Individualized Patient Dosing in Phase I Clinical Trials

André Rogatko & James S. Babb

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Theophrastus Philipus Aureolus Bombastus von Hohenheim

aka, **Paracelsus**,

Birth: Einsiedeln, Switzerland, 1493

Career: no fixed place, throughout Germany,
German- speaking countries, and Switzerland.

Death: Salzburg, Austria, 1541

Scientific Disciplines

Primary: Medicine, Iatrochemistry, Chemistry

Subordinate: Astrology, Natural Philosophy

Means of Support

Primary: Medicine

Secondary: Government

Uses arsenic to treat syphilis with great success.

Some patients were cured,
Some died due to excess treatment toxicity.

current paradigm

dose of a therapeutic agent is not adjusted
to accommodate individual patient differences

the identification of working-dose of new cancer therapies
is mainly restricted to phase I trials

proposed paradigm

dose fine-tuning using patient specific attributes

search for the optimal dose extended beyond phase I
and into phases II and III

GOAL

Demonstrate that

Patient Population is Heterogeneous

in terms of Treatment Tolerance

Patient Characteristics Compete with Dose as Predictors of Acute Treatment Toxicity in Early Phase Clinical Trials

André Rogatko,* James S. Babb,* Hao Wang,*
Michael J. Slifker,*and Gary R. Hudes**

Submitted to JCO

Descriptive Statistics

Sample size: 459 patients

	Mean	Std. Dev	Min.	Max.	Median
Age at First Dose	60.2	11	27	84	62

Gender	Patients	Percentage
Females	153	33.3
Males	306	66.7

Phase	Patients	Percentage
I	275	59.9
I/II	24	5.2
II	160	34.9

Agent	Patients	Percentage
Taxol	245	53.4
Estramustine	154	33.6
Carboplatin	140	30.5
Cisplatin	45	9.8
Taxotere	43	9.4
Irinotecan	36	7.8
Tomudex	36	7.8
R115777	34	7.4
5fu	30	6.5
g-csf	27	5.9
Gemcitabine	19	4.1
Topotecan	14	3.0
Cytoxan	13	2.8
Vinblastine	12	2.6
Bryostatin	12	2.6
Bms-188797	11	2.4
Bms-214662	11	2.4
Docetaxel	5	1.1
Ly335979	3	0.7
Leucovorin	2	0.4

Highest Toxicity	Category	Patients	Percentage
Overall	**No toxicity**	10	2.2
	1	84	18.3
	2	116	25.3
	3	139	30.3
	4	110	24.0
Non-Hematological	**No toxicity**	43	9.4
	1	147	32.0
	2	121	26.4
	3	110	24.0
	4	38	8.3
Hematological	**No toxicity**	114	24.8
	1	68	14.8
	2	105	22.9
	3	80	17.4
	4	92	20.0

Toxicity Index - TI

Properties:

- Score $\geq 3 \Leftrightarrow$ DLT
- Maximum Toxicity Grade $\Leftrightarrow$ Integer Part (TI)
- All toxicity grades are taken into account
- Lower grades contribute little
- $0 \leq TI \leq 5$
- Many toxicities of the same grade

LESS THAN

a single toxicity of the next higher grade

Toxicity Grades of a Subject

$$X_1 \geq X_2 \geq \ldots \geq X_n$$

Toxicity Index – *TI*

$$TI = X_1 + \frac{X_2}{1+X_1} + \frac{X_3}{(1+X_1)(1+X_2)} + \ldots + \frac{X_n}{(1+X_1)\ldots(1+X_{n-1})}$$

$$TI = \sum_{i=1}^{n} w_i X_i, \text{ where } w_i = \prod_{j=1}^{i-1} (X_j + 1)^{-1}$$

Toxicity Index - TI

Example:

Subject with two grade 3 toxicities:

$$TI = 3 + \frac{3}{4} = 3.75$$

Subject with one grade 3 and ten grade 2 toxicities:

$$TI = 3 + \frac{2}{4} + \frac{2}{3 \cdot 4} + \frac{2}{3^2 \cdot 4} + \cdots + \frac{2}{3^9 \cdot 4} \approx 3.74999.$$

$$
\begin{aligned}
TI(n_1, n_2, n_3, n_4) = 5\left(1 - \left(\tfrac{1}{5}\right)^{n_4}\right) \\
+ 4\left(\tfrac{1}{5}\right)^{n_4}\left(1 - \left(\tfrac{1}{4}\right)^{n_3}\right) \\
+ 3\left(\tfrac{1}{5}\right)^{n_4}\left(\tfrac{1}{4}\right)^{n_3}\left(1 - \left(\tfrac{1}{3}\right)^{n_2}\right) \\
+ 2\left(\tfrac{1}{5}\right)^{n_4}\left(\tfrac{1}{4}\right)^{n_3}\left(\tfrac{1}{3}\right)^{n_2}\left(1 - \left(\tfrac{1}{2}\right)^{n_1}\right)
\end{aligned}
$$

GRADE				TI
4	3	2	1	
2	2	2	2	4.95708
2	2	2	1	4.95694
2	2	2	0	4.95667
2	2	1	2	4.95625
2	2	1	1	4.95583
2	2	1	0	4.95500
2	2	0	2	4.95375
2	2	0	1	4.95250
2	2	0	0	4.95000
2	1	2	2	4.94833
2	1	2	1	4.94778
2	1	2	0	4.94667
2	1	1	2	4.94500
2	1	1	1	4.94333
2	1	1	0	4.94000
2	1	0	2	4.93500
2	1	0	1	4.93000
2	1	0	0	4.92000
2	0	2	2	4.91333
2	0	2	1	4.91111
2	0	2	0	4.90667

GRADE				TI
4	3	2	1	
2	0	1	2	4.90000
2	0	1	1	4.89333
2	0	1	0	4.88000
2	0	0	2	4.86000
2	0	0	1	4.84000
2	0	0	0	4.80000
1	2	2	2	4.78542
1	2	2	1	4.78472
1	2	2	0	4.78333
1	2	1	2	4.78125
1	2	1	1	4.77917
1	2	1	0	4.77500
1	2	0	2	4.76875
1	2	0	1	4.76250
1	2	0	0	4.75000
1	1	2	2	4.74167
1	1	2	1	4.73889
1	1	2	0	4.73333
1	1	1	2	4.72500
1	1	1	1	4.71667

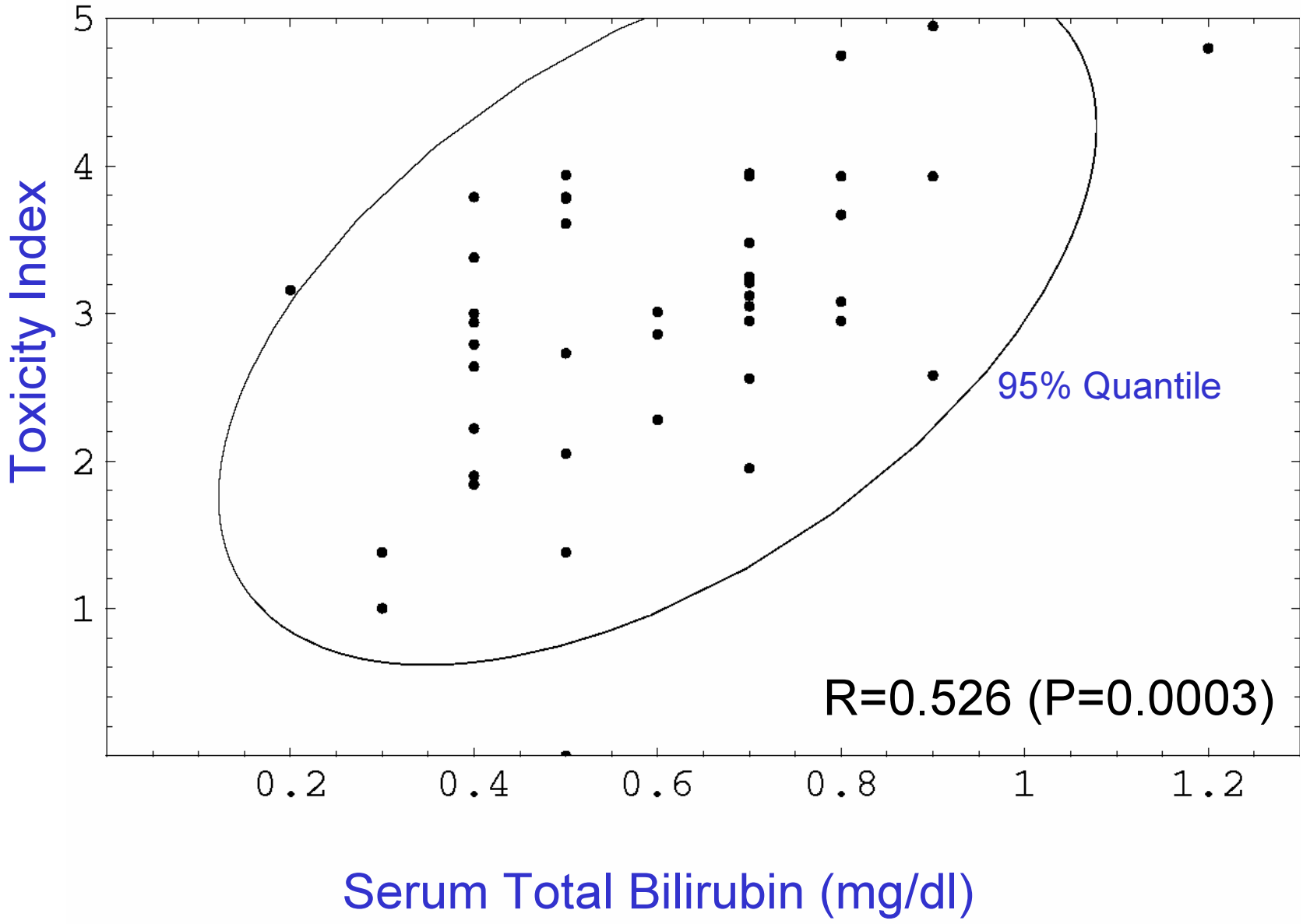
GRADE				TI
4	3	2	1	
1	1	1	0	4.70000
1	1	0	2	4.67500
1	1	0	1	4.65000
1	1	0	0	4.60000
1	0	2	2	4.56667
1	0	2	1	4.55556
1	0	2	0	4.53333
1	0	1	2	4.50000
1	0	1	1	4.46667
1	0	1	0	4.40000
1	0	0	2	4.30000
1	0	0	1	4.20000
1	0	0	0	4.00000
0	2	2	2	3.92708
0	2	2	1	3.92361
0	2	2	0	3.91667
0	2	1	2	3.90625
0	2	1	1	3.89583
0	2	1	0	3.87500
0	2	0	2	3.84375
0	2	0	1	3.81250

