Early Phase Clinical Trial Design in the Era of Targeted Therapy and Immunotherapy

Mark Krailo
University of Southern California
Children's Oncology Group

20 August 2021

CHILDREN'S ONCOLOGY GROUP

Outline

- Dose Seeking Trials
  - Toxicity and biological target considerations
- Efficacy Evaluation
  - Basket trial designs

Dose Seeking Trials

- Evaluate toxicity profile
  - Establish RP2D
- Adverse effects on healthy organs
- Should the target be present in enrollees?
  - Enrichment restricts patient population
  - Invasive procedures without the possibility of benefit

Dose Seeking Trials

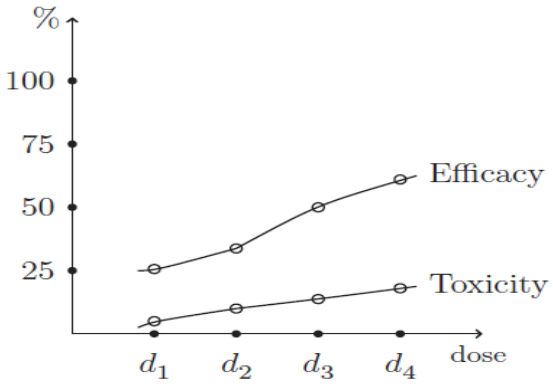
- Booth *et al.* (Eur J Cancer) and LoRusso *et al.* (Clin Cancer Res)
  - Enrichment only if there is a very strong hypothesis and validated markers
  - Biomarkers should be a key part to dose seeking studies

Dose Seeking Trials

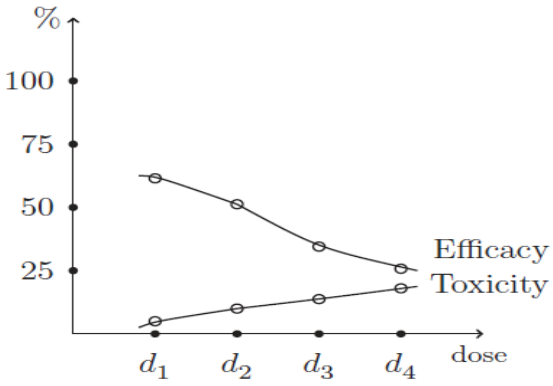
- Patients Evaluated for Two Outcomes
  - Example from Bortezomib (3+3 Design)

Number of Patients Enrolled on Cohort	Action
First cohort of three patients enrolled, none have DLT, three exhibit inhibition	Enroll three more patients at the current dose level
First cohort of three patients enrolled, none have DLT, less than three exhibit inhibition	Escalate to next dose level
Second cohort of three patients, no more than one of six have DLT, five of five or six of six 20S proteasome-evaluable patients exhibit inhibition	Recommended dose established as the current dose level
Second cohort of three patients, no more than one of six have DLT, neither five of five nor six of six 20S proteasome-evaluable patients exhibit inhibition	Escalate to next dose level

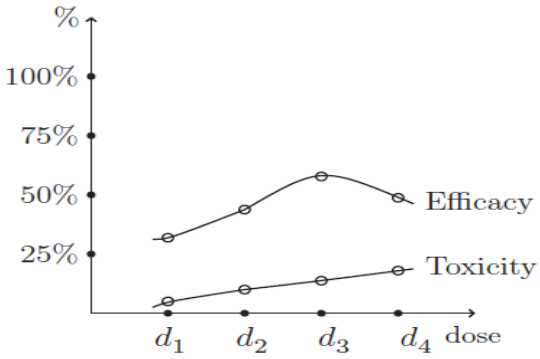
Dose Seeking Trials



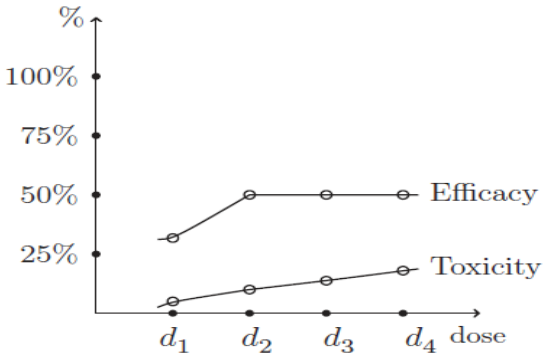
(a) Monotone increasing



(b) Monotone decreasing



(c) Unimodal



(d) Plateau

Dose Seeking Trials

- Model the Relationship Between Toxicity and Biological Outcome and Dose
  - Wages and Tait (2015)
  - Models for both toxicity and biological outcome
    - Escalation to establish doses with acceptable toxicity profile then explore biological activity
    - Update tolerability continuously

