Supplemental Materials

Population pharmacokinetics of melphalan in a large cohort of autologous and allogeneic hematopoietic cell transplantation recipients: Towards individualized dosing regimens.

Gunjan L. Shah, Jaap Jan Boelens, Dean Carlow, Andrew Lin, Ryan Schofield, Nancy Cruz Sitner, Anna Alperovich, Josel Ruiz, Anthony Proli, Parastoo Dahi, Roni Tamari, Sergio A. Giralt, Michael Scordo, Rick Admiraal

Corresponding author:
Rick Admiraal, MD PhD
Princess Maxima Centre for Pediatric Oncology
r.admiraal-4@prinsesmaximacentrum.nl

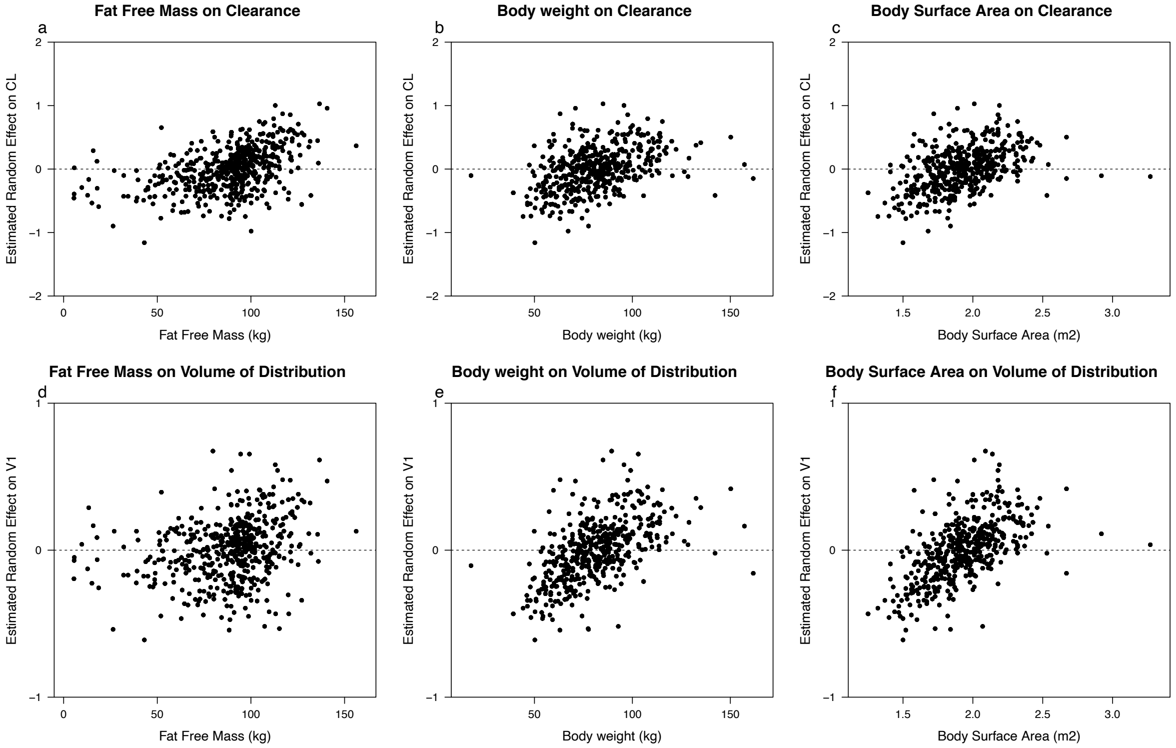


Figure S1: Body size parameters versus interindividual variability on clearance (CL; panels A-C) and central volume of distribution (V1; panels D-F)

