Introduction to Phase I Designs

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Traditional Phase I trials

- Traditionally enroll 12-30 patients
- Aim to find the maximum tolerate dose (MTD)
- Higher dose meant higher efficacy
- Single agent
- Heterogenous population (disease, prior trt)
- Evaluate 5-6 dose levels
- Dose escalation/de-escalation in cohorts of 3 patients

Terminology

- Objectives

to find the maximum tolerated dose (MTD)

- MTD was RP2D
- DLT (dose limiting toxicities: severe grade ≥3) is a binary endpoint measured typically within cycle 1 of treatment

Is the drug safe and at which dose? Which patient population and which drug/regimen to prioritize?

- Success with single agent targeted therapies
- Develop resistance because of multiple genetic alterations and advanced metastatic disease
- Regimens with 1 or more targeted agent
- Many single agents/ combination regimens in the pipeline. Competing Resources

- Minimize # of patients and trial duration

Different objectives

- Targeted agents or combination regimens
- Dose response relationship
- OBD dose: dose that meets a set of endpoints (inhibits a drug target or achieves a target plasma concentration)
- MTD is not necessarily the RP2D
- Dose expansion cohorts (>200 patients)

Why have Phase I trials become so complicated?

Simplest case	More Complex cases
• Single agent • Single schedule • MTD • 5-6 levels • N=20-25	• Combination agents • 2 schedules • MTD (1 or >1) • OBD • multiple disease groups • DLT definition (onset, attribution AE) • starting dose relative to MTD • N=50 – 60 dose escalation • >120 (25-40 per cohort)

Need to use efficient designs

Course Objectives

1. The premise of novel, model based designs
2. Which Phase I design should we be using when?
3. Are some designs better and under what circumstances?
4. What measures of performance should be used to evaluate designs?
5. Theoretical considerations
6. Dose expansion cohorts – large Phase I trials

Course Objectives – Day 2

- More complex clinical problems
  - Efficacy and toxicity
  - Heterogeneous patient populations
- DLT endpoint and uncertainty
- Combination regimens

- Protocol development
  - Design, software, review, amendments

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.

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,

Criticism

- MTD is the dose below the level where ≥ 2/6 DLT
- Generally yields a dose with <30% target toxicity level
- Toxicity rate is estimated for each dose level separately w/o using cumulative data on all dose levels

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%.
- 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

Gemcitabine Trial:
Abbruzzese et al. JCO 1991

Cohort	Dose mg/m^2 10	15	22.5	35	53	80	120	180	225	350	525	790	1000
1	0/3												
2		0/3											
3			0/3										
4				0/3									
5					0/3								
6						0/3							
7							0/3						
8								0/3					
9									1/4				
10										0/3			
11											1/3		
12												1/7	
13													3/6
MTD												****	

Gemcitabine Trial:
Advanced disease, refractory solid tumors

Abbruzzese et al. JCO 1991

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

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

Non model designs

- Similar in concept
- Patient allocation and MTD estimation
- Use all the data (dose-toxicity curve)
- Use the last cohort (the dose below the level at which ≥ 2 DLTs /6 pts)