Dose Seeking Trials

- Wages and Tait
- Bayesian updating
- $Pr(DLT|dose\ i) = p_i^{\beta^*}$
- $K\ competing\ models\ of\ biological$
- $response: Pr(Response|dose\ i) = q_i^{\theta^*}$

Where the “skeleton probabilities” are derived with clinical input

Dose Seeking Trials

Investigator Proposes Plausible Patterns of Biological Response

Model	Pr(E|d1)	Pr(E|d2)	Pr(E|d3)	Pr(E|d4)
1	0.50	0.60	0.75	0.75
2	0.50	0.60	0.60	0.60
3	0.50	0.50	0.50	0.50
4	0.50	0.60	0.70	0.80

Dose Seeking Trials

- First G1 patients used in CRM to establish a set of tolerable doses (G1: 20 for 4 doses) $\{d_1, \ldots, d_i\}$
- In next stage, assign patients in groups of size *g* randomly amongst tolerable doses
- After each group use Bayesian methods to identify the best of the competing models

Dose Seeking Trialss

- After stopping criteria met, select the ‘best’ model
  - Maximum study size
  - Inability to determine a tolerated dose
- Select the lowest dose that gives the highest probability of biological response

Dose Seeking Trials

- Use DLT data collected during response assessment to refine what are ‘tolerable doses’
- Total patients for 4 doses with 4 response models ~60 patients

Dose Seeking Trials

- Background data for putative dose-response models – good pre-clinical data
- Randomized amongst tolerable doses
  - Design entertains that more may not be better

Dose Seeking Trials

- Set of doses with acceptable toxicity changes as the trial proceeds
  - May determine a dose level is “unacceptable” after patients have been assigned and are receiving treatment
- Decision rules set out in protocol prior to enrollment of the first patient
- Requires commitment of analytical team throughout the trial

Features of Model-Based Designs

- Mathematical model relating toxicity to dose
- Updated according to Bayesian methods
- ‘Several’ dose levels support modeling
- Statistical work (simulation studies) required to set tuning parameters

Alternative Approach

- Conventional dose seeking study
  - Enrollment not enriched for patients with the target
- Expansion cohort
  - Enrollment enriched
  - Sufficient sample size to estimate effect on target

