Bayesian Methods for Oncology Clinical Trials

Lili Zhao, Ph.D.

Biostatistics Department, University of Michigan

July 25, 2017

University of Michigan
Medical School

Outlines

Introduction

Goal: Determine a Maximum Tolerated Dose (MTD)

- Doses: $d_1 < d_2 < \cdots < d_K$
- Endpoint: dose-limiting toxicity (DLT) in the observation period
- Treat a small number of patients (< 24)

Trial Designs

Rule-based designs:

- 3+3 Design (Dixon and Mood (1948))
- Rolling 6 Design (Skolnik et al. (2008))- **shorten trial time**

Model-based designs:

- Continual Reassessment Method (CRM) (OQuigley et al. (1990))
- Time-to-Event CRM (TITE-CRM) (Cheung and Chappell (2000))- **shorten trial time**

University of Michigan Medical School

Trial Designs

Rule-based designs:

- 3+3 Design (Dixon and Mood (1948))
- Rolling 6 Design (Skolnik et al. (2008))- **shorten trial time**

Model-based designs:

- Continual Reassessment Method (CRM) (OQuigley et al. (1990))
- Time-to-Event CRM (TITE-CRM) (Cheung and Chappell (2000))- **shorten trial time**

University of Michigan Medical School

Trial Designs

Rule-based designs:

- 3+3 Design (Dixon and Mood (1948))
- Rolling 6 Design (Skolnik et al. (2008))- **shorten trial time**

Model-based designs:

- Continual Reassessment Method (CRM) (OQuigley et al. (1990))
- Time-to-Event CRM (TITE-CRM) (Cheung and Chappell (2000))- **shorten trial time**

University of Michigan Medical School

Trial Designs

Rule-based designs:

- 3+3 Design (Dixon and Mood (1948))
- Rolling 6 Design (Skolnik et al. (2008))- **shorten trial time**

Model-based designs:

- Continual Reassessment Method (CRM) (OQuigley et al. (1990))
- Time-to-Event CRM (TITE-CRM) (Cheung and Chappell (2000))- **shorten trial time**

University of Michigan Medical School

Trial Designs

Rule-based designs:

- 3+3 Design (Dixon and Mood (1948))
- Rolling 6 Design (Skolnik et al. (2008))- **shorten trial time**

Model-based designs:

- Continual Reassessment Method (CRM) (OQuigley et al. (1990))
- Time-to-Event CRM (TITE-CRM) (Cheung and Chappell (2000))- **shorten trial time**

Rule-based Designs

3+3 Design: Treat 3 patients at dose d_j

- If 0/3 DLT, escalate dose
- If 2/3 or 3/3 DLTs, de-escalate dose
- If 1/3 DLT, enroll 3 more patients
  - If 1/6 DLTs, escalate dose
  - If $>$ 1/6 DLTs, de-escalate dose

Declare MTD the highest dose with $\leq 1/6$ DLTs

Rolling 6 Design: No recruitment pause after 3 subjects

- For example, if data was not available for ≥ 1 subjects and 1 DLT, then assign the same dose to the 4th subject

University of Michigan Medical School

Rule-based Designs

3+3 Design: Treat 3 patients at dose d_j

- If 0/3 DLT, escalate dose
- If 2/3 or 3/3 DLTs, de-escalate dose
- If 1/3 DLT, enroll 3 more patients
  - If 1/6 DLTs, escalate dose
  - If $>$ 1/6 DLTs, de-escalate dose

Declare MTD the highest dose with $\leq 1/6$ DLTs

Rolling 6 Design: No recruitment pause after 3 subjects

- For example, if data was not available for ≥ 1 subjects and 1 DLT, then assign the same dose to the 4th subject

University of Michigan Medical School

Rule-based Designs

3+3 Design: Treat 3 patients at dose d_j

- If 0/3 DLT, escalate dose
- If 2/3 or 3/3 DLTs, de-escalate dose
- If 1/3 DLT, enroll 3 more patients
  - If 1/6 DLTs, escalate dose
  - If $>$ 1/6 DLTs, de-escalate dose

Declare MTD the highest dose with $\leq 1/6$ DLTs

Rolling 6 Design: No recruitment pause after 3 subjects

- For example, if data was not available for ≥ 1 subjects and 1 DLT, then assign the same dose to the 4th subject

University of Michigan Medical School

TITE-CRM Design

- MTD is defined as the dose with a probability of DLT closest to some target toxicity rate.
- Working dose-toxicity model:
  - Logistic regression model: $\text{logit}(p_i) = 3 + \beta d_i$
  - Power model: $\log(p_i) = \beta \log(d_i)$
- Weighted Binomial Likelihood:

$$L_n(\beta) = \prod_{i=1}^{n} p(d_i;\beta)^{y_i} \{1 - w_i p(d_i;\beta)\}^{1-y_i}$$

  For subject i, d_i is the dose level, y_i is the DLT outcome, p_i is the toxicity rate, and w_i is the weight (e.g, follwoup/toxicity window)
- Prior: $\beta \sim \text{lognormal}(0, var)$ (var is a tuning parameter).
- Dose allocation is based on estimates of the posterior probability of DLT

TITE-CRM Design

- MTD is defined as the dose with a probability of DLT closest to some target toxicity rate.
- Working dose-toxicity model:
  - Logistic regression model: $\text{logit}(p_i) = 3 + \beta d_i$
  - Power model: $\log(p_i) = \beta \log(d_i)$
- Weighted Binomial Likelihood:

$$L_n(\beta) = \prod_{i=1}^{n} p(d_i;\beta)^{y_i} \{1 - w_i p(d_i;\beta)\}^{1-y_i}$$

  For subject i, d_i is the dose level, y_i is the DLT outcome, p_i is the toxicity rate, and w_i is the weight (e.g, follwoup/toxicity window)
- Prior: $\beta \sim \text{lognormal}(0, var)$ (var is a tuning parameter).
- Dose allocation is based on estimates of the posterior probability of DLT

TITE-CRM Design

- MTD is defined as the dose with a probability of DLT closest to some target toxicity rate.
- Working dose-toxicity model:
  - Logistic regression model: $\text{logit}(p_i) = 3 + \beta d_i$
  - Power model: $\log(p_i) = \beta \log(d_i)$
- Weighted Binomial Likelihood:

$$L_n(\beta) = \prod_{i=1}^{n} p(d_i;\beta)^{y_i} \{1 - w_i p(d_i;\beta)\}^{1-y_i}$$

  For subject i, d_i is the dose level, y_i is the DLT outcome, p_i is the toxicity rate, and w_i is the weight (e.g, follwoup/toxicity window)
- Prior: $\beta \sim \text{lognormal}(0, var)$ (var is a tuning parameter).
- Dose allocation is based on estimates of the posterior probability of DLT

TITE-CRM Design

- MTD is defined as the dose with a probability of DLT closest to some target toxicity rate.
- Working dose-toxicity model:
  - Logistic regression model: $\text{logit}(p_i) = 3 + \beta d_i$
  - Power model: $\log(p_i) = \beta \log(d_i)$
- Weighted Binomial Likelihood:

$$L_n(\beta) = \prod_{i=1}^{n} p(d_i; \beta)^{y_i} \{1 - w_i p(d_i; \beta)\}^{1-y_i}$$

  For subject i, d_i is the dose level, y_i is the DLT outcome, p_i is the toxicity rate, and w_i is the weight (e.g, follwoup/toxicity window)
- Prior: $\beta \sim \text{lognormal}(0, var)$ (var is a tuning parameter).
- Dose allocation is based on estimates of the posterior probability of DLT

University of Michigan Medical School

TITE-CRM Design

- MTD is defined as the dose with a probability of DLT closest to some target toxicity rate.
- Working dose-toxicity model:
  - Logistic regression model: $\text{logit}(p_i) = 3 + \beta d_i$
  - Power model: $\log(p_i) = \beta \log(d_i)$
- Weighted Binomial Likelihood:

$$L_n(\beta) = \prod_{i=1}^{n} p(d_i; \beta)^{y_i} \{1 - w_i p(d_i; \beta)\}^{1-y_i}$$

For subject i, d_i is the dose level, y_i is the DLT outcome, p_i is the toxicity rate, and w_i is the weight (e.g, follwoup/toxicity window)

- Prior: $\beta \sim \text{lognormal}(0, var)$ (var is a tuning parameter).
- Dose allocation is based on estimates of the posterior probability of DLT

University of Michigan Medical School

TITE-CRM Design

- MTD is defined as the dose with a probability of DLT closest to some target toxicity rate.
- Working dose-toxicity model:
  - Logistic regression model: $\text{logit}(p_i) = 3 + \beta d_i$
  - Power model: $\log(p_i) = \beta \log(d_i)$
- Weighted Binomial Likelihood:

$$L_n(\beta) = \prod_{i=1}^{n} p(d_i; \beta)^{y_i} \{1 - w_i p(d_i; \beta)\}^{1-y_i}$$

  For subject i, d_i is the dose level, y_i is the DLT outcome, p_i is the toxicity rate, and w_i is the weight (e.g, follwoup/toxicity window)
- Prior: $\beta \sim \text{lognormal}(0, var)$ (var is a tuning parameter).
- Dose allocation is based on estimates of the posterior probability of DLT

University of Michigan Medical School

TITE-CRM Design

- MTD is defined as the dose with a probability of DLT closest to some target toxicity rate.
- Working dose-toxicity model:
  - Logistic regression model: $\text{logit}(p_i) = 3 + \beta d_i$
  - Power model: $\log(p_i) = \beta \log(d_i)$
- Weighted Binomial Likelihood:

$$L_n(\beta) = \prod_{i=1}^{n} p(d_i; \beta)^{y_i} \{1 - w_i p(d_i; \beta)\}^{1-y_i}$$

  For subject i, d_i is the dose level, y_i is the DLT outcome, p_i is the toxicity rate, and w_i is the weight (e.g, follwoup/toxicity window)
- Prior: $\beta \sim \text{lognormal}(0, var)$ (var is a tuning parameter).
- Dose allocation is based on estimates of the posterior probability of DLT

University of Michigan Medical School

Required Parameters in TITE-CRM design

- Observation window for toxicity (e.g. one or two cycles)
- Target probability (e.g. 0.25 or 0.3) (Investigator)
- Dose-toxicity model (Statistician)
- Initial estimates of toxicities at doses (Investigator)
- Confidence of the initial guesses (i.e, prior for β) (Investigator and statistician)

University of Michigan Medical School

Required Parameters in TITE-CRM design

- Observation window for toxicity (e.g. one or two cycles)
- Target probability (e.g. 0.25 or 0.3) (Investigator)
- Dose-toxicity model (Statistician)
- Initial estimates of toxicities at doses (Investigator)
- Confidence of the initial guesses (i.e, prior for β) (Investigator and statistician)

University of Michigan Medical School

Required Parameters in TITE-CRM design

- Observation window for toxicity (e.g. one or two cycles)
- Target probability (e.g. 0.25 or 0.3) (Investigator)
- Dose-toxicity model (Statistician)
- Initial estimates of toxicities at doses (Investigator)
- Confidence of the initial guesses (i.e, prior for β) (Investigator and statistician)

University of Michigan Medical School

Required Parameters in TITE-CRM design

- Observation window for toxicity (e.g. one or two cycles)
- Target probability (e.g. 0.25 or 0.3) (Investigator)
- Dose-toxicity model (Statistician)
- Initial estimates of toxicities at doses (Investigator)
- Confidence of the initial guesses (i.e, prior for β) (Investigator and statistician)

