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Are We Defining the Right Doses of Targeted Therapy?

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Do We Have a Problem? The Case Study of Cabozantinib

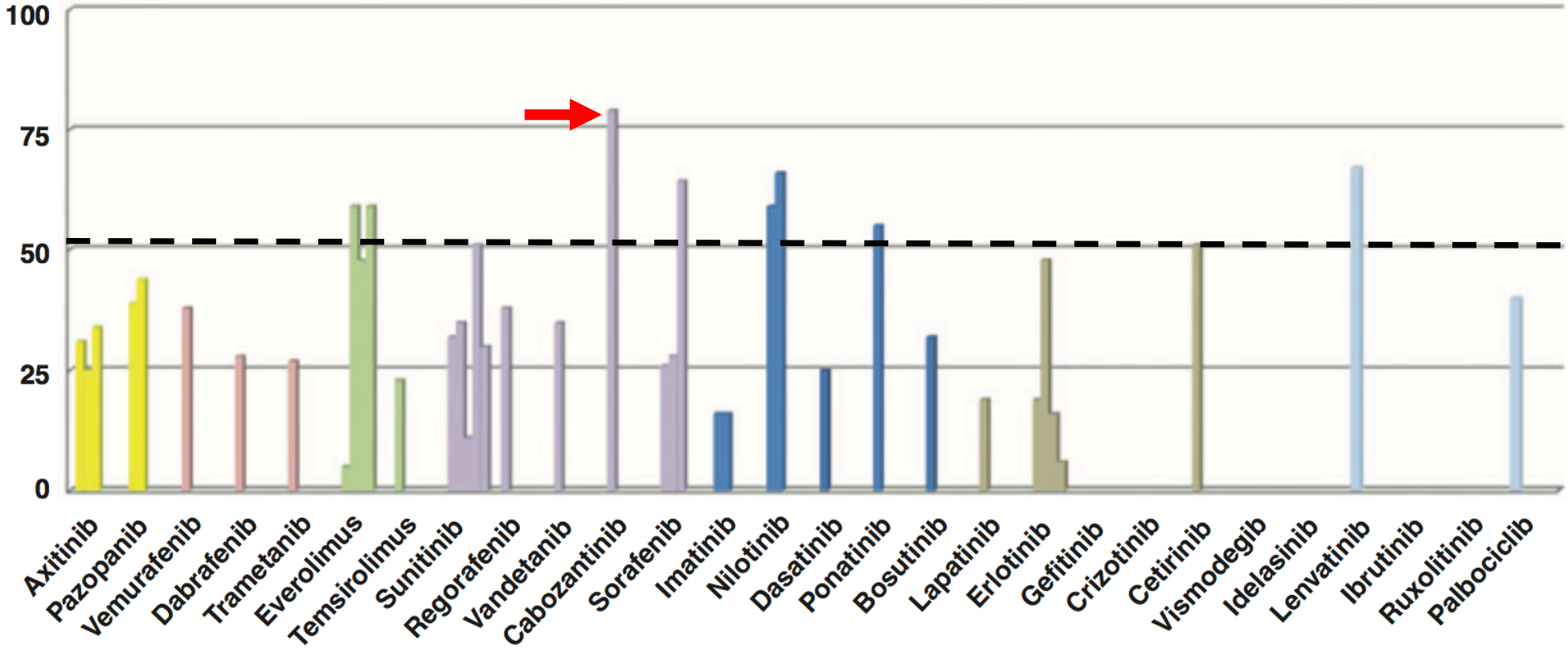
- MTD in first-in-human Phase I 175mg daily
- FDA approved for metastatic medullary thyroid cancer (MTC) at 140mg daily
- Phase III RCT trial in MTC (cabo vs placebo):
  - 330 patients
  - Dose reduction: **79%** vs 9%
  - Median dose delays: **1** vs 0
  - Tox leading to rx discontinuation: 16% vs 8%
- Current studies using 60mg daily
- Does this represent a problem?

Key Questions

- What defines a tolerable dose for targeted therapy?
- Are our Phase I studies defining tolerable doses?
- What are the implications of different dose escalation schema?
- Do Phase I studies identify key toxicity of agents?
- How do we approach differing schedules and drug combinations?

How Widespread is This Phenomena

% Dose Reductions in 34 Phase III Studies of Recently Approved Targeted Agents



7/34 (31%) required dose reductions in >50% of patients

Roda et al, Clin Cancer Res; 22(9) May 1, 2016

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BELLE-2: Fulvestrant ± Buparlisib in ER+ Breast Ca

Patient Disposition, %	Buparlisib + Fulvestrant (n=576)	Placebo + Fulvestrant (n=571)
Treatment phase ongoing	16.1	16.5
Treatment discontinued	83.5	83.2
Primary reason for treatment discontinuation		
Progressive disease	54.3	73.0
Adverse event	13.2	1.8
Patient decision	8.9	3.2
Physician decision	4.0	3.7
Death	1.2	0.9
Other	1.9	0.7

26% discontinue without PD

Exposure to Study Treatment	Buparlisib + Fulvestrant (n=573)	Placebo + Fulvestrant (n=570)
Median duration of treatment exposure, months	4.2	5.0
Buparlisib/placebo median relative dose intensity, %	93.2	100
Buparlisib/placebo dose adjustments, %		
Dose reduction	46.4	7.0
Dose interruption	55.8	31.4

Treatment Exposure Lower

AE Rate: 63.2% (G3), 14.1% (G4)