GRADE				TI
4	3	2	1	
0	2	0	0	3.75000
0	1	2	2	3.70833
0	1	2	1	3.69444
0	1	2	0	3.66667
0	1	1	2	3.62500
0	1	1	1	3.58333
0	1	1	0	3.50000
0	1	0	2	3.37500
0	1	0	1	3.25000
0	1	0	0	3.00000
0	**0**	**2**	**2**	**2.83333**
0	**0**	**2**	**1**	**2.77778**
0	**0**	**2**	**0**	**2.66667**
0	**0**	**1**	**2**	**2.50000**
0	**0**	**1**	**1**	**2.33333**
0	**0**	**1**	**0**	**2.00000**
0	**0**	**0**	**2**	**1.50000**
0	**0**	**0**	**1**	**1.00000**
0	**0**	**0**	**0**	**0.00000**

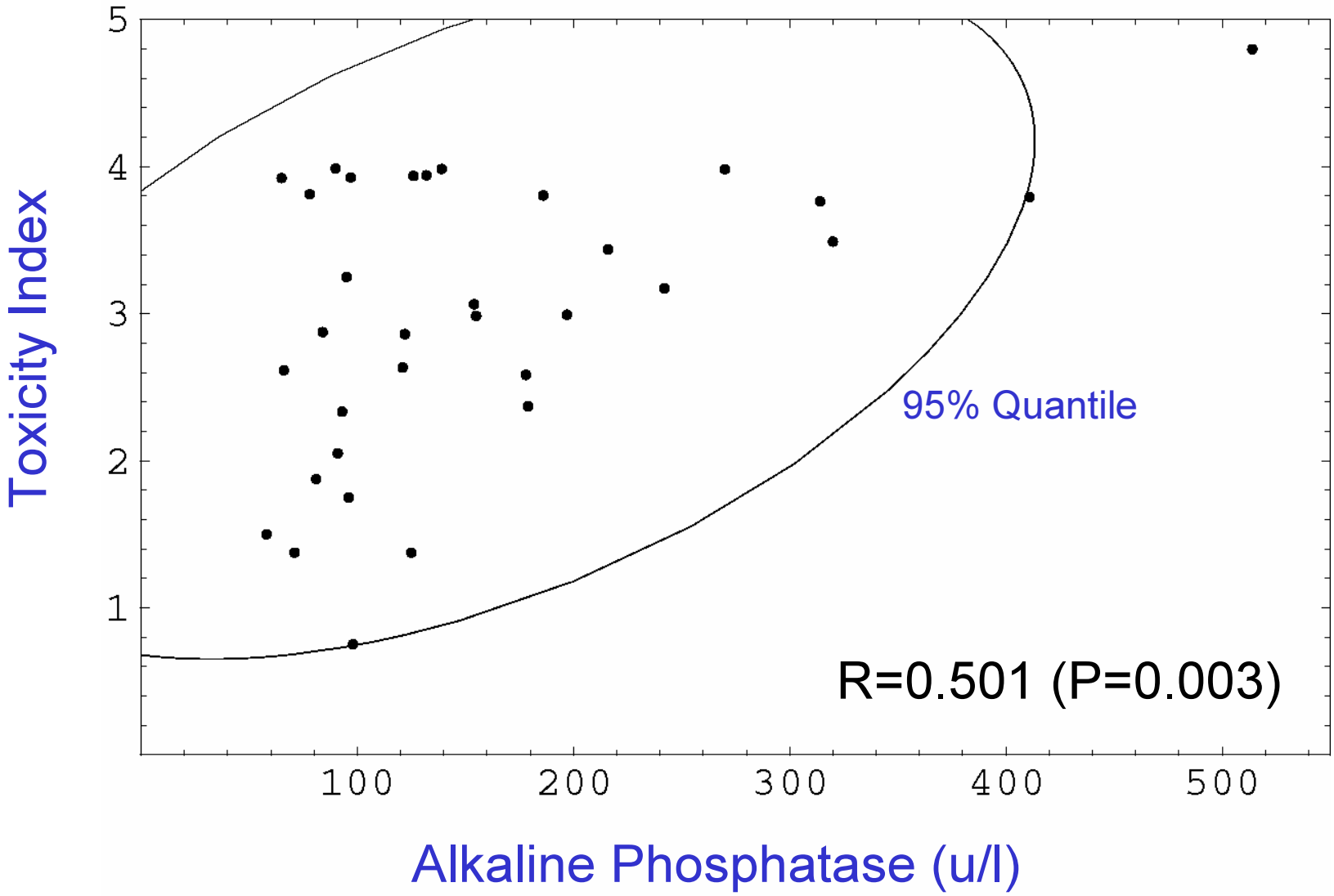
‘Best Subset’ of Covariates for each Agent

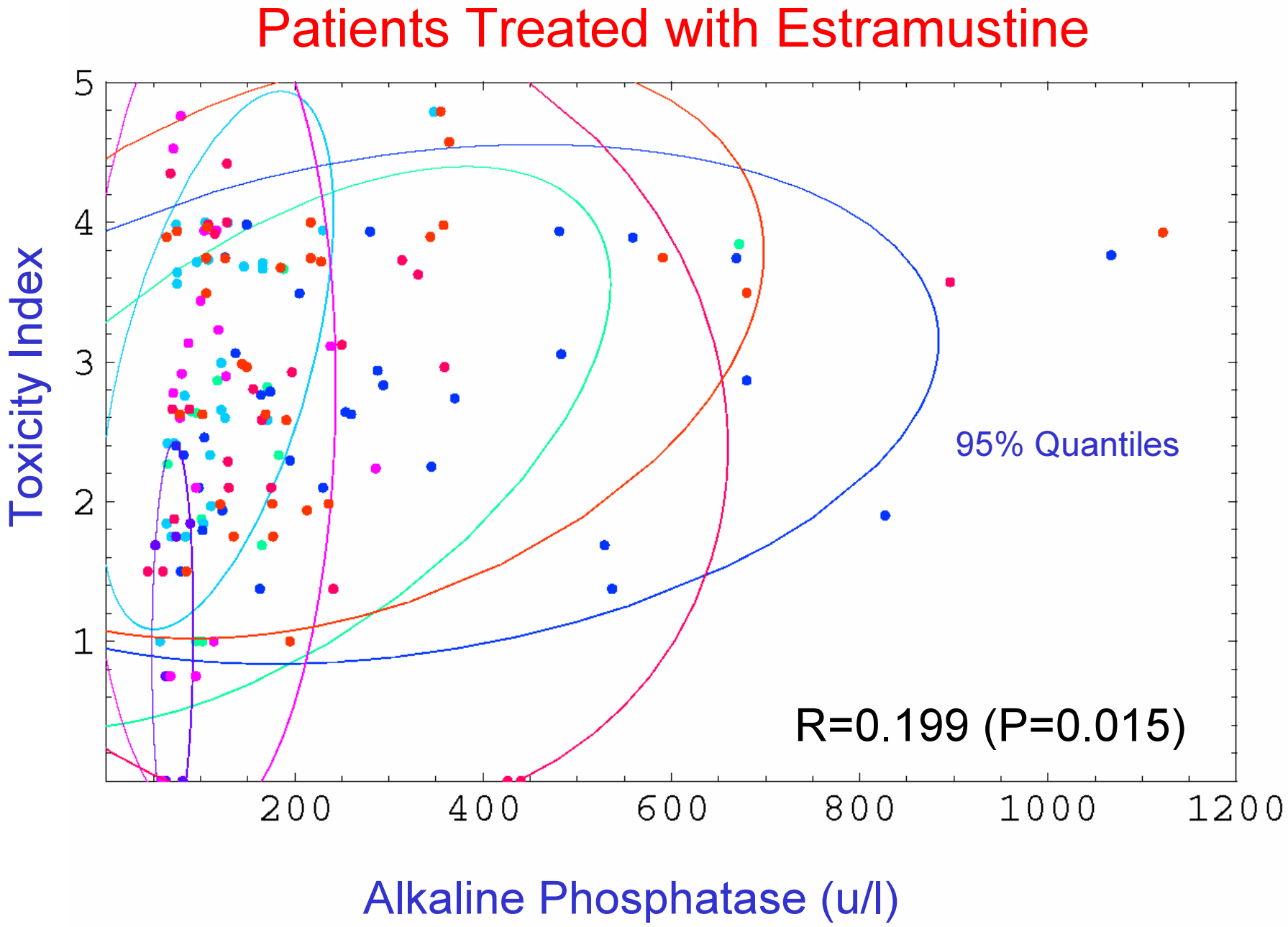
Agent	Number of Patients	Covariate	Significance level
Taxol	245	Dose (mg)	0.0341
		ECOG Performance Status	0.0001
Estramustine	154	Dose (mg/m^2)	0.0041
		Alkaline Phosphatase (u/l)	0.0059
		ECOG Performance Status	0.0001
Carboplatin	140	Dose (AUC)	0.4060
		Serum Total Bilirubin (mg/dl)	0.0057
Cisplatin	45	Dose (mg/m^2)	0.0001
		Alkaline Phosphatase (u/l)	0.0111
Taxotere	43	Dose (mg/kg)	0.0997
		Serum Total Bilirubin (mg/dl)	0.0003
Irinotecan + Tomudex	36	Irinotecan Dose (mg/kg)	0.0001
		Tomudex Dose (mg/kg)	0.1235
		Alkaline Phosphatase (u/l)	0.0006
		Serum Creatinine (mg/dl)	0.1301
		Tobacco Use	0.0005
R115777	34	Dose (mg/m^2)	0.0495
		Alkaline Phosphatase (u/l)	0.0187

