Society for Clinical Trials 34th Annual Meeting

Workshop P8
Recent Developments and Design Considerations in Early Phase Clinical Trials

Sunday, May 19, 2013
1:00 – 5:00 PM
Commonwealth Ballroom

Introduction to Phase I Designs

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Phase I designs

- Objectives: to find the maximum tolerated dose (MTD)

Terminology

- MTD vs RP2D
- DLT (dose limiting toxicities: severe grade ≥3)

Model based vs non model based

Non model based:

- Algorithmic / Rule based
  - 3+3
  - 3+6
  - Rolling 6
  - Up and down
- Biased coin
- Random walk

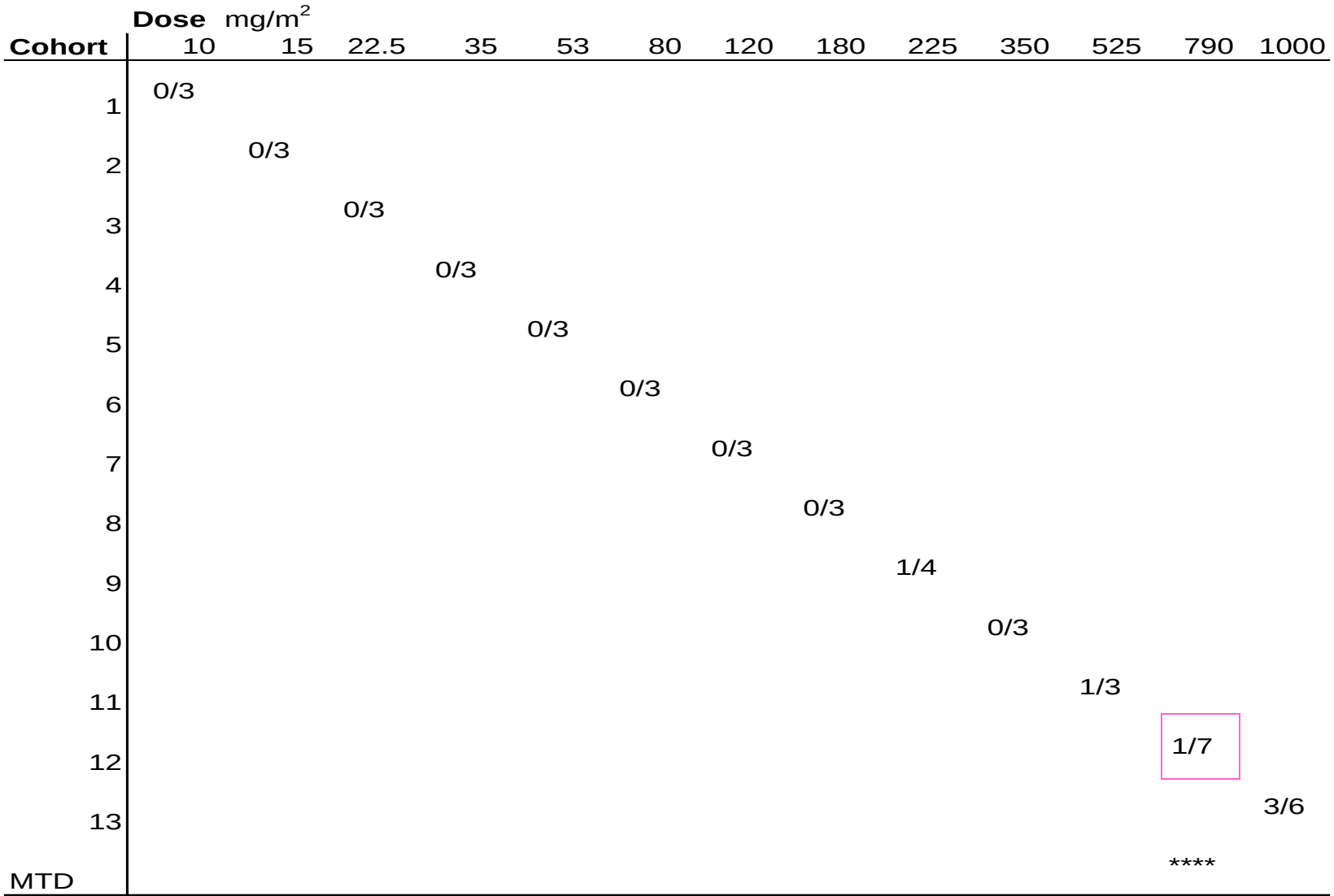
3+3 or standard method

treats 3 patients at each dose level

- Escalates to the next dose level if 0 DLT's are observed.
- Remains at the same level, expands to 6 if there is 1/3 DLT,
- De-escalates if there ≥ 2/6 DLT

- MTD is the dose below the level where ≥ 2/6 DLT

Gemcitabine Trial:
Abbruzzese et al. JCO 1991



Gemcitabine Trial:
Advanced disease, refractory solid tumors

Abbruzzese et al. JCO 1991

- Required 12 dose escalations, N=47;
- DLT rate 6/47 (12.8%)
- Study duration 3 years
- MTD is 79 times the starting dose
- 34 patients/47 received sub-optimal dose

Up and down

- 3+3 is a special case of up and down or A+B
- Different stopping rule
- Does not find a dose with DLT rate ~33% (<33%)
- Underestimates DLT rate –

  Lin and Shih 2001 and others showed that DLT rate varies from 16-30% depending on location of MTD and version of 3+3

Rolling 6

- Instead of waiting for the first 3, add 4^{th}, 5^{th}, 6^{th} patient as they come in at the same dose
- Enables to go on (R6 lower probability to terminate vs 3+3)

Zhao et al (Clin Trials 2011)

- TITE-CRM more accurate than R6
- R6 more pts at levels above MTD depending on accrual rates
- R6 longer trial duration

Other designs

- Random walk (Durham S et al)
- Biased coin up-and-down(Stylianou M, Flournoy N)

  If toxicity, then de-escalate

  If no toxicity, then biased coin with P(heads) ϵ[0,0.5]

  If heads, increase dose

  If tails, stay at same level

Similar in concept

- Unknown or known properties

- Use all the data (dose-toxicity curve)

OR

- Use the last cohort (the dose below the level at which ≥ 2 DLTs /6 pts)

MTD is the dose which, if exceeded, would put patients at unacceptable risk of toxicity

STANDARD (traditional)

If risk can be observed from patient data, then MTD can be identified from the data and no stat considerations are warranted

MODEL BASED

MTD: unknown parameter corresponding to that specified probability of acceptable toxicity and must be estimated.

Use most current data to obtain an updated estimate,

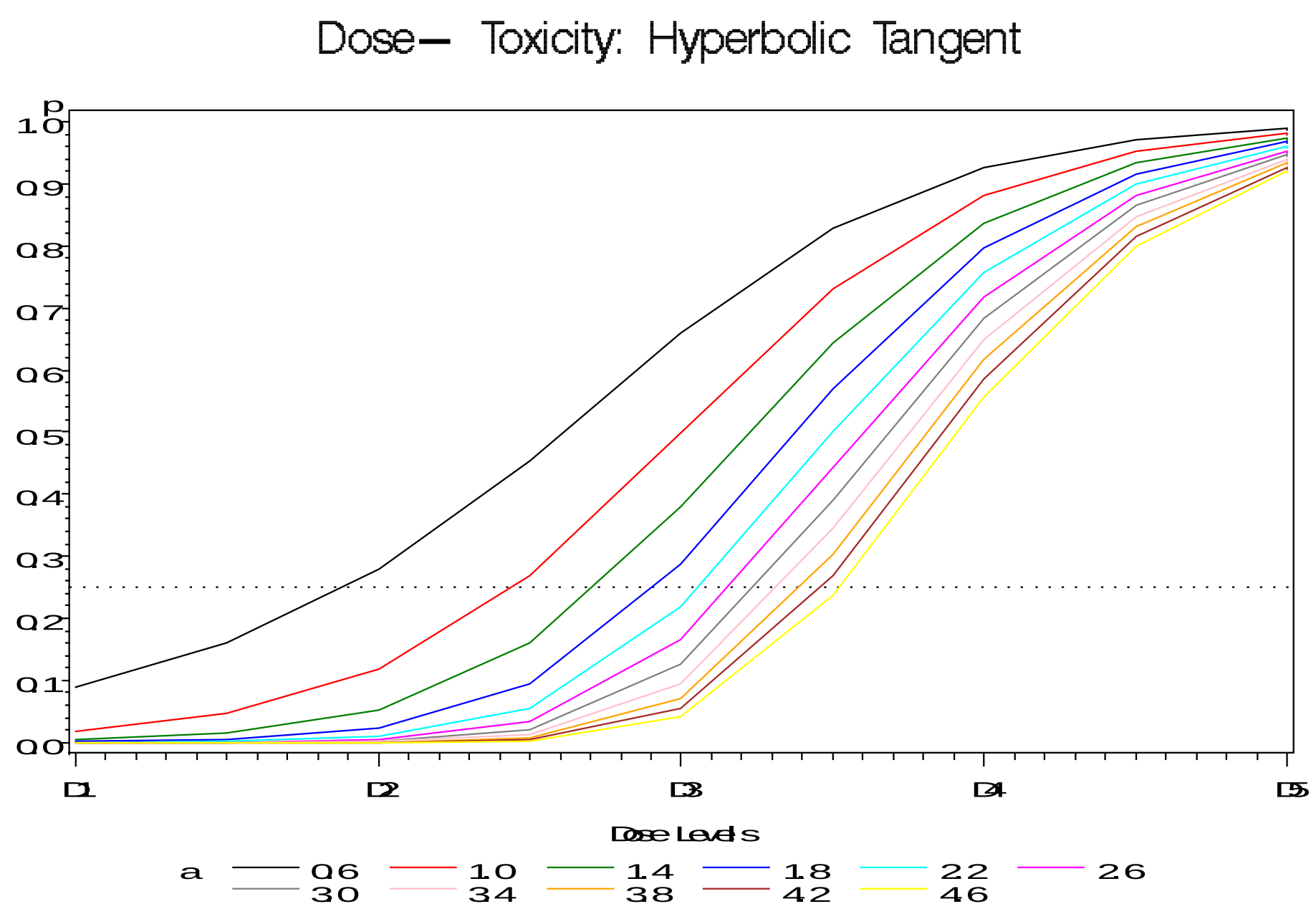
sequentially.

