PHASE 1 CLINICAL TRIALS: DESIGNS AND CONSIDERATIONS

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Hôpital général juif
Jewish General Hospital

Outline

- Introduction
- Goal of Phase I studies in oncology
- Standard 3+3 design
- Other designs
- Patient selection
- Expansion cohort
- Biomarkers

- Particular cases
  - *Molecularly targeted therapies*
  - *Immunotherapy*
  - *Phase 1 combination studies*
  - *Pediatric phase 1 studies*
- The investigator /investigative site

Preclinical

↓

Phase I – Dose finding study

↓

Phase II – Efficacy

↓

Phase III – Randomized comparison to standard of care

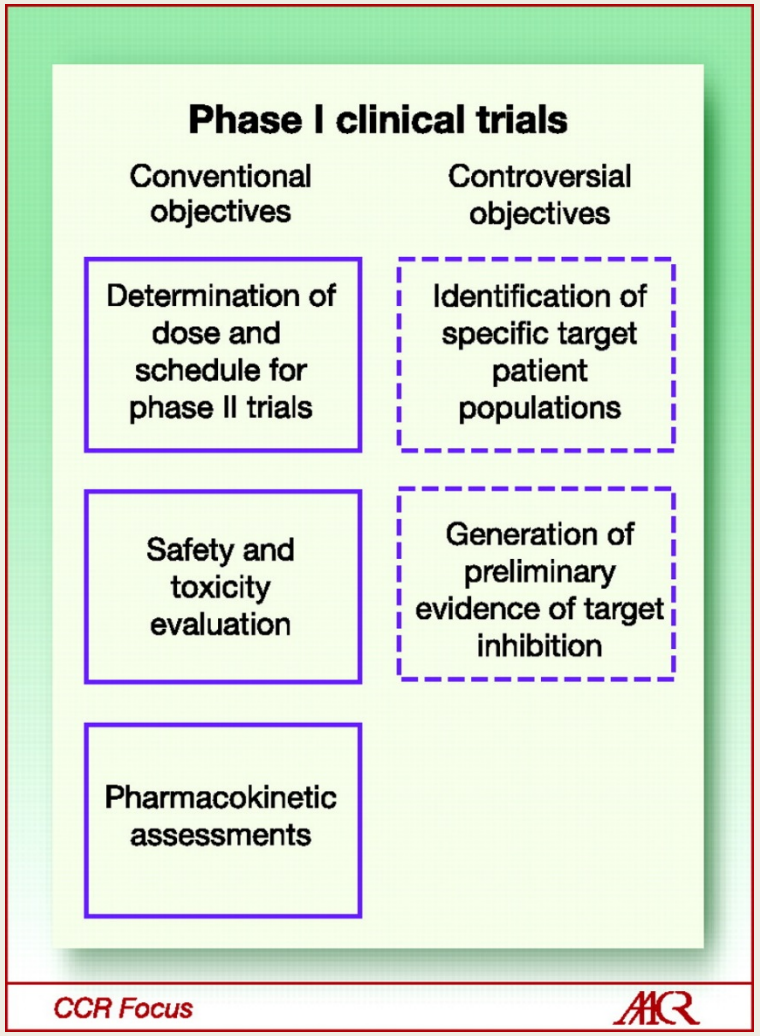
↓

New standard of care

~ 5-7 years of testing

- Phase I trial design
  - *Primary objective*: ***determine dose and schedule***
  - *Endpoints: safety, pharmacokinetics (PK), toxicity profile, modulation of target/biomarker*

Objectives of phase 1 clinical trials.