Patients Treated with Taxotere

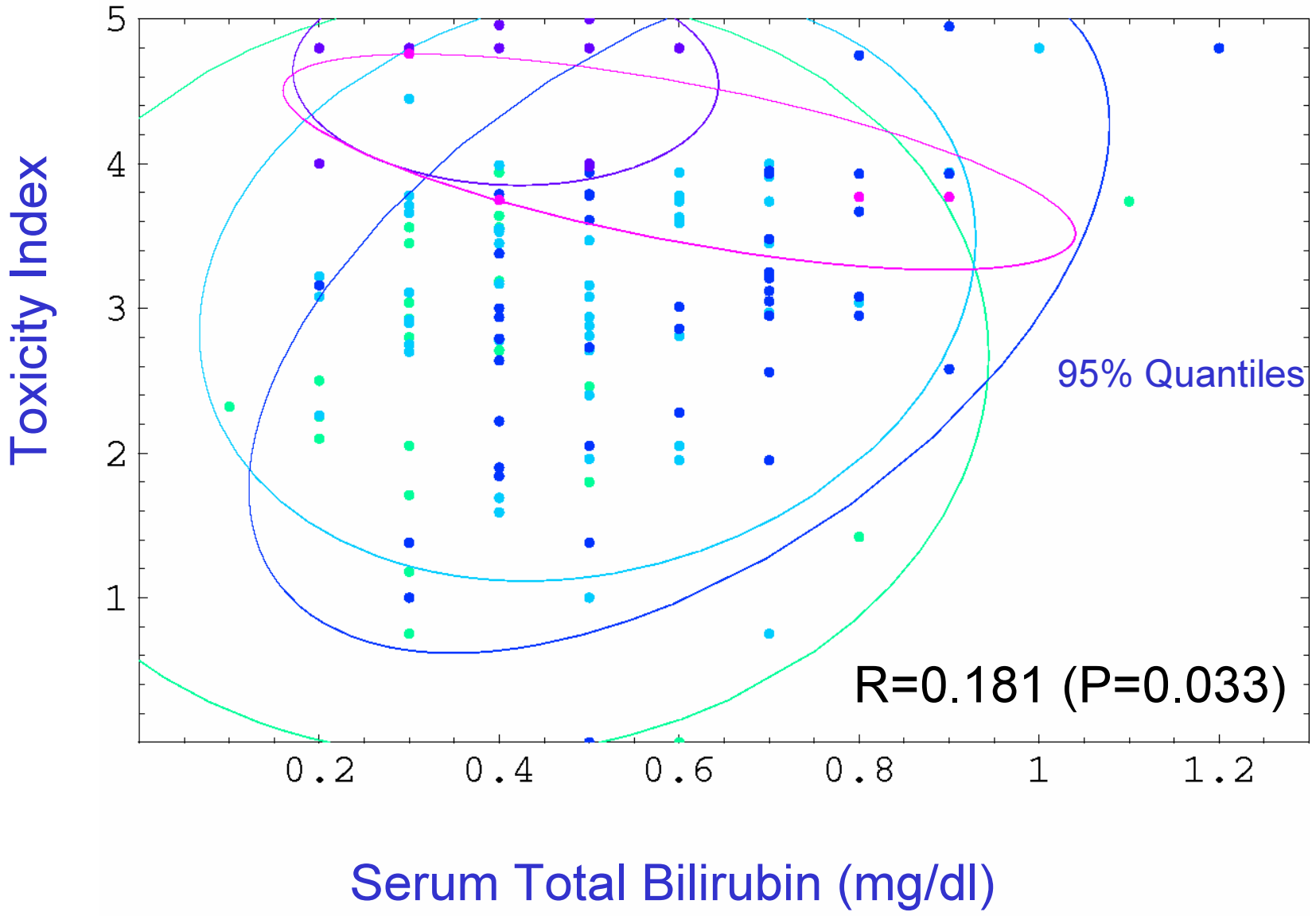


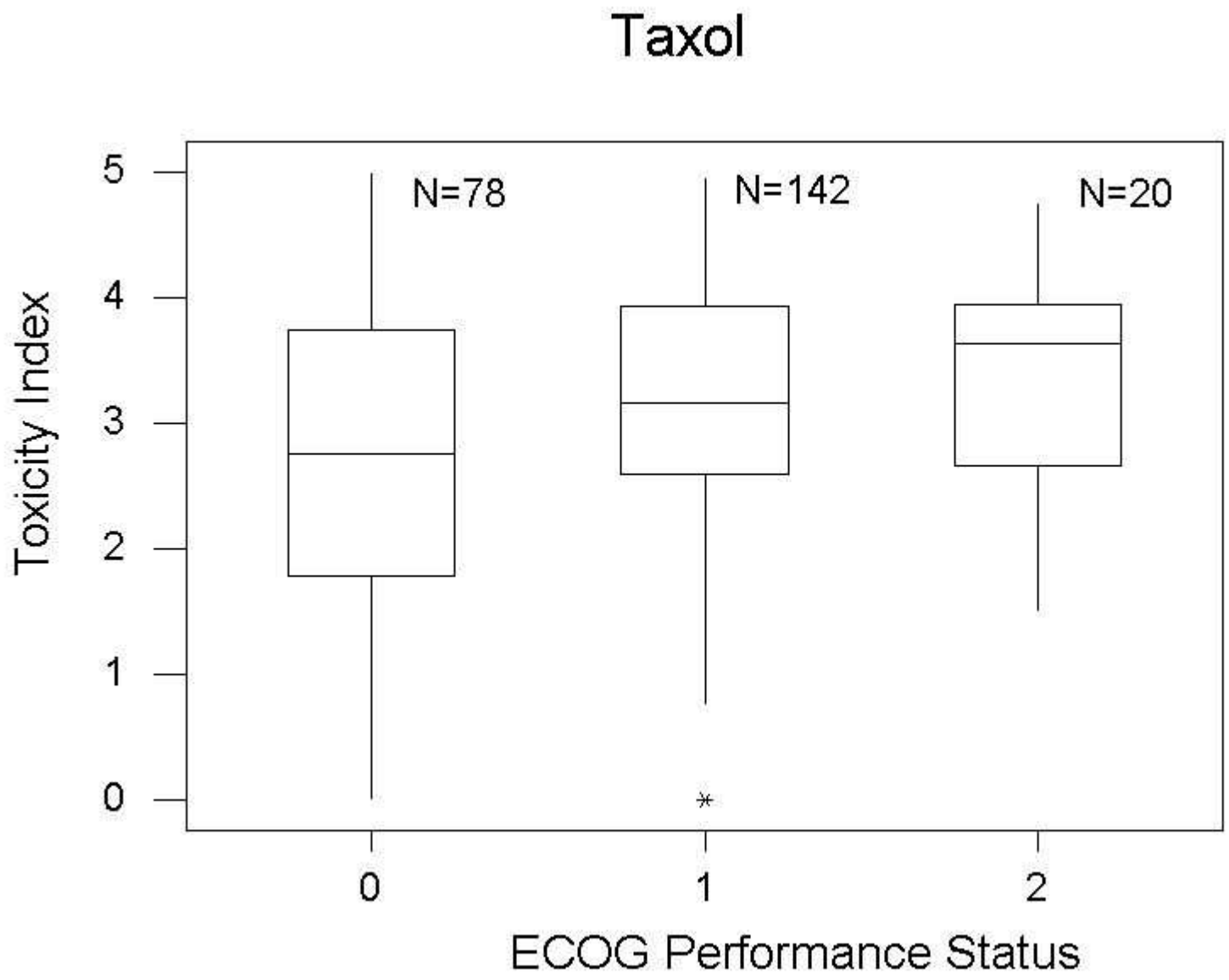
Patients Treated with R115777




Patients Treated with Estramustine
Toxicity Index
5
4
3
2
1
95% Quantiles
R=0.199 (P=0.015)
200
400
600
800
1000
1200
Alkaline Phosphatase (u/l)

Patients Treated with Carboplatin




Taxol
Toxicity Index
5
4
3
2
1
0
N=78
N=142
N=20
0
1
2
ECOG Performance Status

SUMMARY

- Toxicity Index
  Greater sensitivity to uncover potential associations

- For every agent, at least one pre-treatment patient-specific characteristic found to be significant predictor of adverse treatment response

- Generate Hypothesis for Future Trials

EWOC

Escalation with Overdose Control

Overdose Control
Proven Convergence
Confidence Interval for MTD
Flexible Patient Scheduling
Allow Covariate

Personalizing the Phase I Dose EWOC with Covariates

- One Dose Fits ALL Assumption

- Case study - PNU Trial:

  PNU Action moderated by Anti-SEA antibodies

Individualized Patient Dosing in Phase I Clinical Trials: the Role of EWOC in PNU-214936

Jonathan D. Cheng, Corey Langer, Steinar Aamdal, Francisco Robert, Lars Rupert Engelhardt, Olov Fernberg, Joan Schiller, Goran Forsberg, R. Katherine Alpaugh, Louis M. Weiner, James S. Babb and André Rogatko