Baselga et al, San Antonio Breast Cancer Symposium 2015

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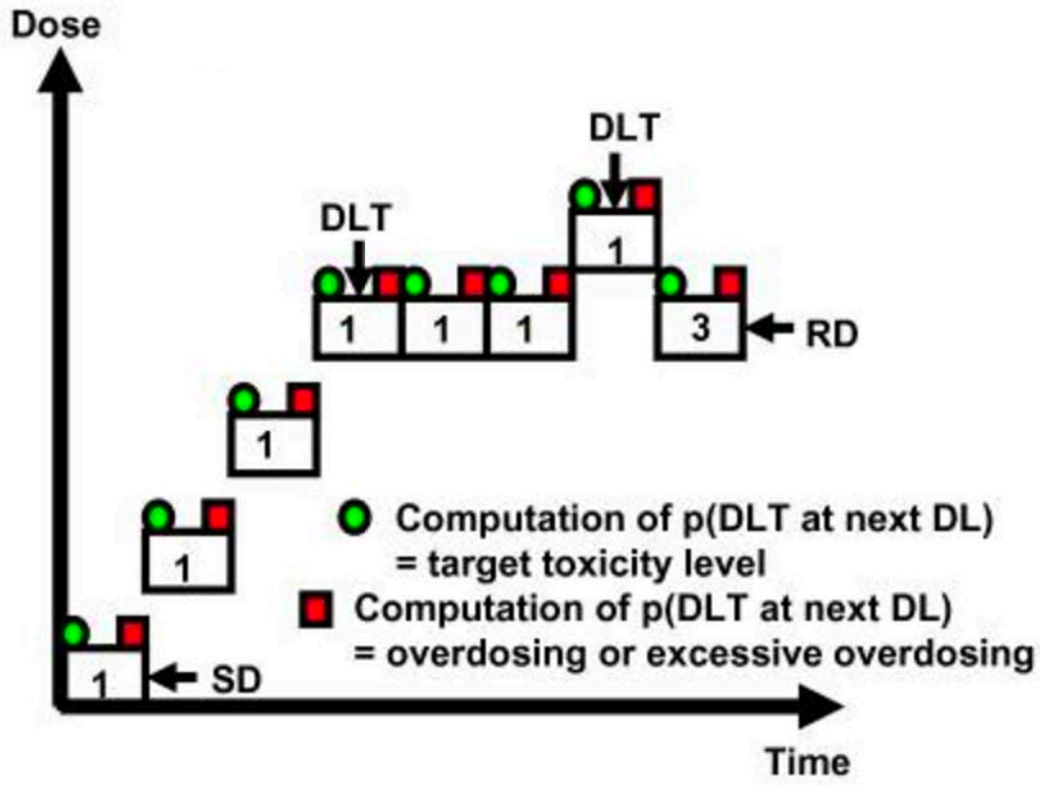
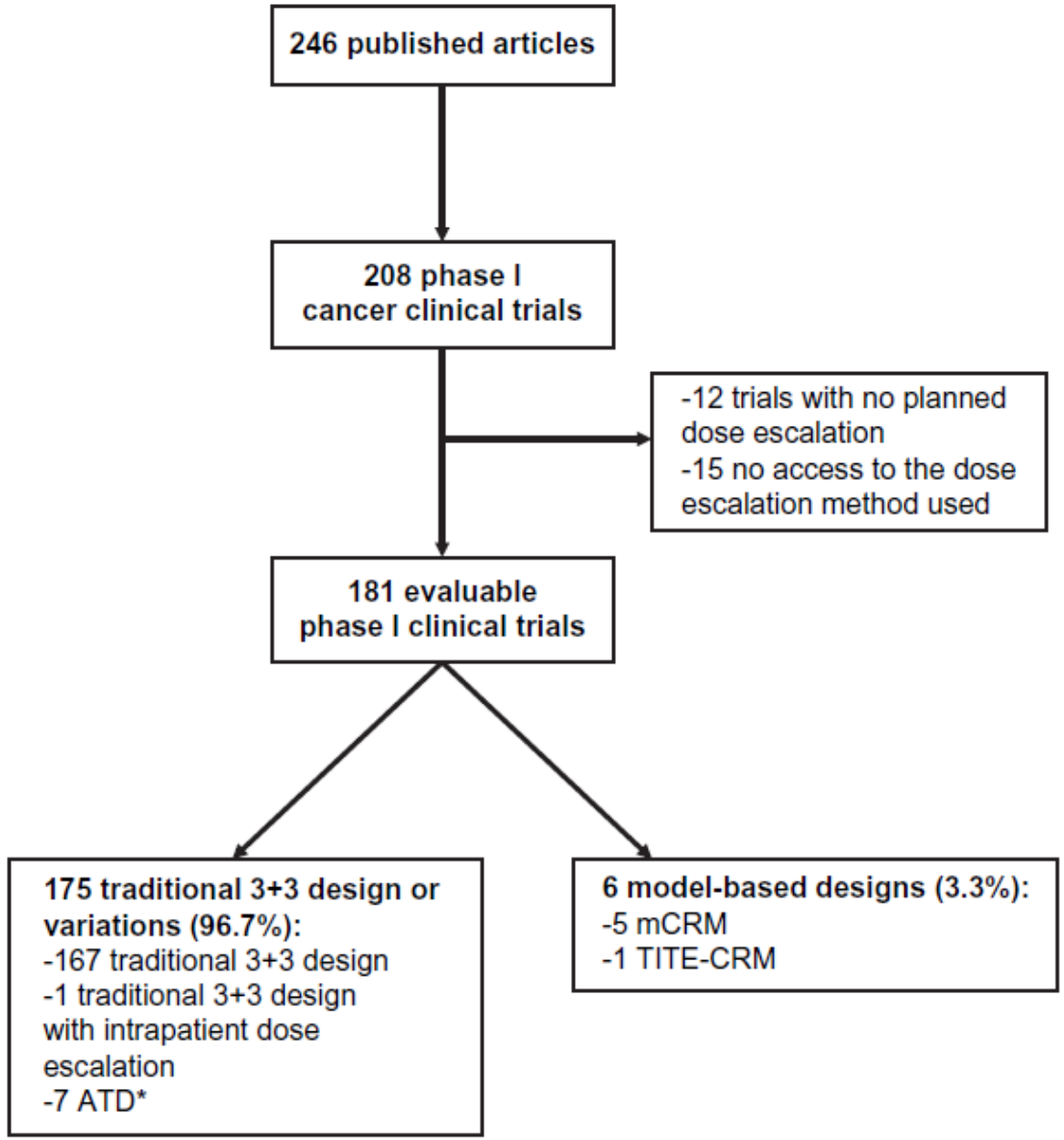
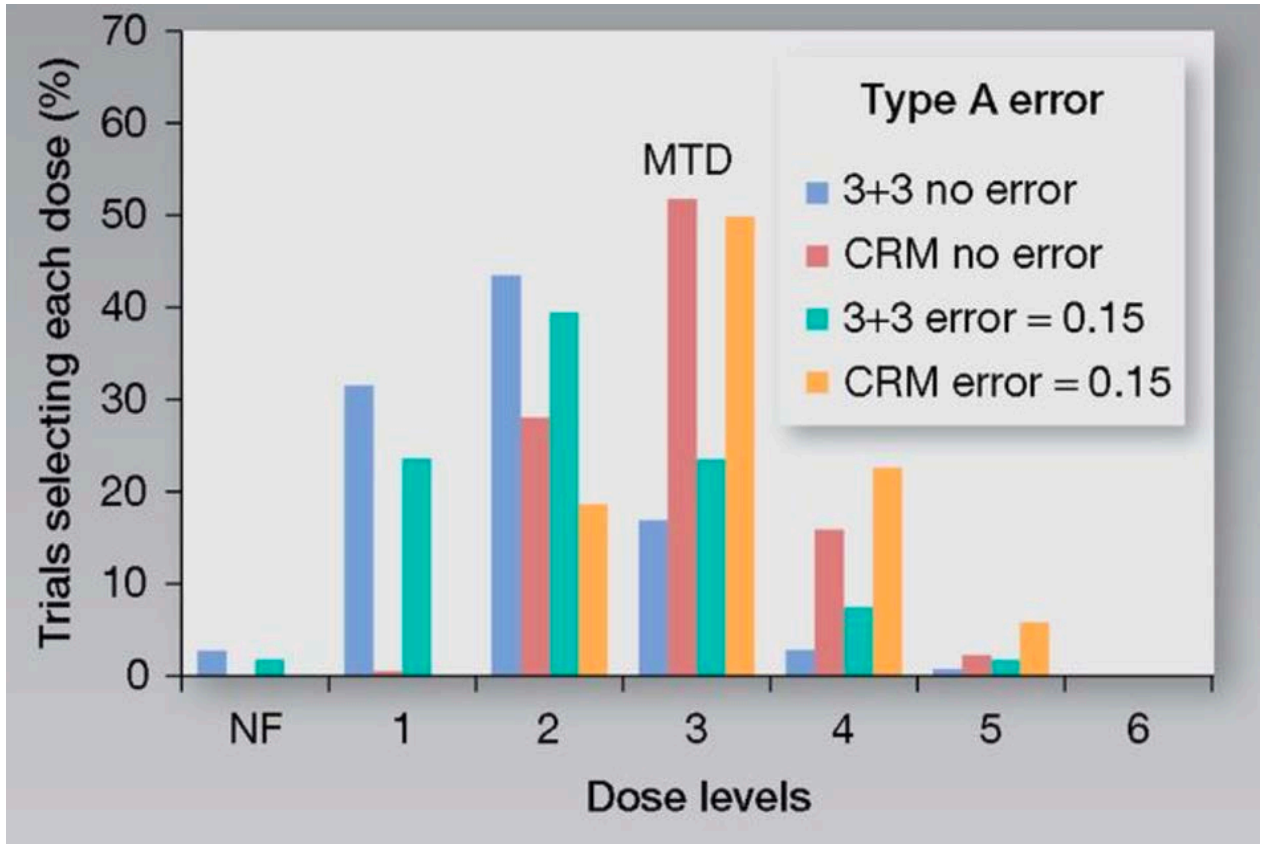
Where Do We Start?
Bayesian Dose Escalation Designs and Adoption