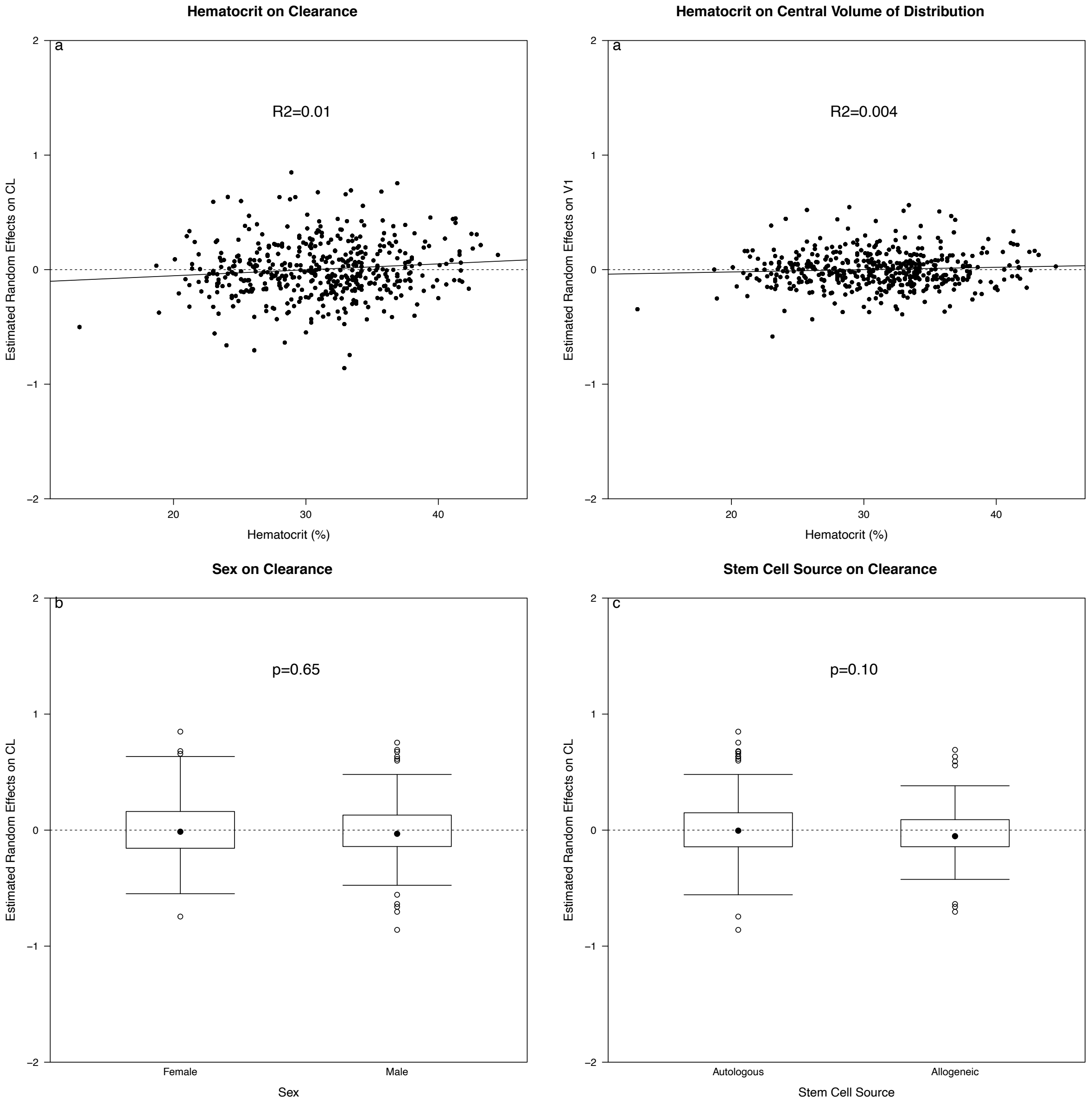


Figure S2: Covariates not