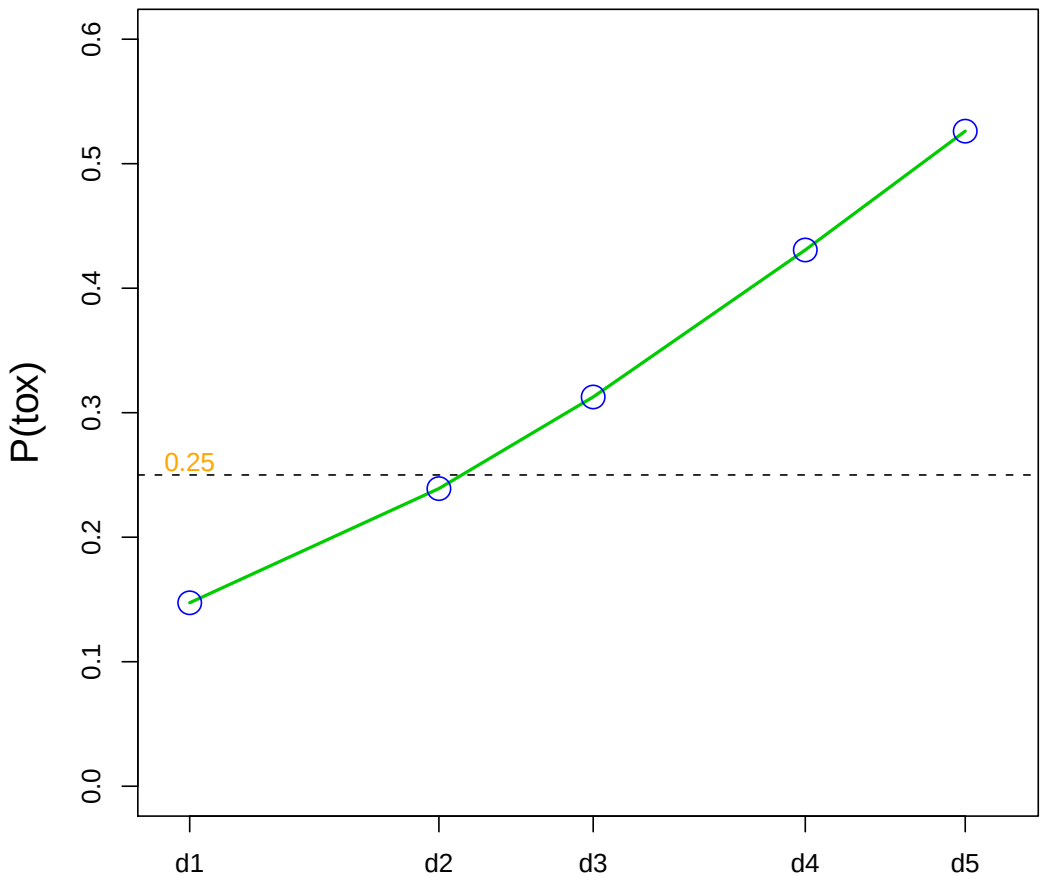
University of Michigan Medical School

Required Parameters in TITE-CRM design

- Observation window for toxicity (e.g. one or two cycles)
- Target probability (e.g. 0.25 or 0.3) (Investigator)
- Dose-toxicity model (Statistician)
- Initial estimates of toxicities at doses (Investigator)
- Confidence of the initial guesses (i.e, prior for β) (Investigator and statistician)

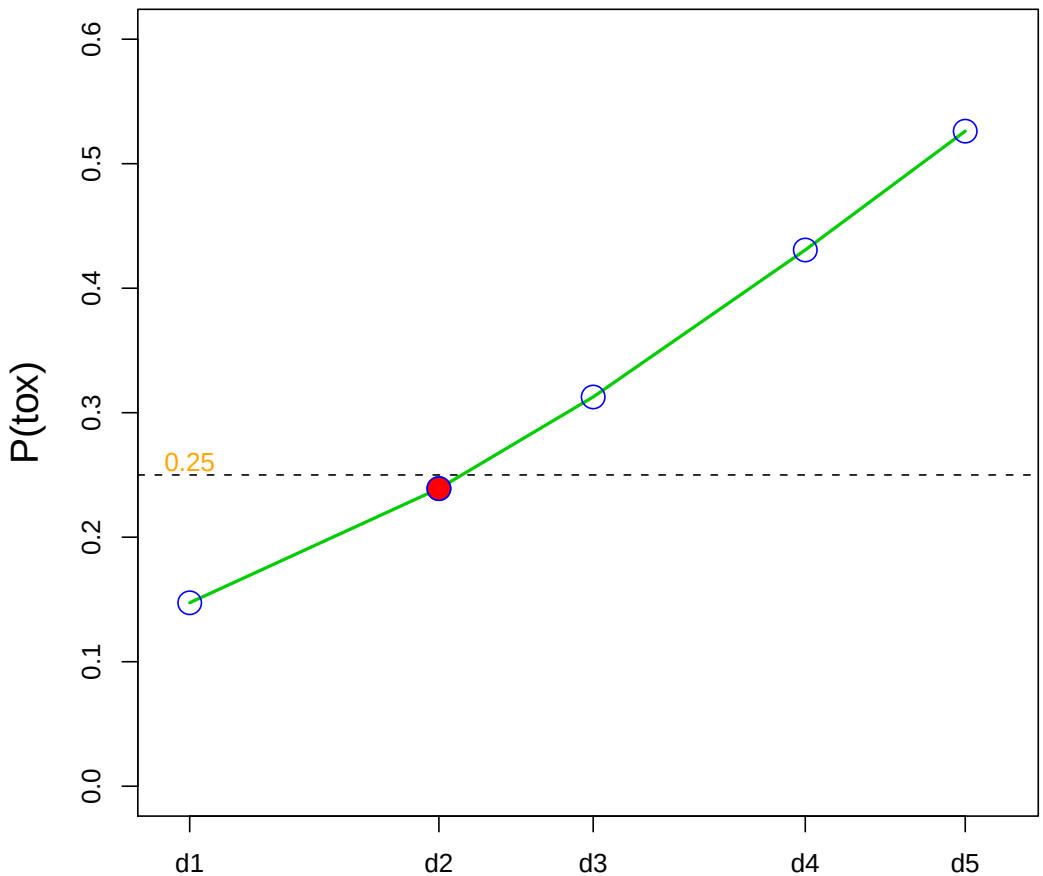
Example: Dose Assignments for the First 3 Patients

- Start at dose 3
- Patient 1
- Patient 2
- Patient 3



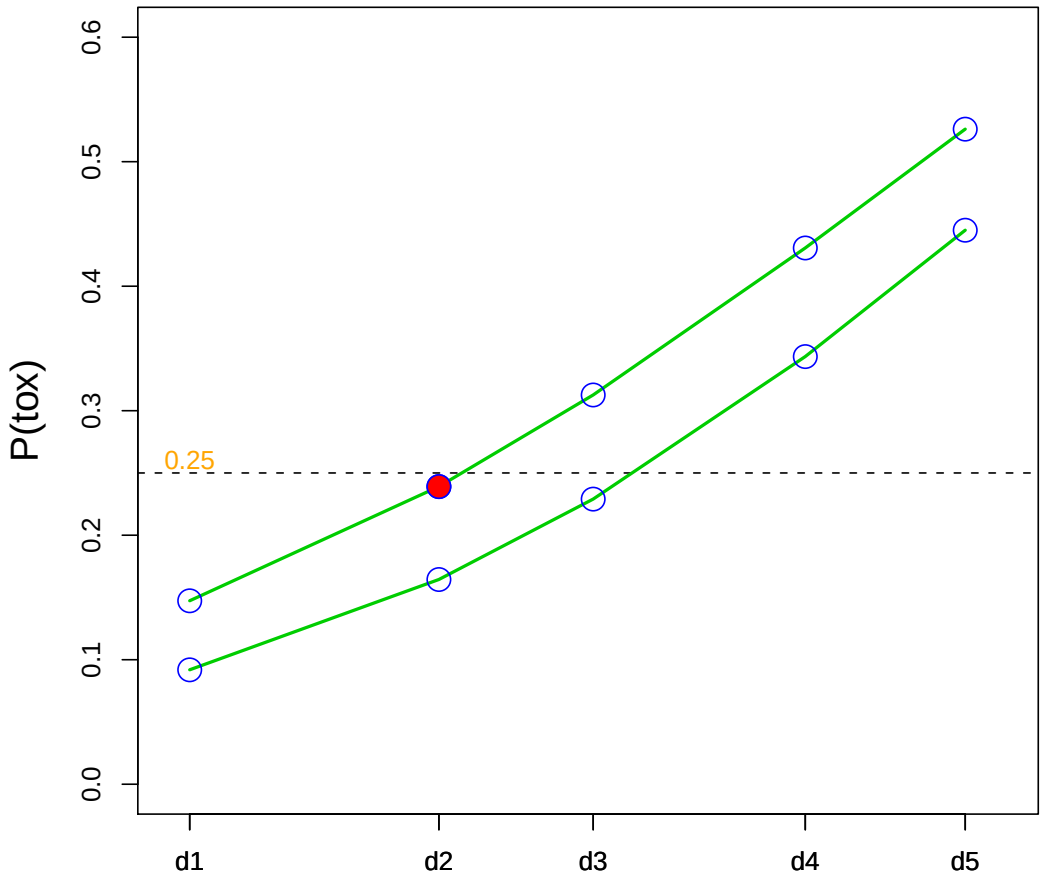
Example: Dose Assignments for the First 3 Patients

- Start at dose 3
- Patient 1
- Patient 2
- Patient 3



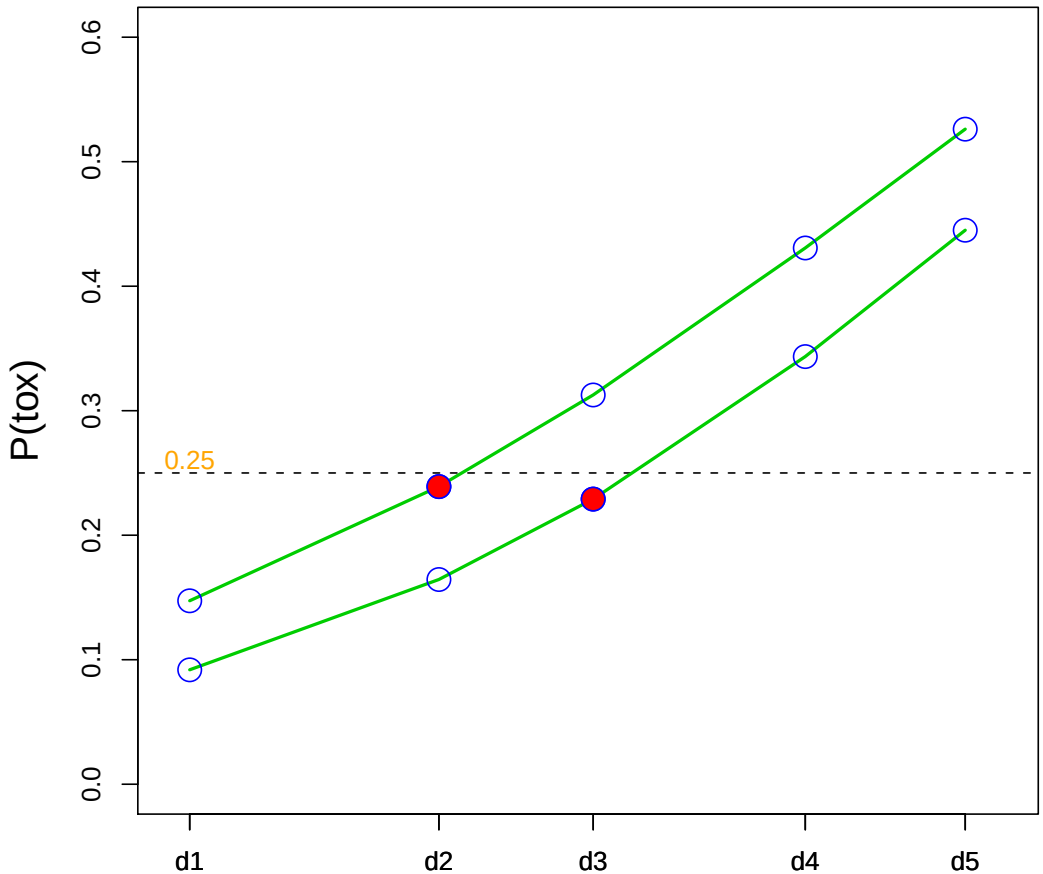
Example: Dose Assignments for the First 3 Patients

