Population Pharmacokinetics of Troxacitabine

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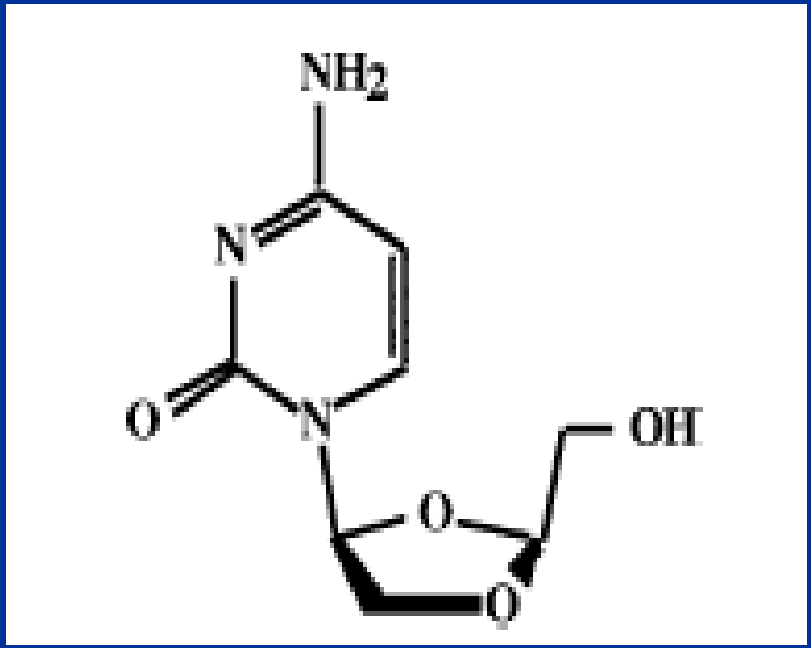
Background

Troxacitabine Pharmacology

- Synthetic L-nucleoside analogue with anti-neoplastic activity in refractory leukemias and solid tumors
- **Mechanism of Action**
  - Intracellular (IC) transport via passive diffusion; nucleoside transport independent
  - Activation by phosphorylation by IC kinases including deoxycytidine kinase
  - Cytotoxic activity via DNA chain termination by incorporating into DNA polymerases
  - Deactivation by endonucleases (APE1); cytidine deaminase resistant



Troxacitabine
(β-L-Odd C or BCH 4556)

Background (2)

Troxacitabine Pharmacology (cont.)

- **Potential Indications**
  - Leukemias; pancreatic, renal & hepatocellular cancers
- **Pharmacokinetics (IV)**
  - Volume of Distribution: 60-78 L (CV%: 32-68)
  - Elimination $T_{1/2}$: 9.8-13 hrs (CV%: 54-85%)
  - Total Clearance: 9.66-11.1 L/hr (CV%: 27-40%); 61-77% dose excreted unchanged in urine within 48 hrs
- **Major Toxicities**
  - Dose Related: neutropenia (AUC related), stomatitis, hand-foot syndrome
  - Other: thrombocytopenia, maculopapular rash
- **Current Development Status**
  - Solid Tumors: Intermittent Dosing - Completed (prostate, colorectal & pancreatic) & ongoing (renal carcinoma & melanoma) Phase II; Continuous IV Infusion - Phase I (48 –120 hr infusion; currently at 72 hrs)
  - Leukemias: Intermittent Dosing - Completed (CML & AML) Phase II; Continuous IV Infusion – Phase I (48 – 168 hr infusion; currently at 144 hrs)

Objective

Develop and validate a population pharmacokinetic (PK) model for troxacitabine using clinical covariates.

Methods

Patient Population

- 111 adult cancer patients from 4 phase I trials
- 83% advanced solid tumors & 17% advanced leukemia
- Patient Covariates: WT, HT, BSA (Mosteller), AGE, SEX, SCR

Serum Troxacitabine Levels

- Dosage: 0.12-12.5 mg/m^2 IV over 30 minutes X 1
- Serum sampling: 12.6 samples per patient (range, 9 -16) obtained 4 min. to 168 hours after start of infusion
- Assay: High-Performance Liquid Chromatography in tandem mass spectrometry (LC/MS/MS) with 0.6-99.9 ng/mL calibration curve

Computer Software

- NONMEM (ver V, level 1.1, UCSF/GloboMax)
- PDx POP (ver 1.1, GloboMax)
- JMP (ver 5.0, SAS Institute)
- EXCEL (ver 2000, Microsoft)