Le Tourneau et al, JNCI Vol. 101, Issue 10, May 20, 2009

How Accurately Do We Estimate the MTD?



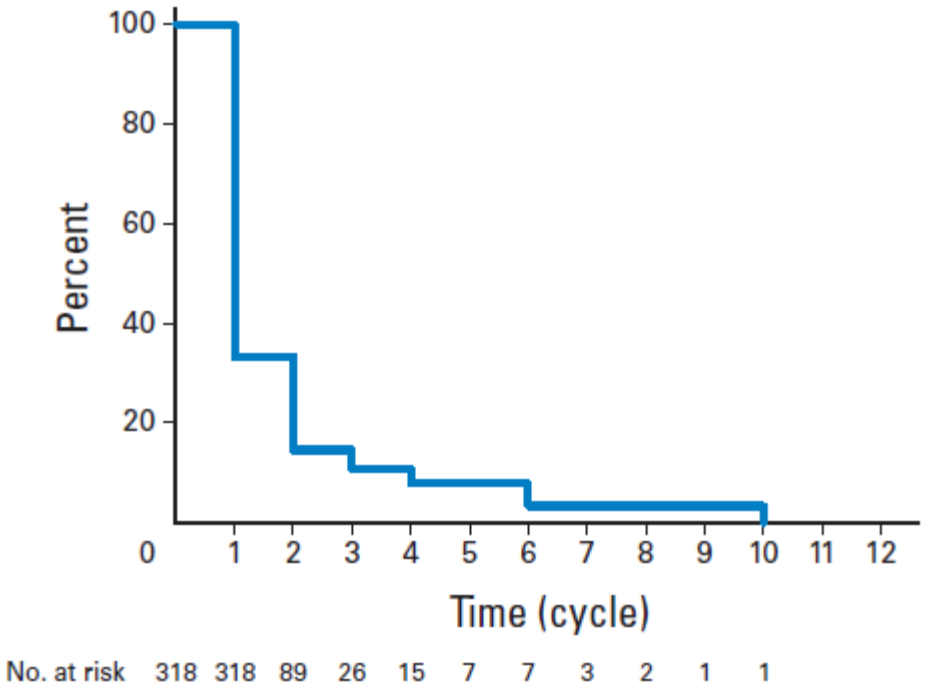
- Even in the absence of attribution error – MTD estimated correctly only 50% of the time (lower with 3+3)
- CRM more robust to introduction of 15% error rate in physician DLT attribution

Iasonos A et al, Clin Cancer Res; 18(19) October 1, 2012

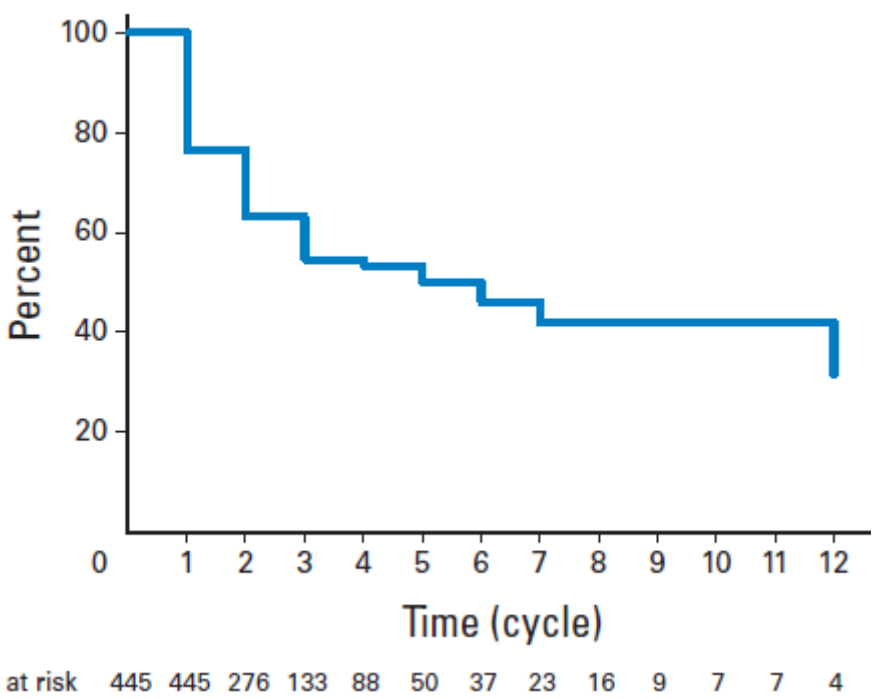
The Core of the Problem: Chronic Toxicity