- Start at dose 3
- Patient 1
- Patient 2
- Patient 3



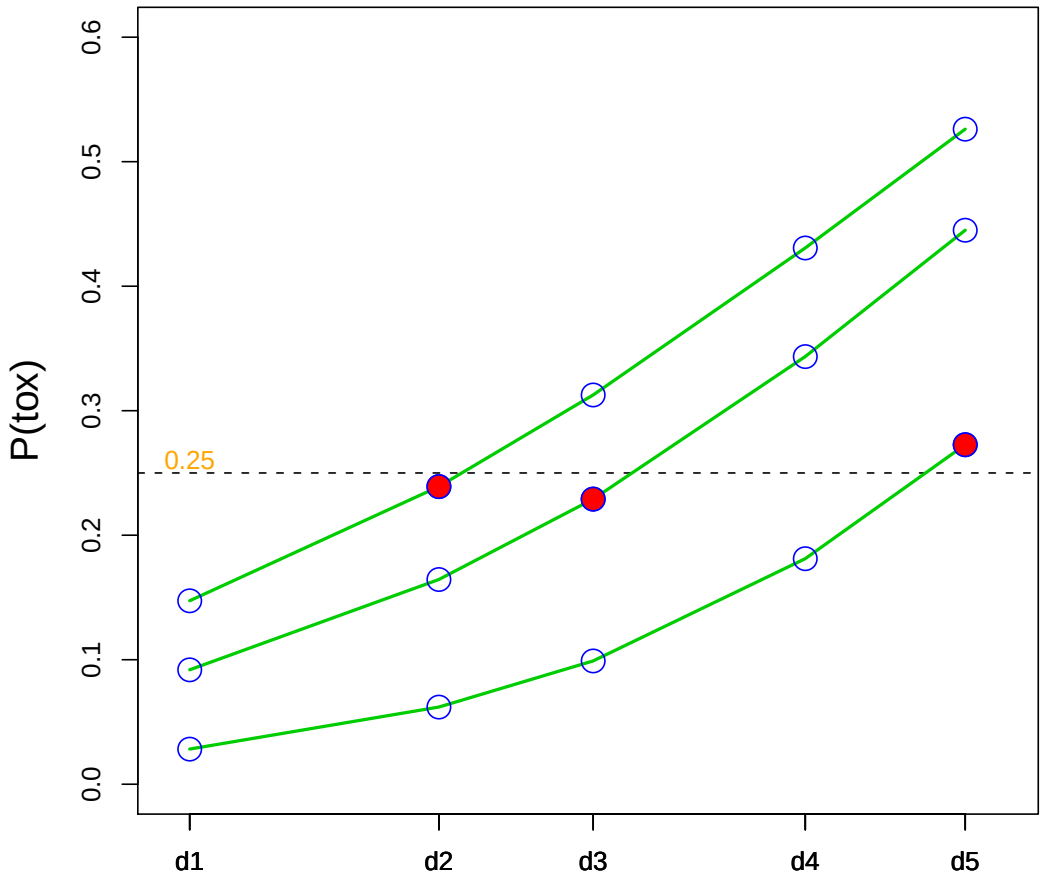
Example: Dose Assignments for the First 3 Patients

- Start at dose 3
- Patient 1
- Patient 2
- Patient 3



Example: Dose Assignments for the First 3 Patients

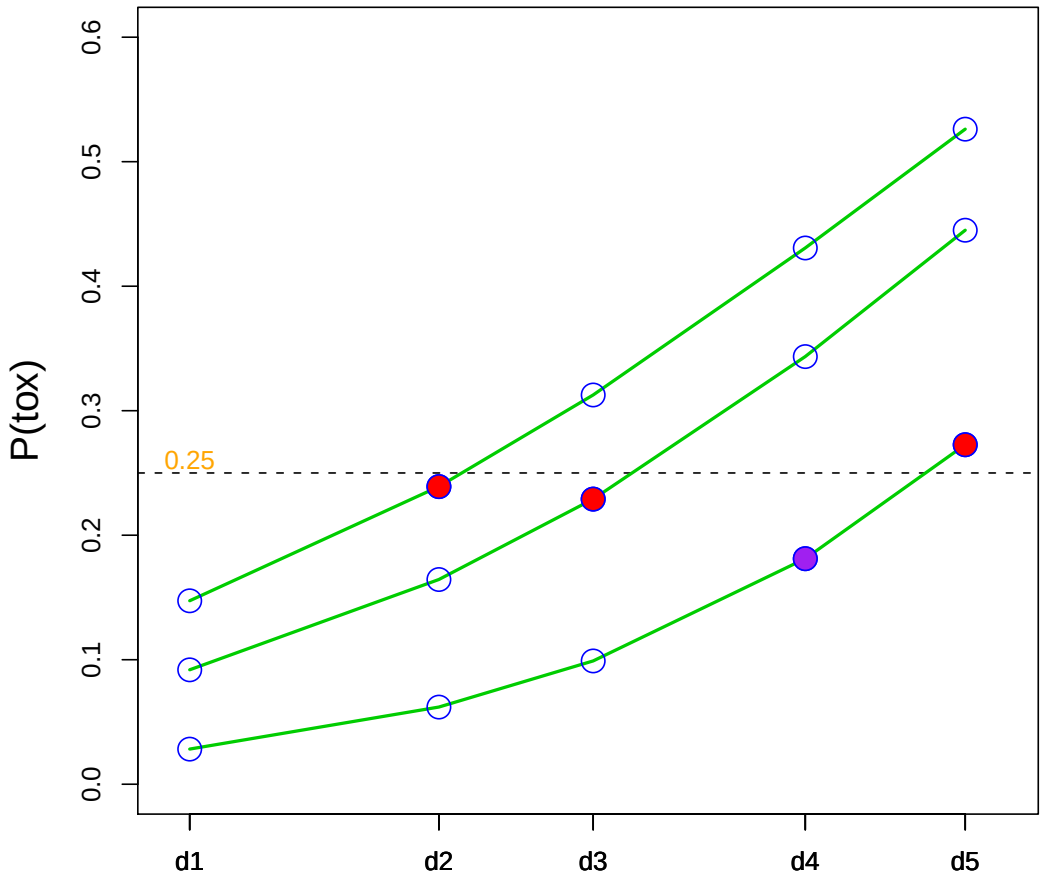
- Start at dose 3
- Patient 1
- Patient 2
- Patient 3



University of Michigan Medical School

Example: Dose Assignments for the First 3 Patients

- Start at dose 3
- Patient 1
- Patient 2
- Patient 3



University of Michigan Medical School

Modifications for Safety

- Start at a lower dose (1 or 2)
- The dose assigned $\leq$ target
- Dose escalation is restricted to one level between adjacent patients
- Escalation was not allowed until at least X patients complete the observation period at the previous dose level.

Modifications for Safety

- Start at a lower dose (1 or 2)
- The dose assigned $\leq$ target
- Dose escalation is restricted to one level between adjacent patients
- Escalation was not allowed until at least X patients complete the observation period at the previous dose level.

Modifications for Safety

- Start at a lower dose (1 or 2)
- The dose assigned $\leq$ target
- Dose escalation is restricted to one level between adjacent patients
- Escalation was not allowed until at least X patients complete the observation period at the previous dose level.

Modifications for Safety

- Start at a lower dose (1 or 2)
- The dose assigned $\leq$ target
- Dose escalation is restricted to one level between adjacent patients
- Escalation was not allowed until at least X patients complete the observation period at the previous dose level.

A Pediatric Trial-Children with Recurrent/Refractory High-risk Neuroblastoma

- Fixed Bortezomib at 1.2mg; Irinotecan at 30,35,40,45,and 50mg
- 24 patients (1/10 days)
- Target probability is 0.25
- Start at 35 Intravenous
- Observation window: 42 days
- Modified TITE-CRM (power model; initial guess is the first column; var is 0.3 in the lognormal prior)

True Probabilities

	1	2	3	4
d_1	0.05	0.05	0.08	0.15
d_2	0.1	0.1	0.15	**0.22**
d_3	0.15	**0.25**	**0.22**	0.3
d_4	**0.25**	0.4	0.3	0.4
d_5	0.35	0.6	0.4	0.5

University of Michigan Medical School

A Pediatric Trial-Children with Recurrent/Refractory High-risk Neuroblastoma

- Fixed Bortezomib at 1.2mg; Irinotecan at 30,35,40,45,and 50mg
- 24 patients (1/10 days)
- Target probability is 0.25
- Start at 35 Intravenous
- Observation window: 42 days
- Modified TITE-CRM (power model; initial guess is the first column; var is 0.3 in the lognormal prior)

True Probabilities

	1	2	3	4
d_1	0.05	0.05	0.08	0.15
d_2	0.1	0.1	0.15	**0.22**
d_3	0.15	**0.25**	**0.22**	0.3
d_4	**0.25**	0.4	0.3	0.4
d_5	0.35	0.6	0.4	0.5

University of Michigan Medical School

A Pediatric Trial-Children with Recurrent/Refractory High-risk Neuroblastoma

- Fixed Bortezomib at 1.2mg; Irinotecan at 30,35,40,45,and 50mg
- 24 patients (1/10 days)
- Target probability is 0.25
- Start at 35 Intravenous
- Observation window: 42 days
- Modified TITE-CRM (power model; initial guess is the first column; var is 0.3 in the lognormal prior)

True Probabilities

	1	2	3	4
d_1	0.05	0.05	0.08	0.15
d_2	0.1	0.1	0.15	**0.22**
d_3	0.15	**0.25**	**0.22**	0.3
d_4	**0.25**	0.4	0.3	0.4
d_5	0.35	0.6	0.4	0.5

University of Michigan Medical School

A Pediatric Trial-Children with Recurrent/Refractory High-risk Neuroblastoma

- Fixed Bortezomib at 1.2mg; Irinotecan at 30,35,40,45,and 50mg
- 24 patients (1/10 days)
- Target probability is 0.25
- Start at 35 Intravenous
- Observation window: 42 days
- Modified TITE-CRM (power model; initial guess is the first column; var is 0.3 in the lognormal prior)

True Probabilities

	1	2	3	4
d_1	0.05	0.05	0.08	0.15
d_2	0.1	0.1	0.15	**0.22**
d_3	0.15	**0.25**	**0.22**	0.3
d_4	**0.25**	0.4	0.3	0.4
d_5	0.35	0.6	0.4	0.5