Methods (2)

Model Development: Step 1: Covariate-Free Model

- Fit data to linear compartmental PK models
- Inter-individual Variability of PK Parameters:
  - Exponential: $PK_i = TVPK_i * EXP(\eta_{iPK})$
- Residual (Intra-subject) Error Models Tested
  - Additive, Proportional, Exponential, & Combination
- Computational Methods Tested
  - FOCE vs. FOCE INTER
- Initial PK Parameter Estimates from Compartmental Modeling
- Final Covariate-Free Model Selection
  - Lowest Aikake Information Criterion (AIC):
    AIC = (-2LL)+2p, where -2LL = NONMEM Objective Function &
    2p = #PK parameters X 2
  - Best Predicted to Actual Serum Concentration Graphical Plot

Model Development: Step 2: Covariate to PK Parameter Relationship

- 2 Different Covariates Groupings
  - Group I: BSA, SEX, AGE, Serum Creatinine (SCR)
  - Group II: WT, HT, SEX, AGE, SCR
- Linear Multiple Regression Analysis on Covariates & PK Parameters
  - Identifies covariates with significant correlation to PK parameters as candidates for covariate model building in the respective groupings
  - Significant Correlation: Prob>F, < 0.1

Methods (3)

Model Development: Step 3: Covariate Model Building

- Covariates added in order of highest to lowest level of significant correlation
- PK Parameter Model Building Order: CL, Vds, Qs
- Continuous Variables (BSA, WT, HT, AGE, SCR): 7 mathematical formulas for CL & Qs; 6 mathematical formulas for Vds
- Categorical Variable (SEX): 3 mathematical formulas
- Criteria for Covariate Addition
  - Successful Program Minimization & Covariate Run Statuses
  - $\geq$ 3.875 $\downarrow$ in objective function (chi square, 1 d.f. & α=0.05)
  - Reduction of PK Parameter Intersubject Variability

Model Development: Step 4: Backward Deletion for Final Models

- Stepwise removal of covariates (in reverse order) from full covariate models from step 3
- Covariate remains in final model when removal of the covariate results in a $\geq$ 10.828 $\uparrow$in objective function (chi square, 1 d.f. & α=0.001)

Results

Patient Characteristics/Covariates

Covariate	Mean (± SD)	Quartiles					Symbol
		Min	25%	Median	75%	Max	
[a]Body Surface Area, m^2	1.92 (0.25)	1.34	1.78	1.95	2.08	2.66	BSA
Weight, kg	78.02 (17.86)	42.6	66.85	78.50	86.4	137	WT
Height, cm	172.76 (8.90)	144.78	167.6	173.0	178	193	HT
Sex, male/female	89/22						SEX
Age, years	59.79 (12.38)	29	50.9	60.0	69.1	83	AGE
Serum Creatinine, mg/dL	1.09 (0.27)	0.49	0.9	1.10	1.25	1.82	SCR
[b]Calculated Creatinine Clearance, mL/min/1.73m^2	62.76 (21.73)	32.57	47.90	56.98	72.52	136.2	

a=Mosteller Method $[(WT \times HT \div 3600)^{0.5}]$
b=Cockcroft Gault Method corrected for BSA

Results (2)

Model Development: Step 1: Covariate-Free

- Model Characteristics
  - Three Compartment Linear Model (ADVAN 11 TRANS 4)
  - Residual Error Model: Combination Additive & Proportional
  - FOCE INTER Computation Method

Model Development: Step 2: Covariate to PK Parameter Relationship (Candidates for Covariate Model Building)

PK Parameter	Group I Covariates*	Group II Covariates*
CL	BSA, SCR, AGE, SEX	WT, SCR, AGE, HT
V1	BSA	HT
V2	BSA, AGE	WT, HT
V3	NONE	NONE
Q2	NONE	NONE
Q3	BSA	WT, HT

***Linear Multivariate Regression, Prob > F, <0.1; order of significance**

Results (3)

Model Development: Step 3: Covariate Model Building

Group I Covariate Model	Decrease in Objective Function*
CL: BSA	27.432
CL: BSA; V1: BSA	12.72
CL: BSA; V1: BSA; V2: BSA	36.347
CL: BSA; V1: BSA; V2: BSA; Q3: BSA	14.143