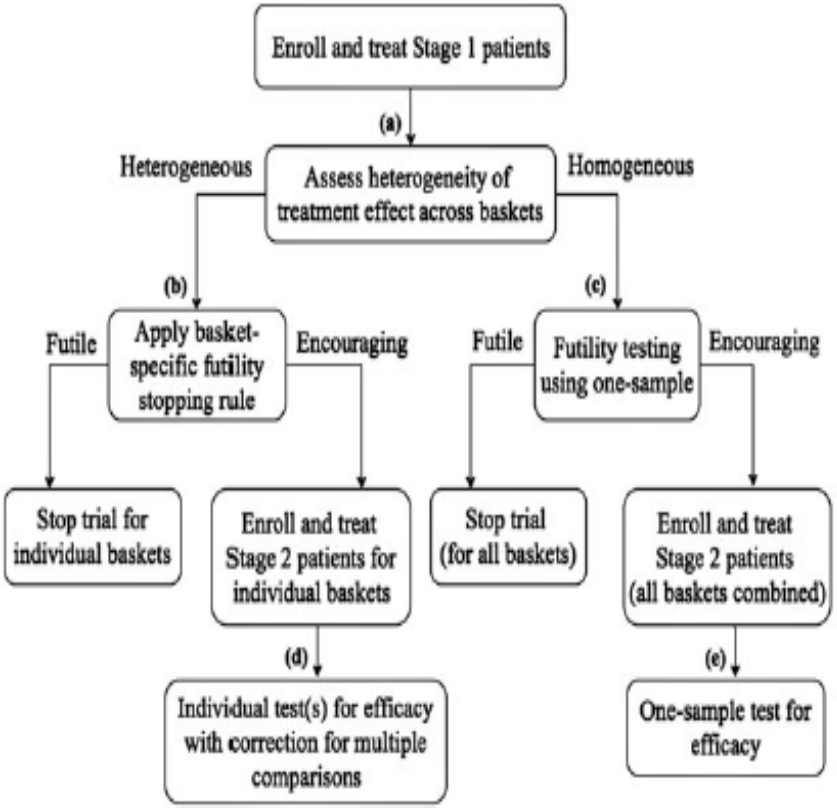
Efficacy Evaluation

- Agents whose effect is believed related to a particular biological feature
- Basket Trial

Basket Trial

- Efficacy assessment
- Acknowledges histology and a specific biological feature
- Adapts as assessment of heterogeneity of effects can be done
- Cunanan *et al.*, 2017

Basket Trial – Cunanan *et al*



Basket Trial – Cunanan *et al*

Table I. Glossary of terms.

Notation	Definition
θ_0	Null response rate
θ_a	Alternative response rate
K	Total number of baskets
A	Number of truly active baskets
ϵ	Target family wise error rate when $A = 0$
$(1 - \beta)$	Target marginal power when $A = 2$ (or 3 depending on K)
$(1 - \beta)_{min}$	Minimum acceptable power when $A = 1$
n_{1k}	Stage 1 sample size for basket k
N_1	Total stage 1 sample size
n_{2k}	Stage 2 sample size for basket k, given heterogeneous design path
N_2	Total stage 2 sample size, given homogeneous design path
γ	Assessment of heterogeneity tuning parameter
r_S	Minimum required number of responses in stage 1 for an individual basket to continue to stage 2, given heterogeneous design path
r_C	Minimum required number of responses in stage 1 across all baskets to continue all baskets to stage 2, given homogeneous design path
α_S	Significance level for final separate analyses (before correction for multiple comparisons), given heterogeneous design path
α_C	Significance level for final combined analysis, given homogeneous design path
FWER	Empirical family wise error rate
P_k	Empirical marginal power (%) for basket $k = 1, \ldots, K$
EN	Expected trial sample size
ET	Expected trial duration (months)

Basket Trials

- Comparison of 5-stratum designs
  - Reference design – analyzed as 5 separate sub-studies
  - Cunanan *et al.* design – 5 strata with the possibility of aggregation

Basket Trials

Table II. Power and expected sample size: equal accrual.

Design	Scenario (*A*)	FWER	Marginal Power* P_1	P_2	P_3	P_4	P_5	EN	ET
Proposed	0 Active	5	2	2	2	2	2	58	7.0
	1 Active		70	7	7	7	7	74	9.5
	2 Active		80	80	11	11	11	83	10.4
	3 Active		84	85	85	17	17	86	10.5
	4 Active		86	85	86	86	23	88	10.2
	5 Active		88	90	88	88	88	78	8.3
Reference	0 Active	5	1	1	1	1	1	58	10.4
	1 Active		79	1	2	1	2	69	13.3
	2 Active		81	82	1	1	1	83	14.8
	3 Active		80	82	81	1	1	96	15.4
	4 Active		82	84	80	80	1	108	15.9
	5 Active		82	81	80	80	82	121	16.3

*Marginal error rates for inactive baskets.
EN, expected trial sample size; ET, expected trial duration; FWER, family wise error rate.

Basket Trial

- Planning is key
  - Examine a wide range of response probabilities and “tuning parameters” (underlying relationship of response rates between tumor groups)
- Simulation (creating *many* synthetic trials under plausible assumptions)
  - Selecting a design that, in most situations, identifies the truth
    - Cost considerations in terms of number of patients required

Summary

- Dose Seeking Trials
  - Narrow dose range (2-3 dose levels) modeling may not be advantageous
  - Bayesian modeling can identify doses based on toxicity and efficacy evaluation
  - Model based designs require substantial simulation studies to set tuning parameters

Summary

- Efficacy Evaluation
  - Basket trial design acknowledges different “phenotype” and provides for aggregation
  - Basket trials require substantial simulation studies to set tuning parameters