Model based designs

Continual Reassessment Method

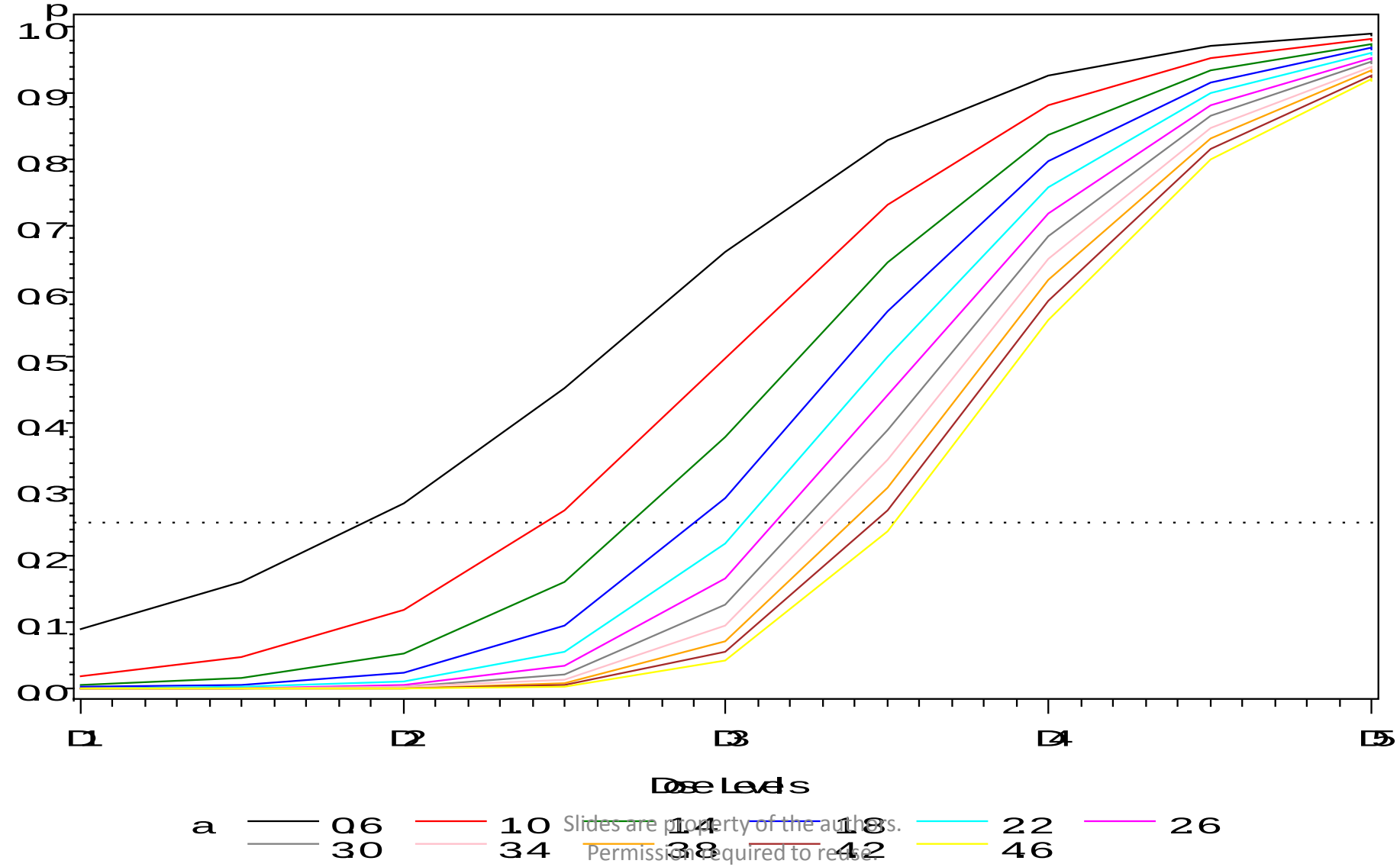
Define MTD as the level closest to an acceptable DLT rate, say 30% (or 20%)

