Three Methods for Phase I/II Clinical Trials, with Application to Allogeneic Stem Cell Transplantation

Peter F. Thall, PhD

Biostatistics Department

M.D. Anderson Cancer Center

Workshop on Clinical Trial Endpoints for Acute Graft-vs-Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation

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Financial Conflicts of Interest

- None

Standard "3+3" Phase I Designs for Oncology

- Objective: Identify the maximum tolerated dose (MTD)
- MTD defined by algorithm: ***Implicitly*** either 17% or 33% grades 3-5 AE
- But the incidence of grade 3 AEs far exceeds 17-33% for BMT patients, so this design is rarely applicable for this population of patients
- Well known to have inferior properties compared to Bayesian adaptive designs

Three Phase I and Phase I-II Designs

Treatment Optimized	Outcome	Decision Criterion	Example
Dose	Bivariate binary (phase I-II)	Efficacy-toxicity trade-offs	GVHD prophylaxis, anergized cells post allotx, etc.
Dose and Schedule	Time to toxicity (phase I)	Pr(toxicity by day t*)	Azacitidine post allotx
Doses of two agents ($dose_1$, $dose_{2)}$	Bivariate ordinal (phase I-II)	Utility of outcome	Bladder cancer

All methods are

Bayesian : Model parameters are considered to be RANDOM quantities

Sequentially Outcome Adaptive :

Choose a treatment

(dose, dose-schedule, dose pair) →

Treat a cohort of patients →

Observe the patients' outcomes

Repeat until a stopping rule says "Stop"

Three Phase I and Phase I-II Designs

Treatment Optimized	Outcome	Decision Criterion	Example
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Dose and Schedule	Time to toxicity (phase I)	Pr(toxicity by day t*)	Azacitidine post allotx
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Dose-Finding Based On Efficacy-Toxicity Trade-Offs

(Thall and Cook, 2004; Thall, Cook and Estey, 2006)

Patient Outcome = {Efficacy, Toxicity}

- each a binary indicator

$\pi_E(x)$ = Pr(Efficacy at dose = x)

$\pi_T(x)$ = Pr(Toxicity at dose = x)

MD must specify:

→ A Lower Limit on $\pi_E(x)$ (minimum response of interest)

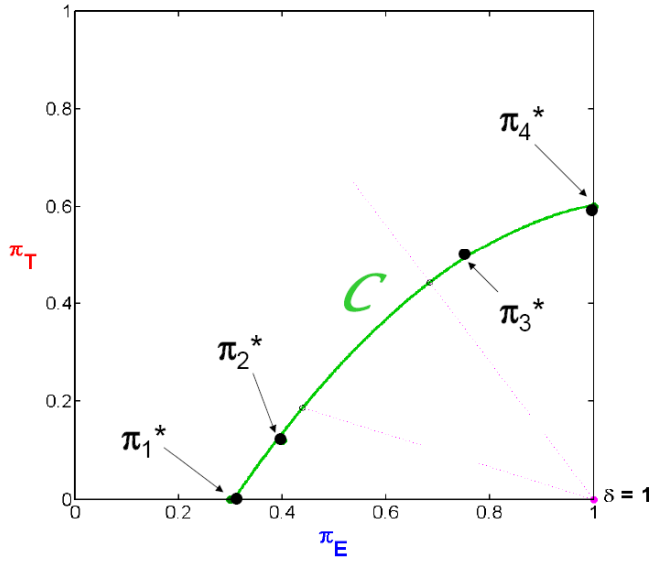
→ An Upper Limit on $\pi_T(x)$(maximum acceptable toxicity)

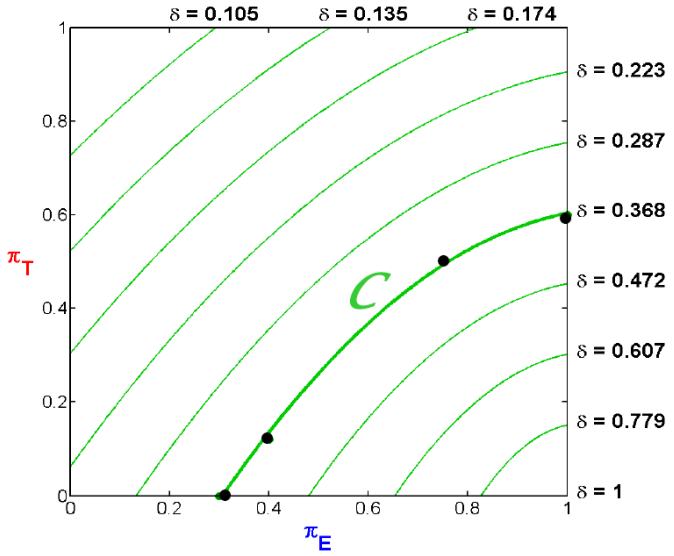
→ Three or more equally desirable (π_E, π_T) targets…