University of Michigan Medical School

A Pediatric Trial-Children with Recurrent/Refractory High-risk Neuroblastoma

- Fixed Bortezomib at 1.2mg; Irinotecan at 30,35,40,45,and 50mg
- 24 patients (1/10 days)
- Target probability is 0.25
- Start at 35 Intravenous
- Observation window: 42 days
- Modified TITE-CRM (power model; initial guess is the first column; var is 0.3 in the lognormal prior)

True Probabilities

	1	2	3	4
d_1	0.05	0.05	0.08	0.15
d_2	0.1	0.1	0.15	**0.22**
d_3	0.15	**0.25**	**0.22**	0.3
d_4	**0.25**	0.4	0.3	0.4
d_5	0.35	0.6	0.4	0.5

University of Michigan Medical School

A Pediatric Trial-Children with Recurrent/Refractory High-risk Neuroblastoma

- Fixed Bortezomib at 1.2mg; Irinotecan at 30,35,40,45,and 50mg
- 24 patients (1/10 days)
- Target probability is 0.25
- Start at 35 Intravenous
- Observation window: 42 days
- Modified TITE-CRM (power model; initial guess is the first column; var is 0.3 in the lognormal prior)

True Probabilities

	1	2	3	4
d_1	0.05	0.05	0.08	0.15
d_2	0.1	0.1	0.15	**0.22**
d_3	0.15	**0.25**	**0.22**	0.3
d_4	**0.25**	0.4	0.3	0.4
d_5	0.35	0.6	0.4	0.5

University of Michigan Medical School

A Pediatric Trial-Children with Recurrent/Refractory High-risk Neuroblastoma

- Fixed Bortezomib at 1.2mg; Irinotecan at 30,35,40,45,and 50mg
- 24 patients (1/10 days)
- Target probability is 0.25
- Start at 35 Intravenous
- Observation window: 42 days
- Modified TITE-CRM (power model; initial guess is the first column; var is 0.3 in the lognormal prior)

True Probabilities

	1	2	3	4
d_1	0.05	0.05	0.08	0.15
d_2	0.1	0.1	0.15	**0.22**
d_3	0.15	**0.25**	**0.22**	0.3
d_4	**0.25**	0.4	0.3	0.4
d_5	0.35	0.6	0.4	0.5

University of Michigan Medical School

A Pediatric Trial-Children with Recurrent/Refractory High-risk Neuroblastoma

- Fixed Bortezomib at 1.2mg; Irinotecan at 30,35,40,45,and 50mg
- 24 patients (1/10 days)
- Target probability is 0.25
- Start at 35 Intravenous
- Observation window: 42 days
- Modified TITE-CRM (power model; initial guess is the first column; var is 0.3 in the lognormal prior)

True Probabilities

	1	2	3	4
d_1	0.05	0.05	0.08	0.15
d_2	0.1	0.1	0.15	**0.22**
d_3	0.15	**0.25**	**0.22**	0.3
d_4	**0.25**	0.4	0.3	0.4
d_5	0.35	0.6	0.4	0.5

University of Michigan Medical School

Conclusion

Compare to Rolling 6, Modified TITE-CRM is

- Identify MTD more accurately
- Treat more patients at or closest to the MTD
- Trial is continually open to accrual and no recruitment pause
- Just as safe: over-dose control

Conclusion

Compare to Rolling 6, Modified TITE-CRM is

- Identify MTD more accurately
- Treat more patients at or closest to the MTD
- Trial is continually open to accrual and no recruitment pause
- Just as safe: over-dose control

Conclusion

Compare to Rolling 6, Modified TITE-CRM is

- Identify MTD more accurately
- Treat more patients at or closest to the MTD
- Trial is continually open to accrual and no recruitment pause
- Just as safe: over-dose control

Conclusion

Compare to Rolling 6, Modified TITE-CRM is

- Identify MTD more accurately
- Treat more patients at or closest to the MTD
- Trial is continually open to accrual and no recruitment pause
- Just as safe: over-dose control

Introduction

- *Goal*: Experimental treatment is more efficacious than a historical control
- *Efficacy Endpoint*: progression-free survival (PFS) rate at t_0 or median PFS (θ)
- *Hypothesis*: $H_0 : \theta \leq \theta_0$ vs $H_1 : \theta \geq \theta_1$

Introduction

- *Goal*: Experimental treatment is more efficacious than a historical control
- *Efficacy Endpoint*: progression-free survival (PFS) rate at t_0 or median PFS (θ)
- *Hypothesis*: $H_0 : \theta \leq \theta_0$ vs $H_1 : \theta \geq \theta_1$

Introduction

- *Goal*: Experimental treatment is more efficacious than a historical control
- *Efficacy Endpoint*: progression-free survival (PFS) rate at t_0 or median PFS (θ)
- *Hypothesis*: $H_0 : \theta \leq \theta_0$ vs $H_1 : \theta \geq \theta_1$

Previous Work

Frequentist methods:

- Simon's two-stage design (1988): search over $n(r)$ and $n_1(r_1)$ to minimize expected/maximum sample size while satisfying the type I and II error constrains
- Extend Simon's two-stage design for time-to-event endpoints (Case and Morgan (2003) and Huang et al (2010))

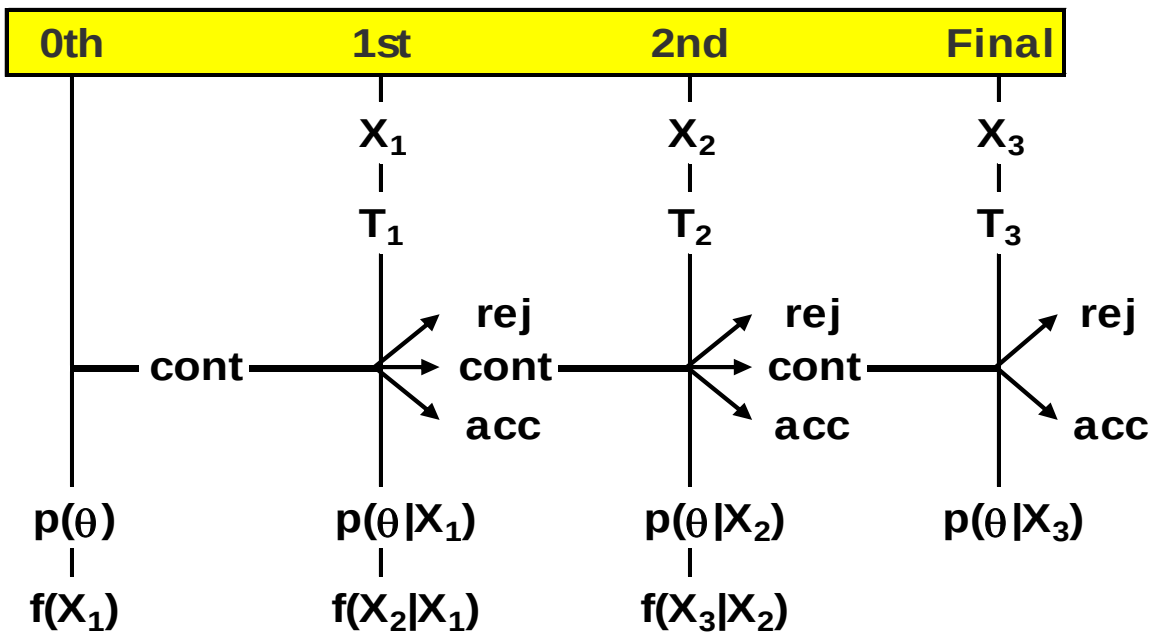
Bayesian methods:

- Follman and Albert (1999); Rosner (2005); Cheung and Thall (2002); Thall et al. (2005)
- Decision rules are based on posterior or predictive distribution: e.g. $p(\theta > \theta_1|X_1) < p_L$ for futility and $p(\theta > \theta_0|X_1) > p_U$ for efficacy

University of Michigan Medical School

A Bayesian Decision Theoretic Design with 2 Interim Looks

Data and information are cumulative



Interim (k)

Data (X)

Information (T)

Actions

Posterior

Predictive

Once Stop, Accept or Reject?

Threshold loss structure:

	True status of the treatment		
	Inferior	Neither	Superior
Decision:	$(\theta < \theta_0)$	$(\theta_0 \leq \theta \leq \theta_1)$	$(\theta > \theta_1)$
Accept H_0	0	0	1
Reject H_0	c_2	0	0

- Risk of accepting H_0: $P(\theta > \theta_1 | X_k)$
- Risk of rejecting H_0: $c_2 P(\theta < \theta_0 | X_k)$

Decision: choose the one with a smaller risk

University of Michigan Medical School

Stop or Continue?

Risk of stopping at interim k :

$$\rho_0(X_k) = \min\{c_2 P(\theta < \theta_0 | X_k), P(\theta > \theta_1 | X_k)\}$$

Risk of continuation:

$$\rho_{K-k}(X_k) = E_{X_{k+1}|X_k}[\rho_{K-k-1}(X_{k+1})] + c_3$$

Two-stage Design with Exponentially Distributed Survival Times

Time-to-progression has an exponential distribution with rate λ

- Prior: $\lambda \sim \Gamma(\alpha, \beta)$
- Likelihood function: $L(\lambda) = \lambda^f e^{-\lambda e}$

  f is total number of events and e is the total exposure time
- Posterior distribution: $\lambda|X_1 \sim \Gamma(\alpha + f, \beta + e)$
- $\theta = e^{-6\lambda}$
- $\rho_0(X_1) = \min\{P(\theta > \theta_1|X_1), c_2 P(\theta < \theta_0|X_1)\}$
- How to estimate the risk of continuation?

$$\begin{aligned}\rho_1(X_1) &= E_{X_2|X_1}[\rho_0(X_2)] + c_3 \\ &= E_{X_2|X_1}[\min\{P(\theta > \theta_1|X_2), c_2 P(\theta < \theta_0|X_2)\}] + c_3\end{aligned}$$

University of Michigan Medical School

Two-stage Design with Exponentially Distributed Survival Times

Time-to-progression has an exponential distribution with rate λ

- Prior: $\lambda \sim \Gamma(\alpha, \beta)$
- Likelihood function: $L(\lambda) = \lambda^f e^{-\lambda e}$

  f is total number of events and e is the total exposure time
- Posterior distribution: $\lambda|X_1 \sim \Gamma(\alpha + f, \beta + e)$
- $\theta = e^{-6\lambda}$
- $\rho_0(X_1) = \min\{P(\theta > \theta_1|X_1), c_2 P(\theta < \theta_0|X_1)\}$
- How to estimate the risk of continuation?

$$\begin{aligned}\rho_1(X_1) &= E_{X_2|X_1}[\rho_0(X_2)] + c_3 \\ &= E_{X_2|X_1}[\min\{P(\theta > \theta_1|X_2), c_2 P(\theta < \theta_0|X_2)\}] + c_3\end{aligned}$$

University of Michigan Medical School

Two-stage Design with Exponentially Distributed Survival Times

Time-to-progression has an exponential distribution with rate λ

- Prior: $\lambda \sim \Gamma(\alpha, \beta)$
- Likelihood function: $L(\lambda) = \lambda^f e^{-\lambda e}$

  f is total number of events and e is the total exposure time
- Posterior distribution: $\lambda|X_1 \sim \Gamma(\alpha + f, \beta + e)$
- $\theta = e^{-6\lambda}$
- $\rho_0(X_1) = \min\{P(\theta > \theta_1|X_1), c_2 P(\theta < \theta_0|X_1)\}$
- How to estimate the risk of continuation?