Group II Covariate Model	Decrease in Objective Function*
CL: WT	21.527
CL: WT & AGE	6.09
CL: WT & AGE; V1: HT	5.147
CL: WT & AGE; V1: HT; V2: WT	30.459
CL: WT & AGE; V1: HT; V2: WT & HT	4.27
CL: WT & AGE; V1: HT; V2: WT & HT; Q3: WT	10.506

*** $\geq$ 3.875 decrease (chi square, 1 d.f. & α = 0.05)**

Results (4)

Model Development: Step 4: Final Models

PK Parameter	Group I Covariates[1]	Group II Covariates[2]
CL (L/hr)	9.19 + 4.73*(BSA–1.95)	9.22*(WT÷78.5)**(0.75)
V1 (L)	13.4*BSA ÷ 1.95	13.1
V2 (L)	14.2*EXP(0.61*(BSA-1.95))	14.1*(WT÷78.5)**(0.606)
V3 (L)	95.3	94.5
Q2 (L/hr)	16.8	16.8
Q3 (L/hr)	5.1*EXP(0.615*(BSA-1.95))	5.13*(WT÷78.5)**(0.566)

1. Covariates could not be deleted
2. Backward Deletion: HT from V2, HT from V1, & AGE from CL

FINAL MODEL REDUCTION IN INTERSUBJECT VARIANCE (CV% decrease)

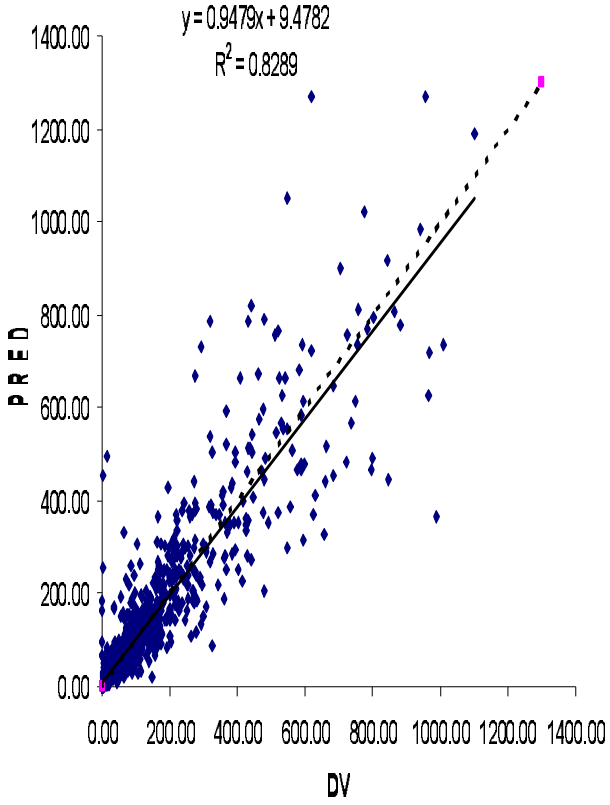
Covariate Group	CL	V1	V2	V3	Q2*	Q3
Group I	26.9% (14.3%)	11.7% (6%)	85.5% (62.3%)	3.15% (1.6%)	N/A (N/A)	33.3% (18.5%)
Group II	19.9% (10.3%)	0% (0%)	79.9% (55.3%)	4.1% (2.13%)	N/A (N/A)	28.3% (15.3%)

N/A= not applicable because intersubject variance value extremely small in Step 1: covariate-free model development (removed from model)

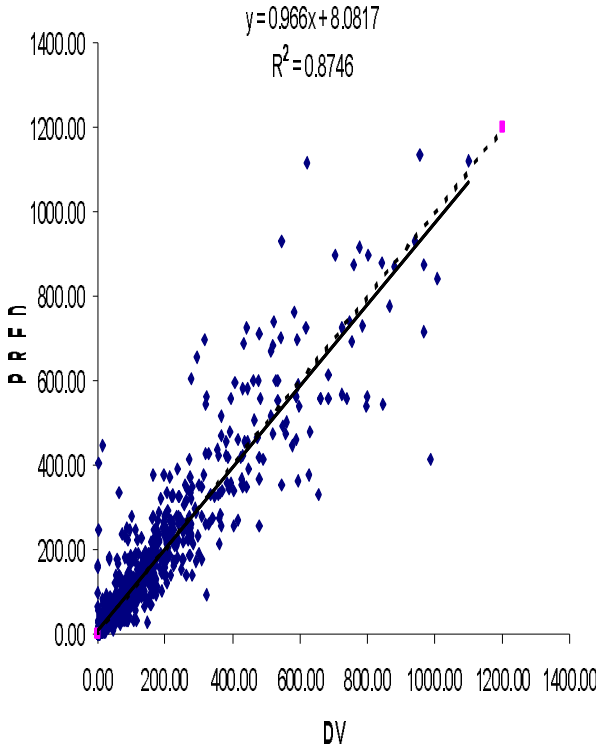
Results (5)