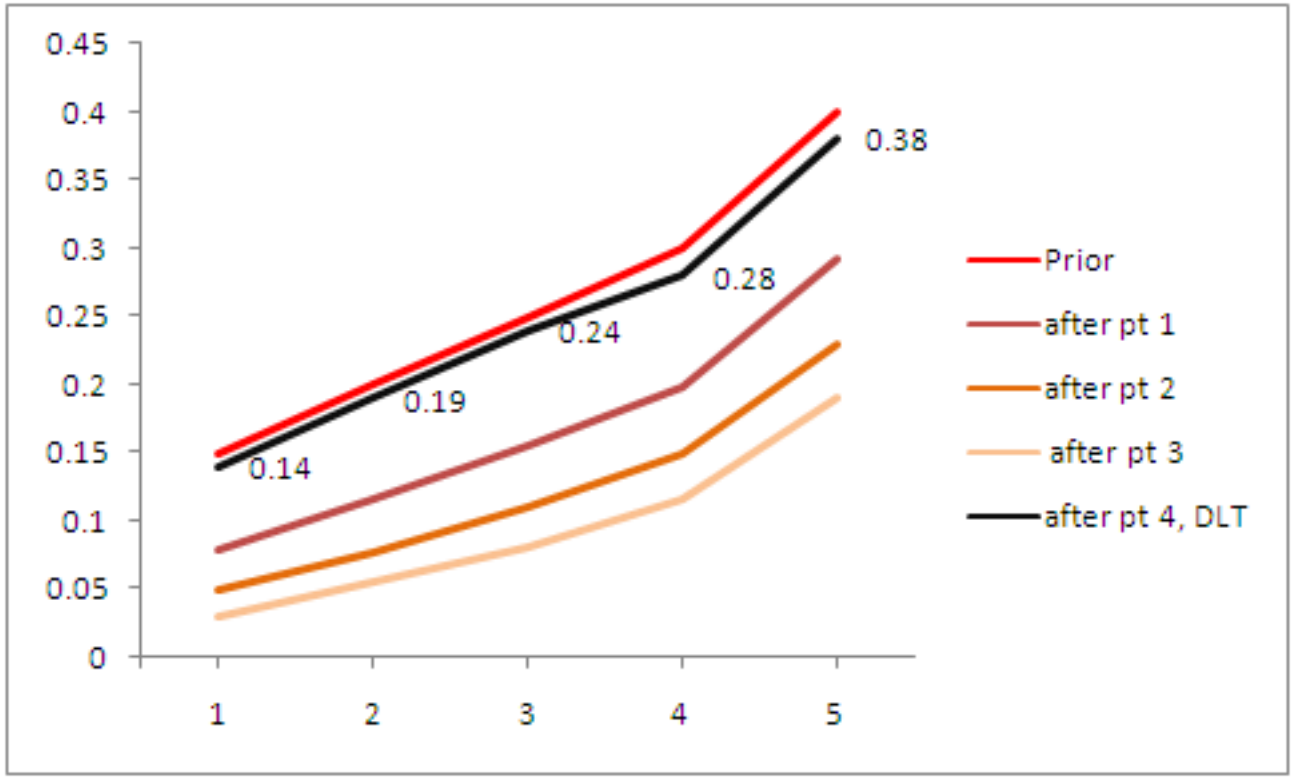
Model based designs

Continual Reassessment Method

Define MTD as the level closest to an acceptable DLT rate, say 30% (or 20%)

We aim to find the dose where no more than 30% of patients experience DLTs


Dose– Toxicity: Hyperbolic Tangent
p
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
1
2
3
4
5
Dose Levels
a
0.6
1.0
1.4
1.8
2.2
2.6
3.0
3.4
3.8
4.2
4.6


0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
1
2
3
4
5
0.38
0.28
0.24
0.19
0.14
Prior
after pt 1
after pt 2
after pt 3
after pt 4, DLT

CRM Scheme - Algorithm

1. CRM assumes a dose-toxicity curve (model)
2. Assume an acceptable toxicity rate (target) which you do not want to exceed (25-30%)
3. Treat first patient
   - at the dose level closest to the target based on the “initial curve”
   - at lowest dose

4. Observe the toxicity outcome (DLT: yes, no) in the first cycle (21-28 days)
5. Update dose toxicity curve

6. The dose closest to the target toxicity rate, based on the “new curve”, will be the dose of the next patient.
7. Repeat until a max *n* is observed

Clinical misconceptions
3+3 vs CRM

3+3

- Simple
- Fewer patients
- Shorter trial duration
- Can proceed faster
- …

CRM

- Complex
- More patients
- Longer trial duration
- Has to wait
- …

Statistical comparison

3+3

- Non model based
- Sample size depends on # of levels and observed DLTs
- Next cohort must wait for previous cohort

CRM

- Model based
- Sample size is usually fixed
- Model can be updated at any time

- Accuracy in finding true MTD
- Safety
- Patients treated
- Group inclusions/ varied cohort size
- Sample Size
- Trial duration

How do we compare methods based on simulations?

We know the true DLT rates at each level

Every patient has the same probability to experience a DLT

Design alone determines the dose allocation

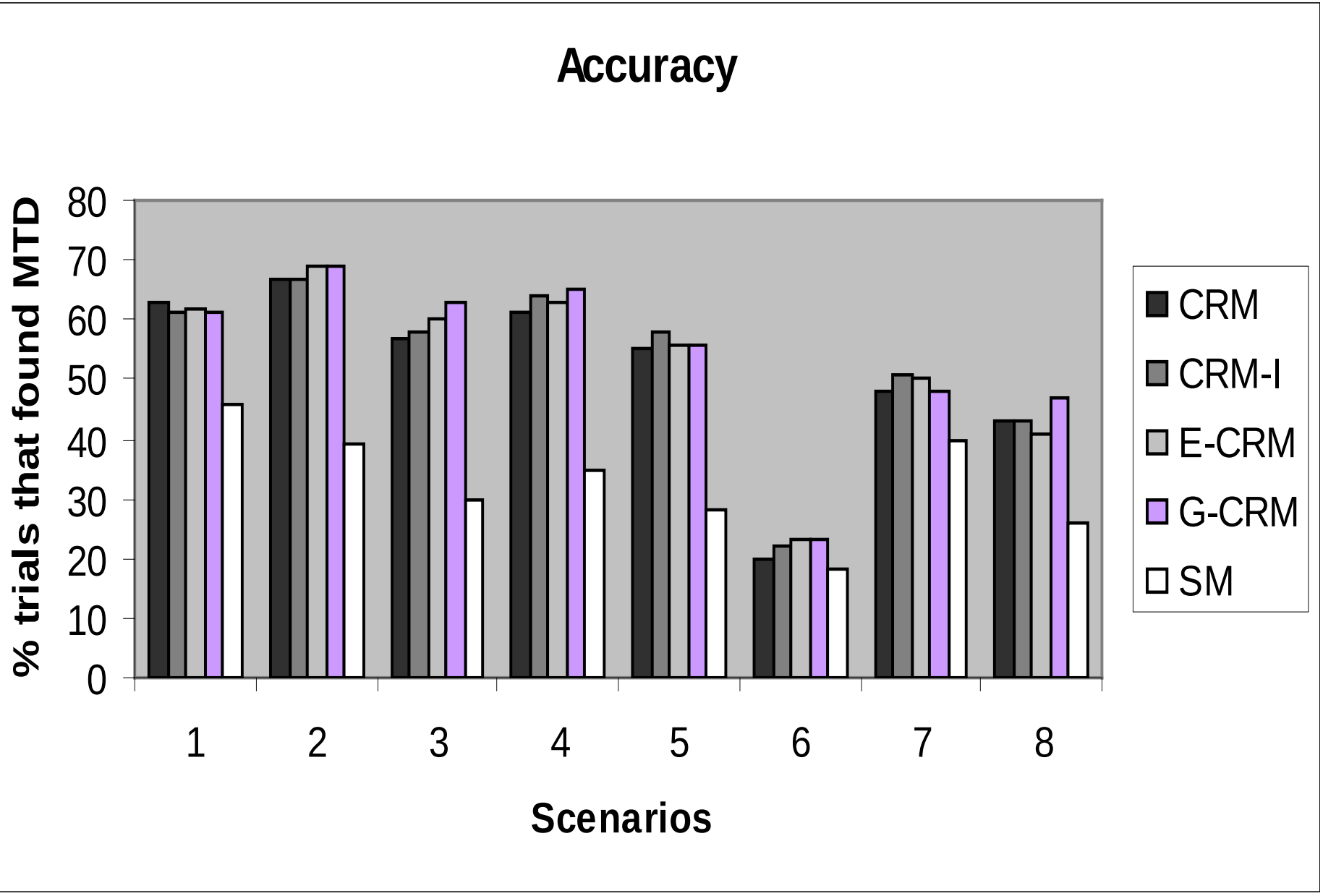
	True Toxicity Rates (*pi*)				
Levels	D_1	D_2	D_3	D_4	D_5
Rates	.03	.05	.10	0.18	0.22