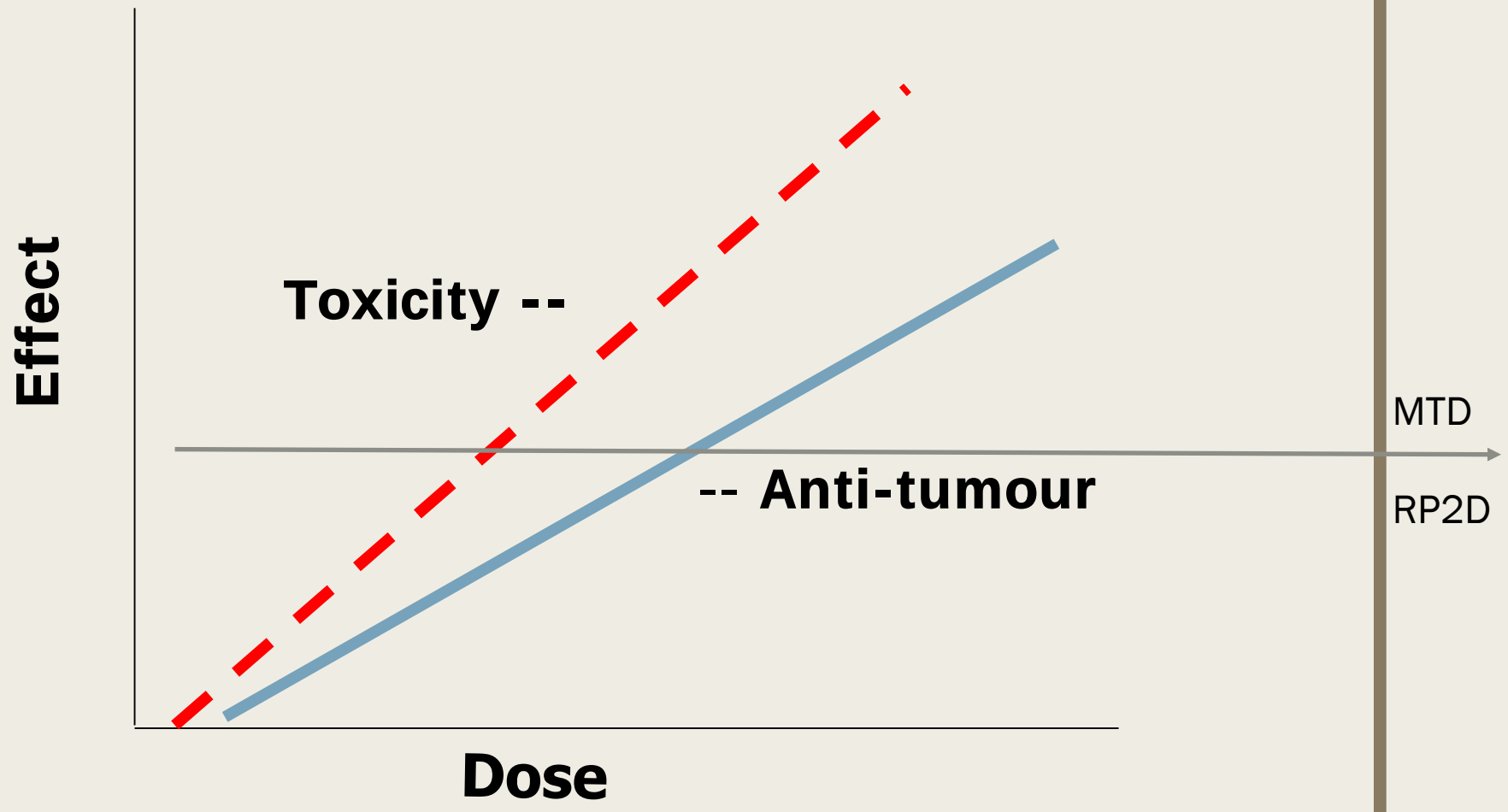


Evidence of antitumor activity

S. Percy Ivy et al. Clin Cancer Res 2010;16:1726-1736

Clinical Cancer Research
AACR American Association for Cancer Research

Assumption: higher dose = greater clinical efficacy



c/o E.Eisenhauer

Some terms

- Primary objective of Phase I study is to determine the recommended phase 2 dose (RP2D) or maximum tolerated dose (MTD) in schedule evaluated
  - *Assumption: higher dose = greater clinical efficacy*
  - *Dose-escalation study to determine an acceptable level of dose-limiting toxicity (DLT) = MTD/RP2D*

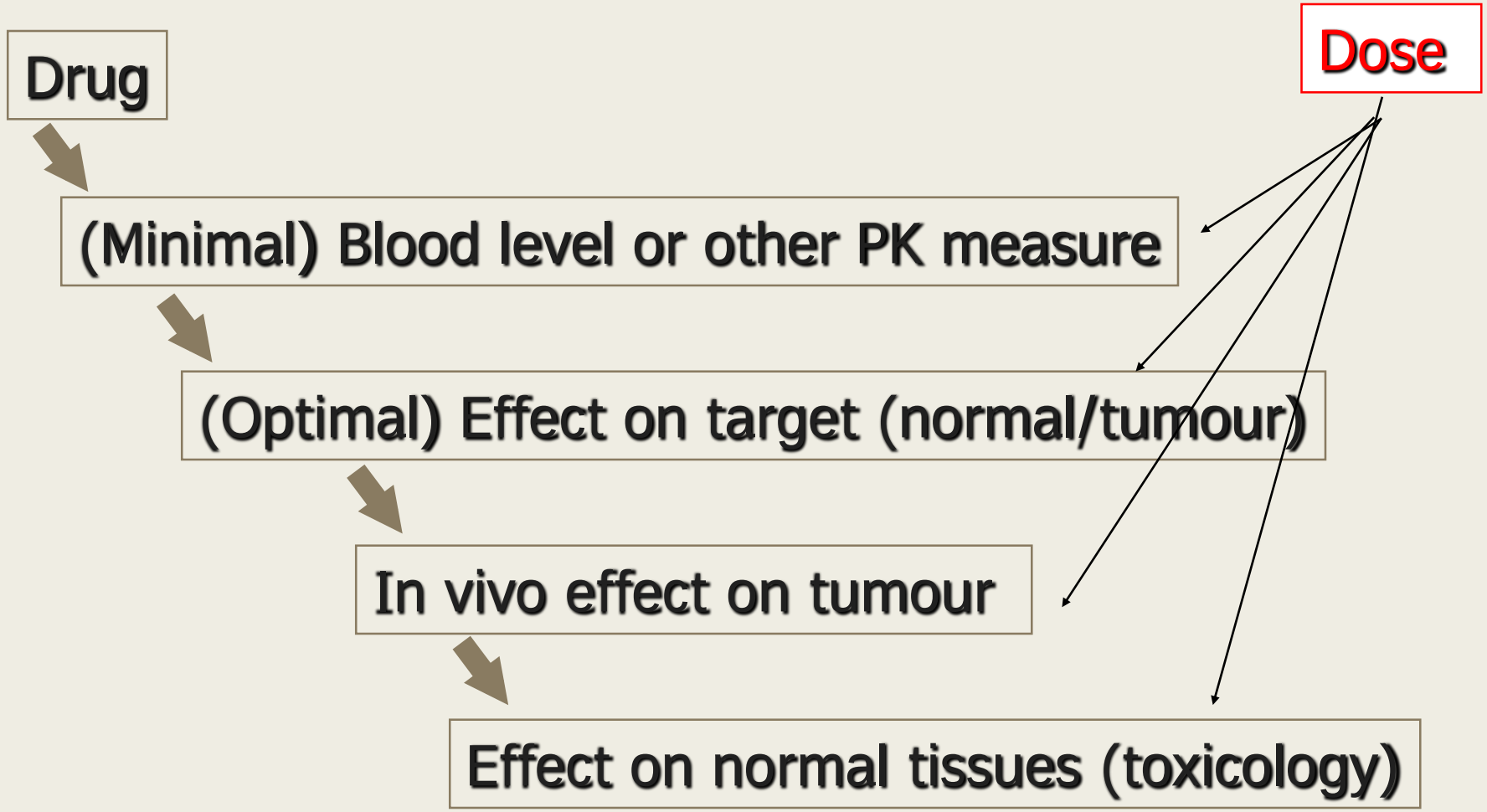
Dose Limiting Toxicity (DLT)

