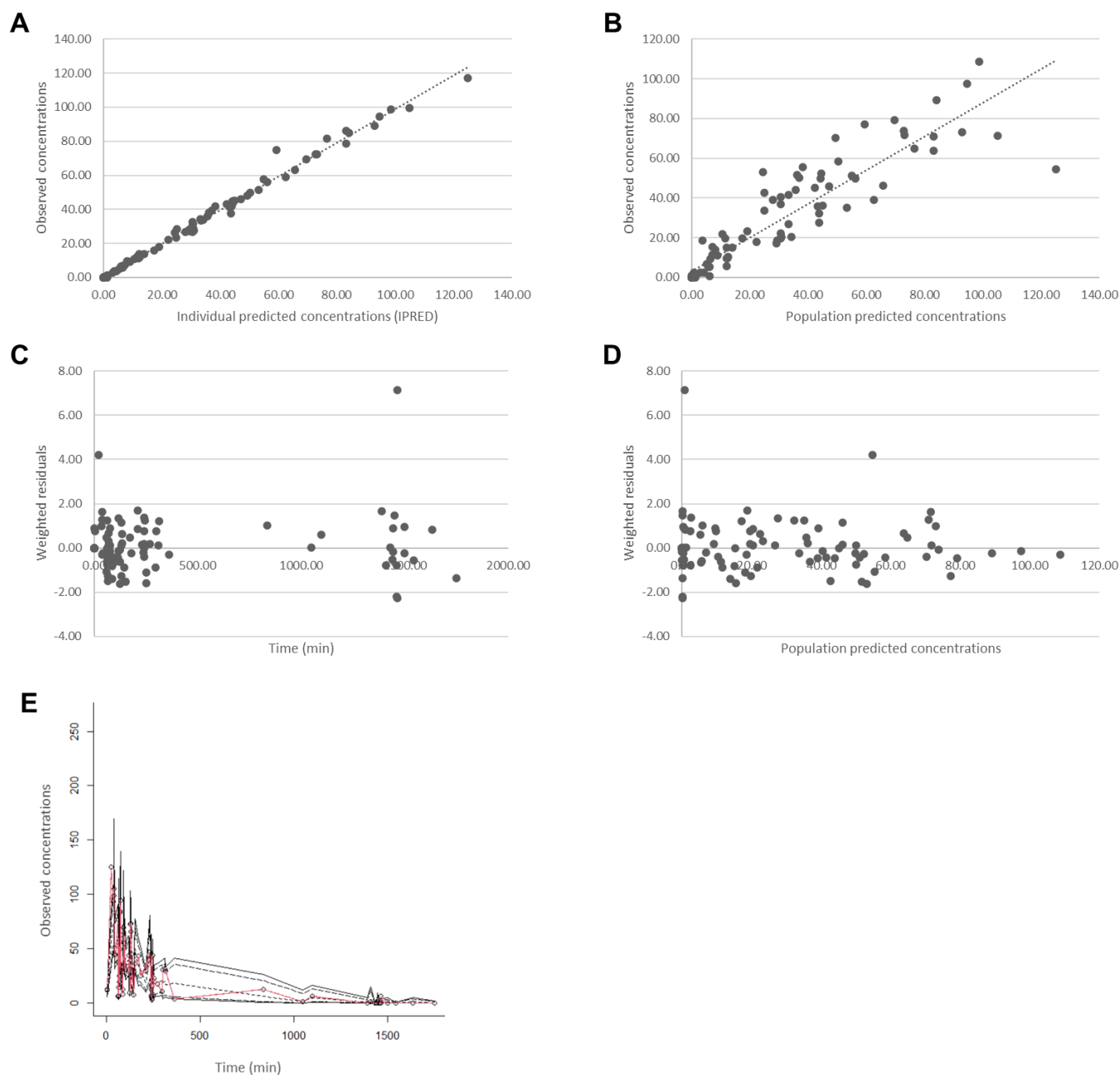


Figure S2 The effect of (A) age, (B) CYP2B6 genotype and (C) weight on cyclophosphamide AUC normalised to dose and (D) weight not normalised to dose. The error bars represent standard deviation, the black dashed line indicates the geometric mean cyclophosphamide normalised AUC of 0.045 (mg/mL.min)/dose and the blue dashed line indicates the geometric mean cyclophosphamide AUC of 12.6 mg/mL.min.