Observed vs. Predicted Concentrations

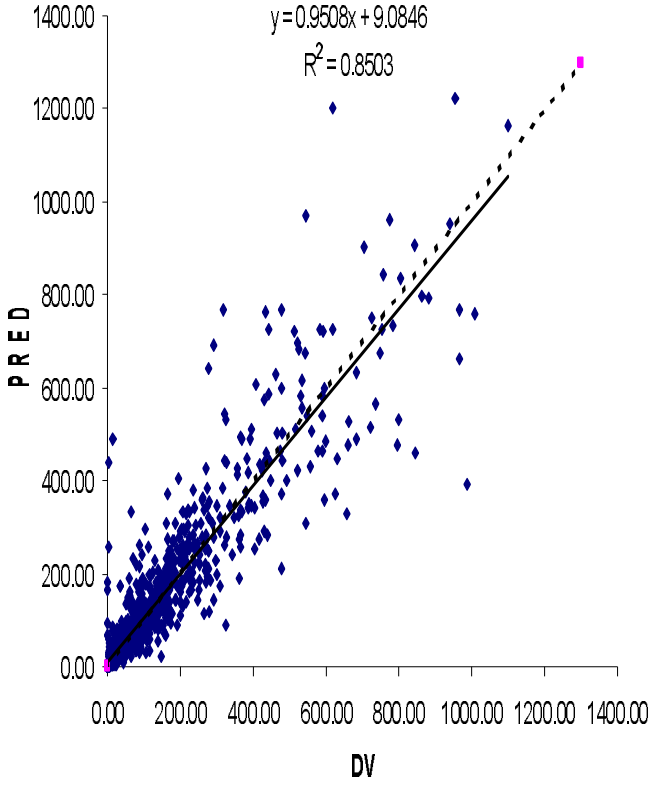
Covariate-Free



Group I



Group II

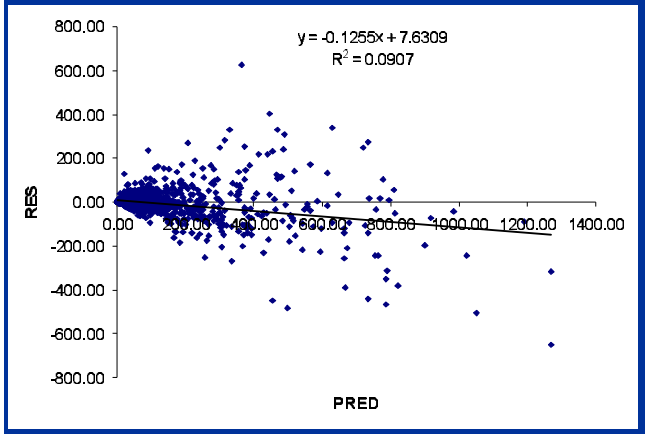


DV = Observed Conc. PRED = Predicted Conc.
Solid line = regression line; Dotted line = line of identity

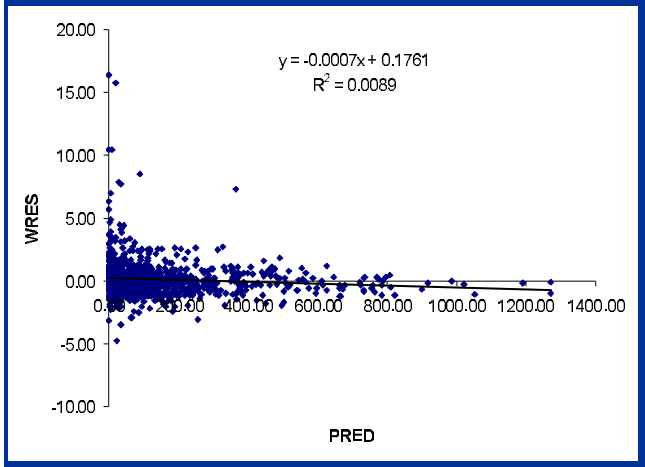
Results (6)