included in the model

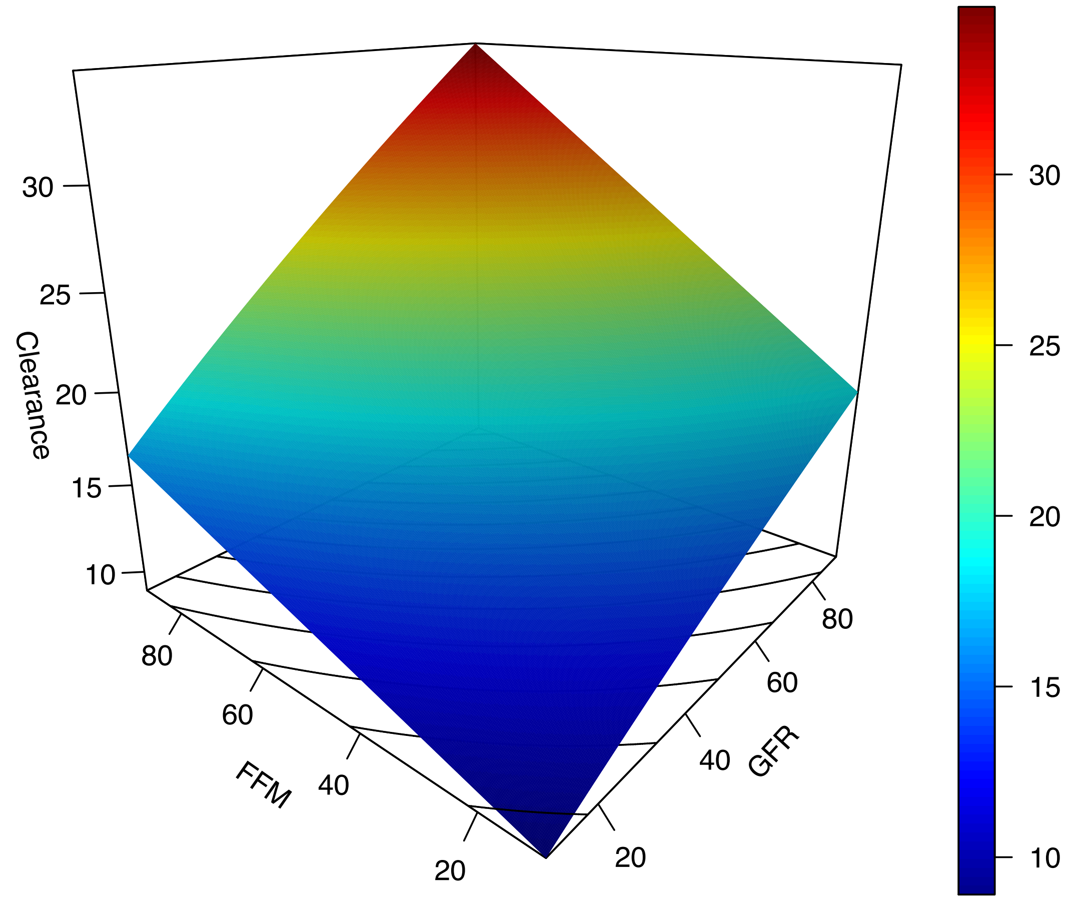