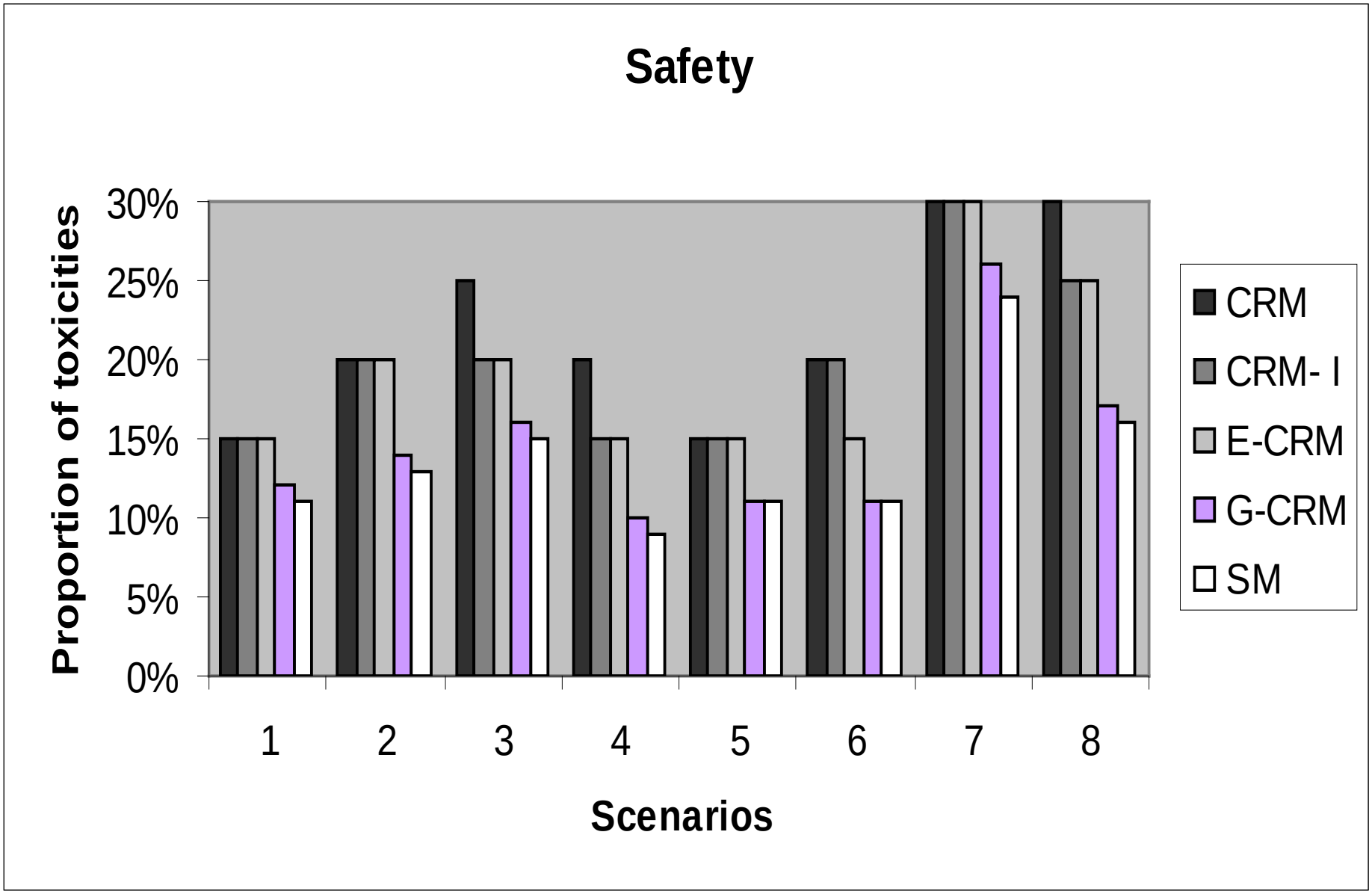
Simulate many trials and report on average

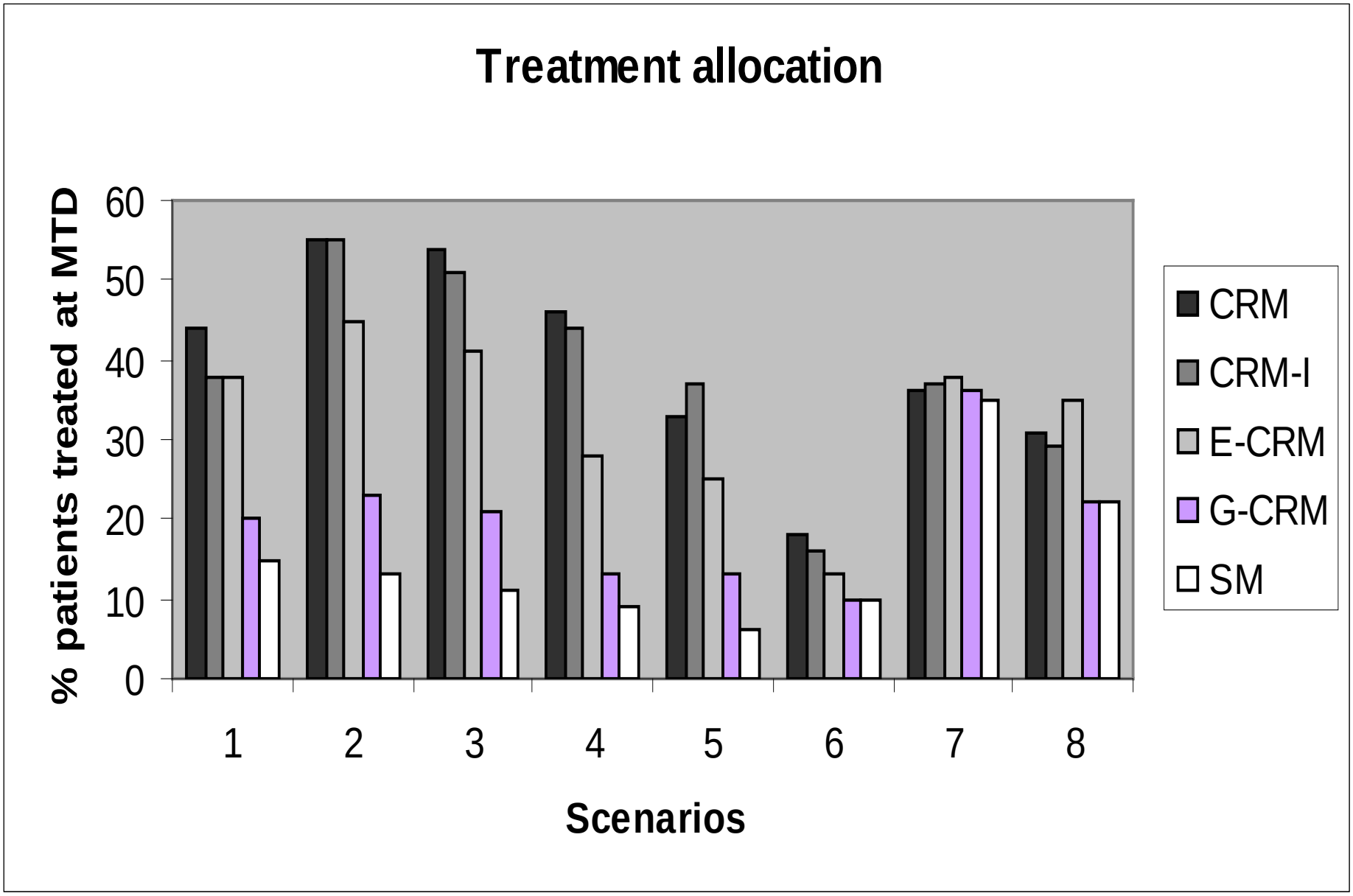
- How many trials recommended which level?
- Where patients were assigned/treated?