Residuals vs. Predicted Concentrations

Covariate-Free

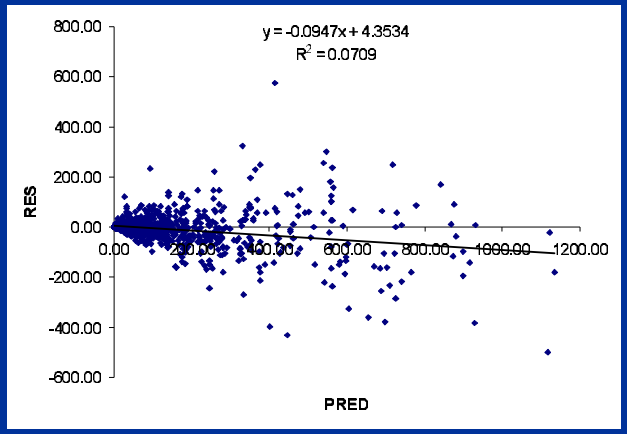


RES range: -650.4 to 624.5

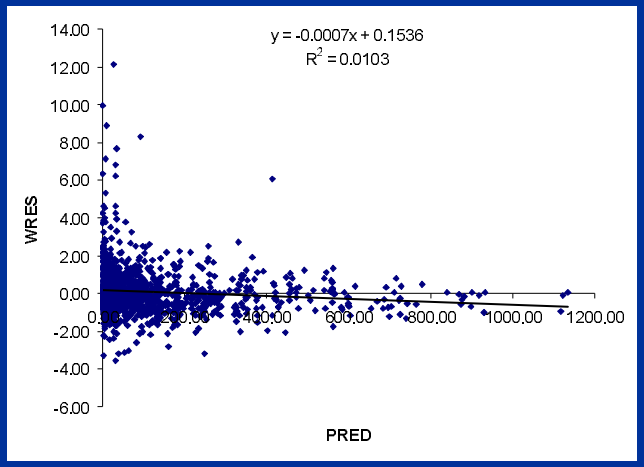


WRES range: -4.77 to 16.38

Group I

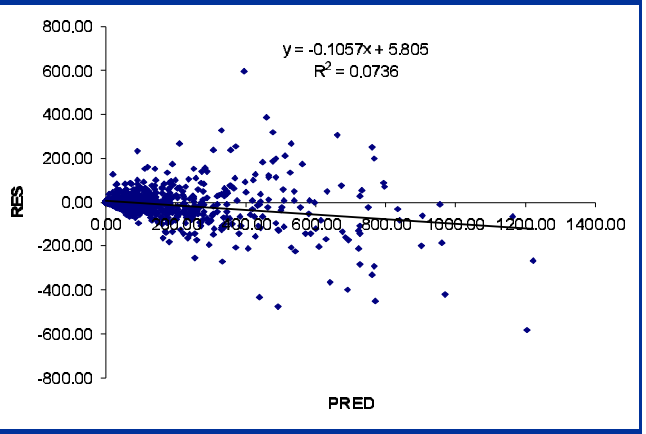


RES range: -497.5 to 574.82

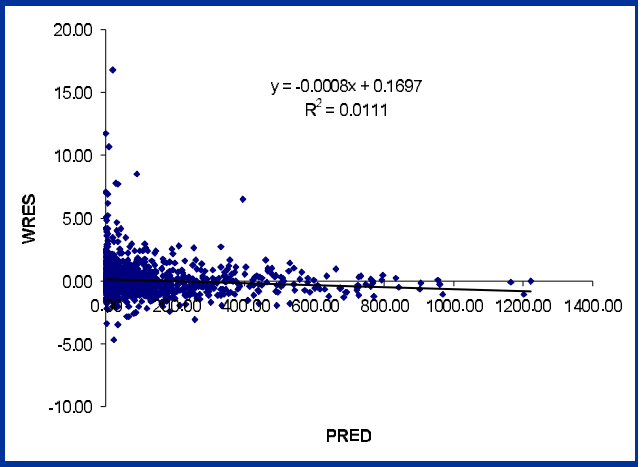


WRES range: -3.53 to 12.16

Group II



RES range: -583.25 to 594.52



WRES range: -4.68 to 16.75

Model Validation

- Internal Cross Validation
- Predictive Performance of PK Parameters
- External Validation