Two Dose Acceptability Criteria

Efficacy Cop

Toxicity Cop

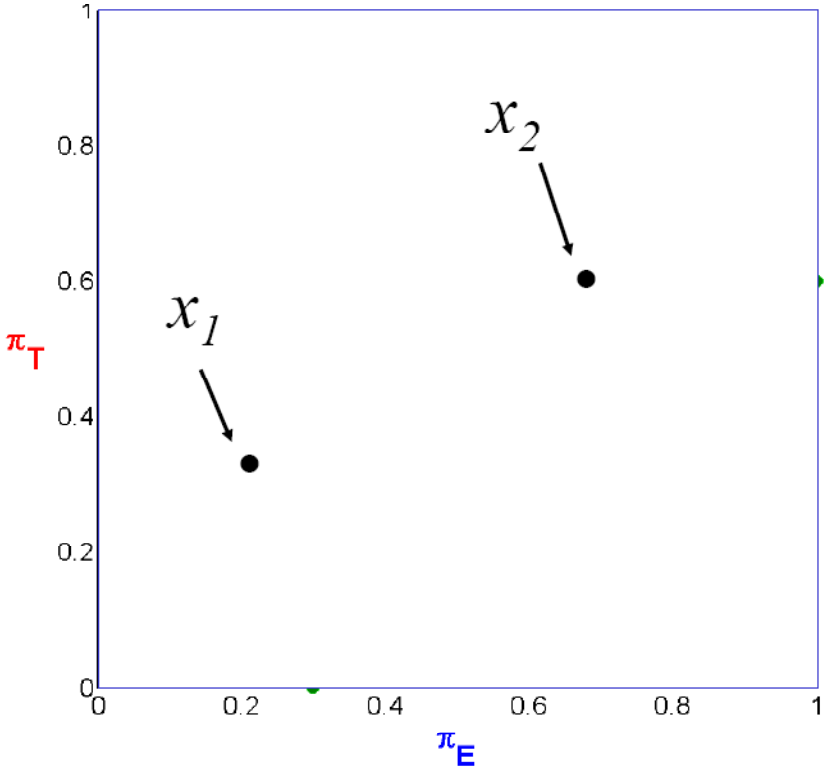


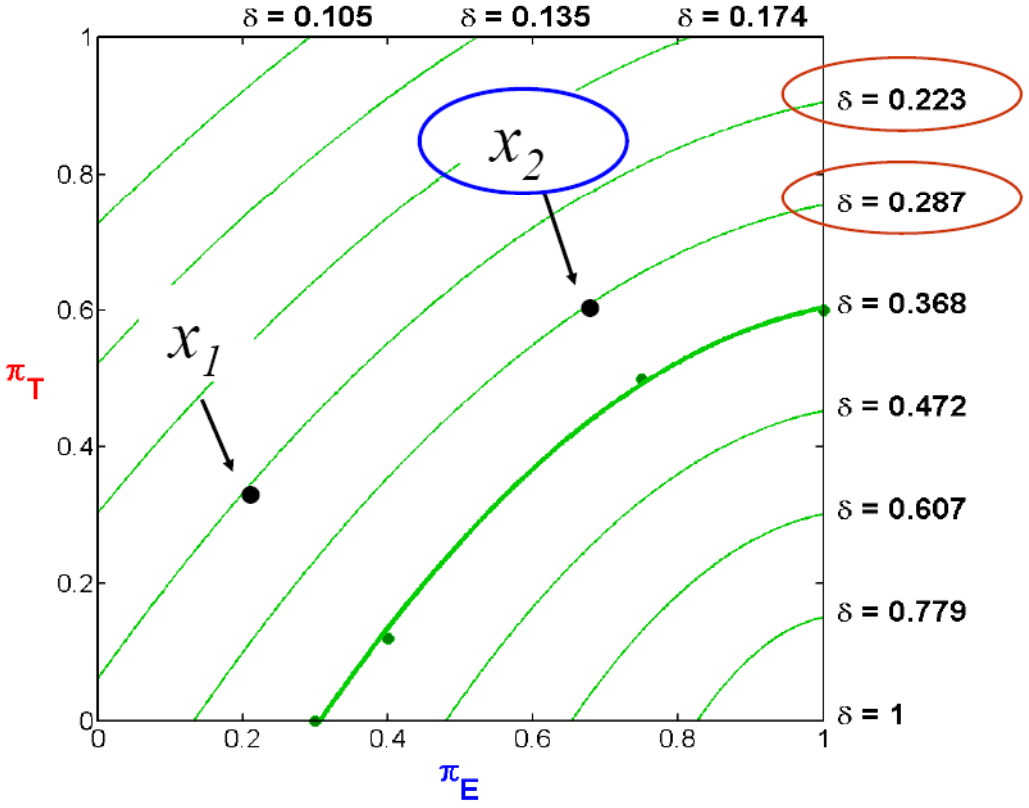


Target pairs are used to construct an Efficacy-Toxicity Trade-off Contour…

and a family of Contours each with desirability, δ, for the (π_E, π_T) pair

Which of these two π pairs is more desirable?





Trial Conduct

1) The physician chooses the starting dose
2) A dose is *Acceptable* if either
   a) it has acceptable π_E & π_T or
   b) it is the lowest untried dose and has acceptable π_T
3) *Treat each cohort at the current most desirable dose*
   a) The dose chosen for the next cohort may be *higher than, the same as, or lower than* the current dose
   b) After de-escalation due to excessive toxicity or low efficacy, if subsequent outcomes at a lower dose are sufficiently safe and efficacious, then *the algorithm may re-escalate*
4) Do not skip untried doses
5) No dose acceptable ➔ *Stop the trial*
6) At the end, select the most desirable dose

Pentostatin for Graft-Versus-Host Disease

Patients with steroid-refractory GVHD after allotx from an HLA-matched donor

Doses : x = .25, .50, .75, or 1.00 mg/m^2

N_{max} = 36, cohort size = 3

First cohort treated at .25 mg/m^2

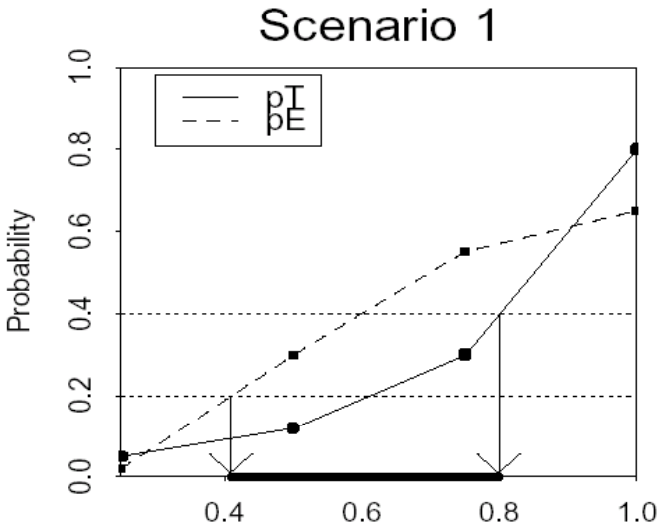
Toxicity = {Infection unresolved by antibiotics, or death, within 2 weeks}