Simulations: Results

Iasonos et al, Clinical Trials 2008


Accuracy
% trials that found MTD
80
70
60
50
40
30
20
10
0
1
2
3
4
5
6
7
8
Scenarios
CRM
CRM-I
E-CRM
G-CRM
SM


Safety
Proportion of toxicities
30%
25%
20%
15%
10%
5%
0%
1
2
3
4
5
6
7
8
Scenarios
CRM
CRM- I
E-CRM
G-CRM
SM


Treatment allocation
% patients treated at MTD
60
50
40
30
20
10
0
1
2
3
4
5
6
7
8
Scenarios
CRM
CRM-I
E-CRM
G-CRM
SM

Conclusions

- CRM is more accurate
- Reaches MTD faster
- Treats more pts at or around MTD
- It is as safe (overdose control etc)
- Does not require larger sample – sample size depends on number of levels

Sample Size

- 15 for 3 levels
- 20-25 for 5-8 levels
- Since we reach the MTD faster, we could test more dose levels

CRM with modifications

The modified versions do not change the operating characteristics.

- Start at lowest dose or dose closest to the target
- Skip dose levels or not (restrict escalation)
- Wait for all patients' responses or not
- CRM with fixed sample or with stopping rules

Which design to use in practice?

Model based vs non model based

- Literature Review
    1. O' Quigley, Pepe, Fisher (1990)
    2. Goodman et al. (1995)- Group inclusions
    3. Shen, O'Quigley (1996) : Asymptotic distribution
    4. O'Quigley, Shen (1996): MLE – Frequentist approach
    5. Moller (1995) Comparisons
    6. Babb et al.(1998) Escalation with Overdose Control
    7. Heyd, Carlin (1999) Adaptive Design improvements
    8. Leung, Wang (2002) Extensions
    9. Rosenberger, Haines (2002) Competing designs
    10. Cheung YK, Chappell R (2002): Model sensitivity
    11. Garrett- Mayer (2007): Review
    12. Iasonos et al (2008): Comparative Review
    13. ….

Original CRM with binary response is often sufficient

Summary

- It is not complex
- It can handle more than just a binary outcome
- Time to event outcome or ordinal outcome (grades)
- Drug combinations, patient heterogeneity, bridging studies

Phase I with Dose Expansion Cohorts

- Ph I objectives:
- Determine (maximum tolerated dose) MTD often in solid tumors
- Evaluate safety profile

Dose expansion cohorts

1. Follow dose escalation design
2. Find MTD
3. Add additional patients (6, 10, 12, 16) at MTD

Escalation Phase

Expansion Phase
at MTD
2nd endpoints

Phase I/II Protocols

- Goals of each phase are separated – pts receive same treatment
- Design
- Analysis

PD1 study – Design
Phase I protocol – 8 amendments

- Dose escalation: 3+3: Doses 1, 3, 10 mg
- Dose expansion: 5 cohorts,16 pts(n=80) at 10mg for melanoma, NSCL, RCC, Prostate, colorectal
- High activity, addl cohorts of 16pts melanoma, LC, RCC randomly assigned at different dose levels
  - 1 and 3mg melanoma then 0.1, 0.3, 1 mg (RR 19-41%)
  - 1, 3, 10 mg for Lung (RR: 6%, 32%, 18%)
  - 10mg fo RCC (RR: 24%)

Stopping rules for safety in expansion cohort (s) in PD1 study

- DLT rate ≥ 33% across all 5 indications

OR

- Within an indication: DLT rates ≥ 33% from the first 6 patients only

Course Objectives

1. The premise of model based designs and the Continual Reassessment Method (CRM)
2. Modified versions of CRM
3. Which Phase I design should we be using when?
4. More complex problems:
   - Drug combinations
   - Multiple schedules
   - Patient heterogeneity

5. Practical considerations - Lessons learned from case studies
6. Protocol development
7. Available Software

QUESTIONS?

Applications

LITERATURE
CRM APPLICATIONS

1: Morita S, Nakata B, Tsuji A, et al. A phase I study of combination therapy of the oral fluorinated pyrimidine compound S-1 with low-dose cisplatin twice-a-week administration (JFMC27-9902 Step2) in patients with advanced gastric cancer using a continual reassessment method. Jpn J Clin Oncol. 2007 Dec;37(12):924-9. PubMed PMID: 18211983.

2: Saji S, Toi M, Morita S, et al. Dose-finding phase I and pharmacokinetic study of capecitabine (Xeloda) in combination with epirubicin and cyclophosphamide (CEX) in patients with inoperable or metastatic breast cancer. Oncology. 2007;72(5-6):330-7. Epub 2008 Jan 12. PubMed PMID: 18187954.

3: Morita S, et al. Application of a continual reassessment method to a phase I clinical trial of capecitabine in combination with cyclophosphamide and epirubicin (CEX) for inoperable or recurrent breast cancer. Jpn J Clin Oncol. 2004 Feb;34(2):104-6. PubMed PMID: 15067105.

4: Pisters PW, et alPhase I trial of preoperative doxorubicin-based concurrent chemoradiation and surgical resection for localized extremity and body wall soft tissue sarcomas. J Clin Oncol. 2004 Aug 15;22(16):3375-80. PubMed PMID: 15310783.

5: Mathew P, Thall PF, et al. . Platelet-derived growth factor receptor inhibitor imatinib mesylate and docetaxel: a modular phase I trial in androgen-independent prostate cancer. J Clin Oncol. 2004 Aug 15;22(16):3323-9. PubMed PMID: 15310776.

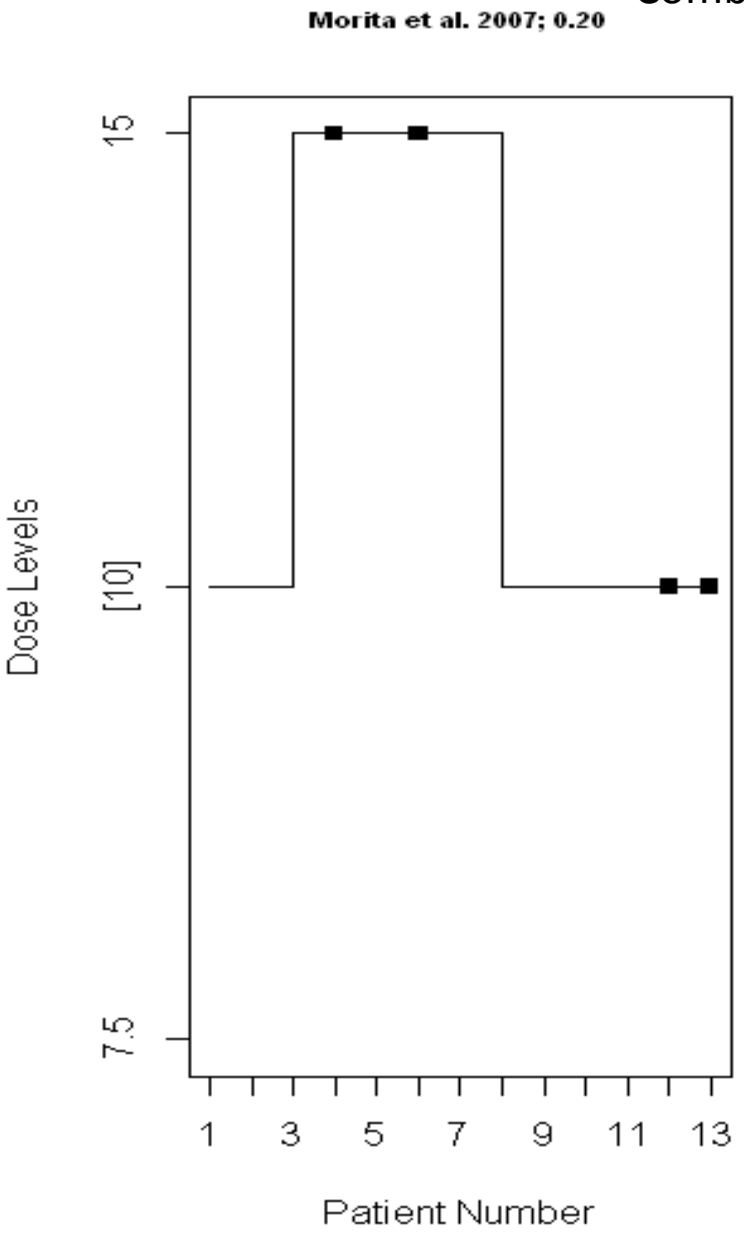
6: Flinn IW, Goodman SN, et al.A dose-finding study of liposomal daunorubicin with CVP (COP-X) in advanced NHL. Ann Oncol. 2000 Jun;11(6):691-5. PubMed PMID: 10942057.