Submitted to JCO

DOSE-TOXICITY MODEL

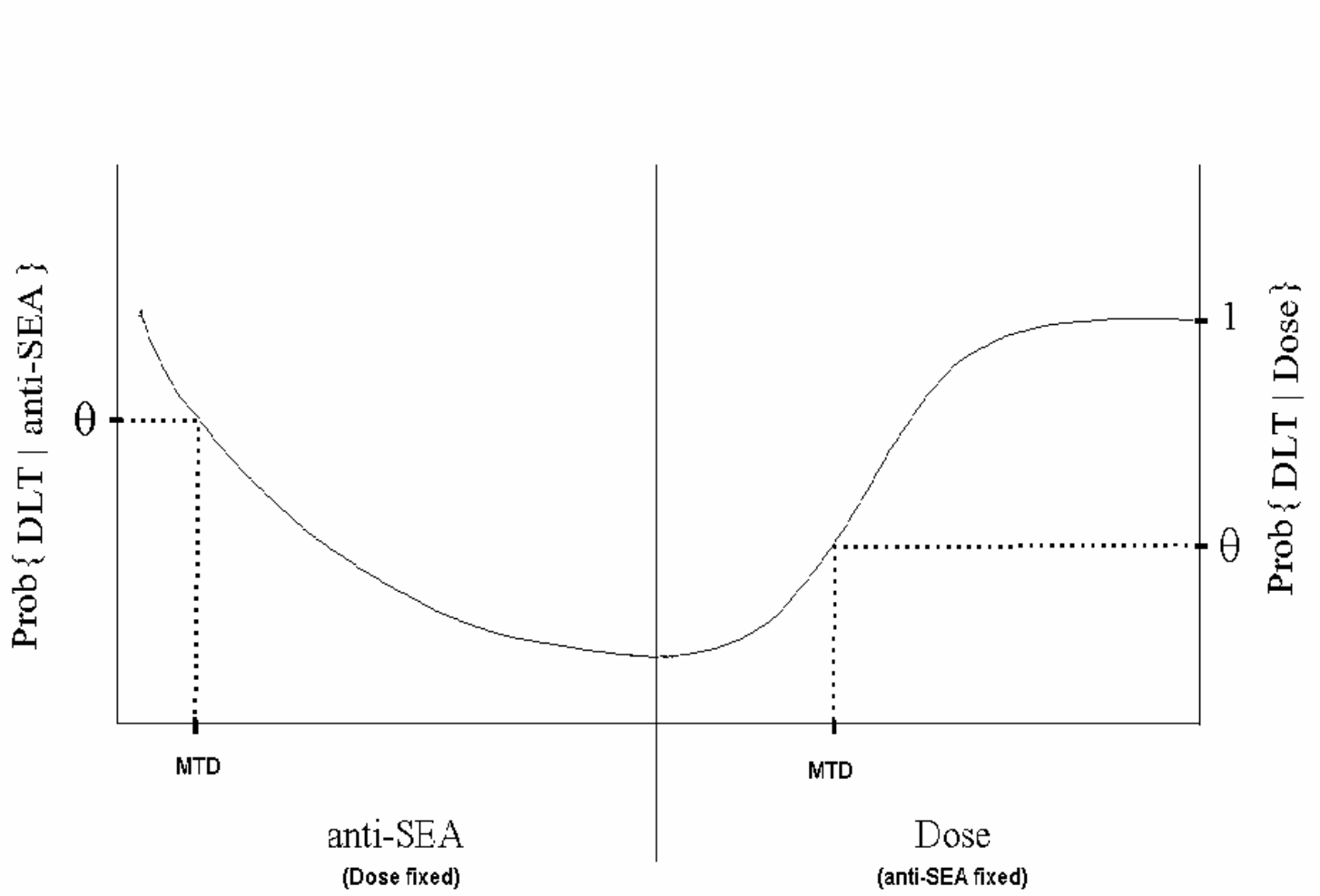
$$p_c(x) \;=\; \text{Prob}[\ \text{DLT}\ |\ \text{Dose}\ = x,\ \text{anti}\ \text{-}\ \text{SEA}\ = c\,]$$

LOGISTIC MODEL

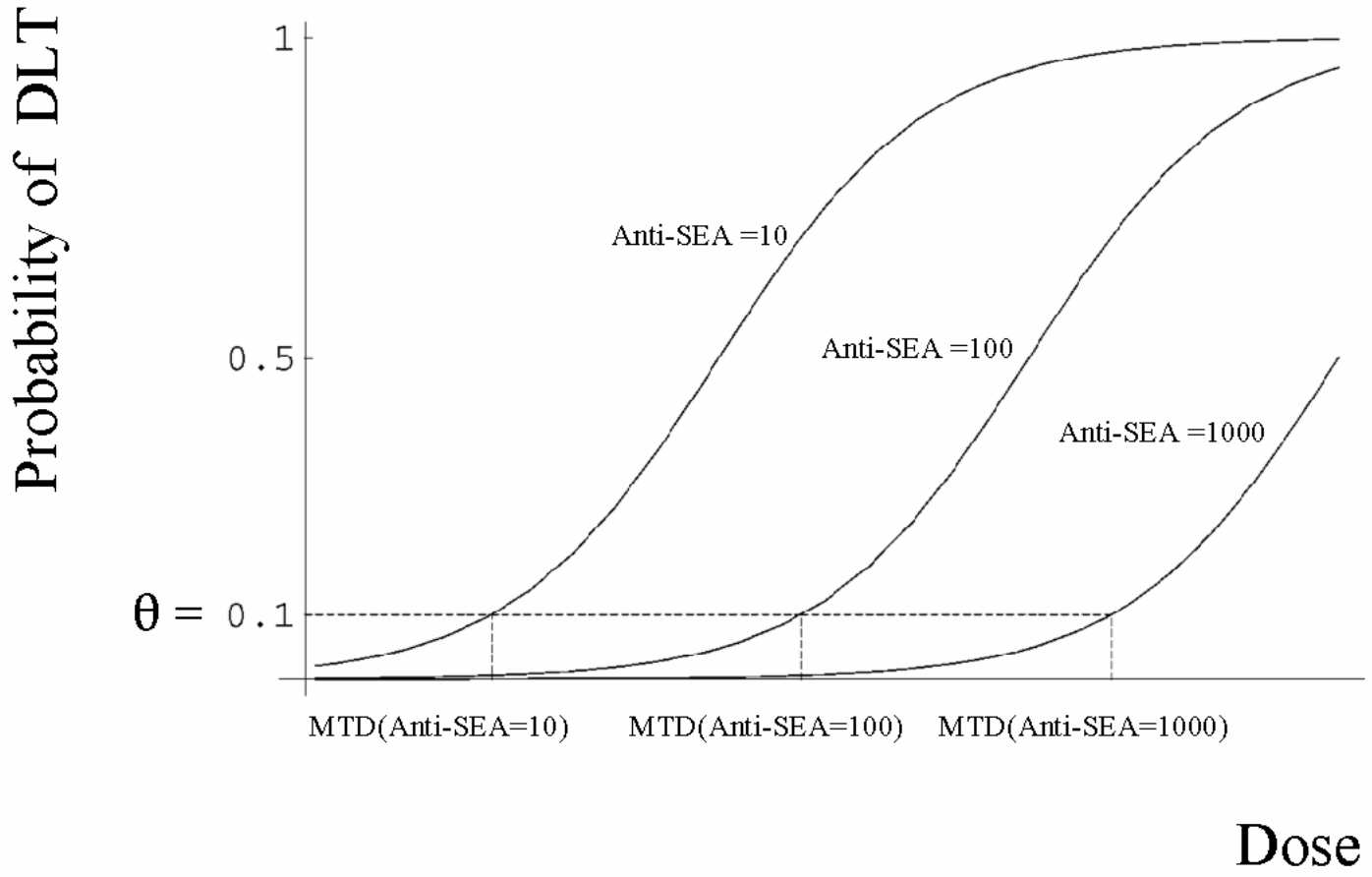
$$\text{Logit}\left[p_c(x)\right] \;=\; \alpha \;+\; \beta \ln(x) \;+\; \delta \ln(c)$$