- What is considered to be beyond the limit of tolerable toxicity
  - Severity – usually using the CTCAE V.4, grade 3 or 4

    AND
  - Duration – too long as to prohibit retreatment within a reasonable timeframe

    OR
  - Organ system involvement
    - *Severe hematologic toxicity for patients with solid tumours (but ok for hematologic cancer)*
    - *Cardiotoxicity, renal or hepatic toxicity*
    - *Toxicity known to be associated with the agent (e.g. diarrhea, skin rash)*

Ideal preclinical information



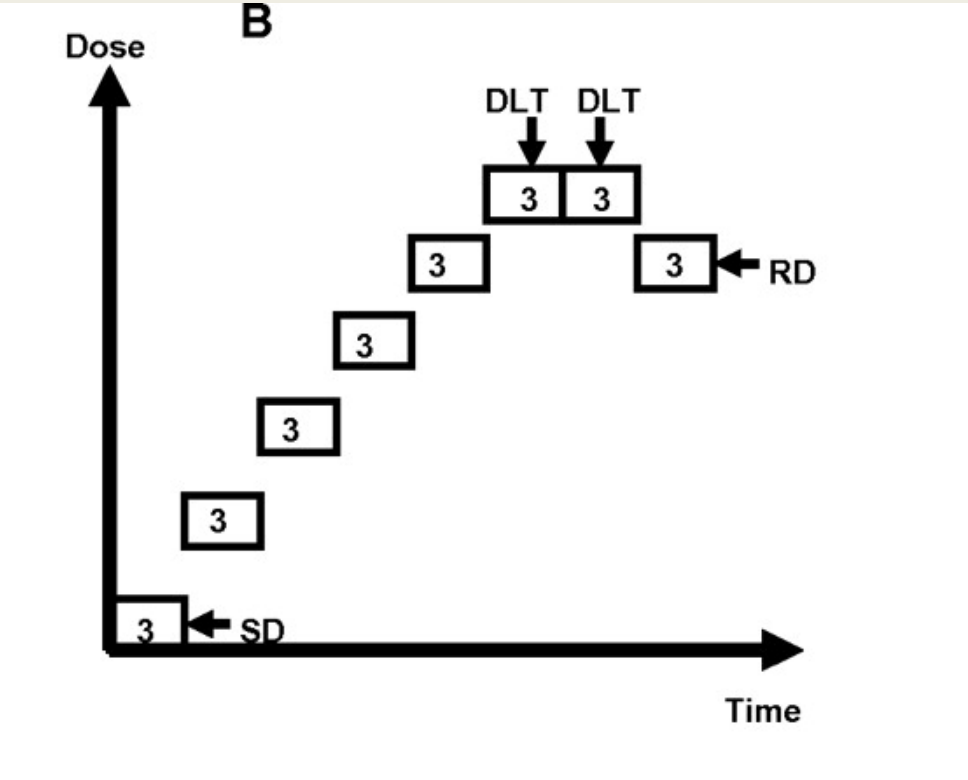
c/o E.Eisenhauer

Starting dose

- Safe, not overly conservative
- Dose by BSA* associated with 10% lethality in mice (MELD10) roughly equivalent to the human MTD
  - *“allometric scaling” – toxicity as a function of body weight or surface area is assumed to be roughly constant across species*
- Initial dose for Phase I trials is taken to be 1/10 the MELD10, or if smaller 1/3 the LD10 in the beagle dog.

*BSA = body surface area

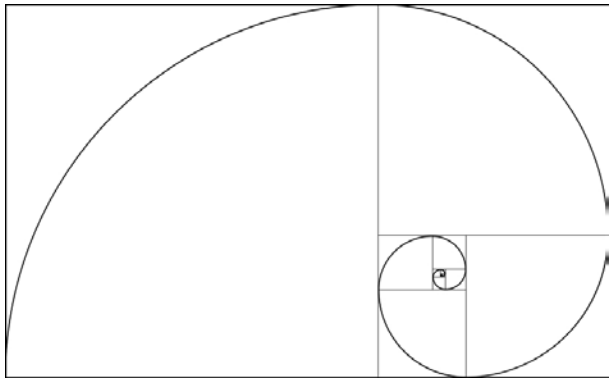
Standard design for phase I cancer clinical trials



Simulations show that for a wide variety of dose-toxicity curves, the probability is approximately 85-90% that the defined MTD will be associated with DLT probability of approximately 10-45%.