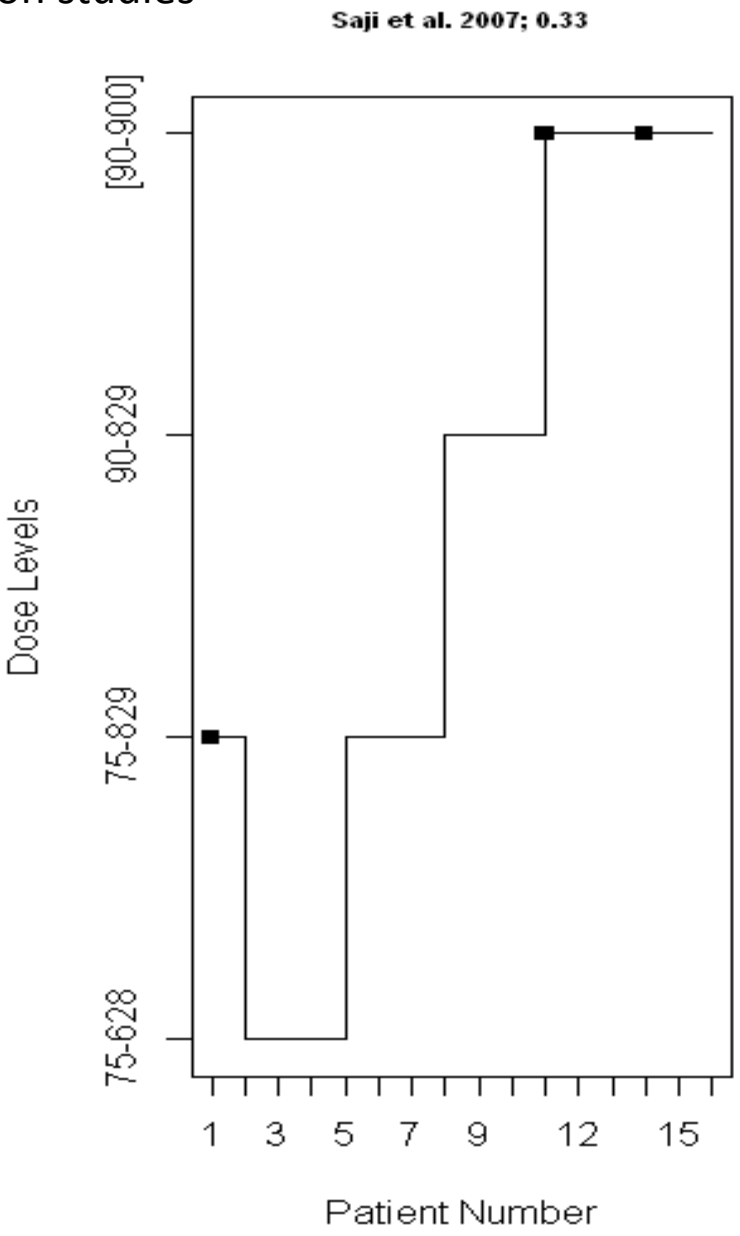
7: Dougherty TB, Porche VH, Thall PF. Maximum tolerated dose of nalmefene in patients receiving epidural fentanyl and dilute bupivacaine for postoperative analgesia. Anesthesiology. 2000 Apr;92(4):1010-6. PubMed PMID: 10754620.

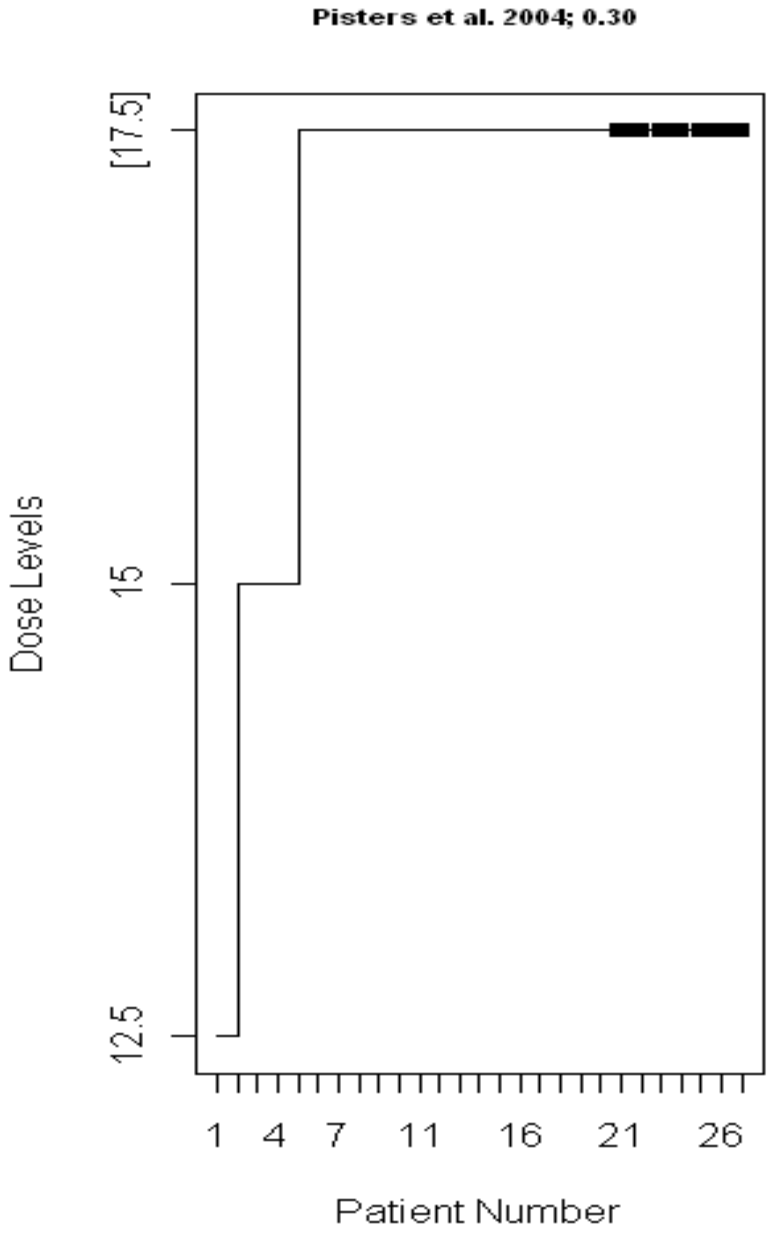
Design Type

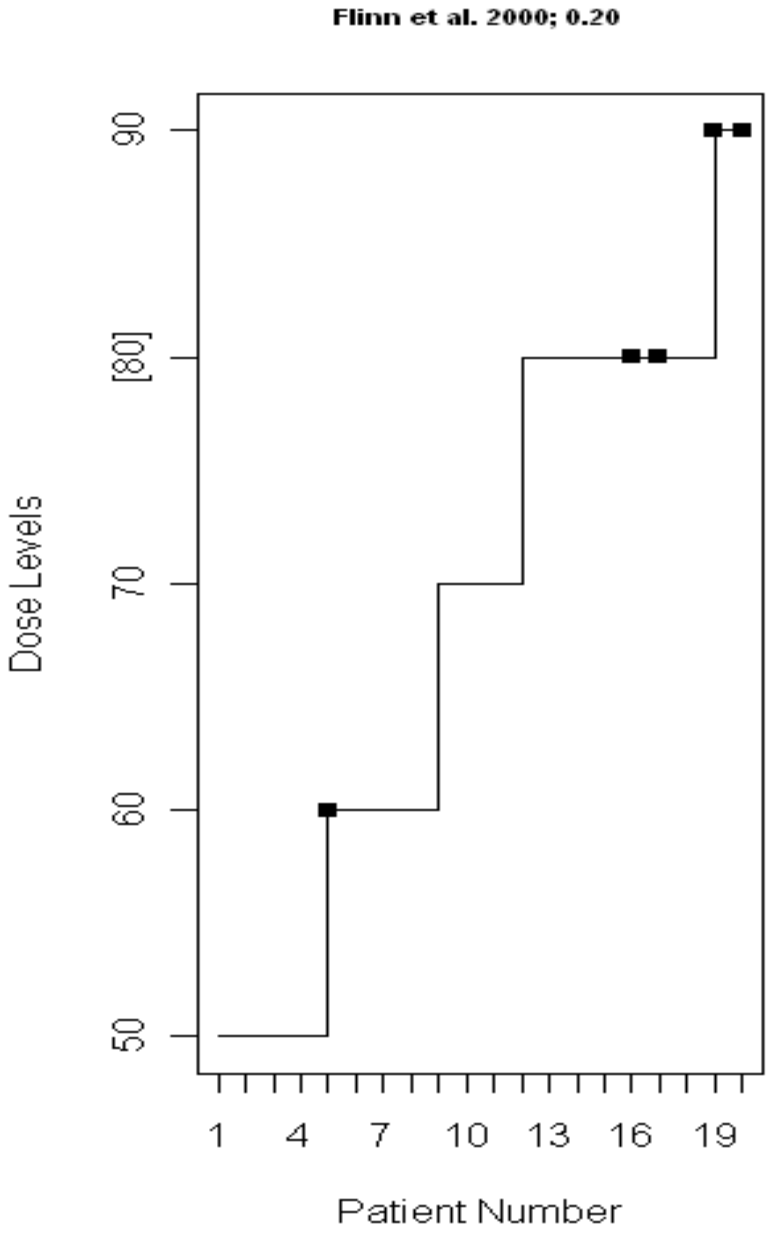
TYPE OF DESIGN	N=35
CRM (O'Quigley 1990)	17/35
TITE CRM (Cheung 2002)	8/35
CRM with continuous dosing (Piantadosi 1998)	7/35
EWOC (Babb, Rogatko et al, 1999)	2/35
Lower grades (Goodman 1995)	1/35