$$\beta > 0,\ \ \delta < 0$$

DOSE-TOXICITY MODEL



Dose-Toxicity Model



PRIOR INFORMATION

PARAMETERS

$$\gamma_{\max} = \gamma(1800)$$

$$\rho_1 = p_{0.05}(0.5)$$

$$\rho_2 = p_{1800}(0.5)$$

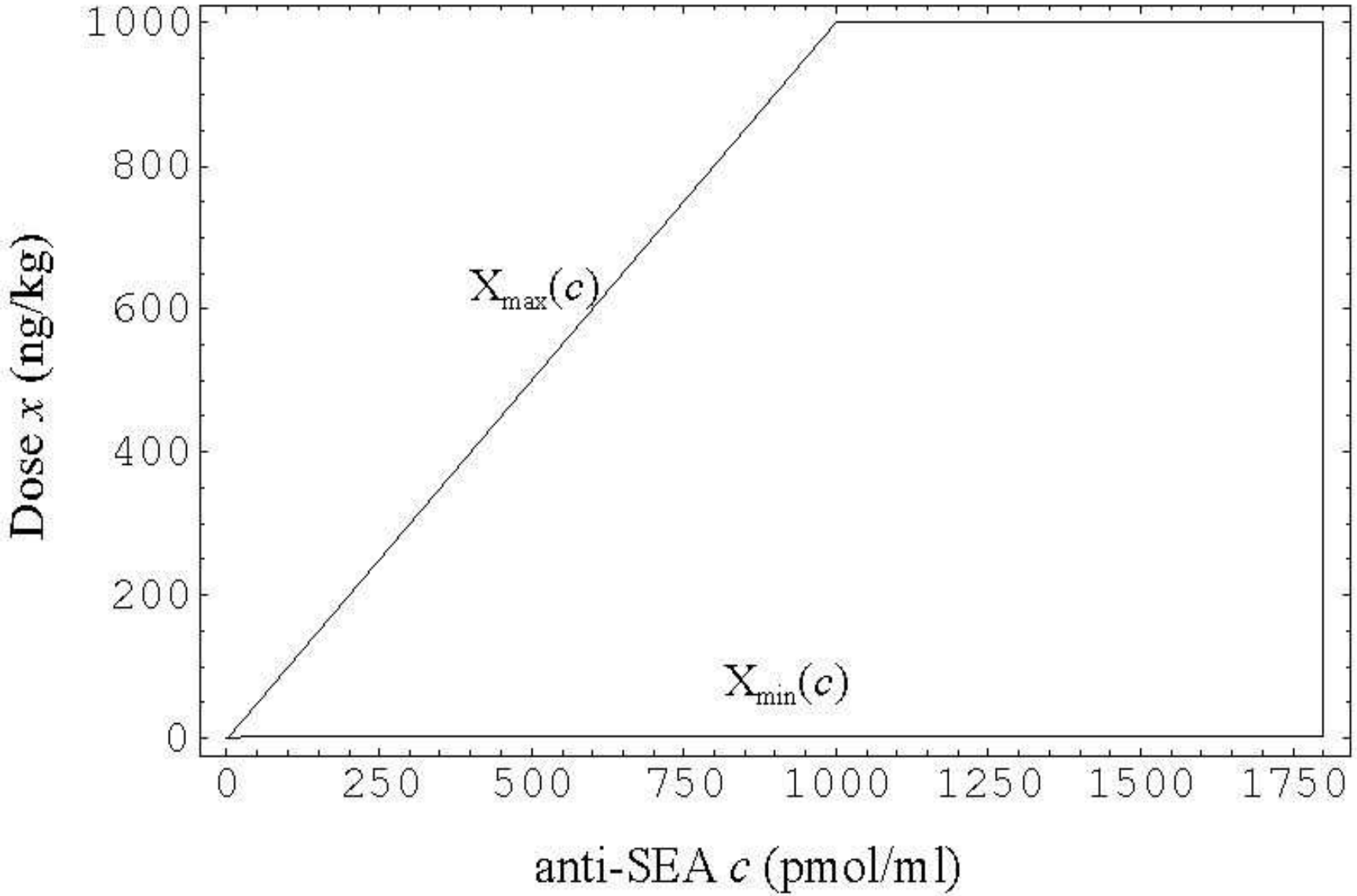
CONSTRAINTS

$$0 \le \rho_2 < \rho_1 \le \theta$$

$$\ln[\gamma_{\max}] \in \Delta$$

$$\Delta = [\ln(3.5), \ln(1000)]$$

Parameter Space



PRIOR DISTRIBUTION

INDEPENDENCE

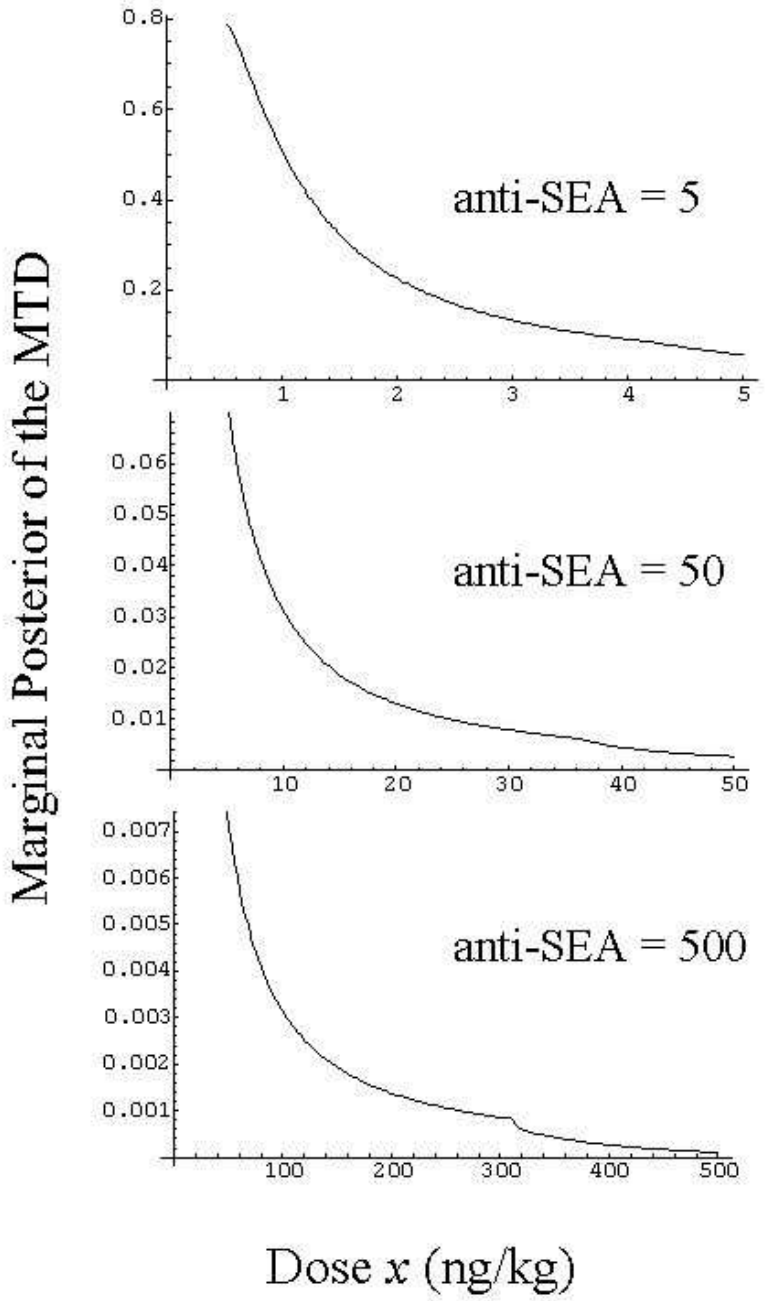
$$\gamma_{\max} \perp (\rho_1, \rho_2)$$

NON-INFORMATIVE

$$(\rho_1, \rho_2) \sim \text{Uniform on } \Omega$$

$$\Omega = \{(\rho_1, \rho_2) : 0 \le \rho_2 \le \rho_1 \le \theta\}$$

$$\ln(\gamma_{\max}) \sim \text{Uniform on } \Delta$$


Marginal Posterior of the MTD
anti-SEA = 5
anti-SEA = 50
anti-SEA = 500
Dose x (ng/kg)

MARGINAL POSTERIOR DISTRIBUTION

$$\gamma(c) = \left(\frac{c}{1800}\right)^{-\delta/\beta} \gamma_{\max}$$

where

$$\frac{\delta}{\beta} = \frac{\ln\left[\frac{\rho_1(\rho_2 - 1)}{\rho_2(1-\rho_1)}\right] \frac{\ln(2\gamma_{\max})}{\ln(36000)}}{\ln\left[\frac{\theta(1-\rho_2)}{\rho_2(1-\theta)}\right]}$$

LOSS FUNCTION

$$L_c(x,\gamma(c)) = \begin{cases} \alpha[\gamma(c) - x] & \text{if } x < \gamma(c), \\ (1-\alpha)[x - \gamma(c)] & \text{if } x > \gamma(c) \end{cases}$$

$$\alpha = 0.25\,(0.05)\,0.5$$

RECOMMENDED DOSES

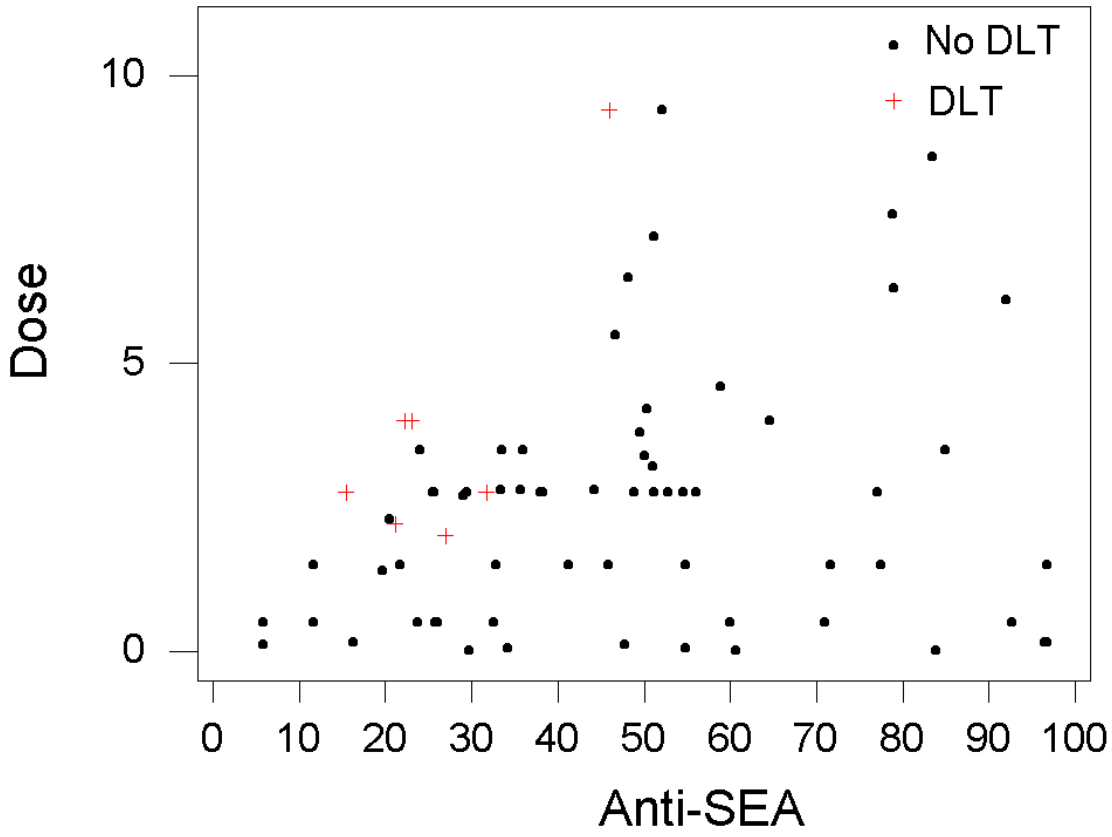
$X_k(c)$ = Dose for patient with anti-SEA c given D_k, the data from k patients.

$F_{k,c}$ = Marginal CDF of $\gamma(c)$ given the data D_k.