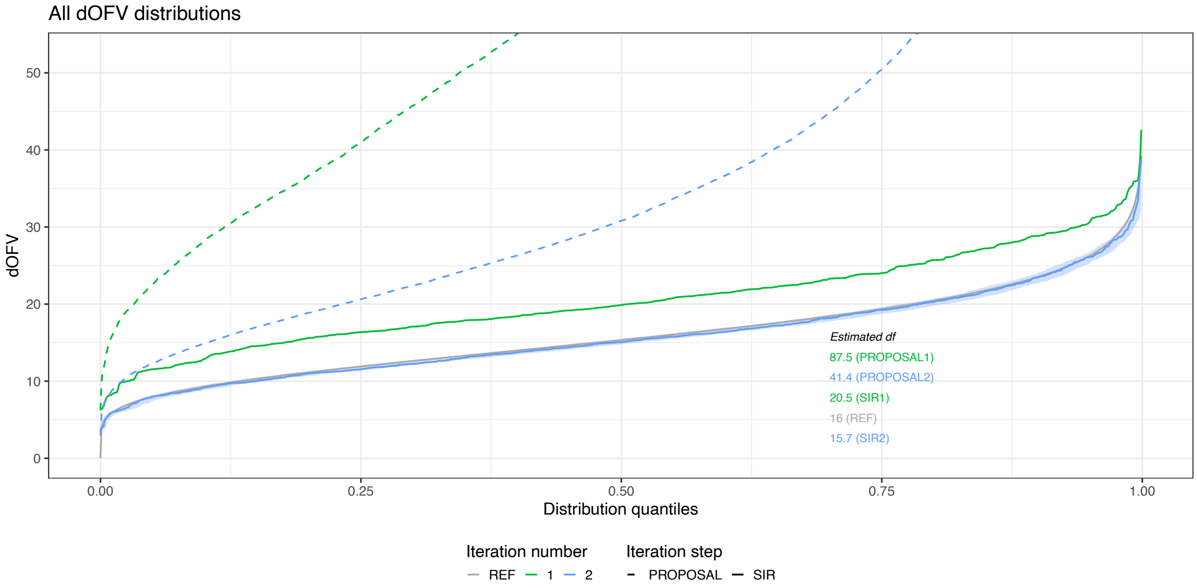
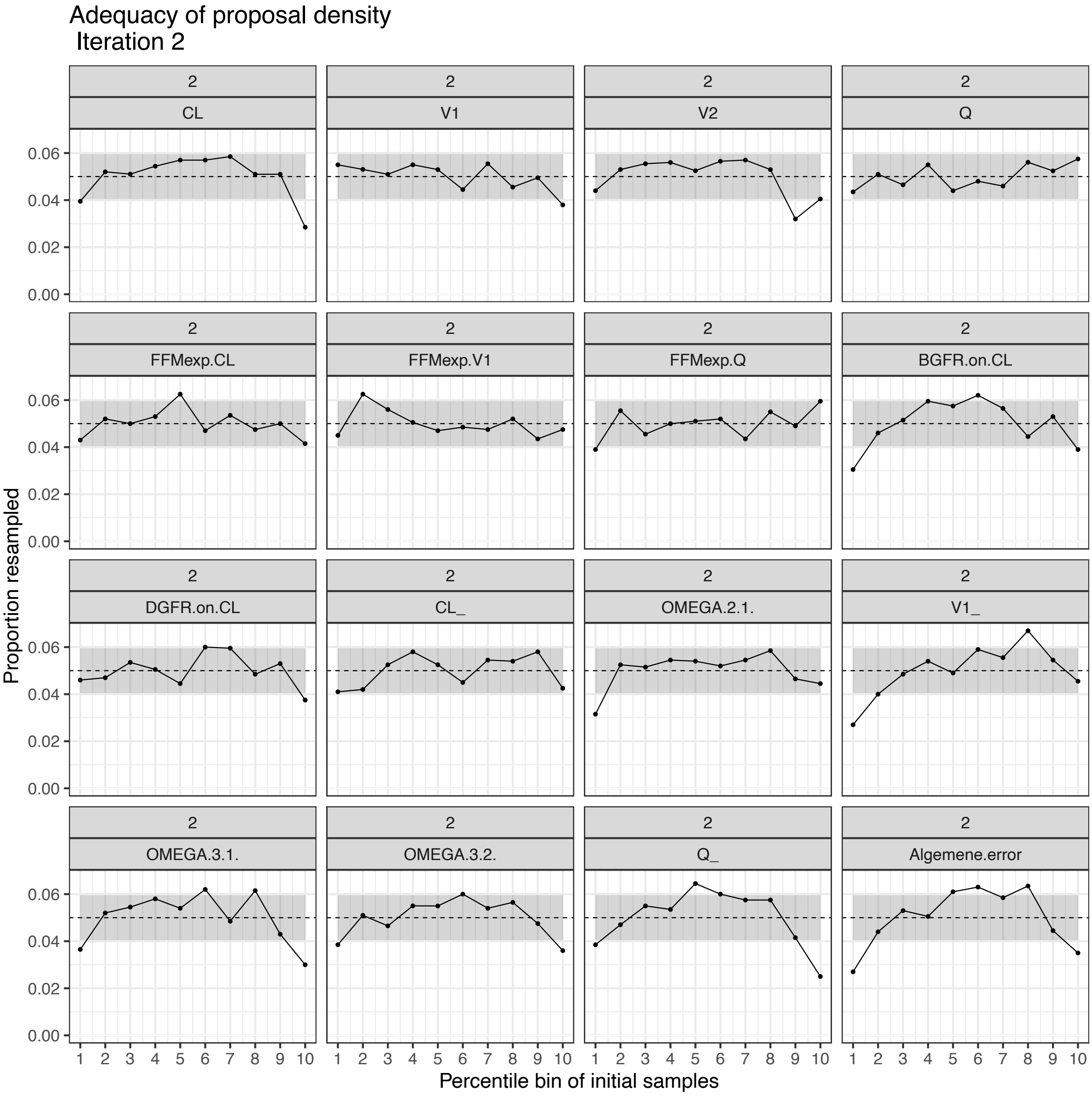