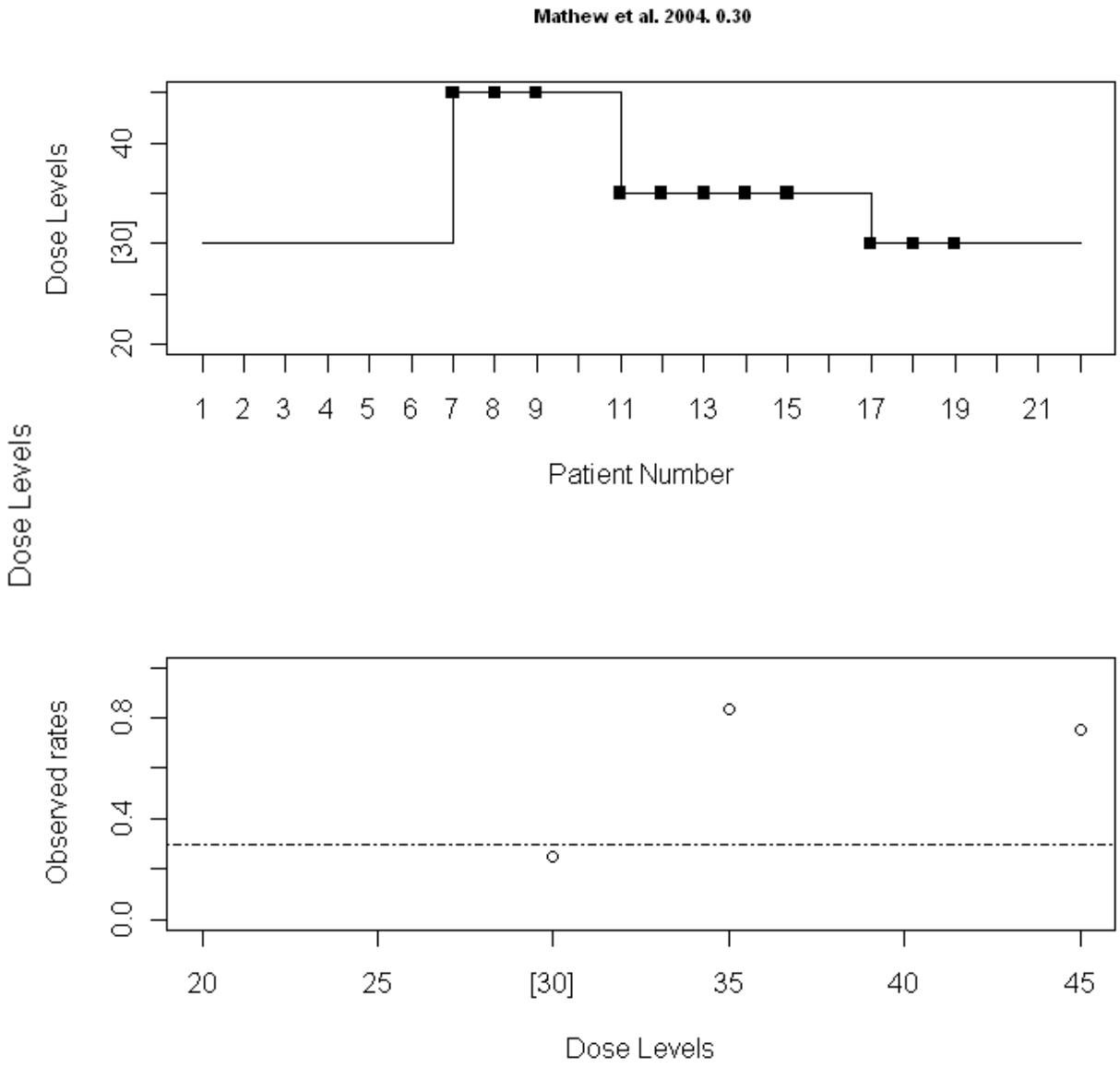
Combination studies






Pisters et al. 2004; 0.30
Dose Levels
12.5
15
[17.5]
1
4
7
11
16
21
26
Patient Number


Flinn et al. 2000; 0.20
Dose Levels
50
60
70
[80]
90
1
4
7
10
13
16
19
Patient Number

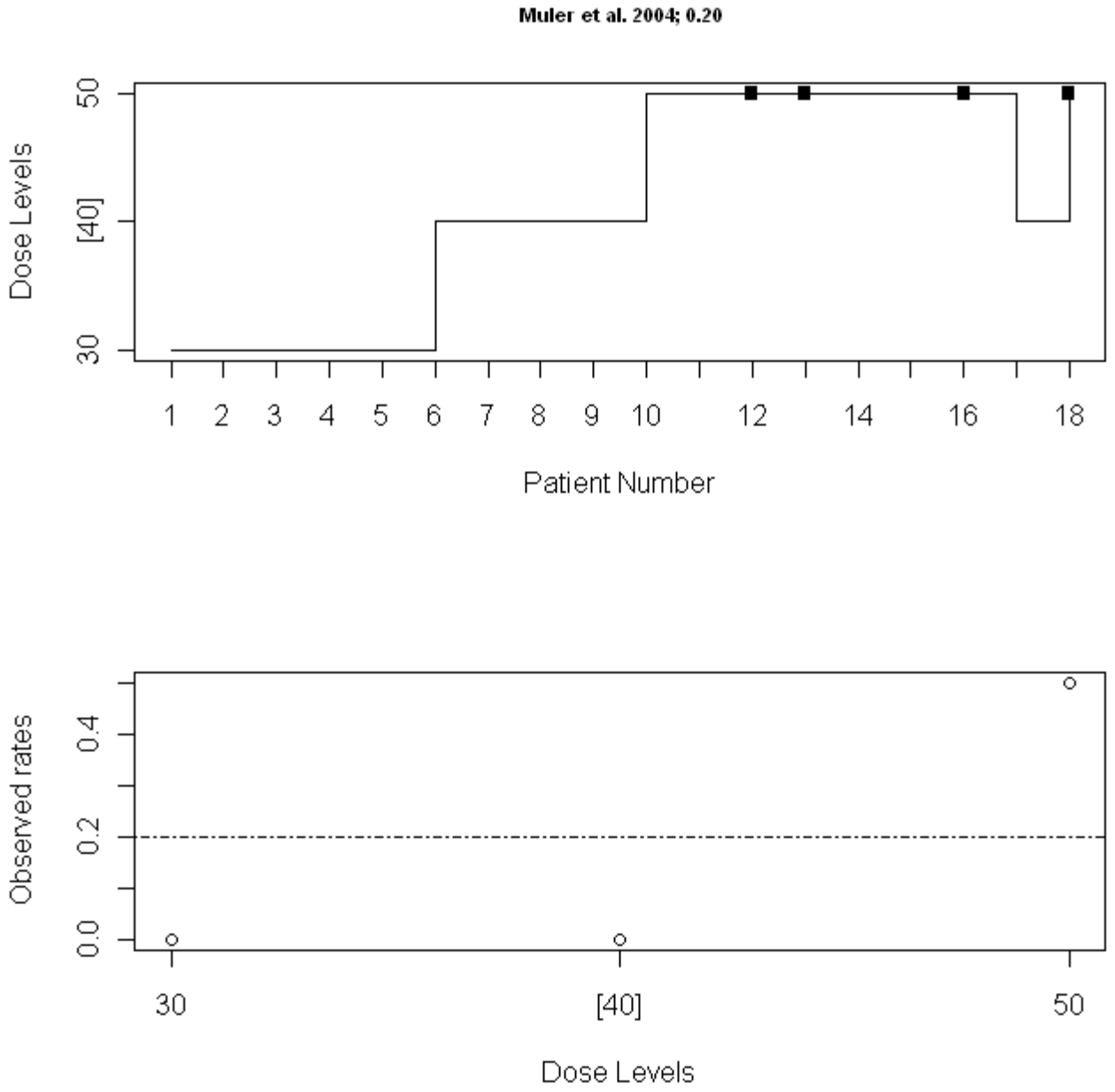

Mathew et al. 2004. 0.30
Dose Levels
20
[30]
40
1 2 3 4 5 6 7 8 9 11 13 15 17 19 21
Patient Number
Dose Levels
Observed rates
0.0
0.4
0.8
20 25 [30] 35 40 45
Dose Levels