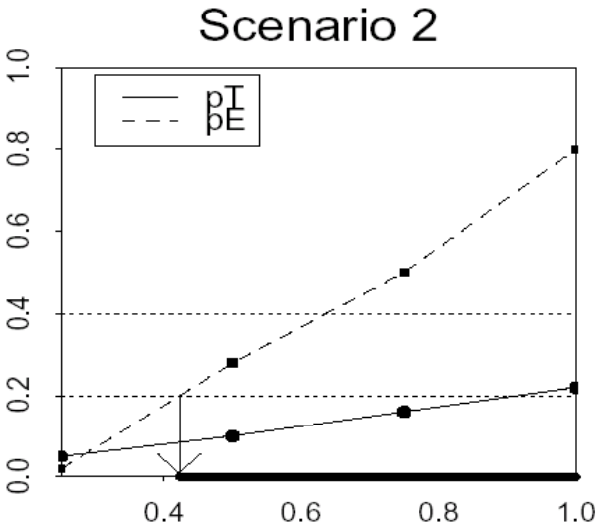
Efficacy = { $\geq$ 1 grade drop in GVHD severity, within 2 weeks}

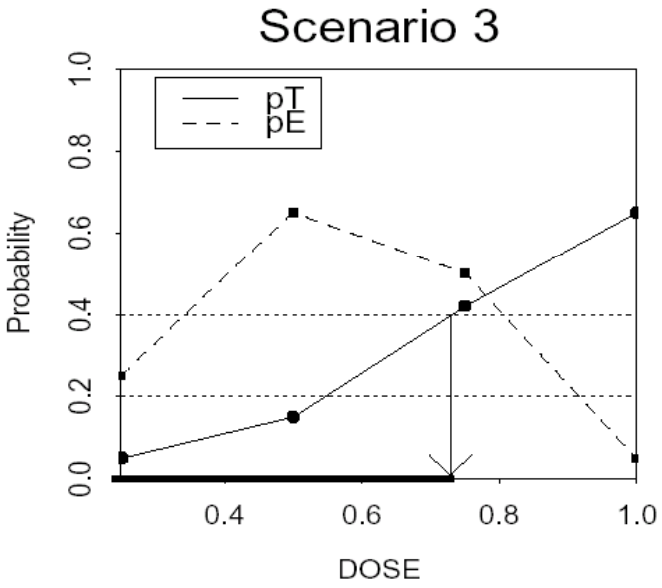
.40 = Upper Limit on $\pi_T(x)$

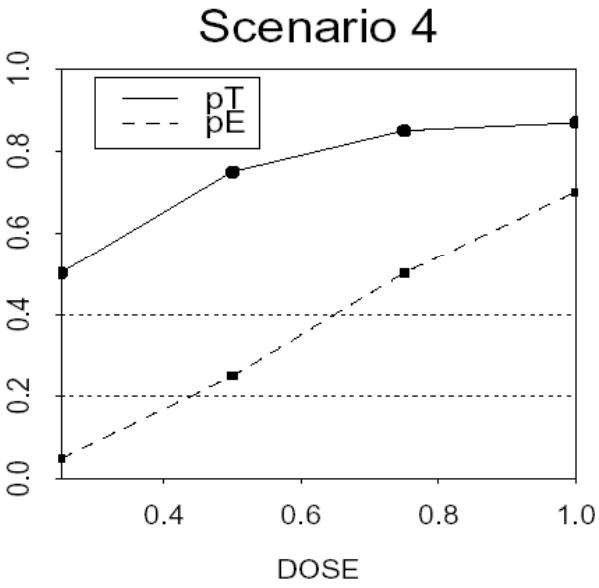
.20 = Lower Limit on $\pi_E(x)$

Simulation Scenarios for the Pentostatin Trial

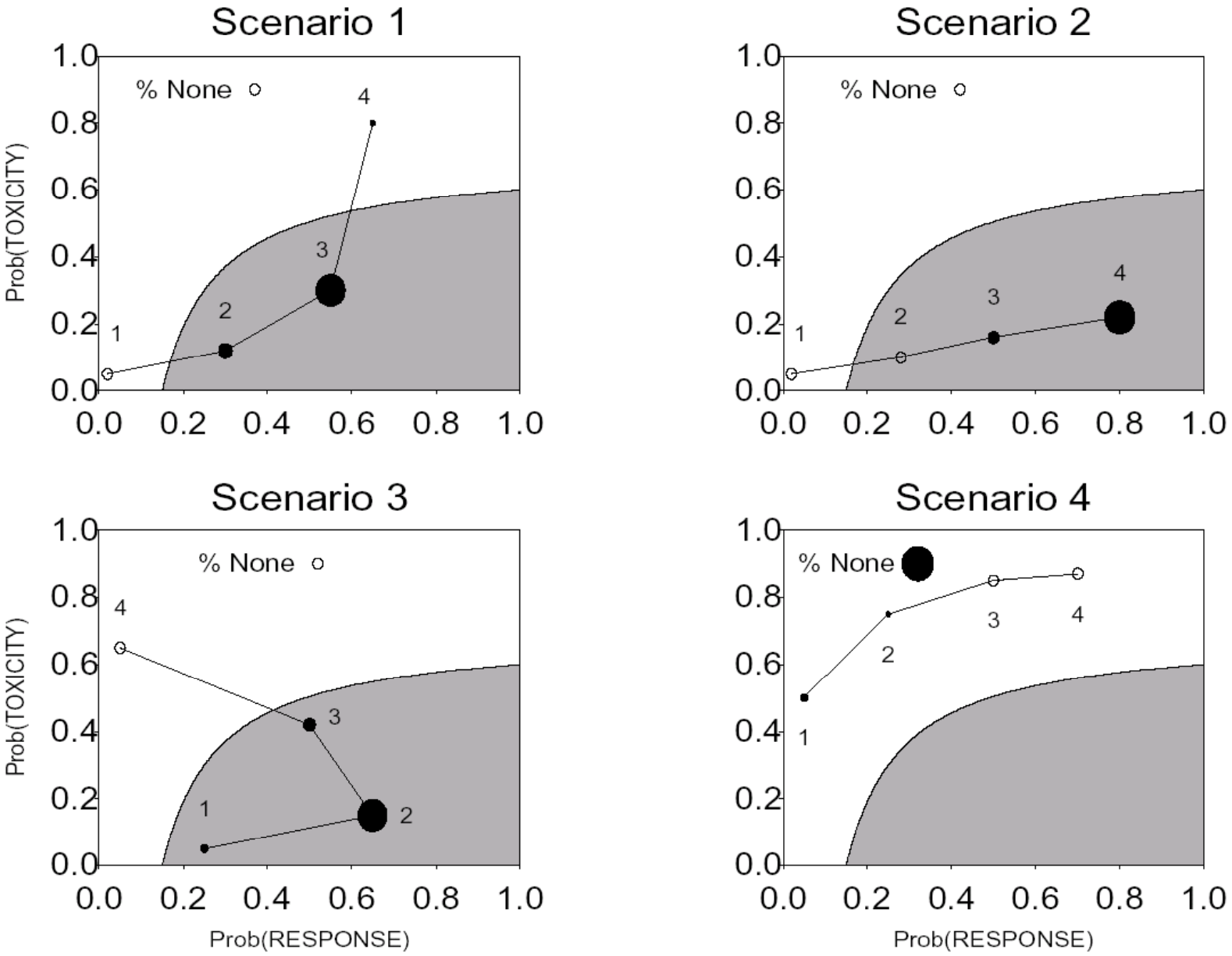








Dose Selection Probabilities



Conclusions

The *Trade-Off-Based Algorithm* reliably

1) Finds Safe Doses having High Efficacy

2) Stops if no dose is acceptable

Implementation is Hard Work, but a free computer program is available!

Three Phase I and Phase I-II Designs

Treatment Optimized	Outcome	Decision Criterion	Example
Dose	Bivariate binary (phase I-II)	Efficacy-toxicity trade-offs	GVHD prophylaxis, anergized cells post allotx, etc.
Dose and Schedule	**Time to toxicity (phase I)**	**Pr(toxicity by day t*)**	**Azacitidine post allotx**
Doses of two agents ($dose_1$, $dose_2$)	Bivariate ordinal (phase I-II)	Utility of outcome	Bladder cancer

Optimizing Dose and Schedule Based On Time to Toxicity