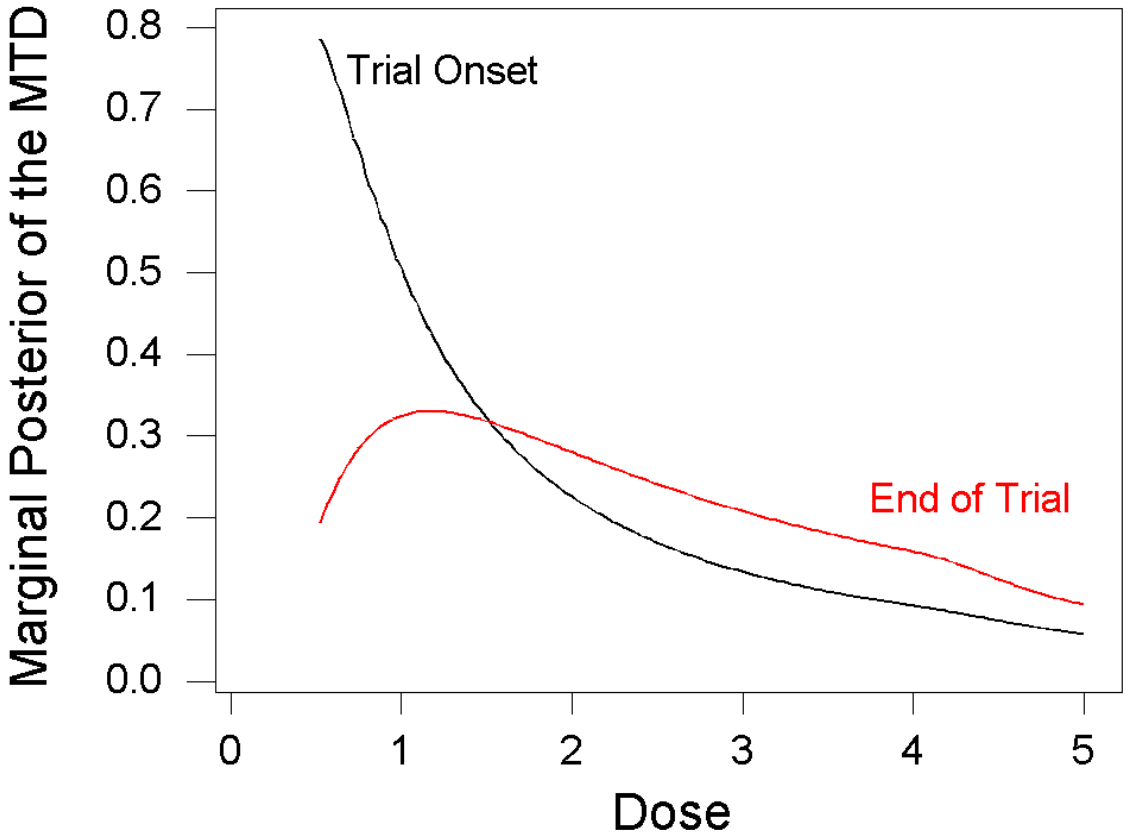
$$X_k(c) = F_{x,c}^{-1}(\alpha)$$

$$\text{Prob}[\, X_k(c) > \gamma(c) \mid D_k \,] = \alpha$$

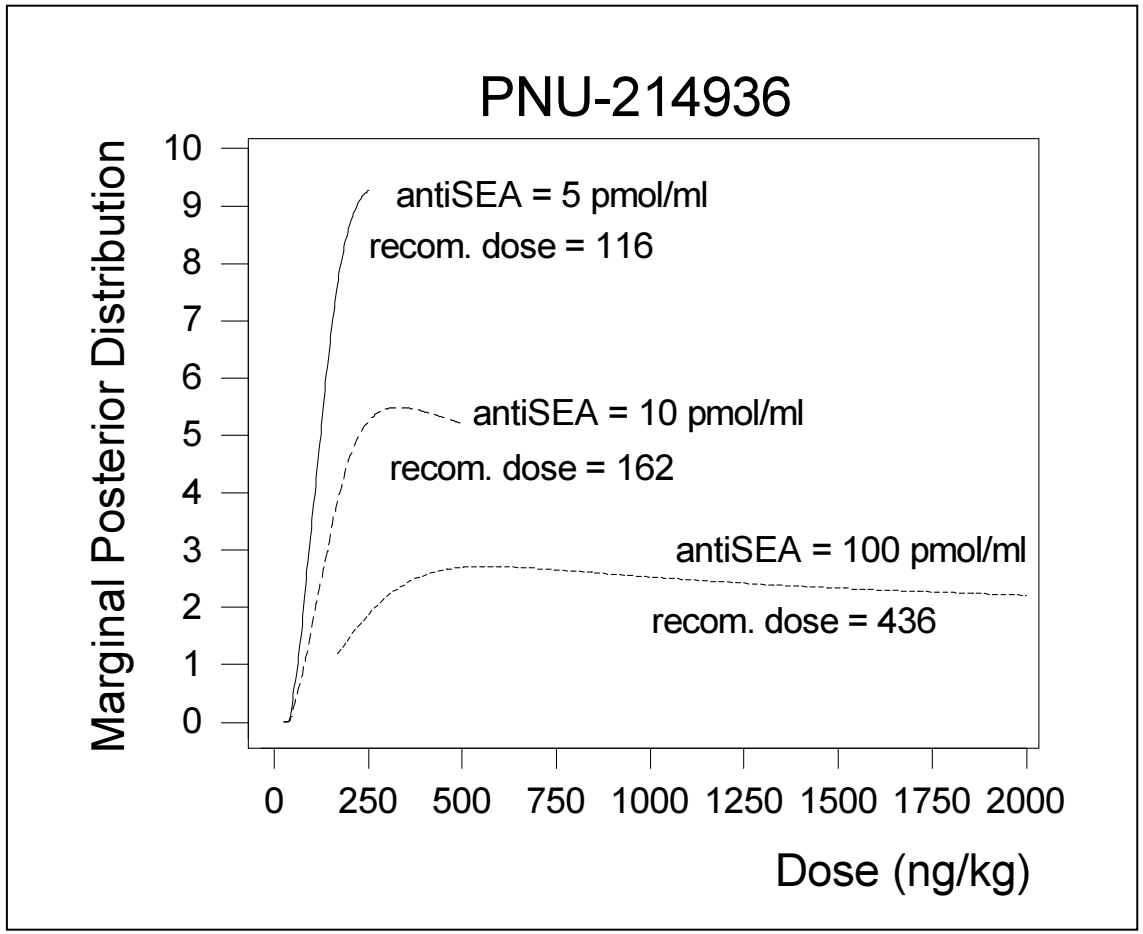
RESULTS



POSTERIOR DISTRIBUTION



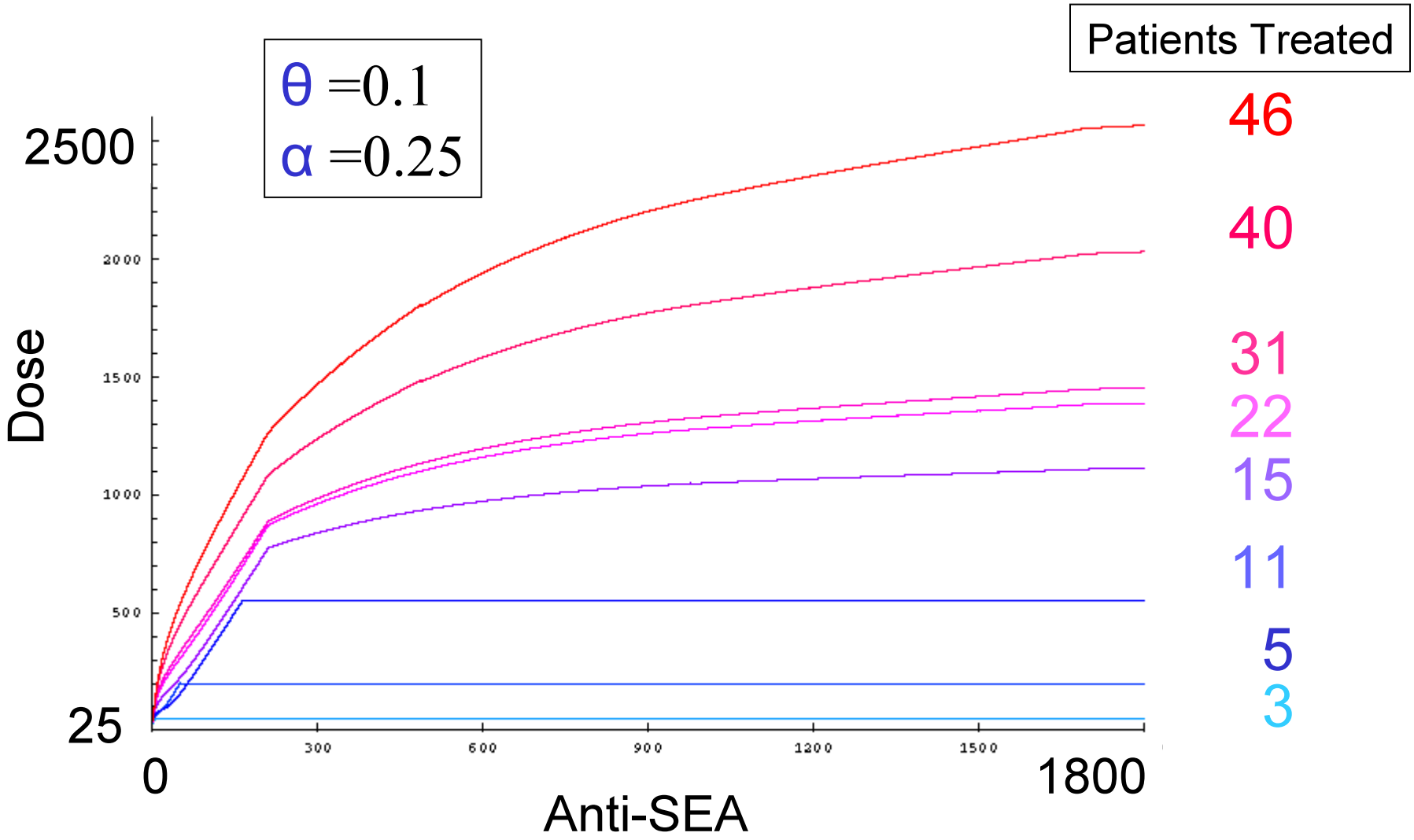
Marginal posterior distribution of the MTD (univariate posterior distribution of the MTD after integrating the joint posterior with respect to all other model parameters) for three selected pre-treatment anti-SEA concentrations.