Points to consider

- Cohort size – 6 can be problematic
- Accrual Rate vs DLT timeframe
- Number of inevaluable patients for toxicity

Compromise

- Sample size vs uncertainty


Muler et al. 2004; 0.20
Dose Levels
30
[40]
50
1
2
3
4
5
6
7
8
9
10
12
14
16
18
Patient Number
Observed rates
0.0
0.2
0.4
30
[40]
50
Dose Levels

Points to consider

- Observed rates of 0 and 100%
- Observed rate 0 and 50%
- Target rate 20 or 30%; which one is closer?

- Use as a GUIDE/ TOOL – auxiliary information
    - Toxicity onset, duration, reversible, pts status

Conclusions

- Careful to select design parameters (cohort size, prior distribution, skeleton)

- Method is rigid once parameters are selected but it is flexible through the choice of parameters

Practical considerations: Protocol development and Software

Protocol development – Step 1

Clinical questions:

1. How many patients?
2. How many dose levels?
3. Actual amount of dosage
4. How long will the trial take to complete?

Cost. Resources.

1. Sample Size

- 15 for 3 levels
- 20-25 for 5-8 levels
- Since we reach the MTD faster, we could test more dose levels w/o increasing the sample too much.
- 3+3 sample size depends on # levels
  - 5 levels : 30 pts
  - 6 levels: 36 pts

Fixed sample size or stopping rules

- Fixed sample size is easier
  - Cost, resources known (RSA)
- Fixed SS with option to stop early if 6 pts at the MTD
- Stopping rules
  - Confidence intervals (practically not useful, unless n>36)
  - Probability(all remaining patients be treated at same level and MTD will be the same)

Stopping rules – confidence intervals

O' Quigley, Pepe, Fisher (1990)

Sample size is not fixed, continue accrual until

CI on unknown dose parameter

$$\int_{a_L}^{a_U} f(a,\Omega_j)da = 1-\gamma$$

$$\{\psi(x_i,a_L),\psi(x_i,a_U)\} \in R, R \text{ neighborhood } \theta$$

$$\mathcal{P}_{j,n} = \Pr\left\{x_{j+1} = x_{j+2} = \cdots = x_{n+1} \middle| \Omega_j\right\}$$

Probability(all remaining patients will be treated at same level and MTD will be the same)

Binary trees (O'Quigley, Reiner 1998)

2. How many levels

- Discrete (often) and pre-specified
- Pre-clinical data gives them an estimate of MTD in other species
- Typically: 5-6 levels (2 below, 2 above)
- Discuss Pre-clinical estimates with PIs

3. Actual amount of dosage

Dose selection

Fibonacci sequence: 1,1,2,3,5,8,13,21,…

% increase: 100, 50, 67, 60, 62,…

Modified Fibonacci: % increase in dose levels
100, 67, 50, 40, 33, 33,…

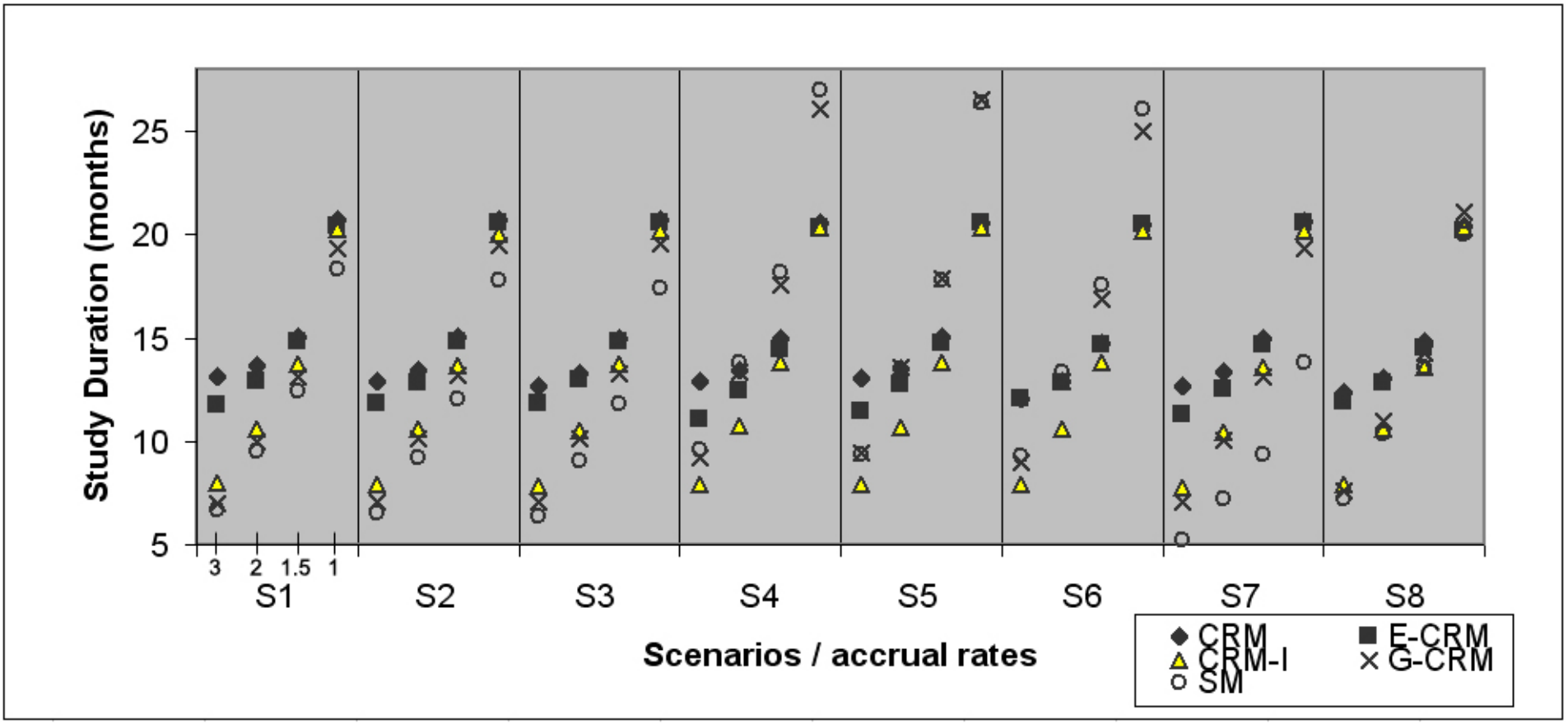
Example: 50mg,100mg, 167mg, 250 mg, 350 mg,..

4. Trial duration

Depends on:

- Accrual rate (1 or 3 pts /month)
- DLT observation period (21, 28 days)
- Grouped inclusions (allow > 1 patient per level)

Trial Duration



CRM	20	20	20	20	20	20	20	20
E-CRM	20	20	20	20	20	20	20	20
CRM-I	20	20	20	20	20	20	20	20
G-CRM	18	18	18	27	27	27	18	21
SM	18	18	18	27	27	27	12	18

Software – Trial duration

1. dfcrm R package (Ken Cheung)
http://cran.rproject.org/web/packages/dfcrm/
dfcrm.pdf
titecrm: one dose assignment
titesim: operating characteristics, trial duration

2. CRM R package (Qianxing Mo)
http://cran.rproject.org/web/packages/CRM/
CRM.pdf
crmsiminc: OC, trial duration

Protocol development – Step 2

Statistical questions:

1. Which model?
2. How many parameters?
3. Bayesian or Likelihood?
4. Prior distribution
5. Skeleton values

Operating Characteristics

- Model, skeleton, prior are chosen
- Evaluate OC
- Define target rate 20-30%
- Cohort size
- Restrict dose jumps to no more than a level

Writing the Statistical section

- No updated formal guidelines by FDA (1994)
- Describe CRM in words and with a model
- Provide OC section (recommended)
  - Committees Review
  - Stage 1 data (True DLT rates)
- Rigid versus flexible
- Fixed sample or stopping rules

Statistical Section

A two-stage CRM will be used at the beginning of a trial until a DLT is observed (accelerated stage), and then the CRM is in effect at the second stage after the first DLT or when dose level 6 (28 mg) is reached, whichever occurs first. During the accelerated stage one patient is accrued at a time, escalation to the next dose is permitted if there is no DLT.