- MTD reflects only Cycle 1 toxicity
- However, targeted agents are administered chronically

Time to Worst Grade Toxicity



Time to 1st Grade 3/4 Toxicity



Postel-Vinay, JCO Vol 29, Num 13, may 1 2011

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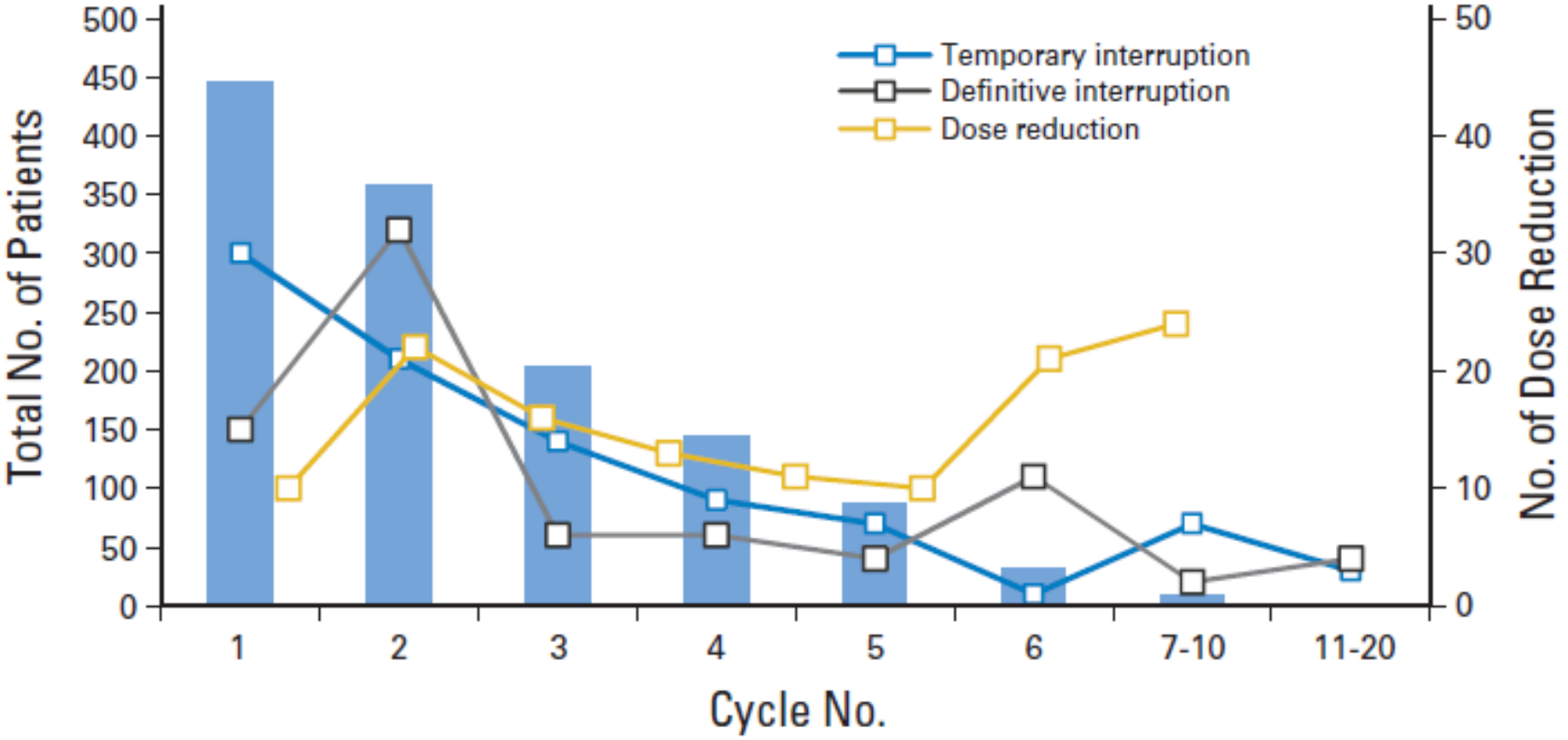
Key Metrics: Treatment Interruption and Reduction



- Treatment interruption / dose-reductions continue after Cycle 1

Postel-Vinay, JCO Vol 29, Num 13, may 1 2011

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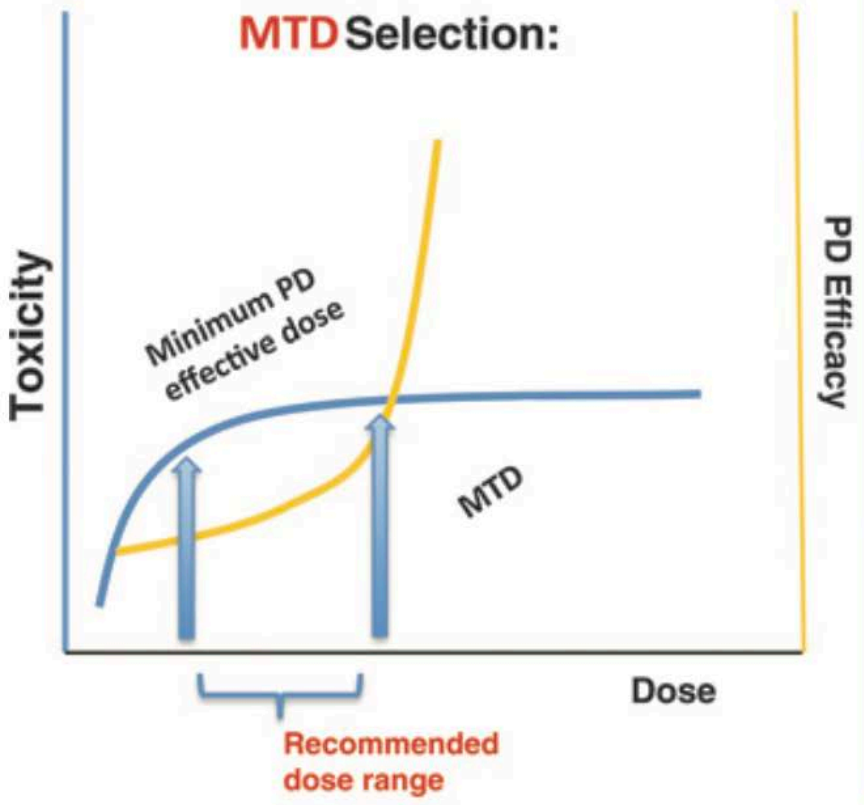
Is There a Better Way?