$$\begin{aligned} \rho_1(X_1) &= E_{X_2|X_1}[\rho_0(X_2)] + c_3 \\ &= E_{X_2|X_1}[\min\{P(\theta > \theta_1|X_2), c_2 P(\theta < \theta_0|X_2)\}] + c_3 \end{aligned}$$

University of Michigan Medical School

Two-stage Design with Exponentially Distributed Survival Times

Time-to-progression has an exponential distribution with rate λ

- Prior: $\lambda \sim \Gamma(\alpha, \beta)$
- Likelihood function: $L(\lambda) = \lambda^f e^{-\lambda e}$

  f is total number of events and e is the total exposure time
- Posterior distribution: $\lambda|X_1 \sim \Gamma(\alpha + f, \beta + e)$
- $\theta = e^{-6\lambda}$
- $\rho_0(X_1) = \min\{P(\theta > \theta_1|X_1), c_2 P(\theta < \theta_0|X_1)\}$
- How to estimate the risk of continuation?

$$\begin{aligned} \rho_1(X_1) &= E_{X_2|X_1}[\rho_0(X_2)] + c_3 \\ &= E_{X_2|X_1}[\min\{P(\theta > \theta_1|X_2), c_2 P(\theta < \theta_0|X_2)\}] + c_3 \end{aligned}$$

University of Michigan Medical School

Estimate the Risk of Continuation

- **Step 1** Sample λ from the posterior distribution of $f(\lambda|X_1)$,

$$f(\lambda|X_1) \sim \Gamma(\alpha_0 + f, \beta_0 + e).$$

- **Step 2** Sample survival times from Exp(λ) for censored patients in stage I and new patients enrolled in stage II (obtain X_2)
- **Step 3** Calculate

$$\rho_0(X_2) = \min\{P(\theta > \theta_1|X_2), c_2 P(\theta < \theta_0|X_2)\}$$

Repeat steps 1 to 3 many times to obtain many $\rho_0(X_2)$ and then average them and plus c_3 to get the risk of continuation

University of Michigan Medical School

Estimate the Risk of Continuation

- **Step 1** Sample λ from the posterior distribution of $f(\lambda|X_1)$,

$$f(\lambda|X_1) \sim \Gamma(\alpha_0 + f, \beta_0 + e).$$

- **Step 2** Sample survival times from Exp(λ) for censored patients in stage I and new patients enrolled in stage II (obtain X_2)
- **Step 3** Calculate

$$\rho_0(X_2) = \min\{P(\theta > \theta_1|X_2), c_2 P(\theta < \theta_0|X_2)\}$$

Repeat steps 1 to 3 many times to obtain many $\rho_0(X_2)$ and then average them and plus c_3 to get the risk of continuation

University of Michigan Medical School

Estimate the Risk of Continuation

- **Step 1** Sample λ from the posterior distribution of $f(\lambda|X_1)$,

$$f(\lambda|X_1) \sim \Gamma(\alpha_0 + f, \beta_0 + e).$$

- **Step 2** Sample survival times from Exp(λ) for censored patients in stage I and new patients enrolled in stage II (obtain X_2)
- **Step 3** Calculate

$$\rho_0(X_2) = \min\{P(\theta > \theta_1|X_2), c_2 P(\theta < \theta_0|X_2)\}$$

Repeat steps 1 to 3 many times to obtain many $\rho_0(X_2)$ and then average them and plus c_3 to get the risk of continuation

University of Michigan Medical School

Estimate the Risk of Continuation

- **Step 1** Sample λ from the posterior distribution of $f(\lambda|X_1)$,

$$f(\lambda|X_1) \sim \Gamma(\alpha_0 + f, \beta_0 + e).$$

- **Step 2** Sample survival times from Exp(λ) for censored patients in stage I and new patients enrolled in stage II (obtain X_2)
- **Step 3** Calculate

$$\rho_0(X_2) = \min\{P(\theta > \theta_1|X_2), c_2 P(\theta < \theta_0|X_2)\}$$

Repeat steps 1 to 3 many times to obtain many $\rho_0(X_2)$ and then average them and plus c_3 to get the risk of continuation

University of Michigan Medical School

Decision Making Process

- At the end of stage I,
  - Compare the risk of stopping vs the risk of continuation

$$\rho_0(X_1) \quad \text{vs} \quad \rho_1(X_1) \ \text{(depends on } X_2 \text{ and } c_3)$$

  - If decide to stop, compare the risk of rejection vs the risk of acceptance given X_1

$$c_2 P(\theta < \theta_0 | X_1) \quad \text{vs} \quad P(\theta > \theta_1 | X_1)$$

- At the end of stage II, compare the risk of rejection vs the risk of acceptance given X_2

$$c_2 P(\theta < \theta_0 | X_2) \quad \text{vs} \quad P(\theta > \theta_1 | X_2)$$

University of Michigan Medical School

Decision Making Process

- At the end of stage I,
  - Compare the risk of stopping vs the risk of continuation

$$\rho_0(X_1) \quad \text{vs} \quad \rho_1(X_1) \ \text{(depends on } X_2 \text{ and } c_3)$$

  - If decide to stop, compare the risk of rejection vs the risk of acceptance given X_1

$$c_2 P(\theta < \theta_0 | X_1) \quad \text{vs} \quad P(\theta > \theta_1 | X_1)$$

- At the end of stage II, compare the risk of rejection vs the risk of acceptance given X_2

$$c_2 P(\theta < \theta_0 | X_2) \quad \text{vs} \quad P(\theta > \theta_1 | X_2)$$

University of Michigan Medical School

Decision Making Process

- At the end of stage I,
  - Compare the risk of stopping vs the risk of continuation

$$\rho_0(X_1) \quad \text{vs} \quad \rho_1(X_1) \ \text{(depends on } X_2 \text{ and } c_3)$$

  - If decide to stop, compare the risk of rejection vs the risk of acceptance given X_1

$$c_2 P(\theta < \theta_0 | X_1) \quad \text{vs} \quad P(\theta > \theta_1 | X_1)$$

- At the end of stage II, compare the risk of rejection vs the risk of acceptance given X_2

$$c_2 P(\theta < \theta_0 | X_2) \quad \text{vs} \quad P(\theta > \theta_1 | X_2)$$

University of Michigan Medical School

Two-stage Design with Weibull Distributed Survival Times

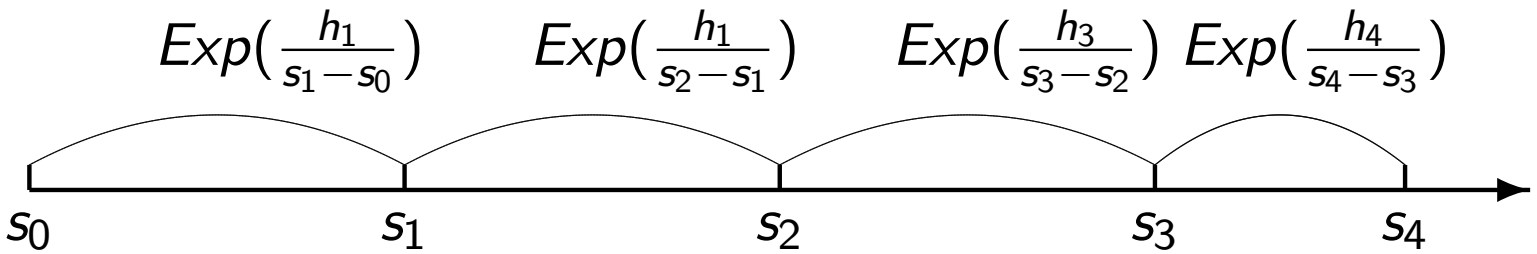
Time-to-progression has a Weibull distribution with parameters γ and α

- $f(t) = \alpha\gamma t^{\alpha-1} e^{-\gamma t^{\alpha}}$ for $\alpha > 0, \gamma > 0$
- The primary endpoint is $\theta = S(t_0) = e^{-\gamma t_0^{\alpha}}$.
- Cumulative hazard function: $H(t) = \gamma t^{\alpha}$
- MCMC method to obtain posterior distribution of γ and α. (Metropolis-Hasting algorithms in Albert (2009))

University of Michigan Medical School

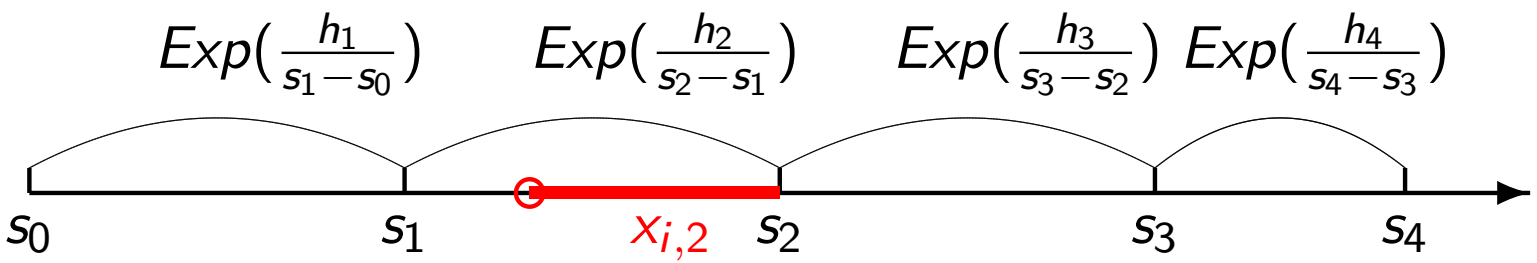
Example of Simulating X_2 Given X_1

Stage I: $h_j = H(s_j) - H(s_{j-1}) = \gamma(s_j^{\alpha} - s_{j-1}^{\alpha}), \quad j = 1, 2, 3, 4$



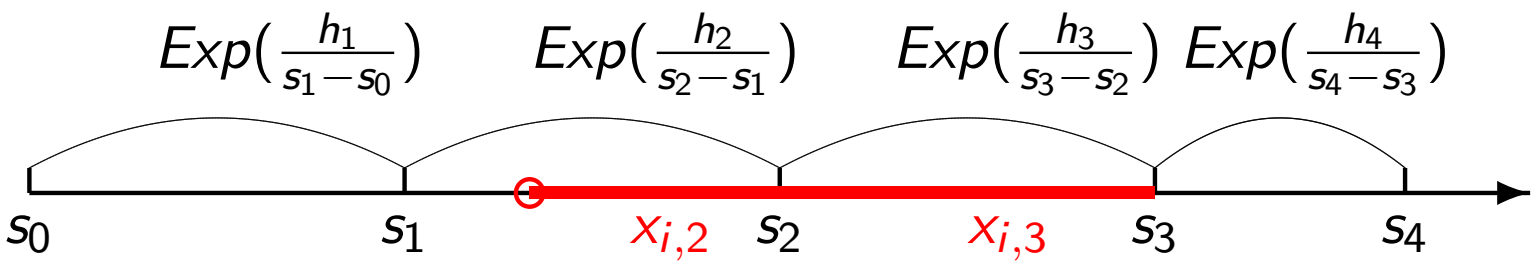
Patient i is Censored at the End of Stage I

At the end of stage one: $h_j = \gamma(s_j^\alpha - s_{j-1}^\alpha), \quad j = 1, 2, 3, 4$