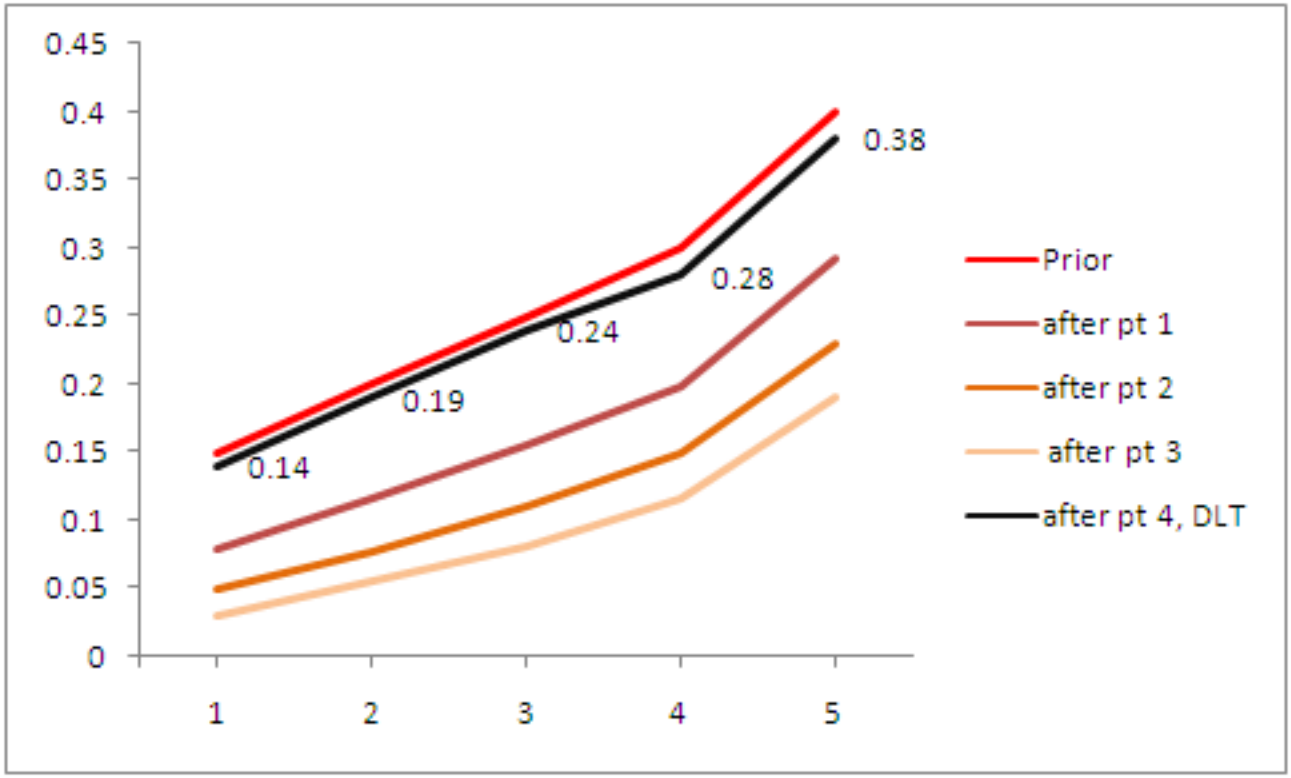
We aim to find the dose where no more than 30% of patients experience DLTs

CRM algorithm

- Assume a dose toxicity curve and refit the curve based on most recent patient data.
- The dose closest to the target toxicity rate, based on the “new curve”, will be the dose of the next patient.
- Repeat sequentially until a max *n* is observed

Dose– Toxicity: Hyperbolic Tangent





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

Ongoing problems

Many model based designs

Evaluated through simulation studies

Which design to use in practice?