We will examine 10 dose levels, 6 during the accelerated stage and the remaining during the model-based phase.

Dose levels	1	2	3	4	5	6	7	8	9	10
Dose mg/m^2	1	2	4	8	16	28	36	40	45	50

Our initial estimates of DLT probabilities are: 0.05, 0.08, 0.1, 0.12, 0.2, 0.25, 0.3, 0.4, 0.45,and 0.5 for doses 1-10, respectively. Thus, our a priori belief is that dose 6 (28 mg/m^2 of drug a) is the MTD which is very conservative. The starting dose level will be dose level 1 at 1 mg/m^2. We assume that the dose-toxicity follows a hyperbolic tangent model as follows:

P(DLT=yes)=((tanhx+1)/2)^a;

where a is the unknown parameter that we need to estimate in order to determine which dose is the MTD and x corresponds to a standardized dose unit. The dose unit x can be solved by setting a=1.0 and using the initial estimates of DLT probabilities shown above for each dose level (0.05, 0.08, 0.1, 0.12, 0.2, 0.25, 0.3, 0.4, 0.45,and 0.5). A value of a=1.0 indicates that our prior beliefs were correct; while a value of a less than 1.0 indicates that the drug is more toxic and a value of greater than 1.0 indicates the drug is less toxic than previously believed. To reflect the uncertainty in our prior probability estimates, we assume an exponential distribution (prior distribution) with mean 1.0 (O'Quigley).

We will enroll 27 evaluable patients; it is expected that the trial will be open to accrual for 18-30 months. The sample size of 27 patients was selected based on simulated studies. All patients will be evaluable for safety analysis if they receive at least one dose of iso-fludelone. Additional subjects will be enrolled to replace any subjects who are enrolled, but do not receive treatment. Patients who die during the study period for reasons not related to toxicity or do not complete the required safety observation time interval (one cycle) will be described and evaluated separately. Patients not meeting the eligibility criteria and other major protocol violations will be described.

Operating characteristics

Through 1000 simulated trials following the methodology referenced in Iasonos et. al with the above parameters we expect the method to behave in the following way, assuming three different hypothetical scenarios for the true toxicity rates at each dose level.

Table 9: Hypothetical True Toxicity Rates

Dose levels	1	2	3	4	5	6	7	8	9	10
Scenario 1	.05	.08	.10	.15	.25	.30	.35	.40	.50	.60
Scenario 2	.05	.07	.08	.10	.15	.20	.25	.40	.45	.50
Scenario 3	.01	.05	.07	.08	.10	.15	.20	.25	0.3	0.33
Scenario 4	.001	.01	.05	.07	.08	.10	.15	.19	.22	.25

Table 10: Percent of simulated trials that selected each dose under each scenario

Dose levels	1	2	3	4	5	6	7	8	9	10
Scenario 1	0	.7	3	18	34	20	18	6	1.4	0
Scenario 2	0	.1	.2	3	15	22	39	18	2	.5
Scenario 3	0	0	0	.5	5	11	24	28	15	17
Scenario 4	0	0	0	.2	.5	3	14	22	18	42

Table 11: Percent of patients treated at each dose under each scenario

Dose levels	1	2	3	4	5	6	7	8	9	10
Scenario 1	6	6	7	16	24	16	15	7	2	1
Scenario 2	5	5	5	8	16	18	24	14	4	2
Scenario 3	4	4	4	6	9	12	19	18	10	13
Scenario 4	4	4	4	4	6	8	15	17	13	26

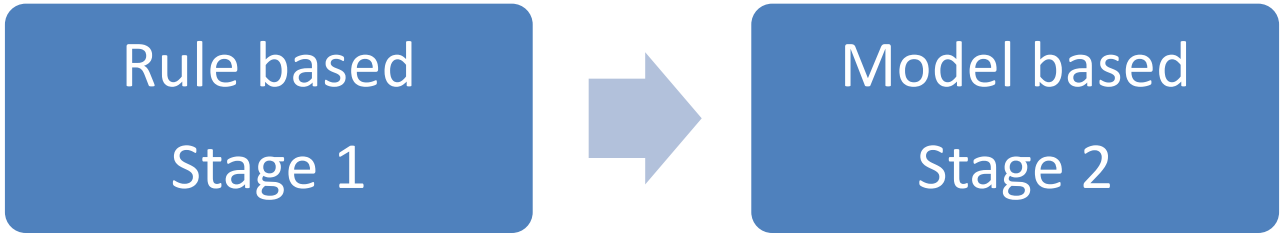
Example ongoing trial at MSKCC

- Investigators wanted to test k=10 dose levels
- Some pre-clinical data suggested the neighborhood of MTD
- Two stage design to eliminate levels far away from MTD
- Accelerated design followed by CRM

Two stage designs

O'Quigley, Shen (1996) Biometrics

1) Why two stage designs?



- 0/3 then escalate
- 1/3 stay and expand to 6
- 2/3 or 2/6 de-escalate

2) switch to stage 2 after the 1st DLT (heterogeneity)

Clinical trial 1

	Accelerated stage					CRM stage				
Dose Levels	d1	d2	d3	d4	d5	**d6**	**d7**	**d8**	d9	d10
Actual dose *(mg/m²)*	10	20	35	50	60	**80**	**100**	**120**	140	160
Skeleton /initial rates	.05	.08	.10	.12	.20	**.25**	**.30**	**.40**	.55	.70

First in humans - No clinical data

Pre clinical data with a lot of uncertainty

140 *mg/m²* was lethal in dogs

80-100 *mg/m²* is expected MTD

Clinical trial 2

	Accelerated stage						CRM stage			
Dose Levels	d1	d2	d3	d4	d5	d6	**d7**	**d8**	**d9**	d10
Actual dose *(mg/m²)*	1	2	4	8	16	28	**36**	**40**	**45**	50
Skeleton /initial rates	.05	.08	.10	.12	.20	.25	**.30**	**.40**	**.45**	.50

- Because this is a different formulation of an approved drug, safety profile is somewhat known
- Area of MTD is believed to be 36 to 45 *mg/m²*

Iasonos and O'Quigley, 2012 Stats Med

- Propose: setting the parameters at the end of stage 1 before modeling initiates
- Use the stage 1 data to inform the choice of CRM tuning parameters
- Until now, parameters for CRM were selected up front, at the design stage

QUESTIONS?

Software

Computational Considerations

R packages

BCRM

- http://cran.r-project.org/web/packages/bcrm/bcrm.pdf

CRM

- http://cran.r-project.org/web/packages/CRM/CRM.pdf

Drug Combinations

http://www.faculty.virginia.edu/model-based_dose-finding/

Wages, Conaway, O'Quigley, Biometrics, 2011

Available R Code:

- Phase I Trials of Combinations of Agents - Implementation
- Phase I Trials of Combinations of Agents - Simulation
- Phase I Trials for Multiple Treatment Schedules - Simulation

- Nonparametric Optimal Benchmark

Software for more advanced problems

- TITE CRM

dfcrm R package (Ken Cheung)

http://cran.rproject.org/web/packages/dfcrm/

Software for more advanced problems

dfcrm R package (Ken Cheung)

http://cran.rproject.org/web/packages/dfcrm/

getprior: skeleton so that OC are met

cohere : coherence status of 2 stage CRM

crmsens: model sensitivity via indifference intervals

Writing your own software

CRM is based on a binomial likelihood

Functions in R to find MLE

optimize

optim

To integrate posterior density

integrate

SIMPLE

CRM: sequential estimation

How to estimate a?

Likelihood CRM:

$$\mathcal{L}_N(a) = \sum_{j=1}^{N} [y_j \frac{\psi'}{\psi}(x_j, a) + (1 - y_j)\frac{-\psi'}{1-\psi}(x_j, a)].$$

Bayesian CRM:

$$f(a, \Omega_{j+1}) = \frac{g(a)\prod_1^j \phi(d_l, y_l, a)}{\int g(u)\prod_1^j \phi(d_l, y_l, u)\, du}$$

where $\phi(d_j, y_j, a) = \psi^{y_j}(d_j, a)\,(1 - \psi(d_j, a))^{(1-y_j)}$

and $g(a)$ is the prior density.

Software Continued

MDAnderson Cancer Center

https://biostatistics.mdanderson.org/

SoftwareDownload/Default.aspx

- CRM Simulator (1990 O'Quigley et al)
- BMA CRM (Yin and Yuan, JASA 2009)
- Bivariate extension of the CRM

Other software

- Babb, J., Rogatko, A., Zacks, S. (1998). EWOC

http://biostatistics.csmc.edu/ewoc/index.php

http://sisyphus.emory.edu/ewoc.html

- Chen Z, et al 2012 "Dose escalation with overdose control using a quasi-continuous toxicity"

THANK YOU

Questions

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