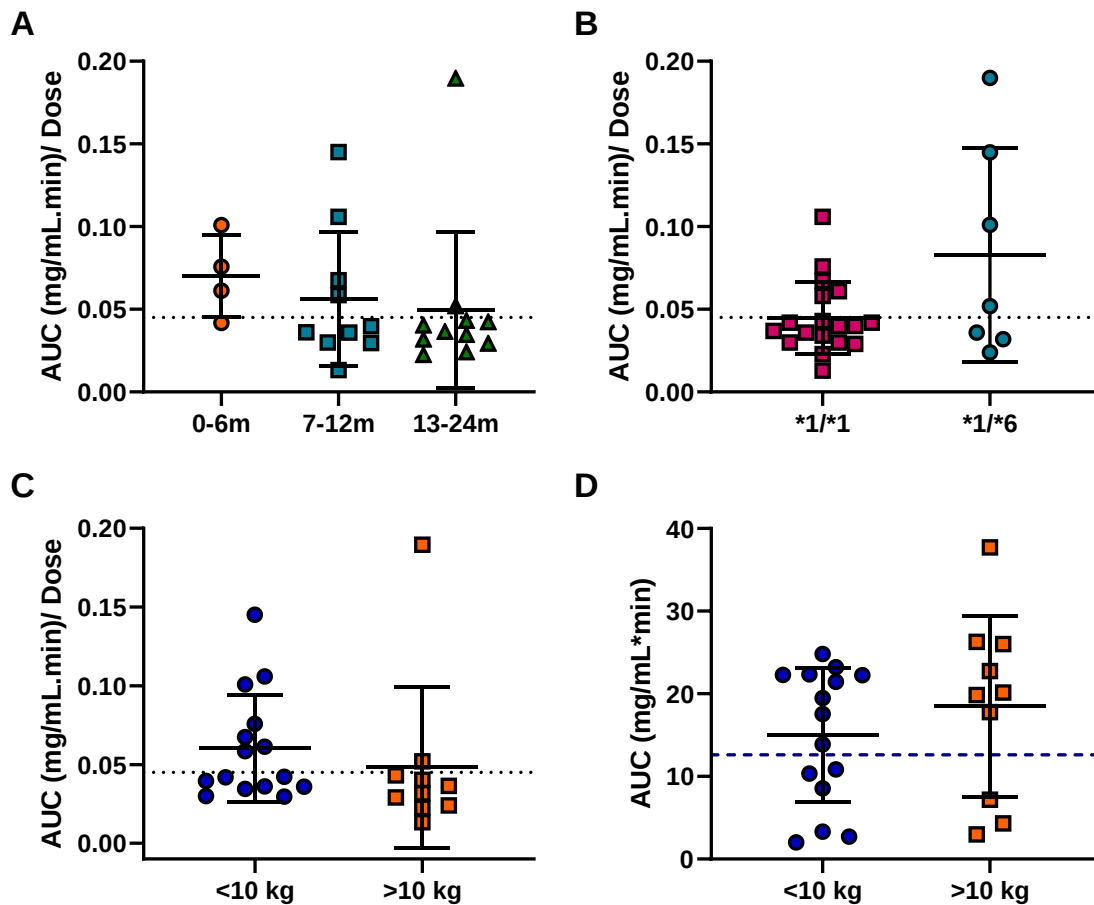


Figure S3 The effect of genotype on clearance using data generated from two studies in childhood cancer patient populations. Error bars represent standard deviation, *** indicates a significance level of $P < 0.0001$.

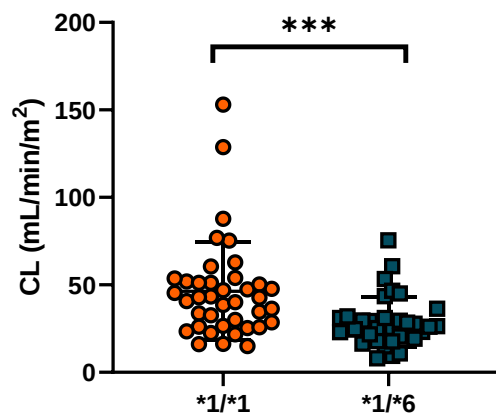


Figure S4 The effect of tumour type on (A) clearance (mL/min/m²) and (B) AUC (mg/mL.min). The tumour type “Other” refers to the remaining tumour types in the study. The error bars represent standard deviation, the blue dashed line indicates the geometric mean Clearance (46.6 mL/min/m²) and AUC (12.6 mg/mL.min).