Classical dose escalation scheme

Modified Fibonacci sequence in which ever higher escalation steps have ever decreasing relative increments



Dose level (cohort)	Dose increment	Dose (mg/m^2)
1	Starting dose	0.10
2	100%	0.20
3	67%	0.33
4	50%	0.50
5	33%	0.67
6	33%	0.89
7	33%	1.18
8	33%	1.57
9	33%	2.08

1	2	3							
4	5	6	7	8	9				
10	11	12	17	18	19	RD			
13	14	15	16	17	…				

x1 x2 x3 Patient Cohort (patient nr. x1, x2, x3, …)

Dose Limiting Toxicities

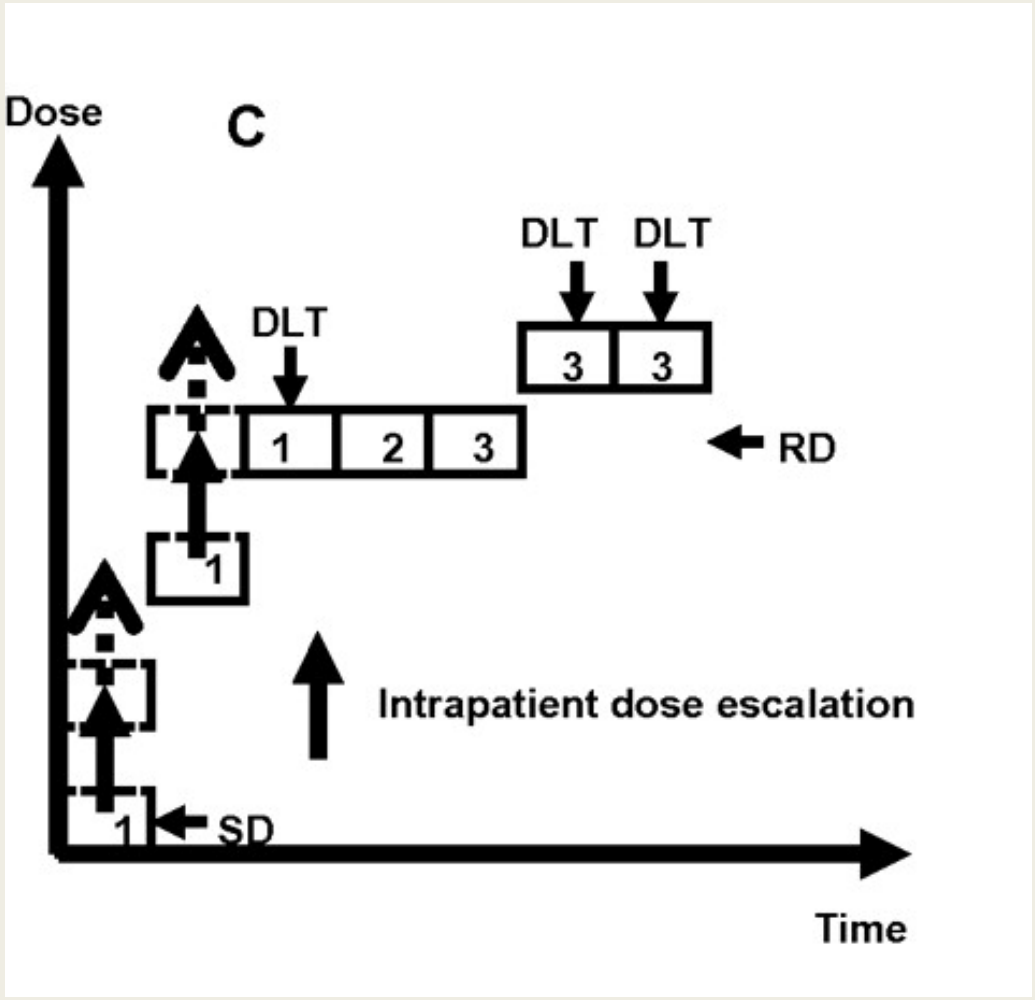
Criticisms of standard design

1. The dose escalation is unnecessarily slow, leading to treatment of excessive numbers of patients at dose levels less likely to be efficacious
2. The MTD definition is unnecessarily imprecise in that it does not make adequate use of all the available first course toxicity data

   - *25% of oncology agents registered with the FDA are labeled at a dose different from that identified in phase I (Letourneau, JCO 2010;28:1401.).*