Internal Cross Validation
Methods

- To evaluate the models' ability to predict concentrations
- Construct 20 different data sets by randomly removing 5-6 subject's observed concentrations from the original 111 subject set as each subject is removed only once
- Run both final models on the 20 data sets to obtain the individual predicted concentrations for subjects with removed concentrations
- Calculate each subject's predicted to observed standardized mean prediction error (SMPE)

  SMPE = MPE ÷ SDMPE, where

  MPE= mean prediction error (mean:PRED-OBS per patient)

  SDMPE = std. dev. MPE
- Calculate the SMPE mean & 95% CI to determine if different from "0"

FDA Guidance on Population PK, Feb 1999, CP1
Vozeh S: J Pharmacokinet Biopharm 1990;18(2):161-73

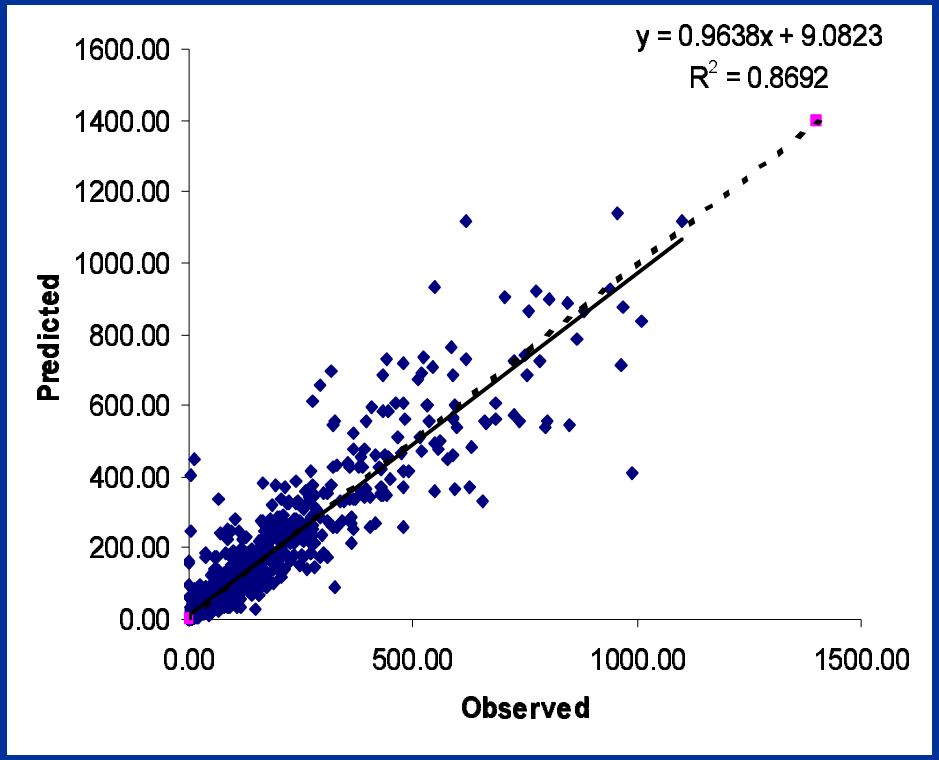
Internal Cross Validation
Results

Final Pop PK Model	SMPE[a] (95% CI)
Group I (BSA)	0.0711 (-0.0406 – 0.183)
Group II (WT/HT)	0.0622 (-0.0483 – 0.173)
Expected Value	0