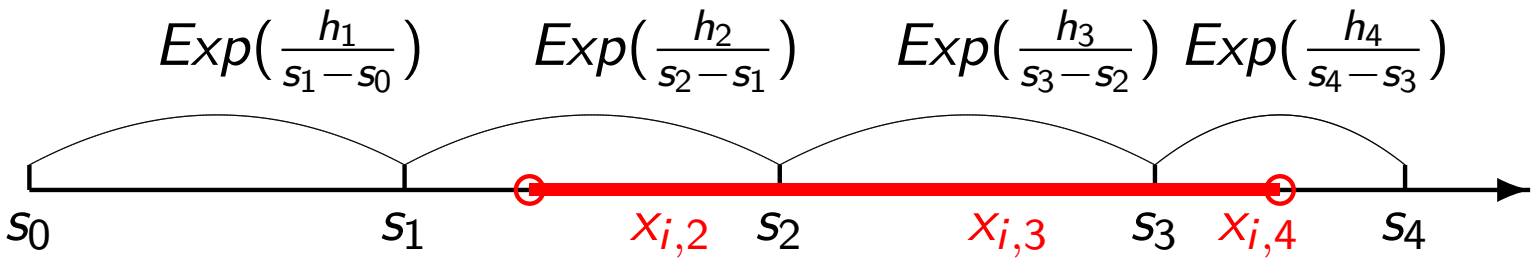
Patient i is Censored at the End of Stage I -continued

At the end of stage one: $h_j = \gamma(s_j^\alpha - s_{j-1}^\alpha), \quad j = 1, 2, 3, 4$



Patient i is Censored at the End of Stage I -continued

At the end of stage one: $h_j = \gamma(s_j^\alpha - s_{j-1}^\alpha), \quad j = 1, 2, 3, 4$



remaining time: $x_{i,2} + x_{i,3} + x_{i,4}$

Simulation Results Given the Same Type I Error and Power

Design	$n(n_1)$	Under H_0			Under H_1		
		PET	EN	ETSL	PET	EN	ETSL
0.2 vs 0.4							
H-ETSL	49(31)	0.66	37	14	0.08	48	21
Optimal	51(17)	0.76	25	13	0.12	47	25
Bayes	28(14)	0.27	24	12	0.04	27	15
0.3 vs. 0.45							
H-ETSL	98(48)	0.67	65	23	0.08	94	37
Optimal	86(29)	0.64	49	22	0.09	81	36
Bayes	54(27)	0.38	44	18	0.04	53	23
0.5 vs. 0.7							
H-ETSL	45(30)	0.70	35	13	0.04	44	21
Optimal	34(11)	0.73	17	11	0.12	31	21
Bayes	20(10)	0.17	18	11	0.02	20	13

University of Michigan Medical School

A Real Sarcoma Trial

- Primary endpoint: 6-month progression-free survival rate
- $\theta_0 = 0.1$ and $\theta_1 = 0.25$
- Accrual: 3 patients per month
- MiniMax Design:
  - Define success: complete 6-month followup and free of progression
  - $n_1 = 24(r_1 > 2)$ and $n = 47(r > 8)$ for type I error of 0.05 and type II error of 0.15.

Running the trial:

- Stage I: the trial was suspended for 2 months until observed 3 successes $\Rightarrow$ Continued to the final stage.
- Stage II: observed 10 successes $\Rightarrow$ reject H_0.

University of Michigan Medical School

Bayesian Decision Theoretic Two-stage Design

		Stage I				Stage II	
$n(n_1)$	Action	Risk	ρ_0	ρ_1	Decision	Risk	Decision
Weibull							
47(24)	Acc	0.64	0.08	0.04	Continue	0.38	Reject
	Rej	0.08				0.02	
32(24)	Acc	0.64	0.08	0.05	Continue	0.75	Reject
	Rej	0.08				0.01	

Conclusion

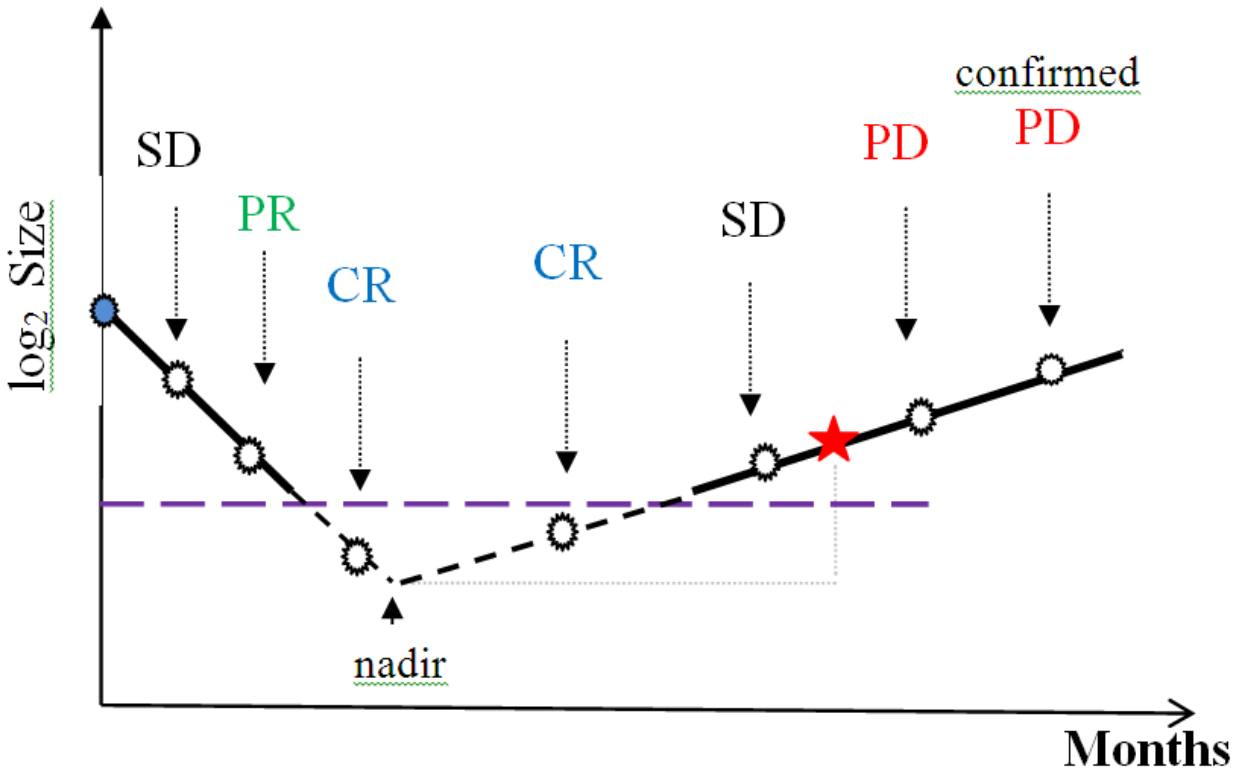
Compared to Simon's design, the Bayesian decision theoretic approach:

- Reduce sample size given the same error rates
- Allow continuous enrollment
- A Flexible design which are based on evidence
- Trial can stop early for efficacy as well as for inferiority
- Can be easily modified to design randomized trials

Efficacy Endpoints in Phase II and III Oncology Trials

- A tumor response rate
- Time-to-progression (TTP)
- Progression-free survival (PFS)

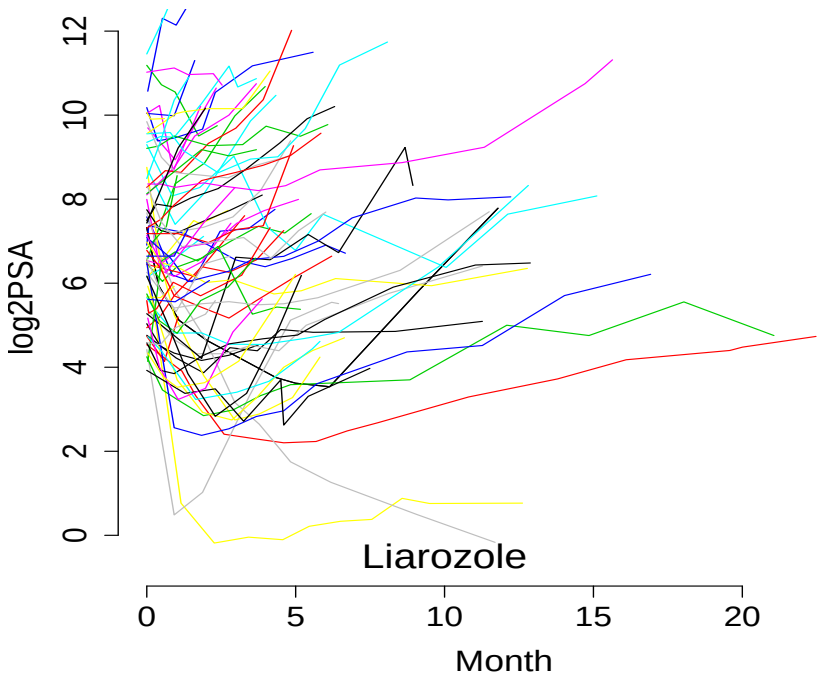
Measure Tumor Response Following Treatment

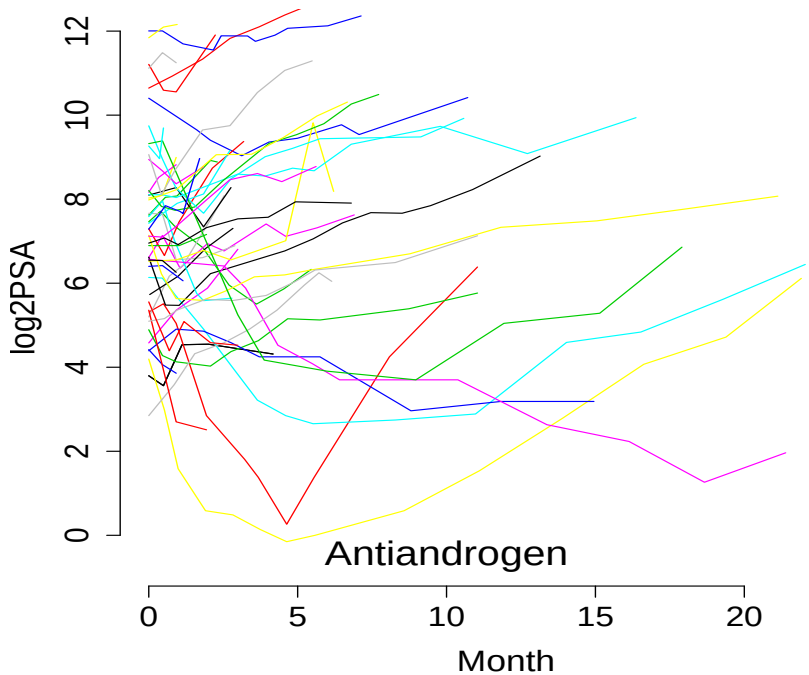


- PR: reduce 30% (ref. baseline)
- CR: all target lesions disappear
- PD: increase 20% (ref. nadir)
- SD: between PR and PD