Escalation cohort

MTD Selection:



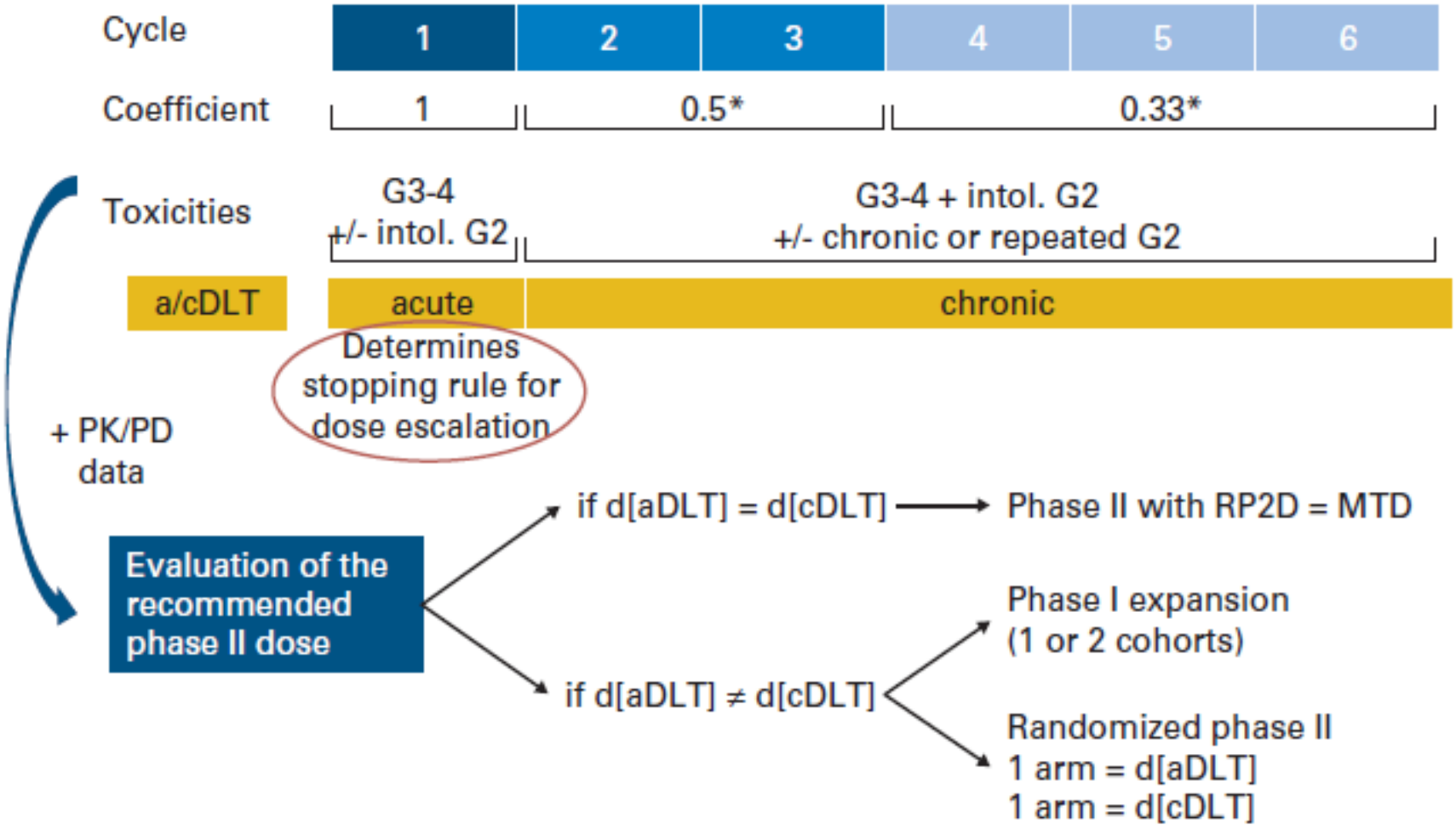
Expansion cohort

To confirm RP2D if:

- Tolerable in 12–20 patients.
- Long observation (2 cycles) should be completed.
- Dose modifications in less than 30% of patients

Roda et al, Clin Cancer Res; 22(9) May 1, 2016

Another Proposal - Defining the "Chronic" MTD



Postel-Vinay, JCO Vol 29, Num 13, may 1 2011

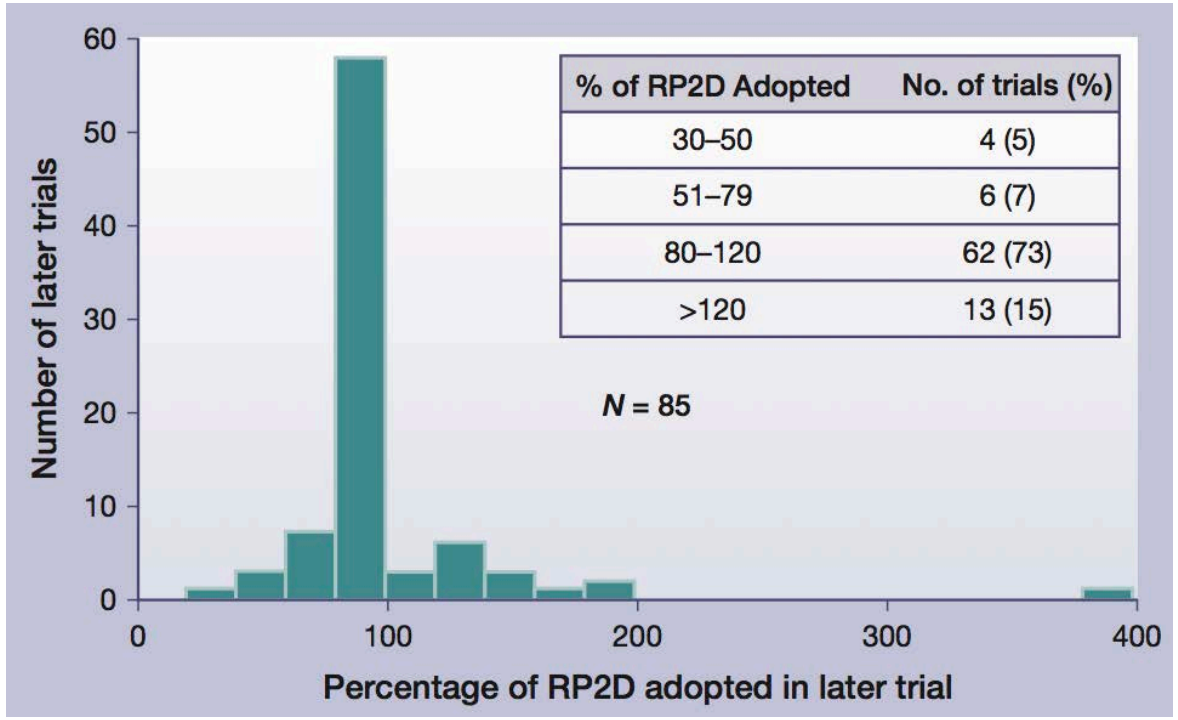
Does Phase I Toxicity Reflect Phase III Toxicity?