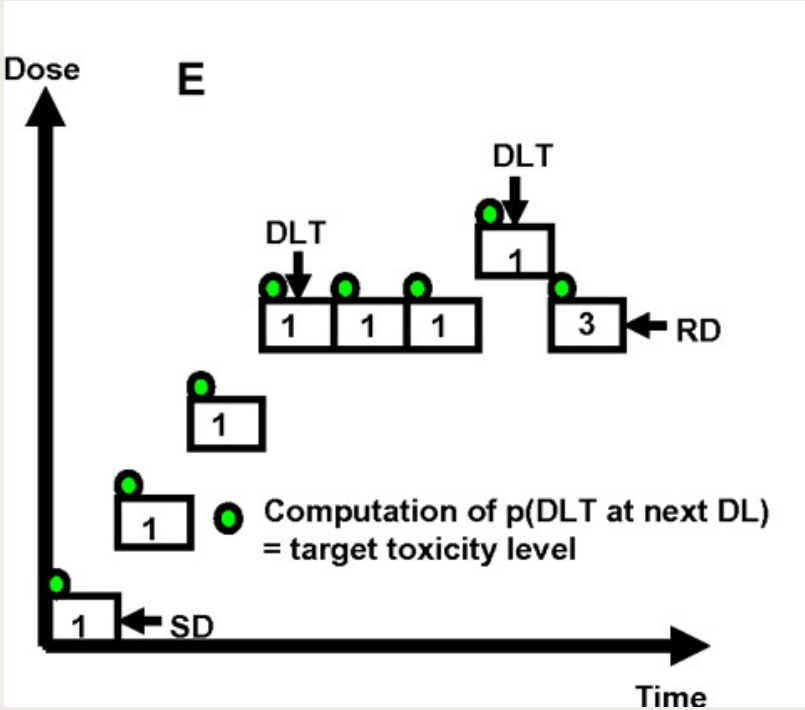
3. Too few patients treated at the MTD

Accelerated titration design



Continual reassessment method for phase I trial design

Each patient is allocated to the dose most likely to be the MTD, according to the current state of the model.
The model is "immediately" updated by incorporating first course toxicity data from each successive patient. The MTD is calculated from the final state of the model.



- Fewer patients treated at suboptimal dose.
- More precise estimate of the MTD.
  - DLT determined based on all available toxicity data.
- Ongoing computational efforts and communication with biostatistician.

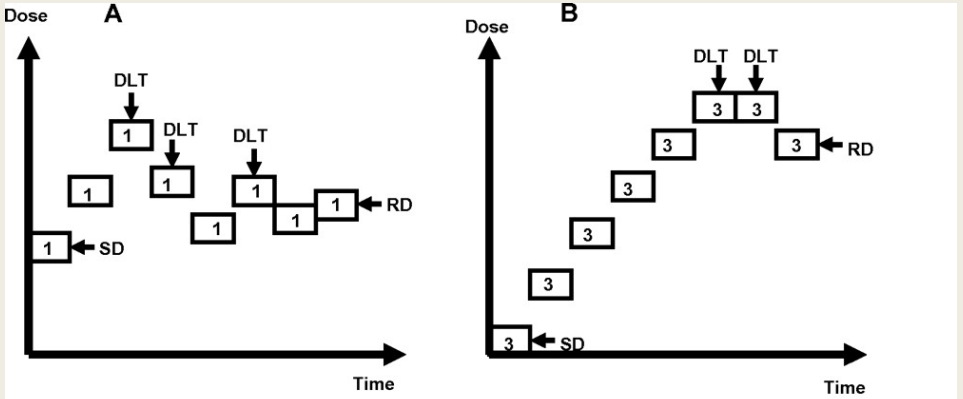
Alternative Endpoints

- Pharmacokinetics
  - *target AUC, minimum trough level, steady state level*
  - *Assures adequate drug delivery to tissues*
- Inhibition of target/pharmacodynamics
  - *In normal tissue*
  - *In tumor tissue*

Graphical depiction of dose escalation methods for phase I cancer clinical trials

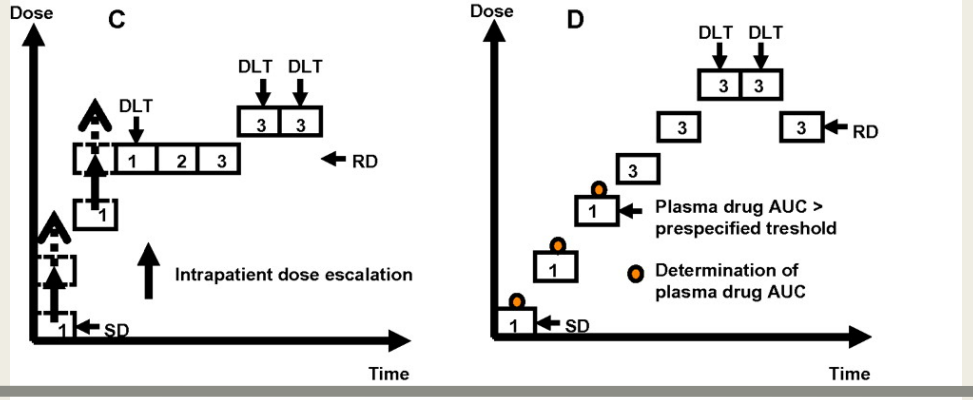
Up & down design

Standard – 3+3



Accelerated titration design

Pharmacologically guided dose escalation

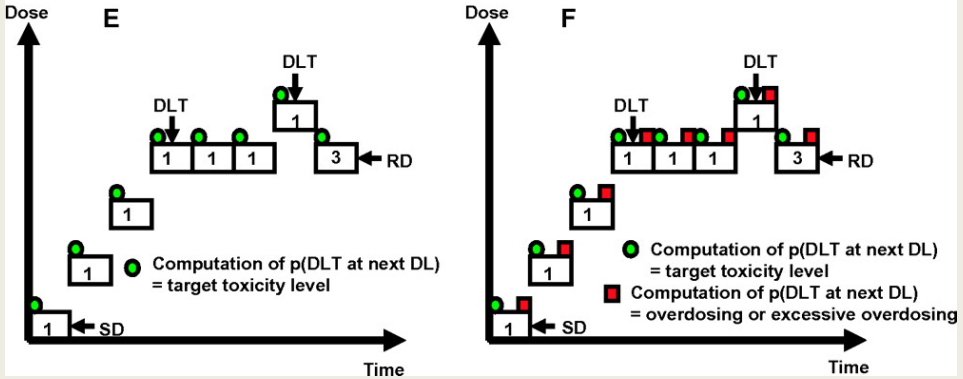


Rule based

Model based

Continual reassessment method

Escalation with overdose control



Le Tourneau, C. et al. J. Natl. Cancer Inst. 2009 101:708

Patient Selection

ALWAYS

- Reasonable performance status (ECOG, Karnofsky)
- Adequate organ function (liver, kidney, heart, marrow, nervous system)
- Not pregnant
- Consent and availability
- (Ability to survive 1 month or 3 months)