Figure S3: 3D-plot of the impact and interaction of the covariates fat free mass (FFM) and renal function (GFR) on clearance. Colors represent the value for clearance, which increases with higher FFM and GFR.


All dOFV distributions
dOFV
0
10
20
30
40
50
0.00
0.25
0.50
0.75
1.00
Distribution quantiles
Estimated df
87.5 (PROPOSAL1)
41.4 (PROPOSAL2)
20.5 (SIR1)
16 (REF)
15.7 (SIR2)
Iteration number
REF
1
2
Iteration step
PROPOSAL
SIR


Adequacy of proposal density
Iteration 2
2
CL
2
V1
2
V2
2
Q
2
FFMexp.CL
2
FFMexp.V1
2
FFMexp.Q
2
BGFR.on.CL
2
DGFR.on.CL
2
CL_
2
OMEGA.2.1.
2
V1_
2
OMEGA.3.1.
2
OMEGA.3.2.
2
Q_
2
Algemene.error
Proportion resampled
0.00
0.02
0.04
0.06
1
2
3
4
5
6
7
8
9
10
Percentile bin of initial samples

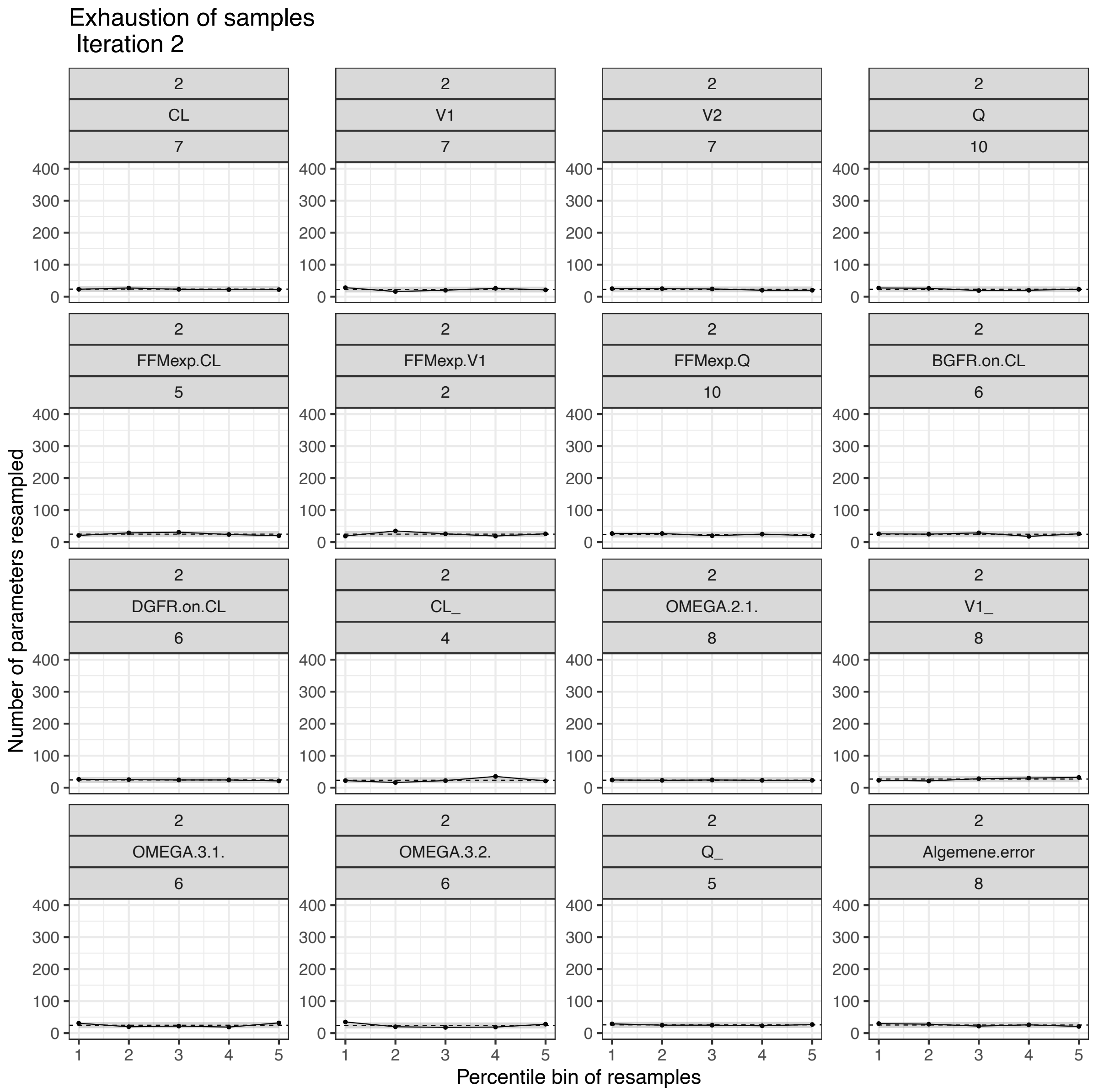


Figure S4: SIR diagnostics

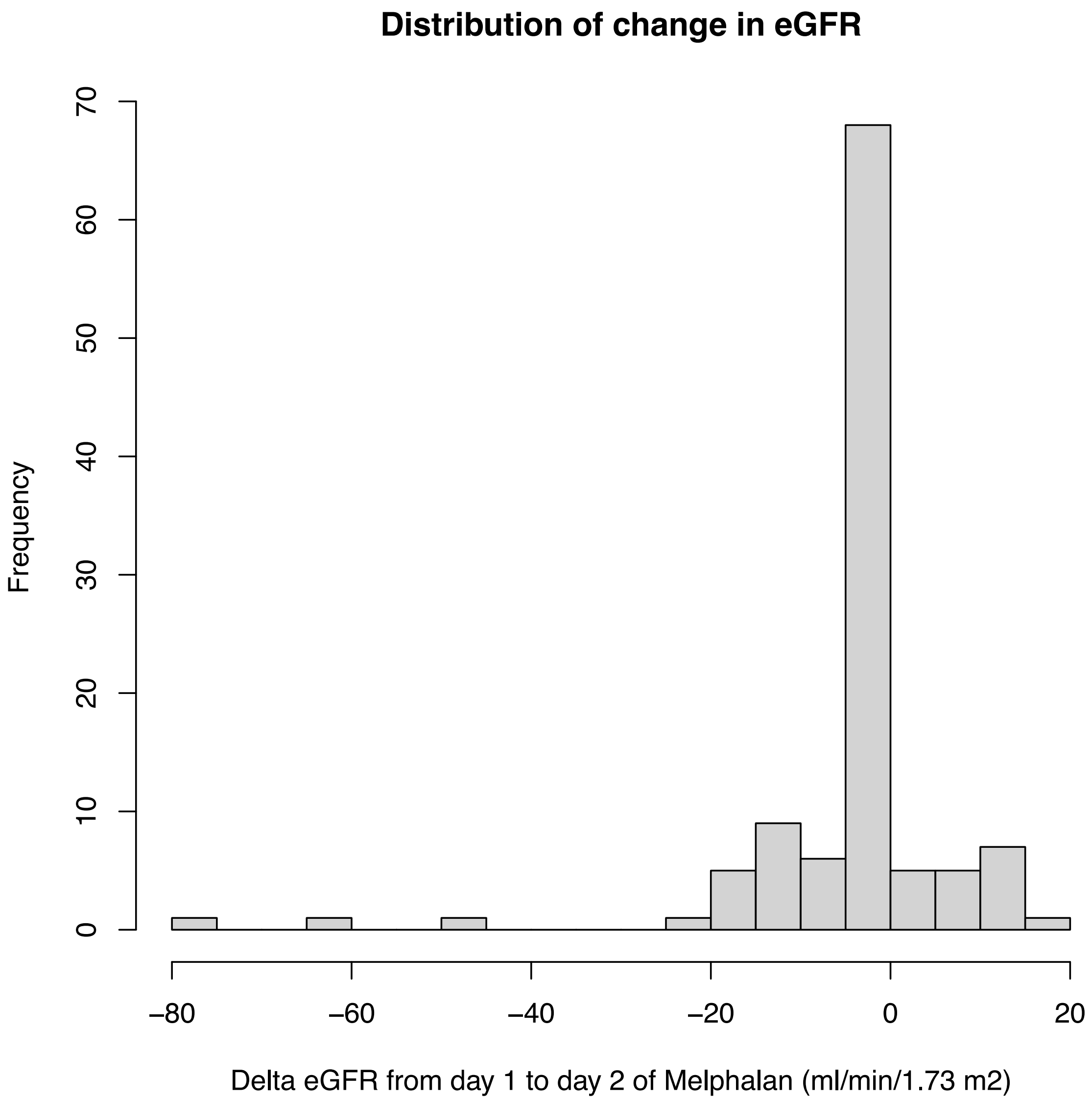


Figure S5: Distribution in changes in eGFR in patients receiving >1 dose of melphalan