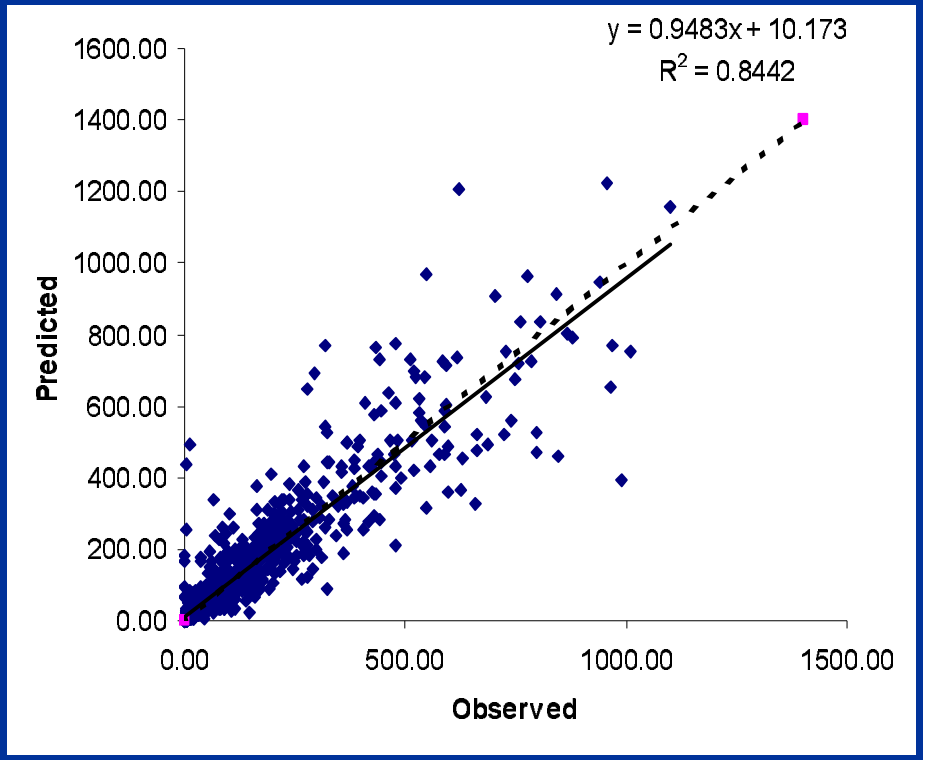
a. SMPE = Standardized Mean Prediction Error, average value for 111 patients. SMPE is expected to be “0” assuming that the model is correct in predicting plasma concentrations.

Internal Cross Validation
Observed vs. Predicted Concentrations

Group I



Group II



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Solid line = regression line; Dotted line = line of identity

Predictive Performance of PK Parameters
Methods

- To evaluate the impact of covariates on model prediction by predictive performance methods (Gallo et.al, & Bruno et.al.)
- Calculate individual % Prediction Error for all PK parameters for covariate-free and final PK models

  $PE_j = (TVPK_j - PK_j) \div TVPK_j \times 100$, where

  $TVPK_j$ = typical (population) PK value for subject j

  PK_j = true PK value for subject j
- Determine if final PK models improve predicting the PK parameters
  - Improvement of individual PK parameter defined:

    $|\text{Final Model } PE_j| < |\text{Cov.Free Model } PE_j|$

Gallo, JM: J Clin Oncol 2000;18(12):2459-67
Bruno, R: J Pharmaco Biopharm 1996:24(2):153-72

Predictive Performance of PK Parameters Prediction Errors Associated with Covariate-Free & Final Pop PK Models

PK Parameter	PE-N Mean (SD)	Group I PE Mean (SD)	Group II PE Mean (SD)	% Pats. Improved (Grp I / Grp II)
CL	-3.26 (25.4)	-2.37 (21.6)	-2.68 (23.4)	65% / 64%
V1	-16.7 (65.2)	-15.3 (61.6)	-17.1 (65.0)	61% / *47%
V2	0.485 (14.9)	0.401 (3.01)	0.521 (4.09)	89% / 88%
V3	-8.84 (53.9)	-8.15 (48.68)	-8.09 (49.3)	*39% / *43%
Q3	-4.21 (29.7)	-2.52 (21.1)	-2.76 (22.4)	68% / 67%

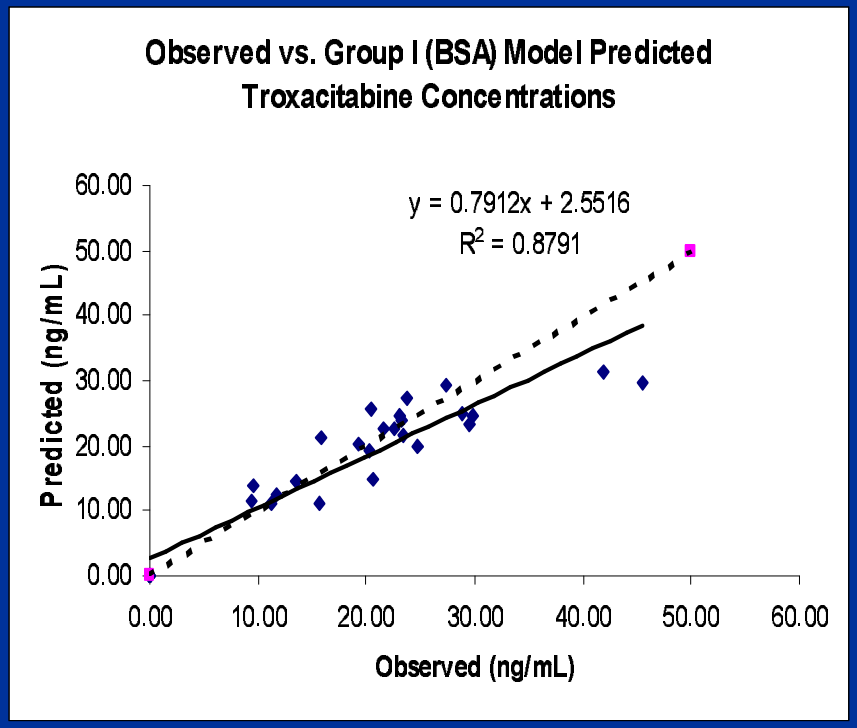
PE-N= covariate-free prediction error; PE= respective group prediction error