University of Michigan
Medical School

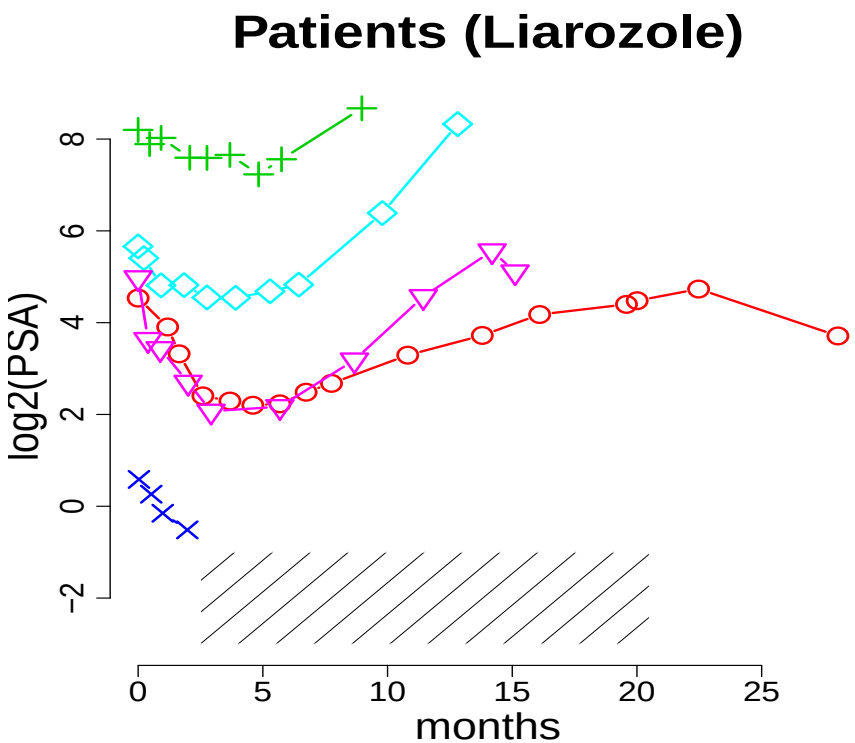
PSA Data in Selected Patients (Buyse 2010)

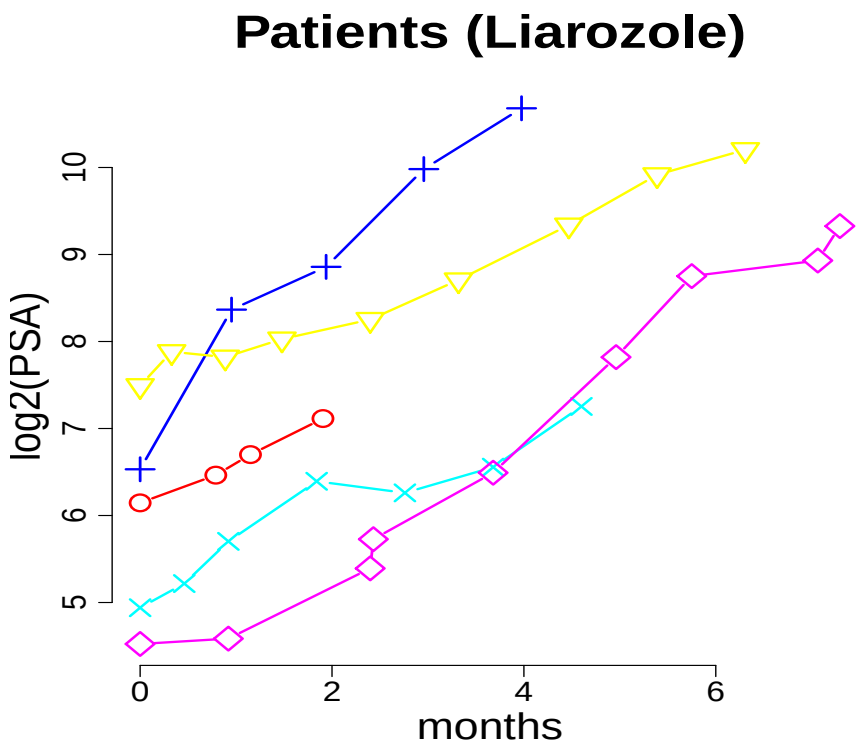




University of Michigan
Medical School

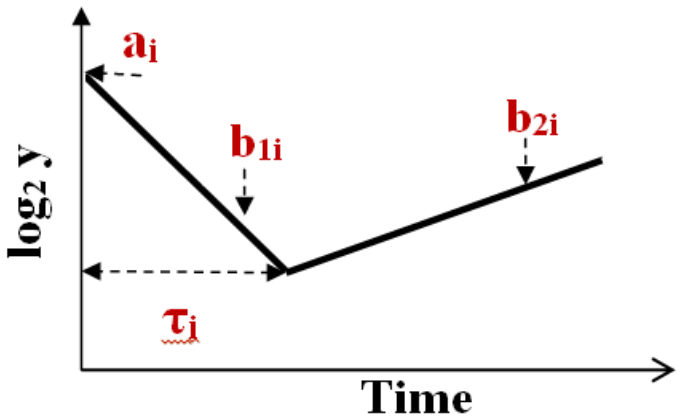
Two Types of Tumor Growth Trajectories:





University of Michigan Medical School

Define Functions Describing Tumor Growth for Subject *i*

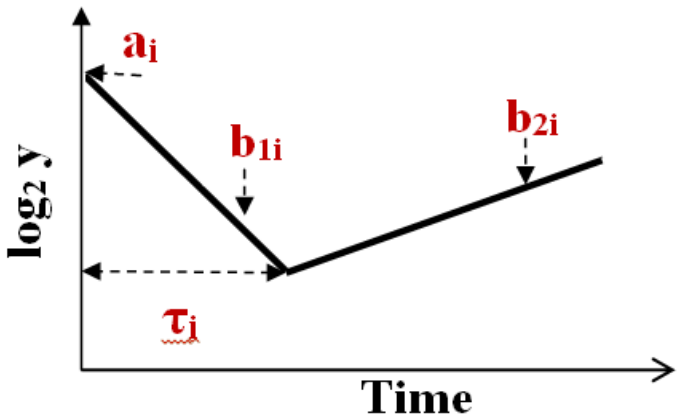


$$y_{ij} \sim N(\mu_{ij}, \sigma^2)$$

$$\mu_{ij} = a_i + b_{1i} t_{ij} \mathbb{I}\{t_{ij} \leq \tau_i\} + b_{1i}\tau_i \mathbb{I}\{t_{ij} > \tau_i\} + b_{2i}(t_{ij} - \tau_i)_+ \quad \text{if} \quad z_i = 1$$

$$\mu_{ij} = a_i + b_{2i} t_{ij} \quad \text{if} \quad z_i = 0$$

Define Functions Describing Tumor Growth for Subject i

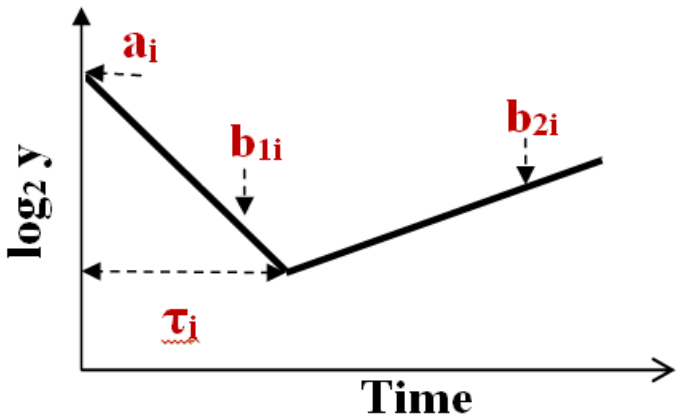


$$y_{ij} \sim N(\mu_{ij}, \sigma^2)$$

$$\mu_{ij} = a_i + b_{1i} t_{ij} \mathbb{I}\{t_{ij} \leq \tau_i\} + b_{1i}\tau_i \mathbb{I}\{t_{ij} > \tau_i\} + b_{2i}(t_{ij} - \tau_i)_+ \quad \text{if} \quad z_i = 1$$

$$\mu_{ij} = a_i + b_{2i} t_{ij} \quad \text{if} \quad z_i = 0$$

Define Functions Describing Tumor Growth for Subject i

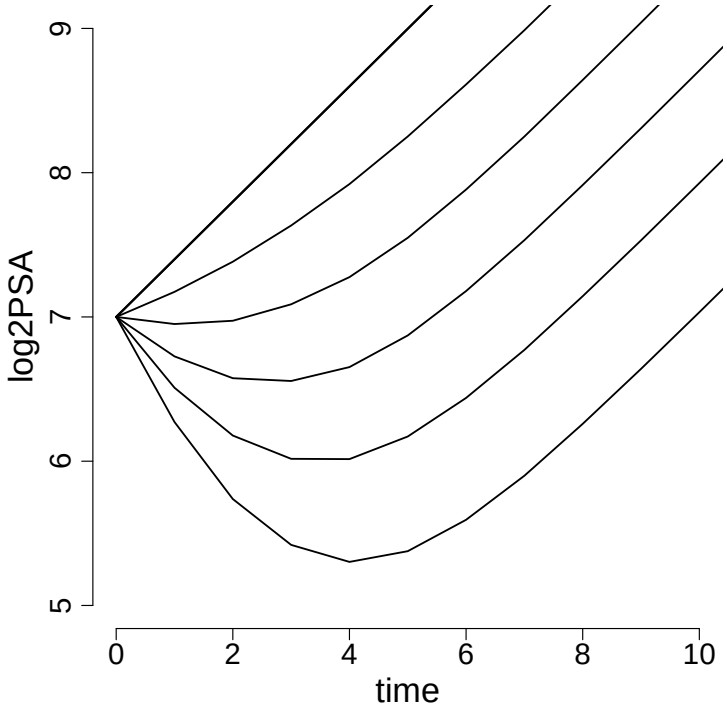


$$y_{ij} \sim N(\mu_{ij}, \sigma^2)$$

$$\mu_{ij} = a_i + b_{1i} t_{ij} \mathbb{I}\{t_{ij} \leq \tau_i\} + b_{1i}\tau_i \mathbb{I}\{t_{ij} > \tau_i\} + b_{2i}(t_{ij} - \tau_i)_+ \quad \text{if} \quad z_i = 1$$

$$\mu_{ij} = a_i + b_{2i} t_{ij} \quad \text{if} \quad z_i = 0$$

Hypothetical Non-linear PSA Trajectories



Each curve is an average over 1000 curves simulated from the mixture model with a mixture probability, p; ranging from 0 to 1, at 0.2 intervals.