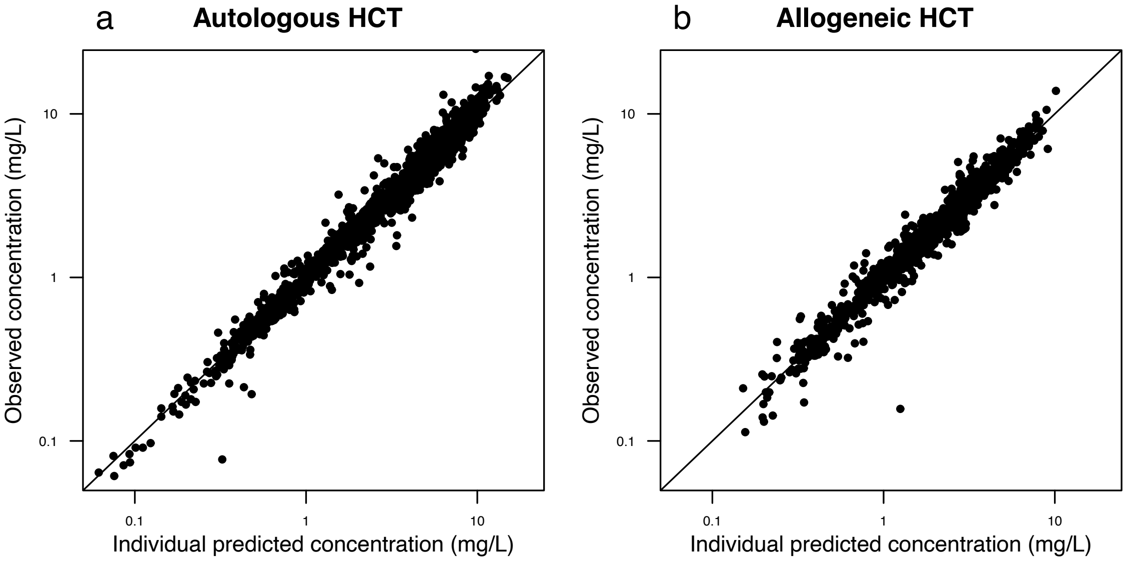


Figure S6: DV vs IPRED final model

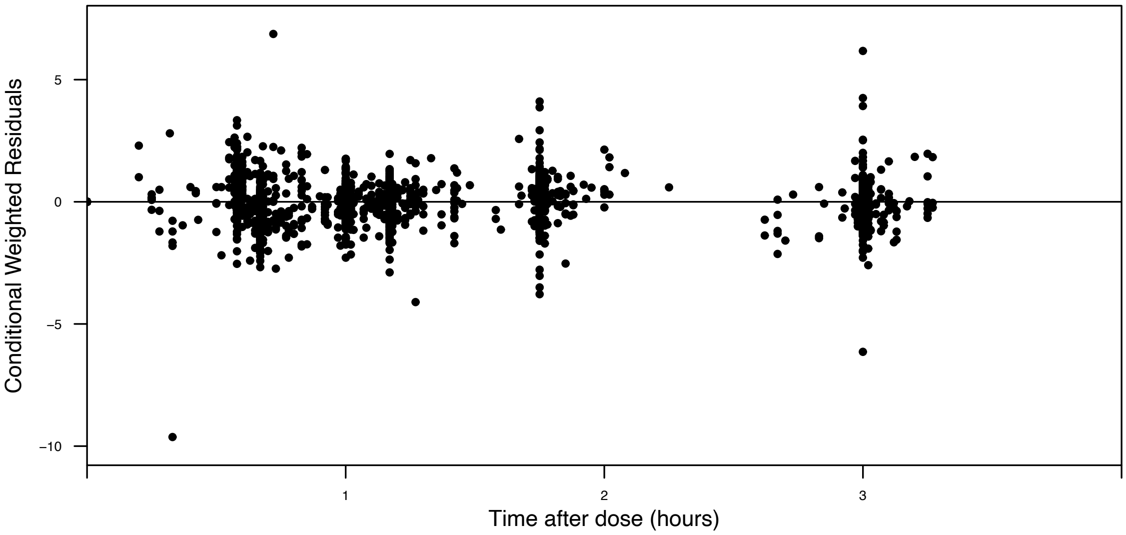


Fig S7: CWRES vs time after dose

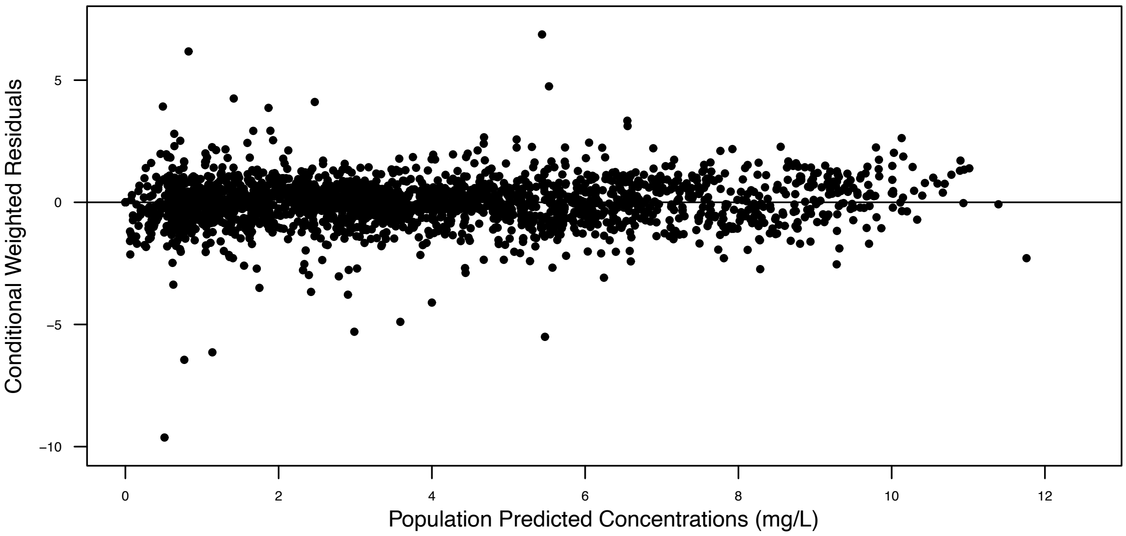


Fig S8: CWRES vs population predicted concentrations

Parameter-Covariate	**Delta OFV**
Forward inclusion relations:	
V1-EGFR	-133.0
V1-COND	-106.8
Q-COND	-95.5
V1-BSA	-88.1
Q-BSA	-70.7
CL-COND	-63.5
CL-BSA	-52.5
CL-AGE	-47.9
CL-HTCR	-30.4
CL-SEX	-18.4
V1-ALBU	-13.2
V1-EFGR	-13.1
V1-AGE	-12.7
Q-SEX	-11.5
CL-CREAT	-11.4
V1-DIAG	-11.1
CL-EGFR	-10.0
CL-FFM	-9.1
Backwards elimination:	
V1-ALBU	6.5
CL-FFM	5.3
V1-AGE	5.0
V1-BSA	4.7
CL-BSA	1.0
V1-EGFR	0.9
Q-BSA	0.0

Table S1: Forward inclusion and backwards elimination of covariates. Legend: V1: central volume of distribution; CL: clearance; Q: intercompartmental clearance; EGFR: estimated glomerular filtration rate; COND: conditioning regimen (categorical); BSA: body surface area; AGE: age; HTCR: haematocrit; ALBU: serum albumin; SEX: sex; FFM: fat free mass; CREAT: serum creatinine. Note: inclusion of a covariate was based on more factors than just the delta OFV in forward inclusion and backward deletion.