Braun, Thall, Nguyen, deLima *Clinical Trials*, 2007

Goal: Optimize **(Dose, Schedule)** **based on Time to Toxicity**

Vidaza® (azacitidine) given post allotx in AML pts

- Dose-toxicity profile of Vidaza® unknown
- Cumulative toxicity of repeated administration (multiple 28-day cycles) unknown

Patient Outcome

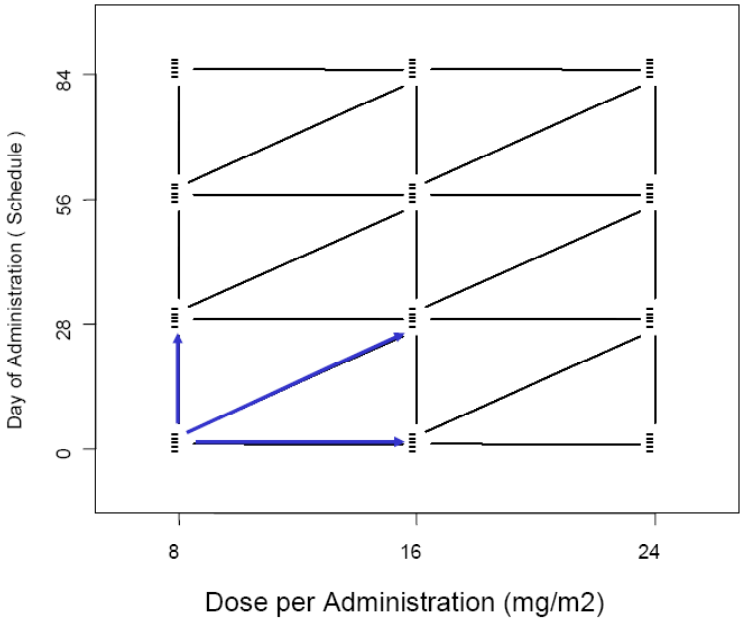
- *T = Time from the start of treatment to toxicity*
- Usual "time-to-event" data, as in a survival time analysis. A patient's outcome consists of

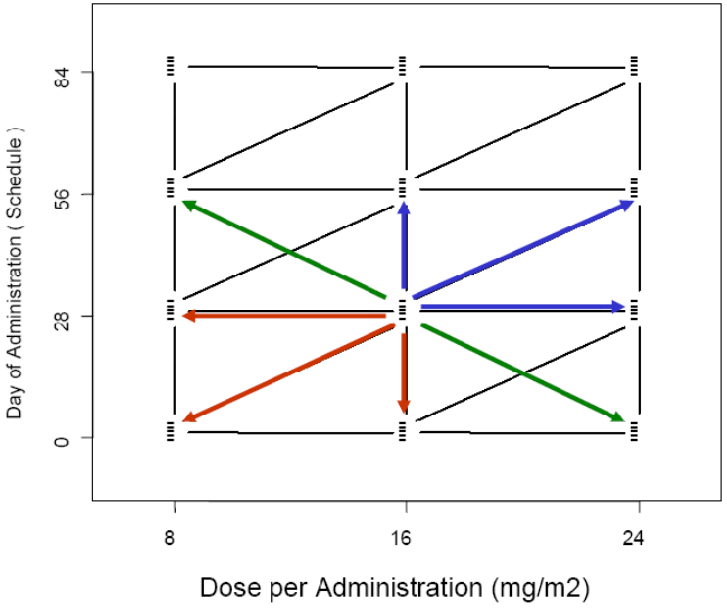
  a) *Time to toxicity* if it occurred, or *Time to last follow up* if toxicity has *not* occurred

  b) An indicator of whether toxicity has occurred
- Why is "time-to-event" better than a binary outcome?
  Using a usual binary (Yes / No) indicator of
  ["Toxicity" within 28 days from the start of therapy]
  - A patient with toxicity at day 27 is scored "Yes"
  - A patient with toxicity at day 29 is scored "No"
  - A patient followed for only 25 days w/o toxicity is inevaluable and ***cannot be scored***