University of Michigan Medical School

Model Parameters

- Subject-level parameters ($i = 1, \cdots, n$):

$$z_i, \quad a_i, \quad b_{1i}, \quad \tau_i, \quad b_{2i}$$

- Treatment-level parameters ($k = 1, \cdots, K$):

$$p_k, \quad \beta_{1k}, \quad \mu_{\tau k}, \quad \beta_{2k}$$

- Population-level parameters

$$\alpha, \quad \sigma^2$$

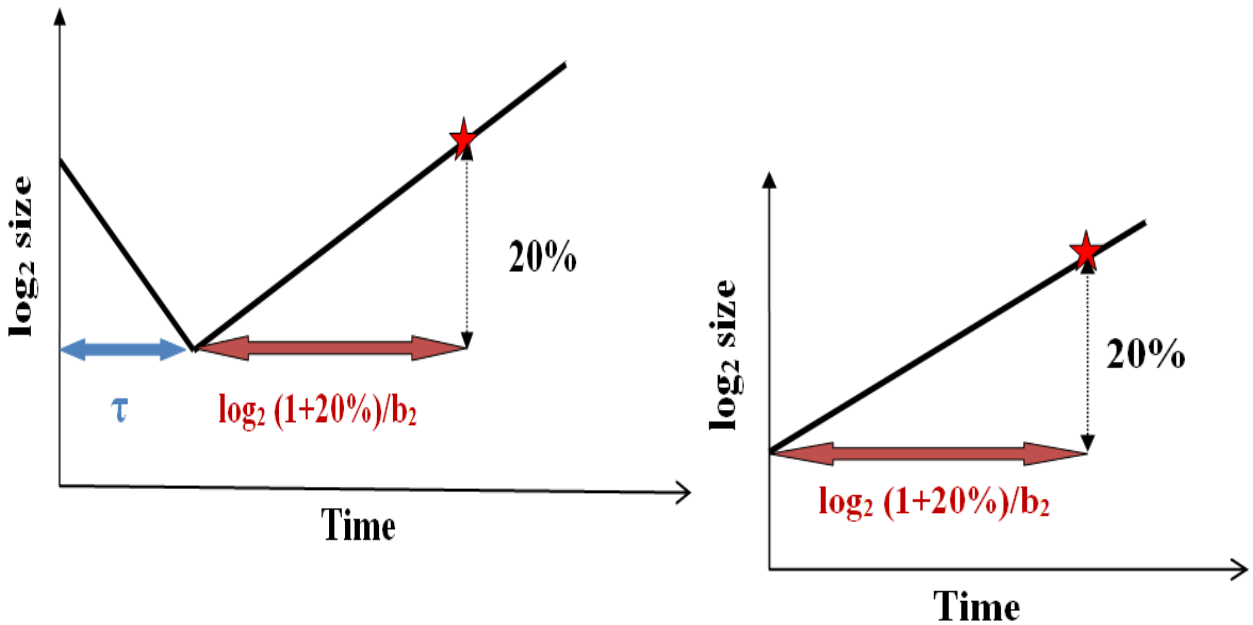
University of Michigan Medical School

Sampling Algorithm

- Conjugate normal forms
- τ_i :Slice sampling (Neal 2003)
- z_i Pseudoprior approach (Carlin&Chib 1995) and Reversible Jump MCMC (Green 1995)
- Sampling constrained parameters (Gelfand 1992)
- Below the limit of detection: $y_{ij}|\mu_{ij}, \sigma^2, \sim N(\mu_{ij}, \sigma^2)\mathbb{I}(y_{ij} < c)$.

Endpoints of TTP and Response Rate

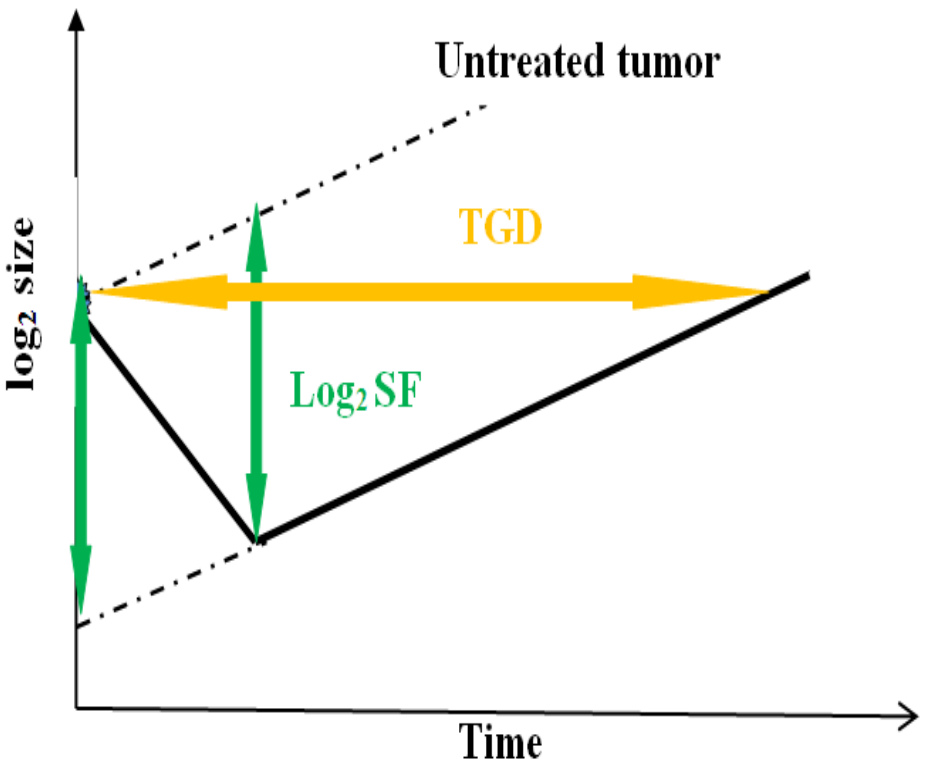
Progression is defined for a $X\%$ increase in biomarker relative to nadir



$$\text{TTP}_k = p_k \mu_{\tau k} + \log_2(1 + 20\%)/\beta_{2k}$$

where p_k is the response rate in treatment k

Endpoints of Cell Killing Fraction and Tumor Growth Delay



(*Demidenko,2010*)

- $\mathrm{LSF}_k = p_k \times \mu_{\tau k}(\beta_{1k} - \beta_2)$
- $\mathrm{KF}_k = 1 - 2^{\mathrm{LSF}_k}$
- $\mathrm{TGD}_k = -\mathrm{LSF}_k/\beta_2$

University of Michigan Medical School

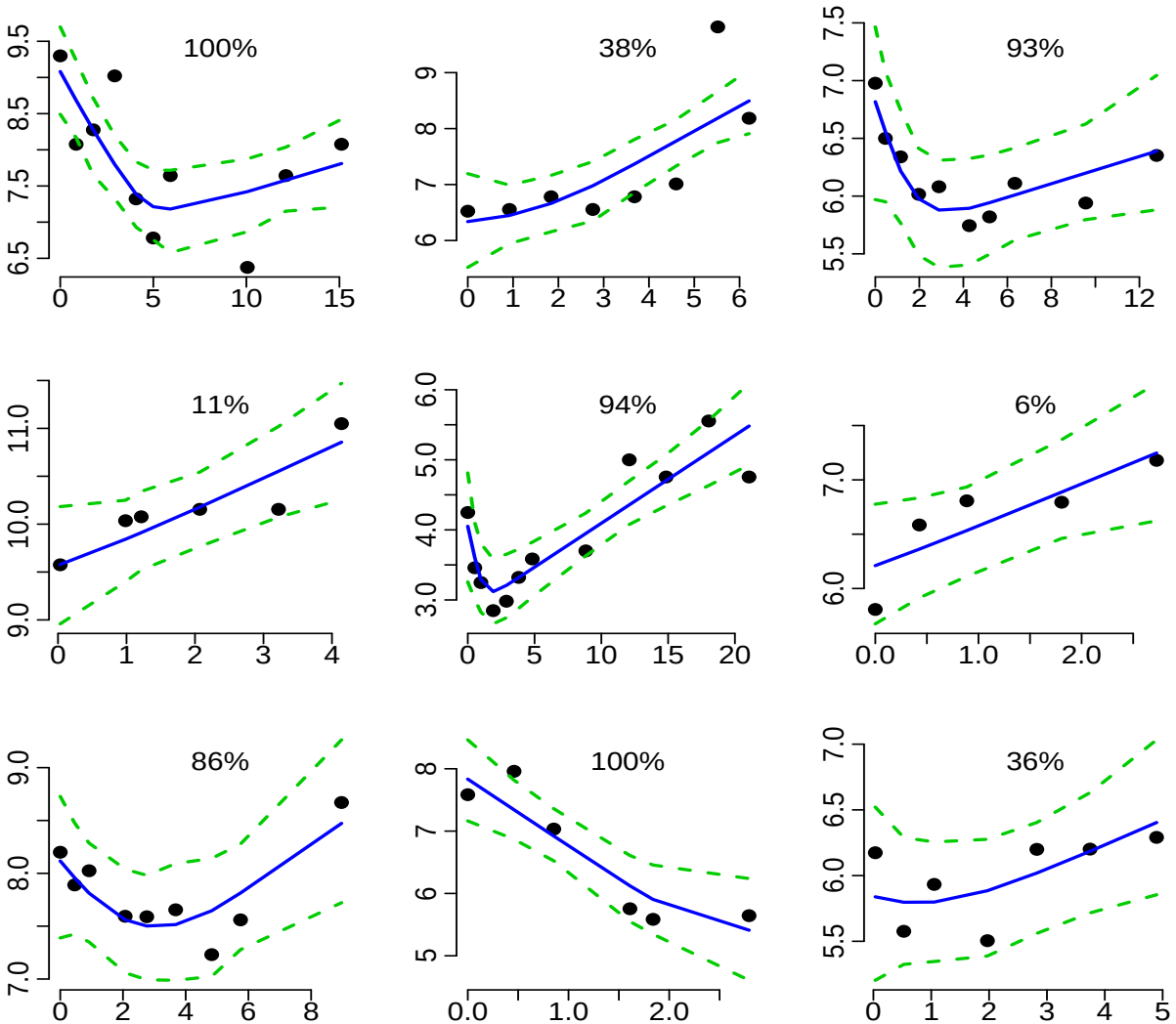
A Prostate Cancer Trial

Table: Posterior mean with 95% HPD intervals .

Compare Parameters	**Antiandrogens**	**Liarozole**	**Difference**
P	0.40(0.33,0.48)	0.43(0.35,0.50)	(-0.08,0.13)
μ_τ	2.02(1.57,2.46)	4.09(3.28,4.96)	(1.12,3.07)*
β_1	-0.76(-0.97,-0.57)	-0.74(-0.90,-0.59)	(-0.25,0.27)
β_2	0.37(0.33,0.42)	0.35(0.32,0.39)	(-0.07,0.04)
TTP	2.39(2.15,2.67)	3.41(2.94,3.87)	(0.46,1.53)*
KF	0.46(0.38,0.55)	0.73(0.63,0.82))	(0.13,0.39)*
TGD	2.50(1.90,3.18)	5.30(3.95,6.81)	(0.28,4.48)*

University of Michigan Medical School

Fitted Curves for Some Subjects



Conclusion

- Use more data information to estimate response rate and TTP
- Estimate biologically meaningful endpoints
- Limitation: need enough data before and after the changepoint

THANK YOU

References

- Zhao L and Woodworth G. (2009). Bayesian Decision-Theoretic Group Sequential Analysis with Survival Endpoints. *Statistics in Medicine*, 28:13391352.
- Zhao L, Morgan MA, Parsels LA, Maybaum J, Lawrence TS, and Normolle D. (2011). Bayesian Hierachical Changepoint Methods in Modeling the Tumor Growth Profiles in Xenograft Experiments (with discussions). *Clinical Cancer Research*, 17(5): 1-7.
- Zhao L , Lee J, Mody, R and Braun TM.(2011). The Superiority of the Time-to-Event Continual Reassessment Method to the Rolling Six Design in Pediatric Phase I Cancer Trials. *Clinical Trials*, 8(4):361-369.
- Zhao L, Taylor JMG, and Schuetze SM. (2012). Bayesian Decision Theoretic Two-stage Design in Phase II Clinical Trials with Survival Endpoints, *Statistics in Medicine*, 31(17):1804-1820.
- Zhao L, Feng D, Neelon B and Buyse M. (2015). Evaluation of Treatment Efficacy Using a Bayesian Mixture Piecewise Linear Model of Longitudinal Biomarkers. *Statistics in Medicine*, 34(10): 1733-1746.

University of Michigan
Medical School