SOMETIMES

- Measurable disease
- Eligibility for special drug administration
- Specific tumor type ± biomarker (vs. all comers with cancer)
- Restriction on number/type of prior therapies

Expansion cohort

- Gain more experience at the MTD
- Establish early signs of efficacy in different disease cohorts
  - *Pembrolizumab KEYNOTE001- phase I with dose expansion in metastatic melanoma and NSCLC-led to accelerated approval of drug (n=1200 pts)*
- Establish efficacy in cohort selected based on molecular target
  - *Ceritinib development – Phase 1 dose expansion in ALK positive NSCLC led to FDA approval*
- Safety expansion cohort
  - *Patients with poorer ECOG, CNS metastases, etc.*

Example of expansion cohort

Table 4 Dose Confirmation Rules

	Number of Subjects Treated at Current Dose										
Number of Toxicities	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
0	S	E	E	E	E	E	E	E	E	E	E
1	S	S	S	S	S	S	E	E	E	E	E
2	D	S	S	S	S	S	S	S	S	S	S
3	DU	D	D	S	S	S	S	S	S	S	S
4	DU	DU	DU	D	D	D	S	S	S	S	S
5		DU	DU	DU	DU	DU	D	D	S	S	S
6			DU	DU	DU	DU	DU	DU	D	D	D
7				DU	DU	DU	DU	DU	DU	DU	D
8					DU	DU	DU	DU	DU	DU	DU
9						DU	DU	DU	DU	DU	DU
10							DU	DU	DU	DU	DU
11								DU	DU	DU	DU
12									DU	DU	DU
13										DU	DU
14											DU

E = Escalate to the next higher dose
S = Stay at the current dose
D = De-escalate to the next lower dose
DU = The current dose is unacceptably toxic
Target toxicity rate = 30%
Noninformative prior is used: a=1; b=1;
k1=1; k2=1.5; pow=1 per [1]

The Oncologist

Editorial

Approval After Phase I: Ceritinib Runs the Three-Minute Mile

BRUCE A. CHABNER
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Disclosures of potential conflicts of interest may be found at the end of this article.


Bruce A. Chabner

The old saw that phase I is all about safety and phase II is all about efficacy no longer applies. Phase I is all about Proof of Principle and efficacy, once a safe dose is reached.

Biomarkers

- Patient selection based on expression of molecular target
  - *NSCLC, CML, Her2neu+ breast cancer*
- Molecular profiling with NGS
  - *Personalized medicine phase I programme (MD Anderson)*
  - *Molecular tumour boards*

*presence of an alternation in known oncogene does not necessarily imply it is the main driver

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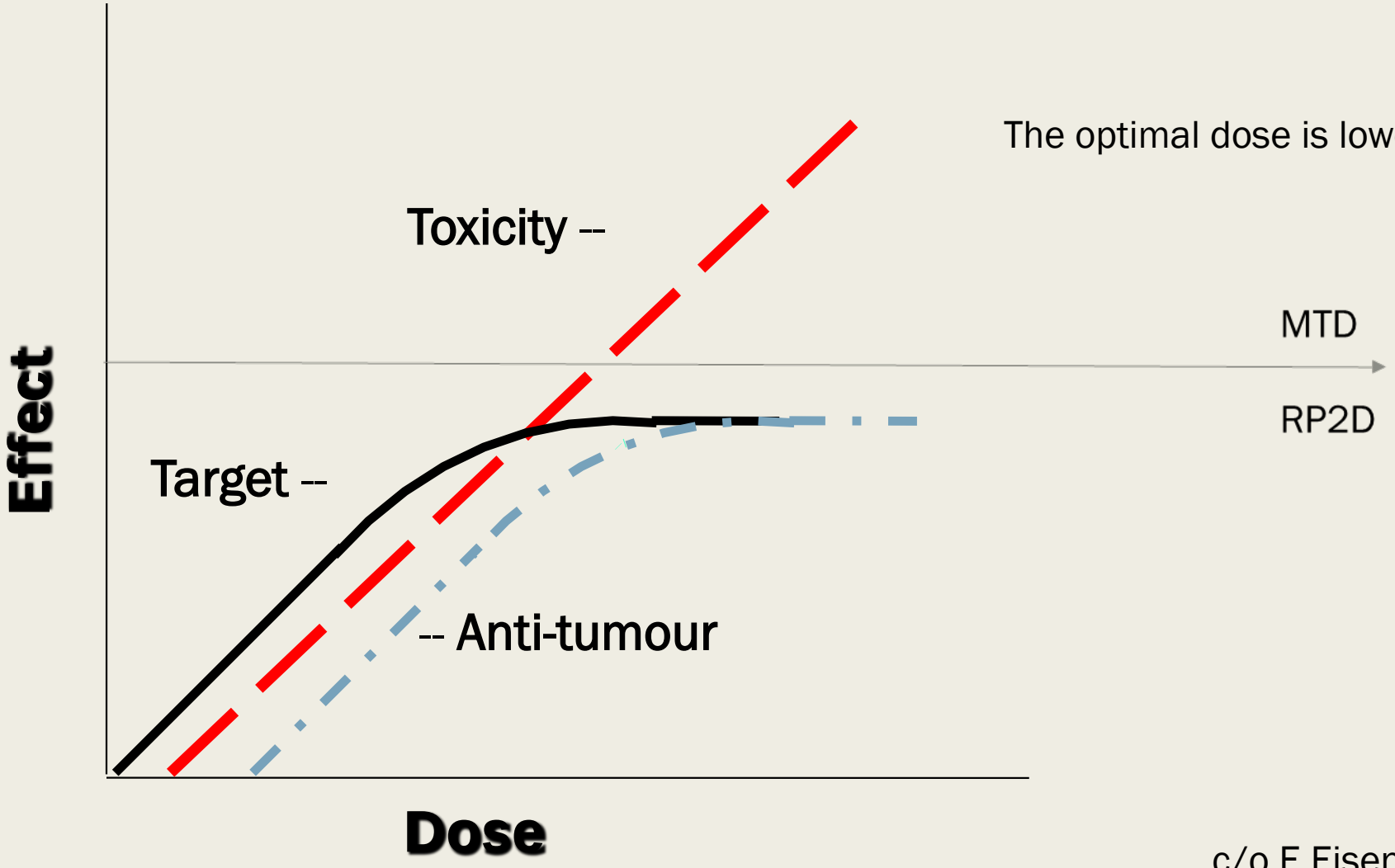
Molecularly targeted agents