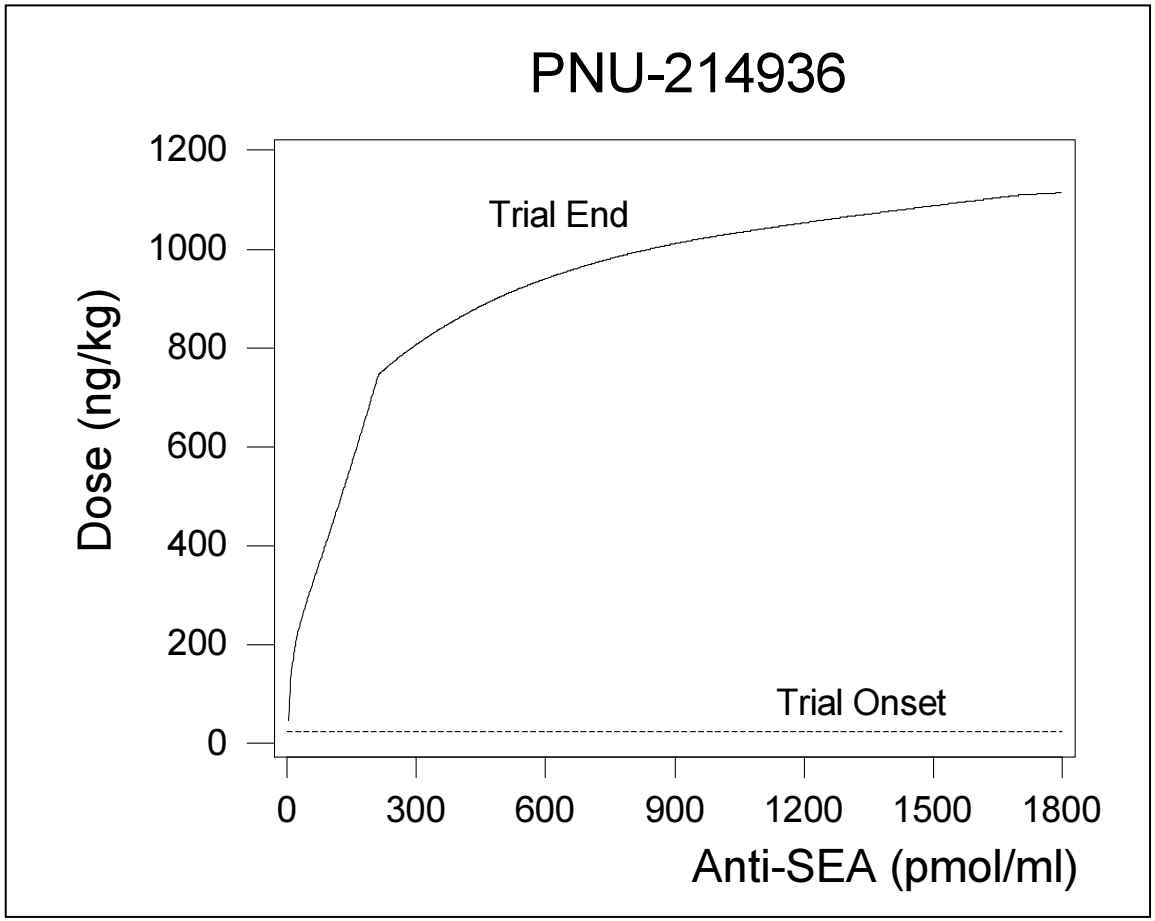
The MTD is defined to be the dose of PNU-214936 that when administered to patients with a particular level of anti-SEA Ab results in a probability equal to 0.10 that DLT occurs.

The recommended dose is determined for each antiSEA level so that the probability that it exceeds the MTD is 0.25.

Phase I Study of PNU based on pre-treatment anti-SEA concentration in Patients with Advanced Non-small Cell Lung Cancer



Use of Covariate in Prospective Clinical Trial



Recommended dose (ng/kg) as a function of
pre-treatment anti-SEA concentration (pmol/ml)
at the beginning (dotted line); and end of the trial (solid line)

Proposition

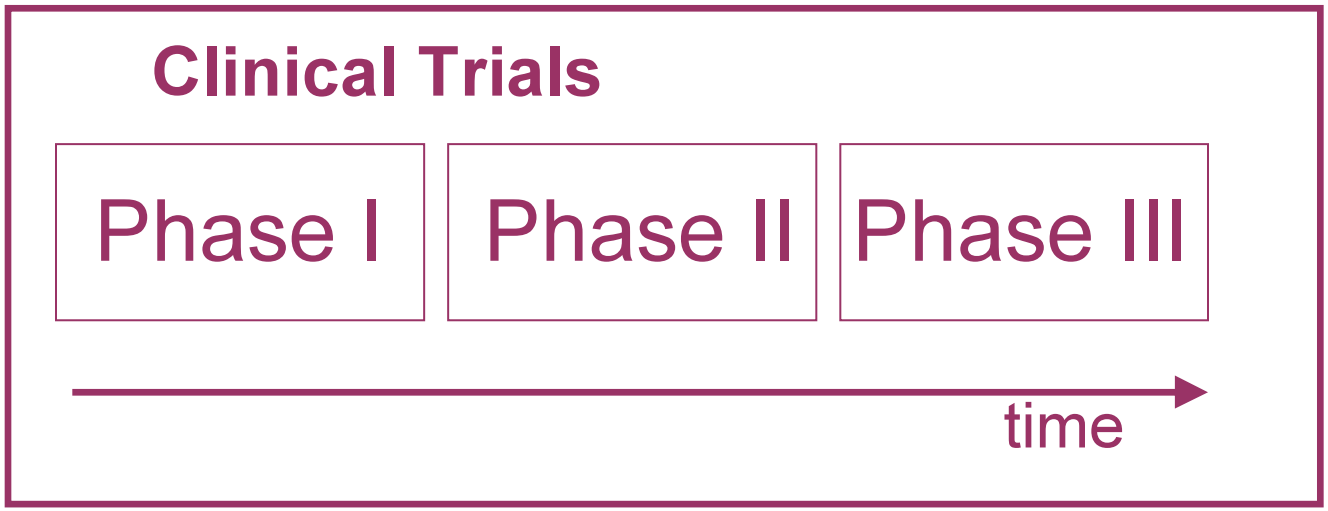
IF

- Target θ during ALL Phases of Treatment Evaluation
- Tailor Dose Levels to the Individual Patient

THEN

- Each Patient at Each Stage will be provided with the Best Dose
- More Patients will be Treated with Therapeutic Doses
- Fewer Patients will be Overdosed and Suffer from Treatment's Toxic Effects

Standard Paradigm



Proposed Paradigm

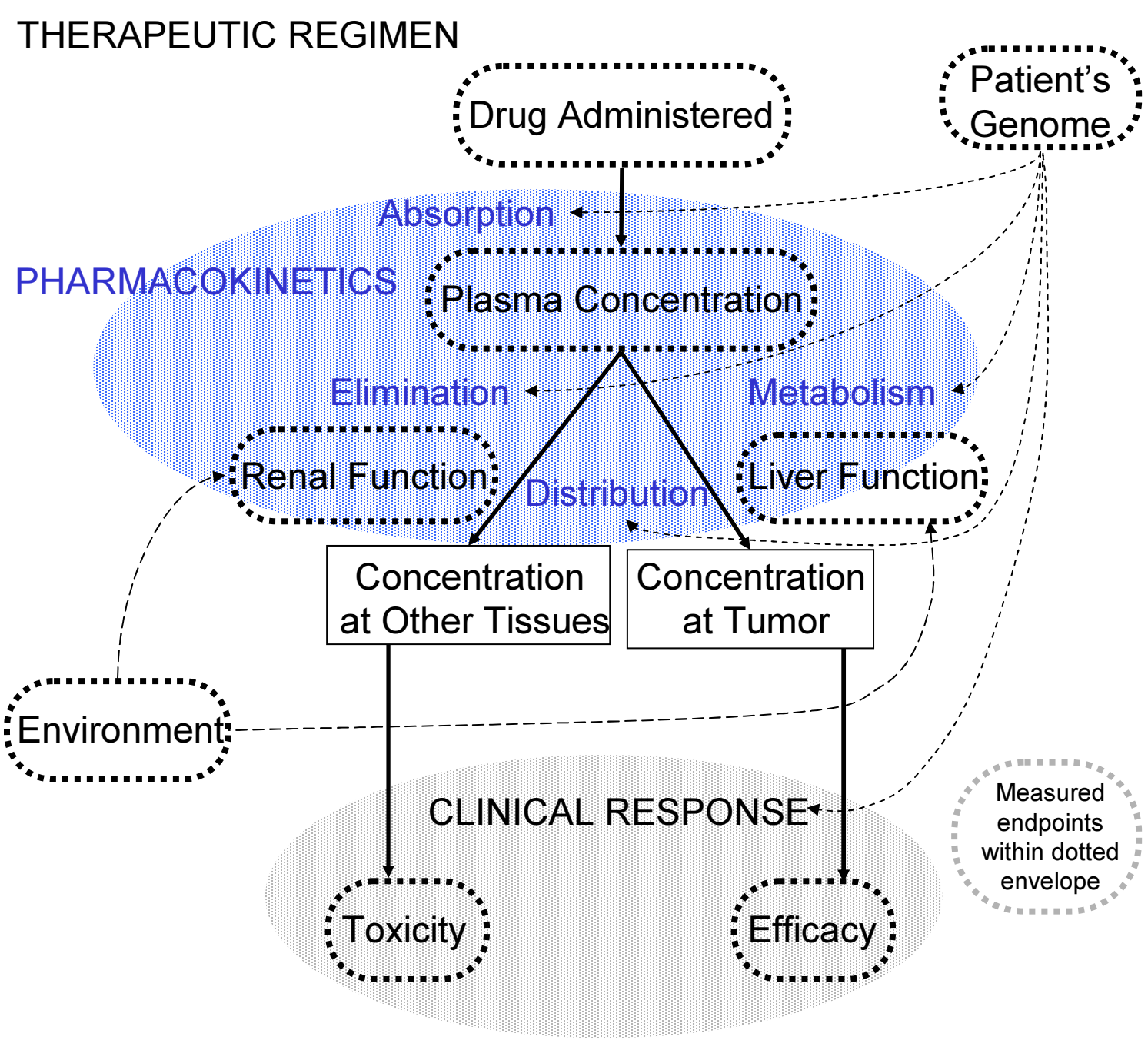
Preliminary Results Summary

- How data can be used to identify patient specific characteristics that affect or predict patient susceptibility to the adverse effects of cancer therapy
- How this information can be exploited to improve cancer treatment in the clinical setting