Parameter	Dataset [estimate (RSE)]	Shrinkage (%)
Structural model		
CL_{pop} (L/h)	15.1 (2%)	
$V1_{pop}$ (L)	23.3 (2%)	
$V2_{pop}$ (L)	14.7 (6%)	
Q_{pop} (L/h)	13.9 (4%)	
Random variability		
Inter-individual variability on CL (%)	34.8% (3.9%)	2%
Inter-individual variability on V_1 (%)	22.9% (9.7%)	9%
Inter-individual variability on Q (%)	43.5% (11.1%)	17%
Proportional residual error (%)	16.2% (5.5%)	

Table S2: Parameter estimates of base model. *RSE* relative standard error, *CL* linear clearance, V_1 central volume of distribution, V_2 peripheral volume of distribution, Q intercompartmental clearance

Dose Level	n	AUC
Melphalan 1 dose 100mg/m2	33	8.5 (7.4-10)
Melphalan 1 dose 140mg/m2	216	10.6 (8.3-13)
Melphalan 1 dose 200mg/m2	99	14.3 (12-17)
Melphalan 2 doses 70mg/m2	66	9.8 (8.3-11)
Melphalan 2 doses; AUC 13.5; first dose 20mg/m2	10	17.0 (14.9-17)
Melphalan 2 doses; AUC 13.5; first dose 100mg/m2	35	14.6 (13.3-16)

Shown as median (quantiles) unless otherwise specified

Table S3: Area under the curve for Melphalan at different dose levels