	Was DLT represented in the four most frequent grade 3/4 adverse events of later trials?[a]			Were the clinically significant toxicities on later trials described on the respective phase I trial?[b]		
Trial/agent characteristic	***N***	***N* "yes" (%)**	***P***	***N***	***N* "yes" (%)**	***P***
Overall	75	54 (72)		84	68 (81)	
Drug class						
Cytotoxic	36	29 (81)	0.12[c]	36	32 (89)	0.23
Targeted	33	21 (64)		37	29 (78)	
Other	6	4 (67)		11	47 (64)	
Route[d]						
IV	43	30 (70)	0.68	47	37 (79)	0.60
PO	31	23 (74)		36	30 (83)	
Monotherapy or not						
Single agent	62	45 (73)	0.81	70	55 (79)	0.21
Combination	13	9 (69)		14	13 (93)	
Number of patients						
11–36	37	28 (76)	0.48	42	30 (71)	**0.026**
37–153	38	26 (68)		42	38 (90)	

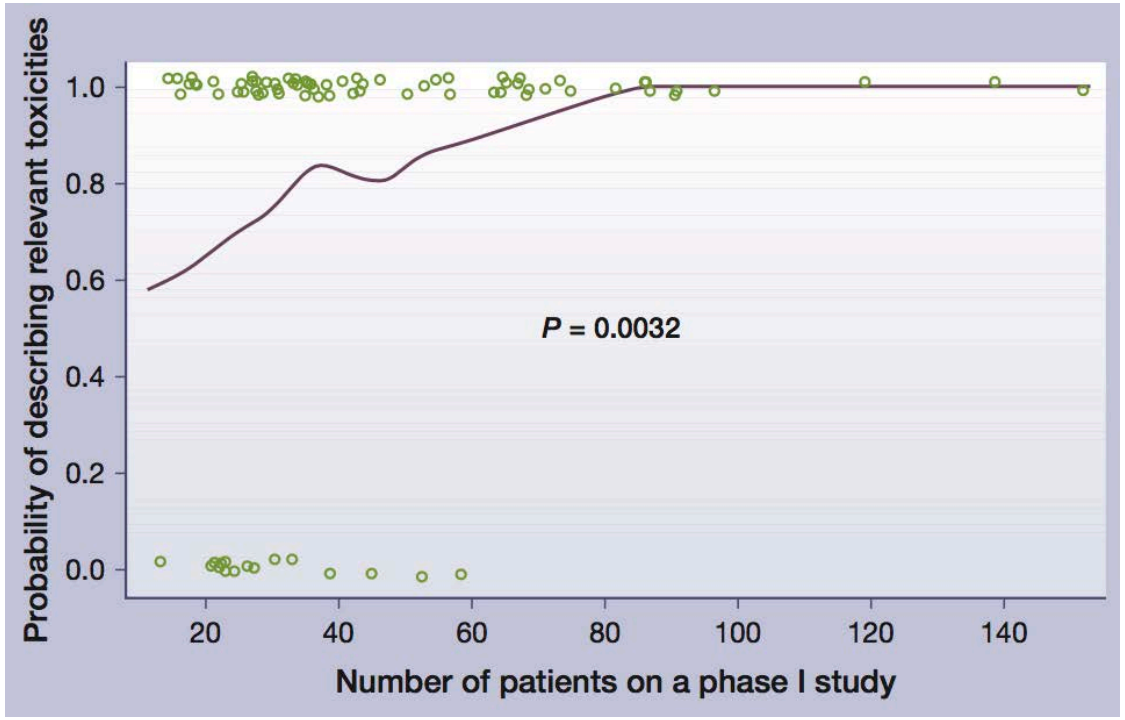
- More Patients on Phase I = Better Toxicity Estimation

Jardim et al, Clin Cancer Res; 20(2) January 15, 2014

Does Phase I RP2D Reflect Phase III Dose Selection?



% of RP2D Adopted	No. of trials (%)
30–50	4 (5)
51–79	6 (7)
80–120	62 (73)
>120	13 (15)