The optimal dose is lower than the MTD

c/o E.Eisenhauer

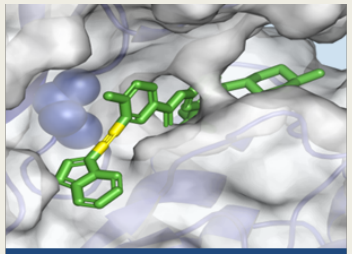
Molecularly targeted agents (MTAs)

- Maximally administered dose (MAD) is determined instead of the MTD
- MTAs can demonstrate delayed or cumulative low-grade toxicities that are not captured within the DLT-assessment window
  - *Chronic toxicities due to drug target in normal tissues*
  - *20% of dose reductions with MTAs occur beyond the usual DLT-assessment period*

…

- RP2D of MTAs should incorporate toxicity data from all cycles of therapy, as well as symptomatic grade 2 toxicities
- DLT window should be prolonged
- Efficacy endpoint can help in the process of dose escalation

Ponatinib



triple bond (*yellow*) is a unique structural feature that evades the T315I gatekeeper mutant (*blue spheres*)

In Vitro IC50 Values (nM) with CCyR Rate Prediction Overlaid

BCR-ABL MUTANT	ICLUSIG™	IMATINIB	NILOTINIB	DASATINIB	BOSUTINIB
Native	3	201	15	2	71
M244V	3 √	287	12 √	2 √	147
L248R	8	10000	549	6	874
L248V	4	586	26	5 √	182
G250E	5 √	1087	41√	4 √	85
Y253H	5	4908	179 X	3 √	40
E255K	6 √	2487	127 √	9 X	181
E255V	16	8322	784	11 X	214
V299L	4 √	295	24	16	1228
T315A	4	476	50	59	122
T315I	6 √	9773	8091 √	10000 √	4338
F317C	3	324	16	45	165
F317I	7	266	25	40	232
F317L	4 √	675	21 √	10 √	82
F317V	10	1023	26	104	1280
M351T	4	404	15 √	2 √	97
E355A	7	441	18	3	74
F359C	6	728	47	2 √	70
F359I	11	324	64	3 √	76
F359V	4 √	346	41 X	2 √	59
H396R	4 X	395	23 X	2 √	60
E459K	5	612	38	4 √	127

Criteria Used to Classify Drug Potency

Predicted response rate		
≥25% CCyR	√	Indicates correct prediction
0-24% CCyR	X	Denotes incorrect prediction
0% CCyR	X, √	Symbol color indicates the correct category

- Phase 1
  - *DLT – amylase, lipase elevation and pancreatitis*
  - *Other toxities – hematologic and rash*
  - *Median follow up 56 weeks*
  - *RP2D 45 mg daily*