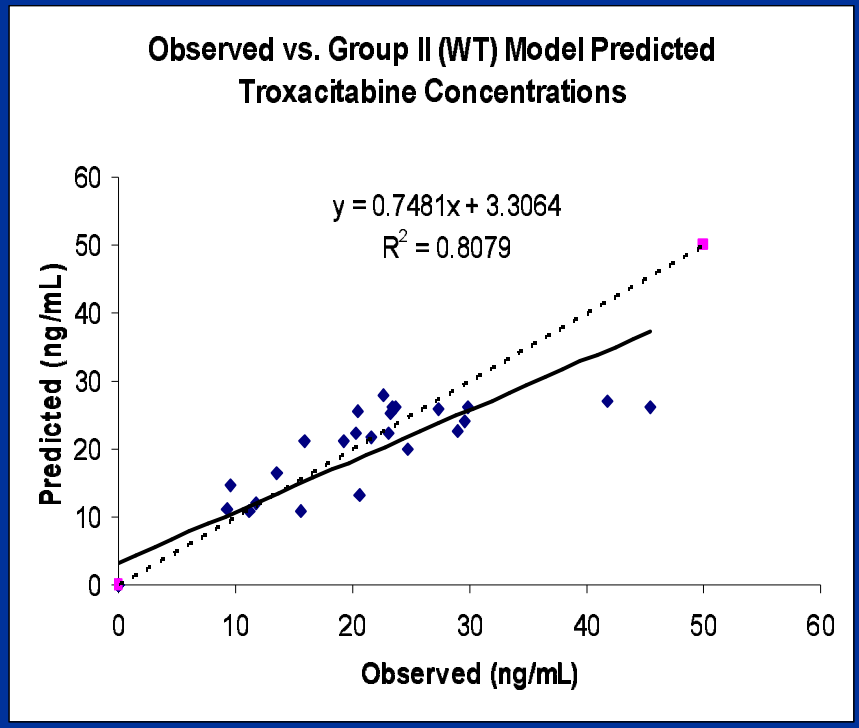
* PK parameter with no covariate added

External Validation
Methods

- To evaluate the BSA & WT final model predictions of troxacitabine concentrations on data obtained from a new trial
- PK data from an open-label, phase I continuous infusion study in patients with advanced solid tumors
  - Doses: 3 mg/m^2/DAY IV up to 24, 48, and 72 hours
  - Serum sampling: 4, 23.5, 47.5, & 71.5 hrs after infusion
  - Data from 7 patients run on BSA final model
- Compare model predicted to observed concentrations

External Validation
Results





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Discussion

- Group I (BSA) Final Model Preferred
  - Better Inter-individual PK Parameter Variance Reduction
  - Better Diagnostic Plots
  - Better Model Validation Results
- Appears to Predict Levels with Continuous Infusion Dosing (up to 72 hrs)
- Serum Creatinine (sCr) Not Included in Models Despite Drug's Renal Clearance Characteristics
  - Majority of patients with normal renal function at baseline
    - 3 of 111 patients with sCr >1.5 mg/dL or GFR < 45 mL/min/1.73m^2
- Future Directions
  - Inclusion of more female & renal compromised patients
  - PK-PD modeling of dose limiting toxicities (neutropenia in solid tumors; stomatitis & hand-foot syndrome in leukemias)

Conclusion

Covariate population modeling supports the use of BSA in current dosing strategies for troxacitabine.

Acknowledgements

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