Practical and logistical challenges

Targeted therapy

Combination regimens

Challenges for targeted combinations

1. Which combinations among many to explore?

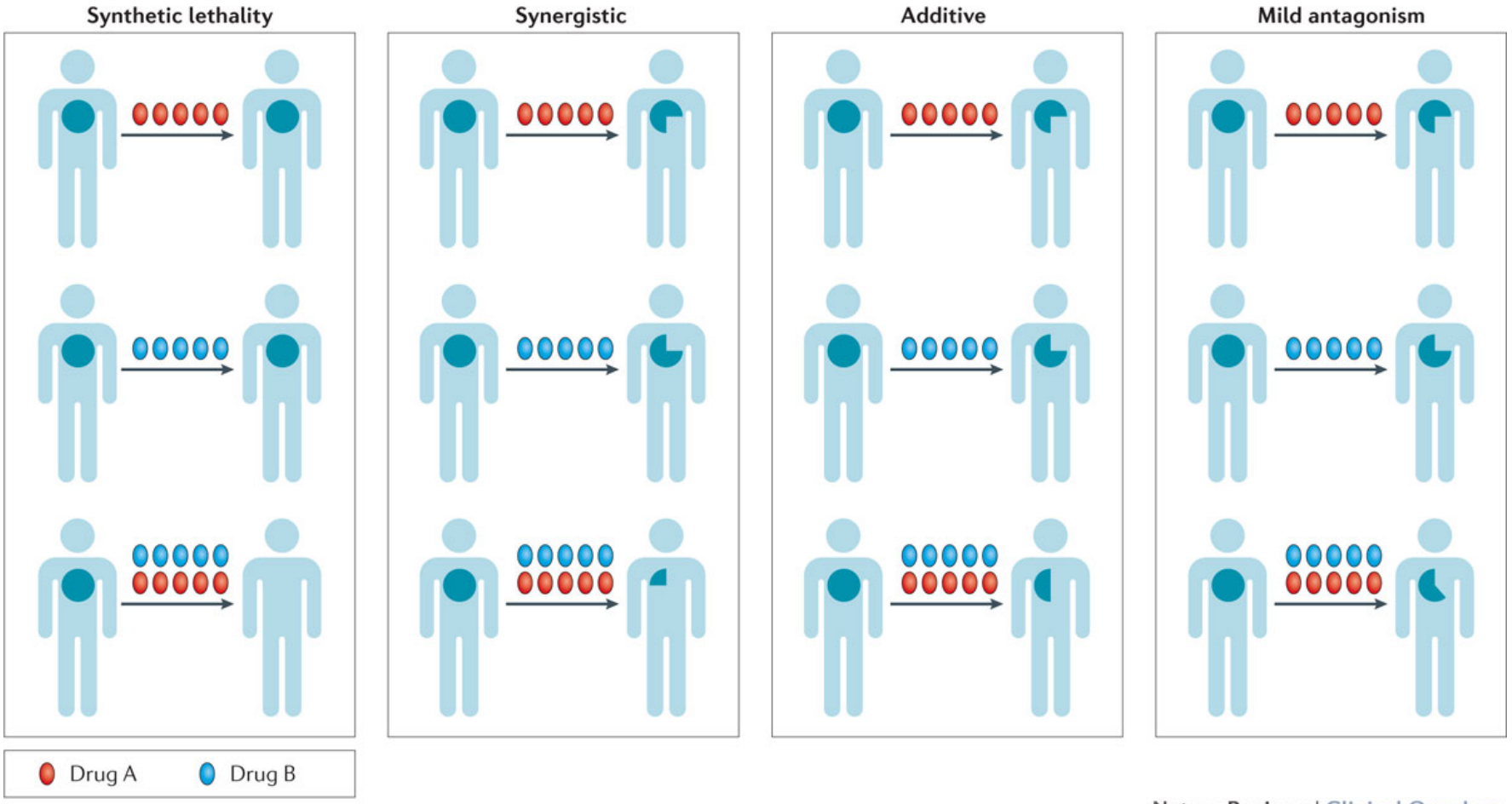
2. How to develop and test the combination?
   - How – dose levels / schedules
   - When – disease state
   - Whom – patient population

1. Which combinations among many to explore?

- Multiple single-hypothesis-testing combination studies are expensive and timely
- Experimental models to discover and prioritirize optimal combinations are needed
- High-throughput systems; cell lines to discover synergestic interactions; modeling to predict tolerability; synthetic lethality and siRNA, RNA interference; systems biology
- Patient derived xenographs (PDXs)

Lopez and Banerji,
NR Clin Onc 2017

How to develop successful combinations?