- More Patients on Phase I = Better Dose Estimation

Jardim et al, Clin Cancer Res; 20(2) January 15, 2014

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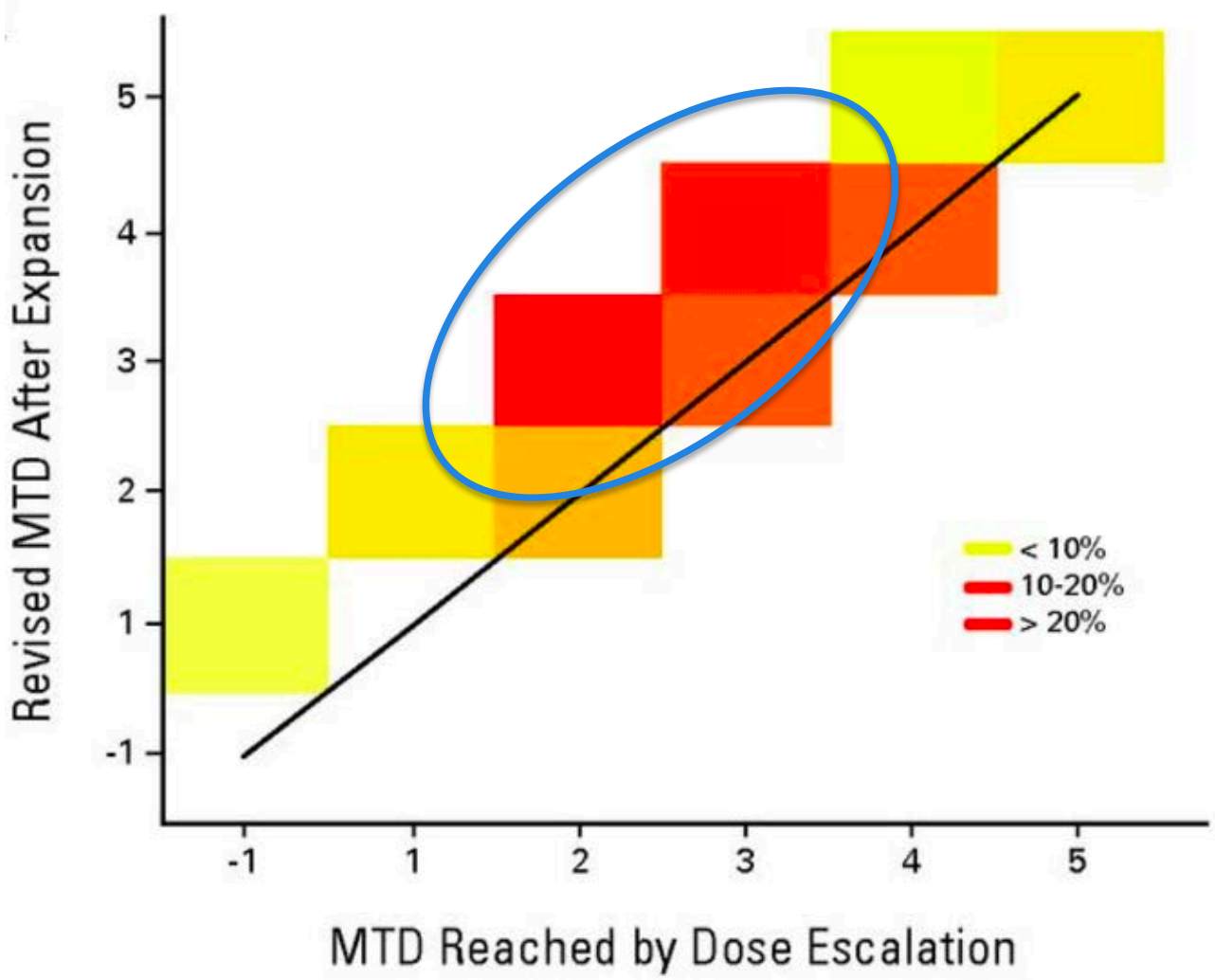
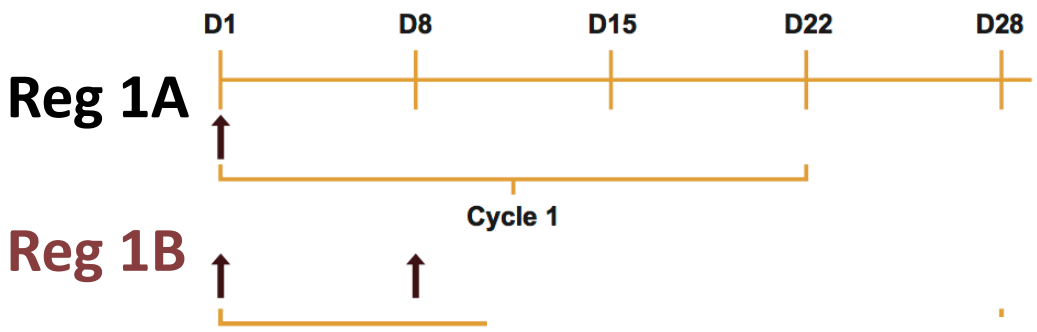
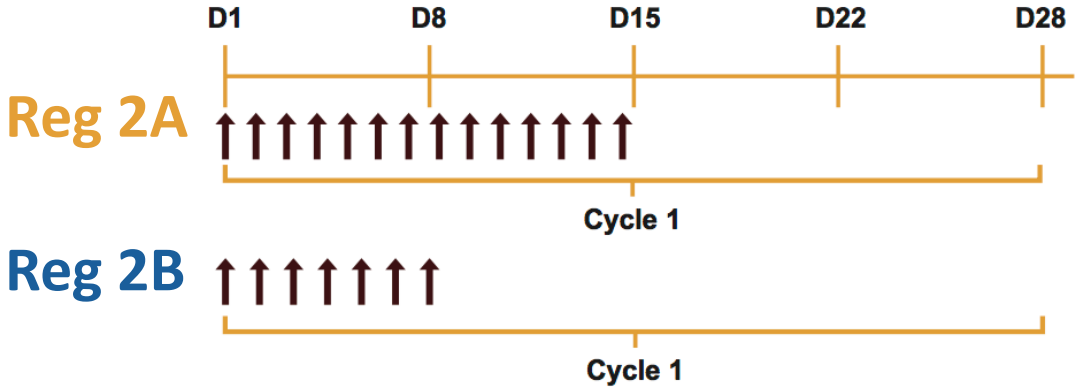
Incorporating Dose Expansion Toxicity to Improve MTD Estimates