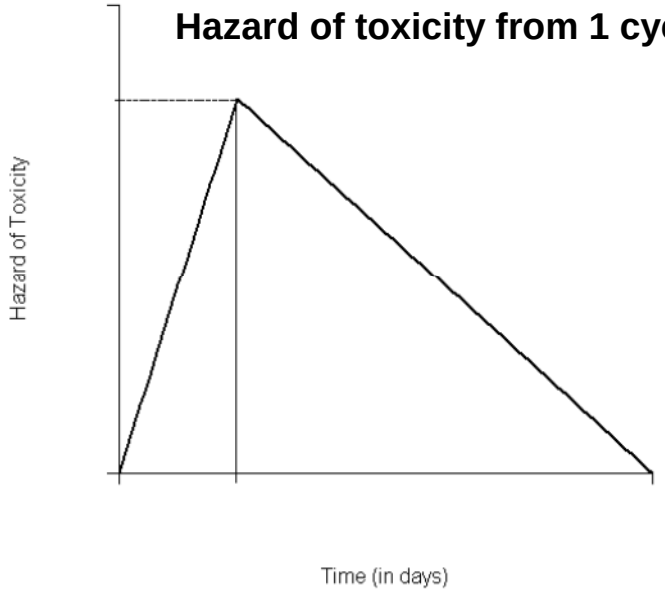
Trial Conduct

1) Treat 1st patient at the lowest (dose, schedule)
2) Using current **Time-to-Toxicity data**, treat each patient at the (dose, schedule) pair with **ptox** = Pr(Toxicity by day t* | dose, schedule) closest to the target max toxicity rate
3) Do not "skip" untried (dose, schedule) pairs
4) If no (dose, schedule) pair is acceptable → Stop the trial

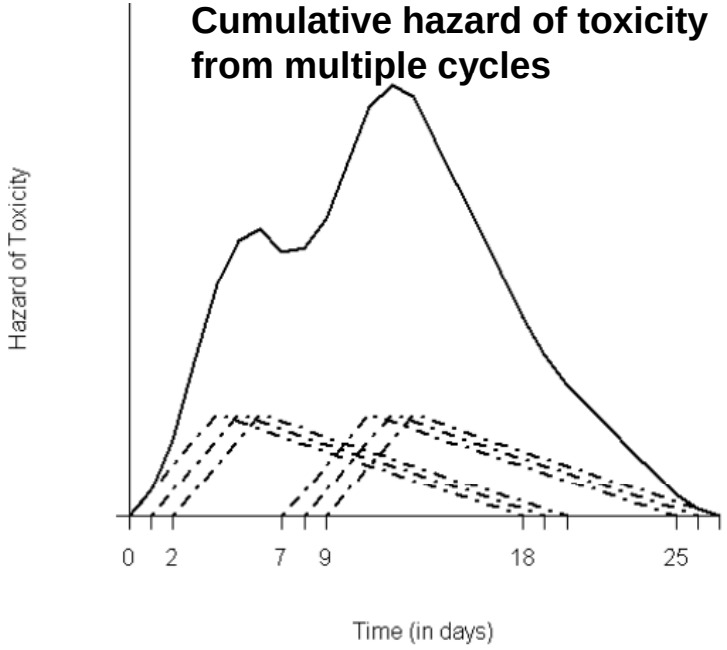




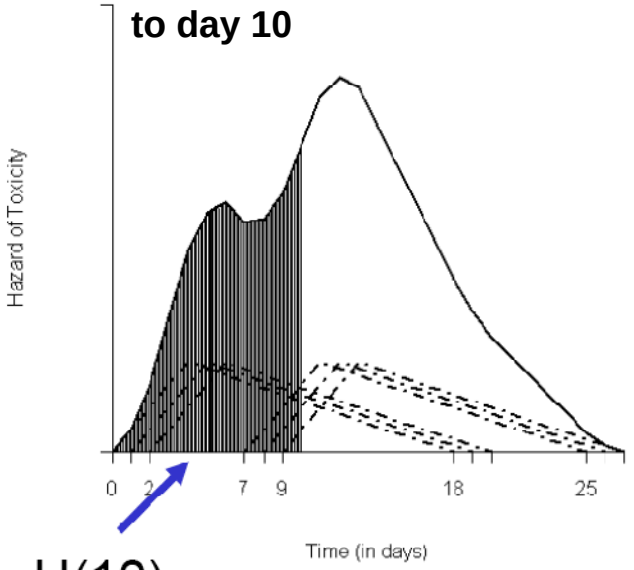
Hazard of toxicity from 1 cycle



Cumulative hazard of toxicity from multiple cycles



Cumulative hazard of toxicity to day 10



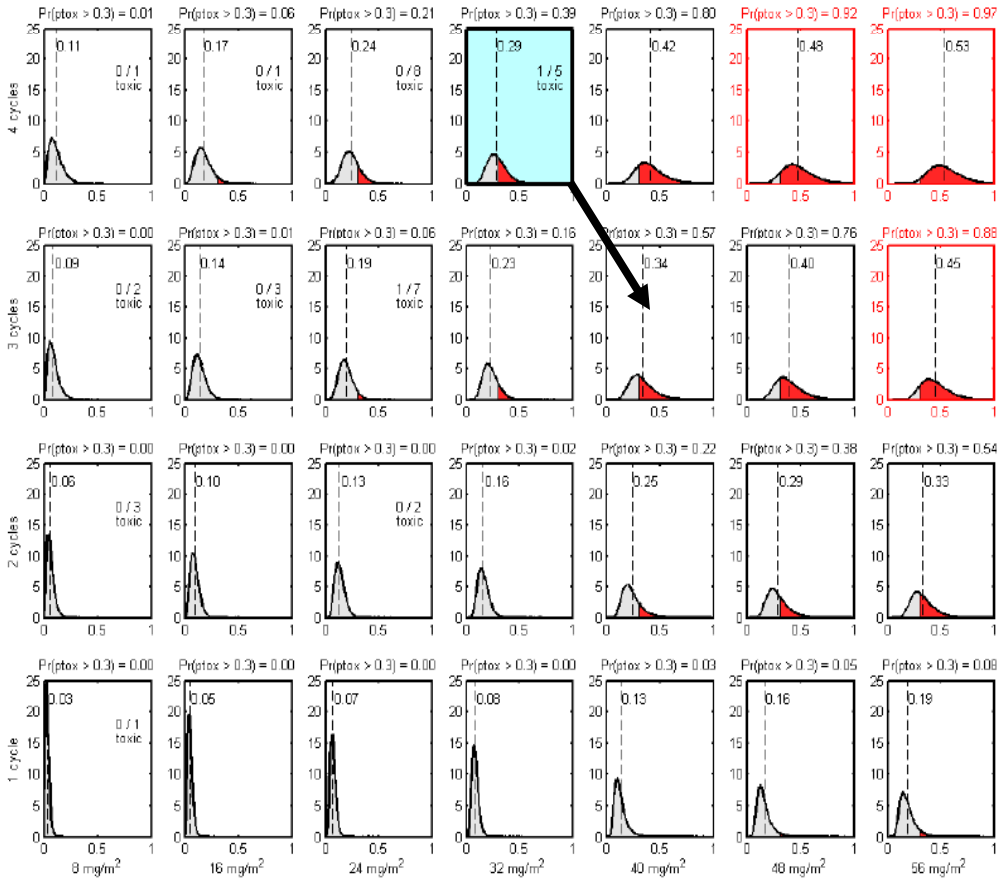
H(10)