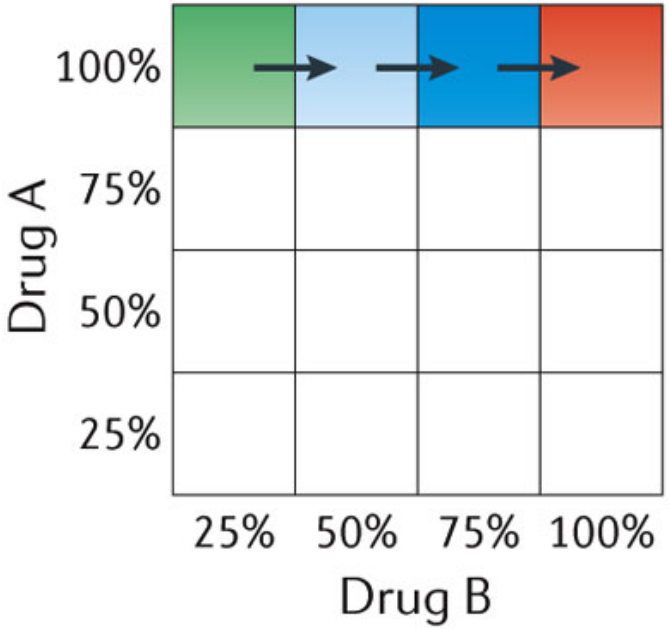


Clinical impact of drug combinations on the tumour

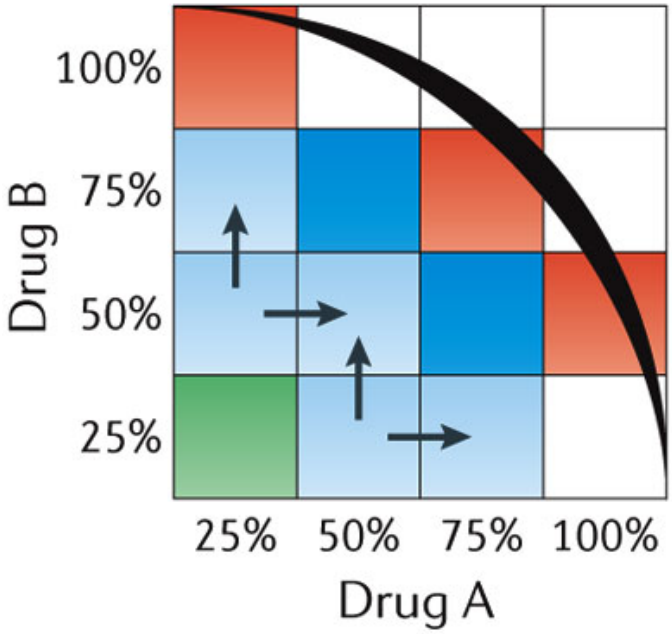
Lopez, J. S. & Banerji, U. (2016) Combine and conquer: challenges for targeted therapy combinations in early phase trials
Nat. Rev. Clin. Oncol. doi:10.1038/nrclinonc.2016.96

2. How to develop the combination?

- How to combine 2 drugs?
  - dose levels (2x3, 3x3, 4x4 etc)



% are OBD of single agent of drug



% are MTD of single agent of drug

Lopez and Banerji 2017

Phase I/Ib study of ibrutinib with ABT-199 in relapsed/refractory mantle cell lymphoma

	Ibrutinib (mg/day)	280	420	560
ABT-199 (mg/day)	400	d3	d5	d6
	200	d1	d2	d4

Group combinations into zones with increasing toxicity
Escalate to higher zones in the absence of DLT
If multiple combinations in zone, randomize to combo in zone
20-28 patients; Partial Order CRM

NCT02419560- UVA
Blood 2016 ; initial report.

Optimal dose combination

- **Objective: determine optimal dose combination** based on binary toxicity/efficacy

  defined as the combination with highest response rate and acceptable level of toxicity.

- Primary outcomes guiding accrual decisions:

  Toxicity: DLT's based on protocol-specific adverse events

  Efficacy: response (CR+PR) at 2 months

NCT02419560- UVA (open for accrual)
Blood 2016; initial report

Complexity increases with number of levels

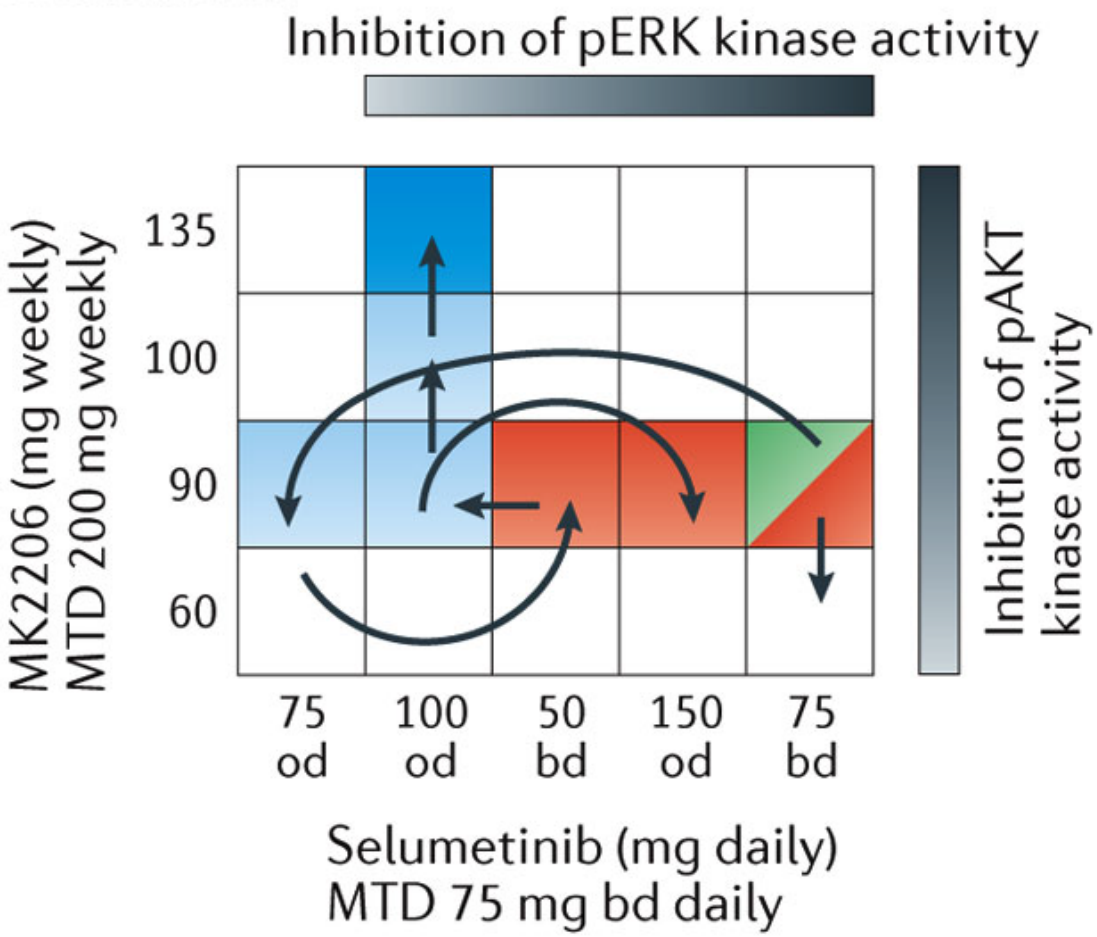
	Ibrutinib (mg/day)	280	420	560
ABT-199 (mg/day)	400	[3]	[5]	[6]
	200	[1]	[2]	[4]

	Ibrutinib (mg/day)	280	420	560
ABT-199 (mg/day)	400	[2]	[4]	[6]
	200	[1]	[3]	[5]

5 paths for 6 (2x3) levels; 24 paths for 9 (3x3) levels
144 paths for 12 (3x4) levels

Explore multiple doses / schedules

Lopez and Banerji 2017



Methods for different schedules and groups

- Two Schedules/routes of administration
  - one schedule is less toxic than the other

    once vs twice daily of an equal dosage
  - unknown how the schedules are related in terms of higher toxicity

- Two patient populations:
  - heavily vs non heavily pretreated patients
  - different histologic subtypes
  - pediatric and adult patients

How can we overcome these challenges?

- Toxicity ordering no longer holds
- Multiple agents /doses / schedules
- Efficacy (+ safety simultaneously)
- Patient populations – heterogeneity
- Attribution or late onset AE (fractional DLTs)

A model based design can accommodate these multiple components

How to develop and test the combination?

- How – dose levels / schedules
- When – disease state
- Whom – patient population

When to treat patients?