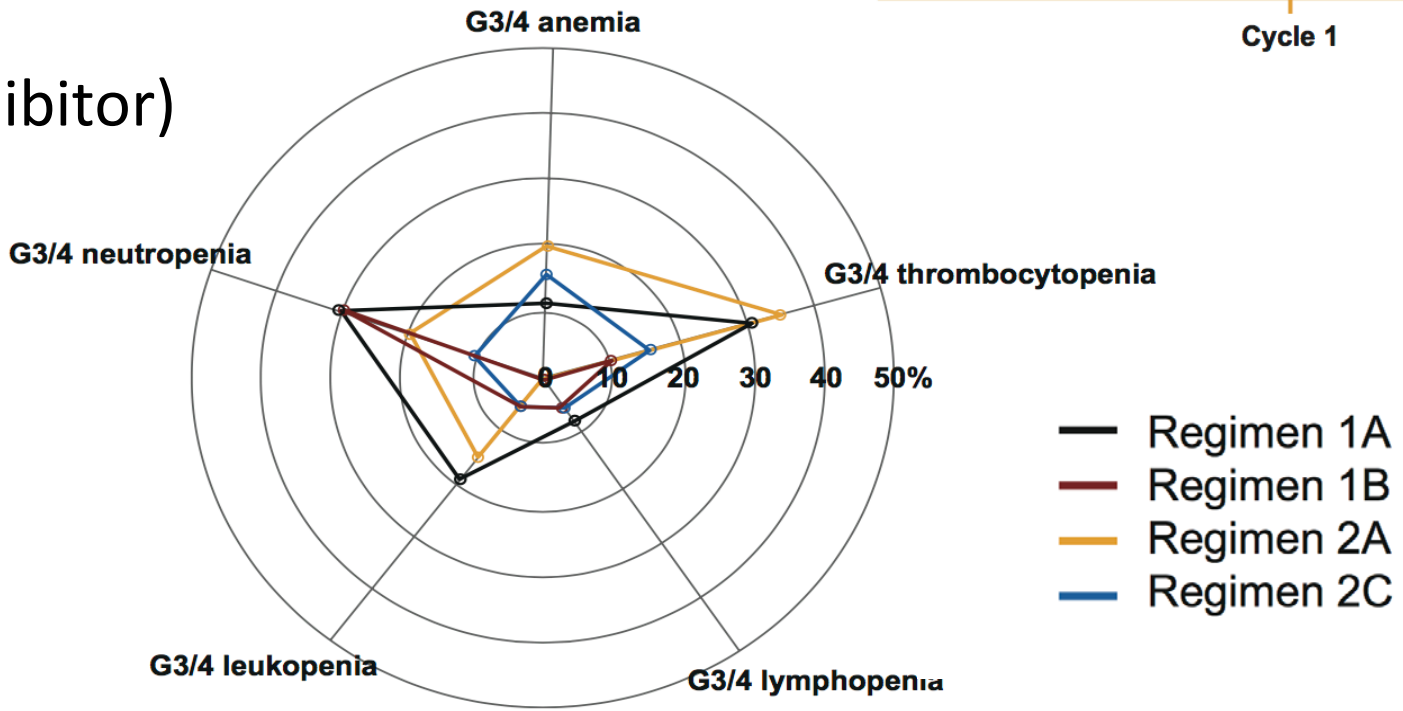
Iasonos et al, J Clin Oncol 31:4014-4021

Schedule Adds Another Dimension of Complexity- Can Impact Therapeutic Index and Efficacy



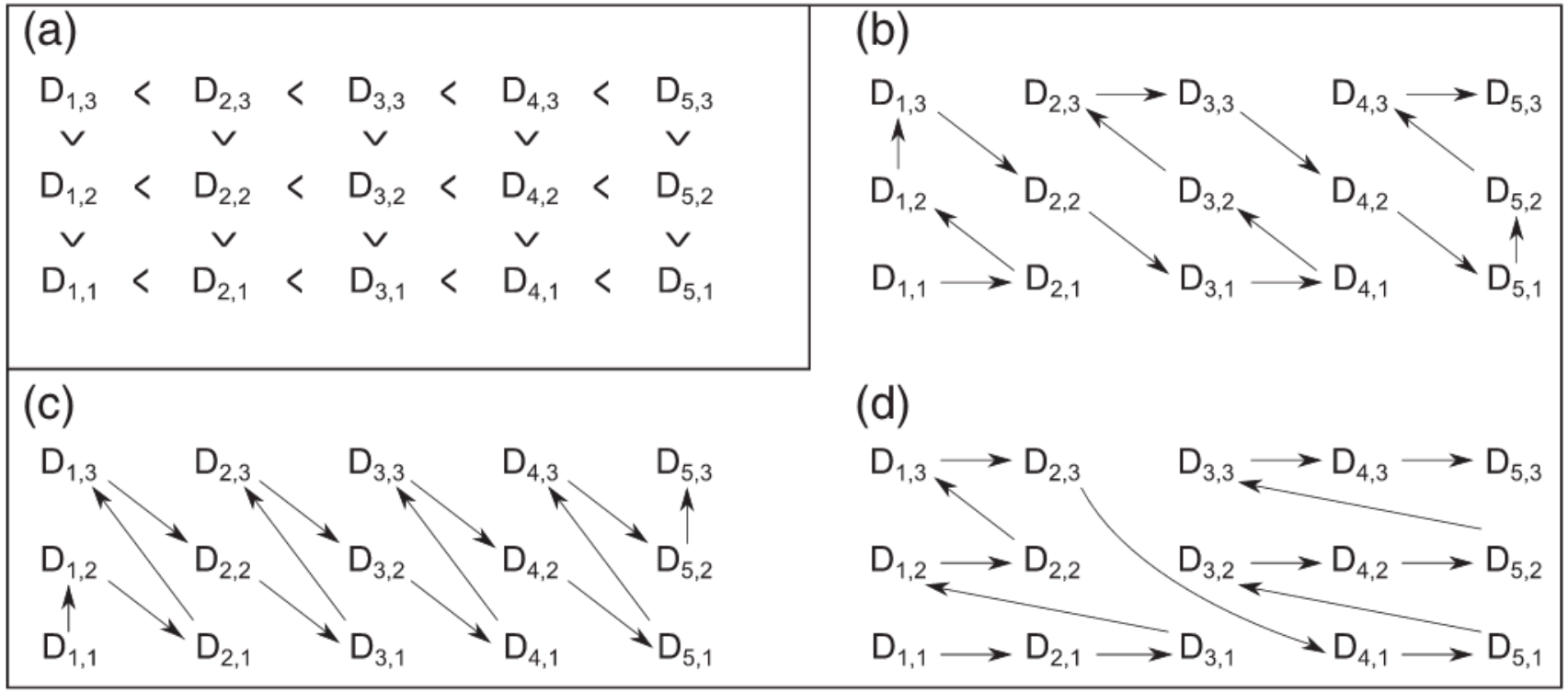


HDM201 (MDM2 Inhibitor)



Hyman et al, EORTC-NCI-AACR Molecular Targets, 2016

Defining Doses of Combination Therapy – Endless Permutations



- Cannot be purely empiric, must be guided by mechanism and pharmacodynamics

Riviere, Statist. Med. 2015, 34 1–12

Conclusions

- Bayesian dose escalation offers advantages over 3+3 design
- 'MTD' is an outdated concept for chronically dosed targeted therapy
- Defining tolerable doses must include information on the rate of interruption/reduction/discontinuation
- Absence of robust PD for the majority of targets make defining a biologically effective dose challenging
- Schedule is an often underappreciated and difficult to study dimension of therapeutic index and efficacy
- Doses of combinations must be driven by mechanism and not empiricism