Prob(Toxicity by day 10) = 1 - $e^{-H(10)}$

What Actually Happened in the Vidaza® Trial?

- Treatment parameters
  - Vidaza doses 8, 16 or 24 mg/m^2 daily x 5 in each cycle
  - Given for 1, 2, 3 or 4 28-day cycles
- Definition of toxicity
  - Severe (NCI grade 3 or 4) kidney, liver, heart, lung or neural toxicity
  - Severe GVHD
  - Systemic infection not resolved by antibiotics within two weeks
  - Severe haematologic toxicity
- **ptox** = Pr(Toxicity by day 116 | dose, schedule) closest to the tox target 0.3
- Only 1 toxicity in 27 patients, so 4 more dose levels 32,40,48,56 added
- Optimal dose-schedule identified after **44** patients:
  (40 mg/m^2 x 3 cycles)

After N=33 patients



Conclusions

The *Dose-Schedule Algorithm* reliably

1) Finds (Dose,Schedule) pairs having specified Pr(Toxicity by day t*)

2) Stops if no (Dose,Schedule) is acceptable

Implementation is Hard Work, but a free computer program is available!

Three Phase I and Phase I-II Designs

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Dose	Bivariate binary (phase I-II)	Efficacy-toxicity trade-offs	GVHD prophylaxis, anergized cells post allotx, etc.
Dose and Schedule	Time to toxicity (phase I)	Pr(toxicity by day t*)	Azacitidine post allotx
Doses of two agents ($dose_1$, $dose_2$)	**Bivariate ordinal (phase I-II)**	**Utility of outcome**	**Bladder cancer**

Optimizing the dose pair of a two-agent combination based on elicited utilities of (Toxicity,Efficacy) outcomes

Houede, Thall, Nguyen, Paoletti and Kramar. *Biometrics*, In press

Goal: Optimize **(Dose of 2 agents) based on Toxicity and Efficacy**

Treatment of bladder cancer with a combination of chemotherapy (c) and a biologic (b) where optimal doses in combination are unknown

Dose-Combination (b_x,c_Y) Matrix

(1,3)	(2,3)	(3,3)	(4,3)
(1,2)	(2,2)	(3,2)	(4,2)
(1,1)	(2,1)	(3,1)	(4,1)