Next Steps

- Prospective Trials

- Generalize EWOC for more than 1 Covariate for Time to Event


THERAPEUTIC REGIMEN
Drug Administered
Patient's Genome
Absorption
PHARMACOKINETICS
Plasma Concentration
Elimination
Metabolism
Renal Function
Distribution
Liver Function
Concentration at Other Tissues
Concentration at Tumor
Environment
CLINICAL RESPONSE
Measured endpoints within dotted envelope
Toxicity
Efficacy

Pharmacogenetics

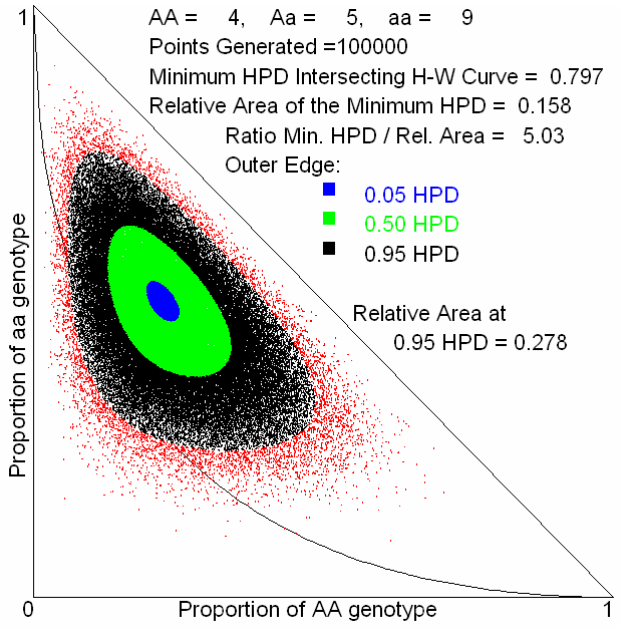
Individuals with
variant capacity to metabolically inactivate taxanes
are at risk for toxic reactions (low capacity)
or inefficacious therapy (high capacity)

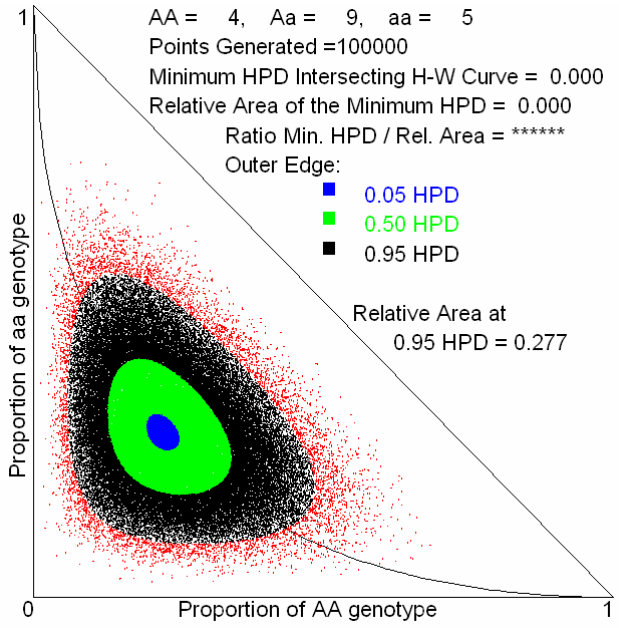
- **CYP2C8**
- **3A4**
- **3A5**
- **UGT1A1-** uridinediphosphate glucuronosyltransferase
- **p53**

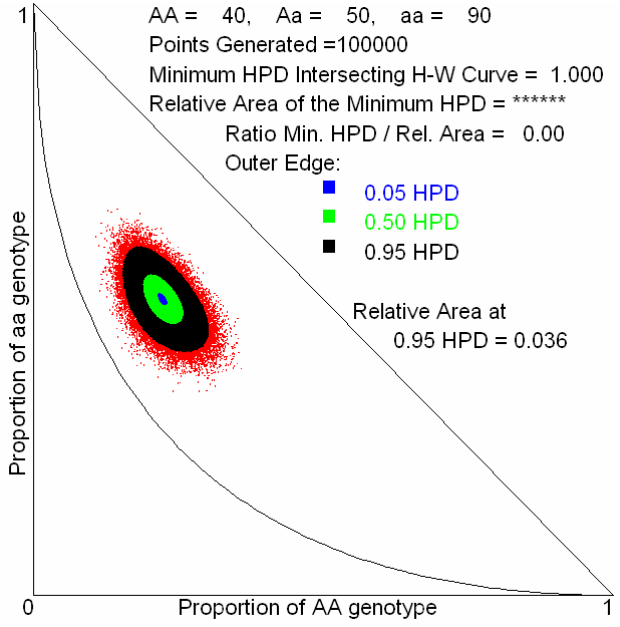
Rogatko, A., Slifker, M.J., Babb, J.S.

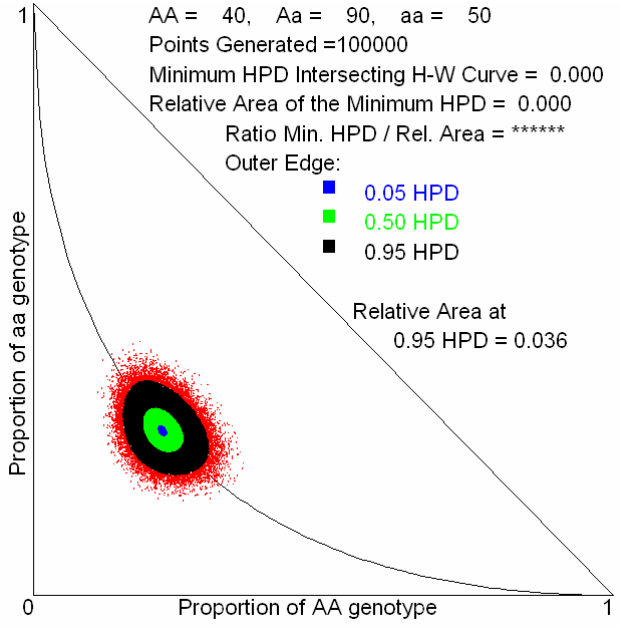
Hardy-Weinberg equilibrium diagnostics.

Theor. Popul. Biol. 62:251-257, 2002.

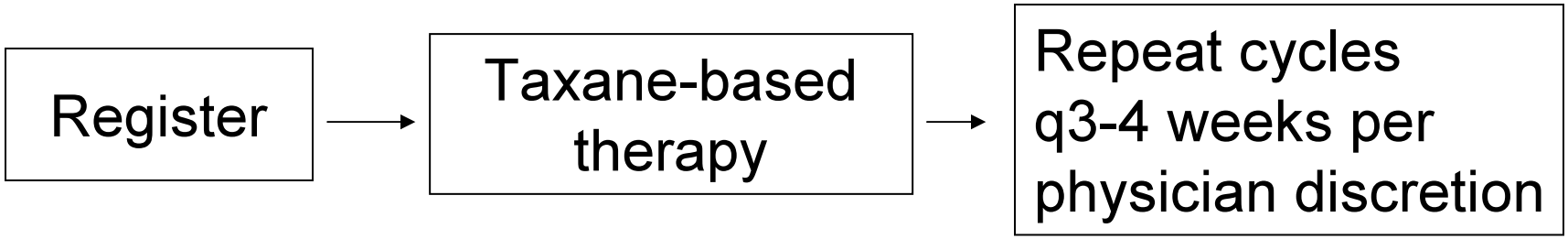








Schema



Any taxane-based treatment
PS 0-2

Baseline Labs
PBMC Collection
Pharmacokinetics (limited sampling)

Toxicity assessment (each cycle)
Response assessment (q 2-3 cycles recommended)

Planned accrual: 1000 patients over 4 years

OBJECTIVES
Specific Aim 1
Cohort Study
Pharmacogenetics Lab.
Pharmacokinetic Lab.
Statistical Analyses
Specific Aim 2
Population Model
Validation
Specific Aim 3
Prediction Model
Prediction Model Validation
Tailored Dose Model
Tailored Dose Model Validation
Specific Aim 4
Statistical Analyses

EVALUATION OF PATIENT CHARACTERISTICS AS PREDICTORS OF ACUTE TREATMENT TOXICITY

Clinical
Hudes, G.
Langer, C.
Cohen, R.
Cianfrocca, M.
Treat, J.
Cheng, J.
Goldstein, L.
VonMehren, M.
Schilder, R.
Haas, N.
Millenson, M.

Biostatistics
Rogatko, A.
Babb, J.
Tighiouart, M.
Wang, H.

Pharmacogenetics
Blanchard, R.
Carlini, L.

Pharmacokinetics
Gallo, J.
TBN - Scientific Technician

Protocol Management
Coackley, S
Kelly, D.
TBN - Protocol Nurse
TBN - Data Manager

Facilities:

- Biosample Repository
- Cancer Prevention Biomarker and Genotyping
- Protocol Support Lab

Phase I studies assume that dose is the significant determinant of toxicity. However, a retrospective analysis of 459 patients enrolled in 23 investigator initiated therapeutic phase I and II studies at the Fox Chase Cancer Center revealed that dose is not always a significant predictor of toxicity. Even with conventional patient selection criteria that included the requirement for normal or near-normal hepatic and renal function, patient characteristics had greater predictive value than dose for the toxicity for several agents. These results are in agreement with recent improvements in our understanding of pharmacokinetics and the genetics of drug metabolism. They indicate that cancer therapies need to accommodate intrinsic patient differences in drug tolerance. Such methods would adjust the dose level according to measurable patient characteristics in order to obtain an individualized target drug exposure. A first step in this direction was the development of a patient specific dose escalation scheme utilizing a Bayesian model of Escalation with Overdose Control (EWOC). This approach was implemented to establish the maximum-tolerated dose of PNU-214936 in advanced non-small cell lung cancer. Methods, results, and ongoing developments will be presented in the design of cancer clinical trials that not only guide dose escalation but also permit personalization of the dose level for each specific patient. This adaptive method adjusts doses according to patient-specific characteristics and allows the dose to be escalated as quickly as possible while safeguarding against overdosing.