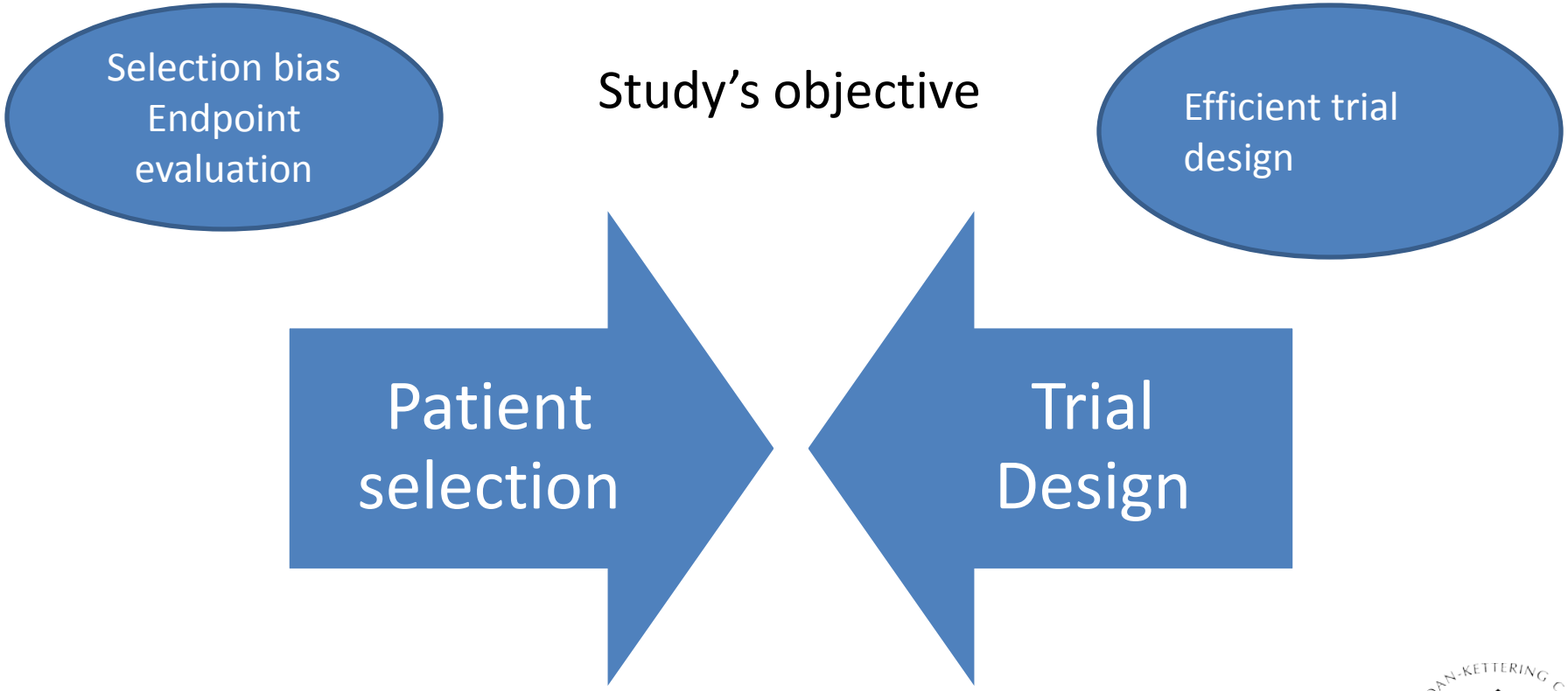
- The setting should be guided by the hypothesis being tested:
  - Goal: delay the onset of resistance or increase degree of tumor shrinkage?
  - Is the combination being tested to show that a degree of de novo resistance to one of the drugs might be reversed by the addition of the 2nd drug?
- Advanced stage disease , late stage metastatic disease
- Frontline adjuvant or first line met disease?

Lopez, J. & Banerji, U. (2016) *Nat. Rev. Clin. Oncol.*

Patient population to test the combination

- Whom to test?
  - Biomarker specific: mutated genes, amplifications, translocations, alterations
  - Knowledge from single agent to combinations
  - BRAF and PIK3CA are biomarkers for MEK and AKT inhibition; KRAS mutations are a biomarker for combinations with MEK/P13K/AKT inhibitors

Patient selection and Trial Design are complementary and need to be optimized



Hyman DM et al
JCO 2014
https://www.mskcc.org/nomograms/clinical_trials

QUESTIONS?
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