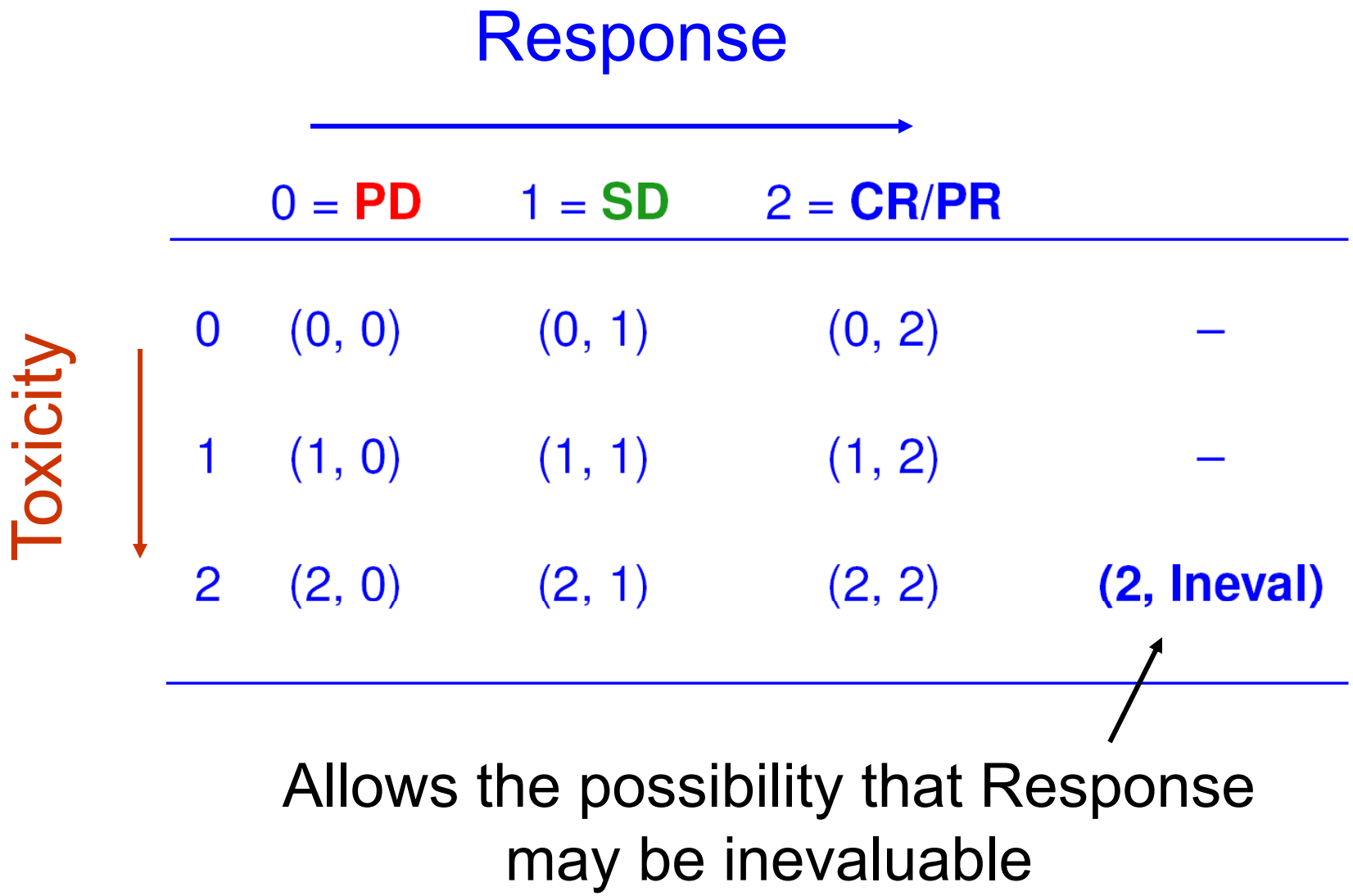
c_Y ↑

b_x →

b_x = dose of biologic agent

c_Y = dose of chemo agent

Patient Outcome is (Response, Toxicity)



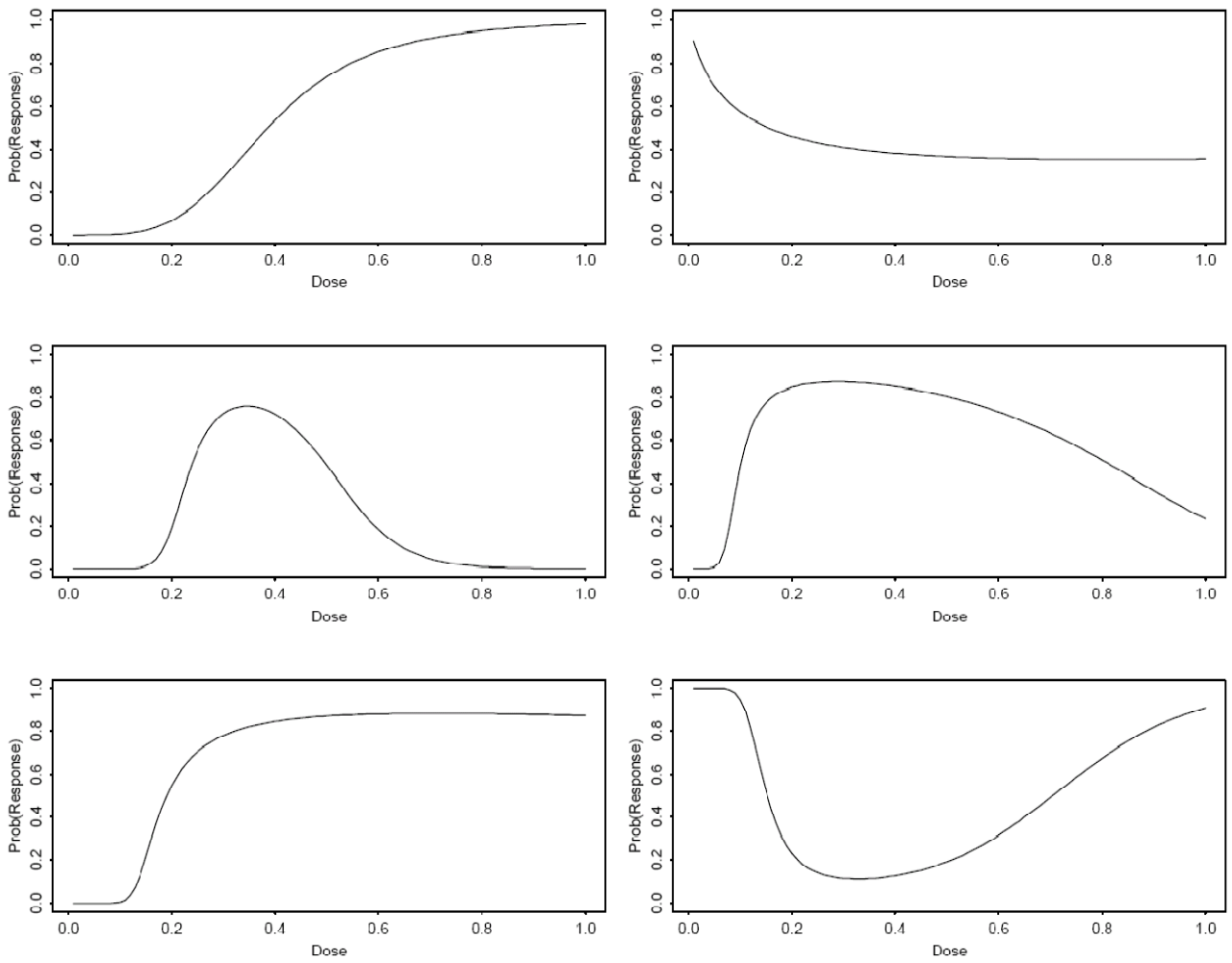
Elicited Consensus Utilities

Response →

Toxicity ↓

	PD	SD	CR/PR	Inevaluable
	25	76	100	–
	10	60	82	–
	2	40	52	0

Very Flexible Dose-Outcome Model



Trial Conduct

Choose each cohort's dose pair to

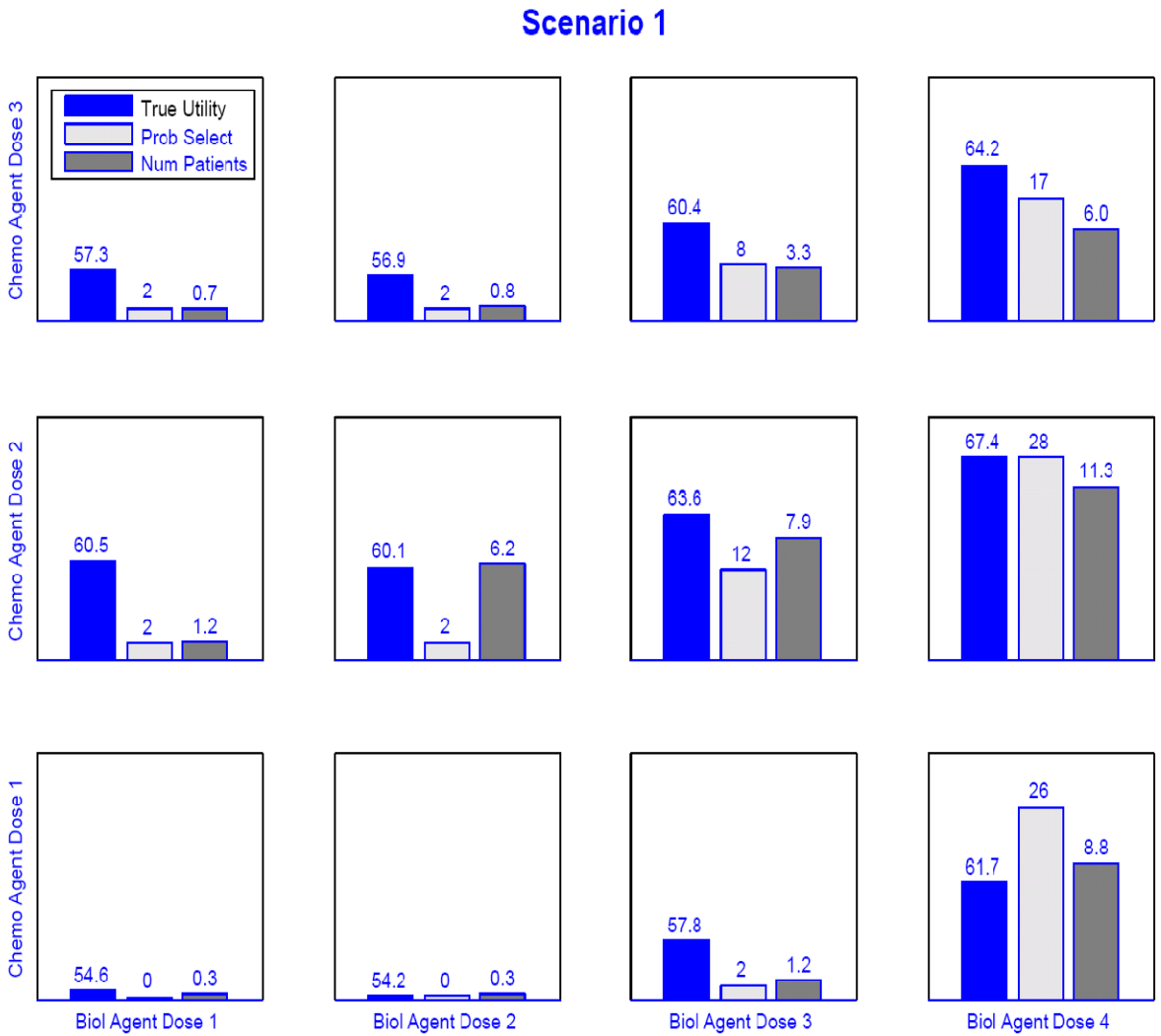
Maximize the Posterior Expected Utility

based on the data observed so far

Do Not Skip Untried Doses:

If (b_1,c_1) is the current dose pair, then escalation is allowed to as yet untried pairs (b_2,c_1), (b_1,c_2), or (b_2,c_2)

Stop the trial if all dose pairs are unacceptably toxic


Scenario 1
True Utility
Prob Select
Num Patients
Chemo Agent Dose 3
Chemo Agent Dose 2
Chemo Agent Dose 1
57.3
2
0.7
56.9
2
0.8
60.4
8
3.3
64.2
17
6.0
60.5
2
1.2
60.1
2
6.2
63.6
12
7.9
67.4
28
11.3
54.6
0
0.3
54.2
0
0.3
57.8
2
1.2
61.7
26
8.8
Biol Agent Dose 1
Biol Agent Dose 2
Biol Agent Dose 3
Biol Agent Dose 4

Application to Trials Monitoring GVHD

Toxicity =

0 if NO GVHD

1 if grade 1,2 GVHD

2 if grade 3,4 GVHD

or

0 if NO grade 3,4 GVHD

1 if grade 3,4 GVHD but resolved in <2 wks

2 if grade 3,4 GVHD not resolved in < 2 wks

Application to Trials Monitoring GVHD

Efficacy =

0 if dead, or alive but no response at day 100

1 if alive and engrafted with PR at day 100

2 if alive and engrafted with CR at day 100

(e.g. for CLL transplantation trials)

or

0 if dead, or no plt recovery in 100 days

1 if alive with 20 < plt < 50 at day 100

2 if alive with plt>50 by day 100

(e.g. for cord blood transplantation trials)

Extensive Computer Simulations Show that the Utility-Based Dose-Finding Method is

Very Reliable and Very Safe

Implementation is Hard Work, but a free computer program is available!

Phase I and I/II Designs for GVHD Trials

Design	Objective	Comments
3+3	MTD	Easy to do, poor properties, rarely applicable to BMT patients
Accelerated titration	MTD	Acceptable for relatively nontoxic agents, but rarely applicable (like 3+3)
CRM, mCRM	MTD	Stat-intensive, flexible for toxicity target, find dose based on toxicity
Time-To-Tox	Max tolerated dose and schedule combo	Stat-intensive, flexible for toxicity target, finds dose and schedule
Eff-Tox	Best dose based on toxicity and efficacy	Stat-intensive, optimizes efficacy and toxicity jointly
Doublet Studies	Best combo based on toxicity and efficacy	Stat-intensive, optimizes efficacy and toxicity jointly

References

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Houede H, Thall PF, Nguyen H, Paoletti X, Kramar A. Utility-based optimization of combination therapy using ordinal toxicity and efficacy in phase I/II trials, 2009. To appear in *Biometrics*

Software at: http://biostatistics.mdanderson.org/SoftwareDownload