Phase 2 study

Table 4. Treatment-Related Adverse Events.*

Event	Chronic-Phase CML (N=270)		Accelerated-Phase CML (N=85)		Blast-Phase CML (N=62)		Ph-Positive ALL (N=32)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)							
Nonhematologic events								
Rash†	107 (40)	10 (4)	25 (29)	3 (4)	15 (24)	2 (3)	6 (19)	1 (3)
Dry skin	104 (39)	5 (2)	21 (25)	1 (1)	10 (16)	1 (2)	7 (22)	0
Abdominal pain	74 (27)	20 (7)	15 (18)	4 (5)	6 (10)	1 (2)	6 (19)	2 (6)
Headache	63 (23)	5 (2)	10 (12)	0	7 (11)	1 (2)	4 (12)	0
Increased lipase	57 (21)	27 (10)	12 (14)	11 (13)	8 (13)	7 (11)	3 (9)	2 (6)
Fatigue	51 (19)	4 (1)	17 (20)	1 (1)	7 (11)	2 (3)	3 (9)	0
Constipation	53 (20)	3 (1)	11 (13)	1 (1)	3 (5)	0	6 (19)	1 (3)
Myalgia	46 (17)	3 (1)	16 (19)	0	7 (11)	0	2 (6)	0
Arthralgia	45 (17)	6 (2)	16 (19)	1 (1)	8 (13)	0	1 (3)	0
Nausea	38 (14)	1 (<1)	9 (11)	0	12 (19)	0	1 (3)	0
Increased alanine aminotransferase	31 (11)	9 (3)	10 (12)	2 (2)	5 (8)	2 (3)	1 (3)	1 (3)
Pancreatitis	19 (7)	17 (6)	7 (8)	5 (6)	3 (5)	2 (3)	0	0
Hypertension	25 (9)	6 (2)	6 (7)	3 (4)	1 (2)	1 (2)	1 (3)	1 (3)
Increased aspartate aminotransferase	24 (9)	5 (2)	8 (9)	3 (4)	4 (6)	1 (2)	1 (3)	1 (3)
Increased blood amylase	16 (6)	4 (1)	6 (7)	3 (4)	3 (5)	2 (3)	1 (3)	0
Increased γ-glutamyltransferase	11 (4)	4 (1)	7 (8)	2 (2)	2 (3)	1 (2)	0	0
Dyspnea	13 (5)	4 (1)	6 (7)	0	4 (6)	1 (2)	0	0
Cardiac failure	3 (1)	2 (<1)	1 (1)	1 (1)	2 (3)	2 (3)	0	0
Hematologic events								
Thrombocytopenia	111 (41)	86 (32)	36 (42)	28 (33)	17 (27)	16 (26)	3 (9)	2 (6)
Neutropenia	44 (16)	38 (14)	22 (26)	22 (26)	14 (23)	11 (18)	4 (12)	4 (12)
Anemia	27 (10)	15 (6)	14 (16)	8 (9)	14 (23)	13 (21)	5 (16)	4 (12)
Decreased white-cell count	11 (4)	7 (3)	7 (8)	5 (6)	0	0	1 (3)	1 (3)
Pancytopenia	2 (1)	2 (1)	3 (4)	2 (2)	3 (5)	3 (5)	0	0
Febrile neutropenia	1 (<1)	1 (<1)	2 (2)	2 (2)	2 (3)	2 (3)	2 (6)	2 (6)

* Treatment-related adverse events were defined as events that the site investigators deemed to have a possible, probable, or definite relationship to ponatinib. Listed are the treatment-related adverse events that were reported in at least 10% of the patients, along with any incidence of grade 3 or 4 events in more than 1% of the total study population.
† Rash includes erythematous and papular rash.

15 month median follow-up

Cumulative and exposure-adjusted incidences of AOEs and VTEs

- Median time to onset for AOEs in total and CP-CML patients was 11.5 (0.1–44.0) months and 14.1 (0.3–44.0) months, respectively
- Median time to onset for VTEs in total and CP-CML patients was 5.8 (0.1–40.1) months and 22.2 (2.0–40.1) months, respectively

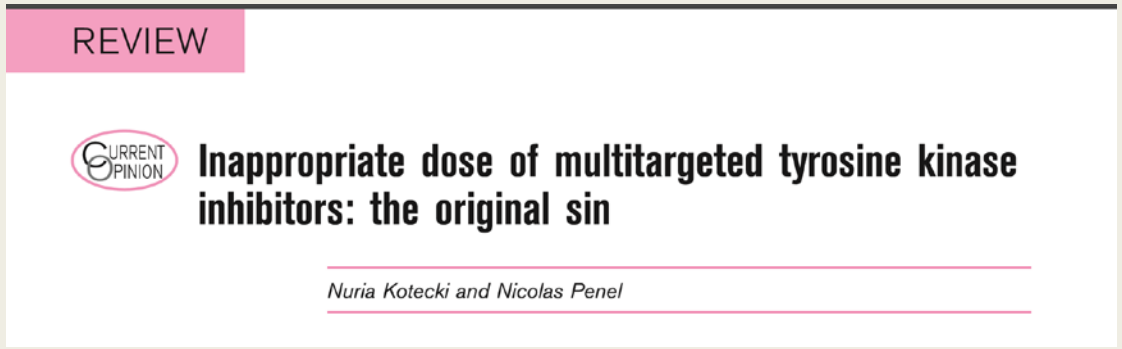
	CP-CML n=270		All n=449	
	All grades	SAEs	All grades	SAEs
AOEs, n (%):	77 (29)[a]	63 (23)[b]	104 (23)[c]	83 (19)[d]
Cardiovascular	39 (14)	30 (11)	56 (13)	41 (9)
Cerebrovascular	33 (12)	26 (10)	39 (9)	31 (7)
Peripheral vascular	31 (11)	25 (9)	40 (9)	31 (7)
Exposure-adjusted AOEs, no. of patients with events per 100 patient-years	14.2	10.9	14.1	10.7
VTEs	13 (5)	12 (4)	25 (6)	22 (5)
Exposure-adjusted VTEs, no. of patients with events per 100 patient-years	2.0	1.8	2.9	2.5

Cortes. EHA 2015. Abstract P234; Cortes et al, ASCO 2016 Abstract 7013

Data as of 3 August 2015

*Categorization of AOEs and VTEs is based on a broad collection of >400 MedDRA preferred terms related to vascular ischemia or thrombosis;
[a]41 patients had >1 AOE; [b]25 patients had >1 serious AOE; [c]51 patients had >1 AOE; [d]32 patients had >1 serious AOE.
SAEs=serious adverse events
AOE –Arterial occlusive events

Headlines



REVIEW

CURRENT OPINION

Inappropriate dose of multitargeted tyrosine kinase inhibitors: the original sin

Nuria Kotecki and Nicolas Penel

special article

Annals of Oncology 26: 1808–1812, 2015
doi:10.1093/annonc/mdv266
Published online 18 June 2015

Statistical controversies in clinical research: requiem for the 3 + 3 design for phase I trials

X. Paoletti[1,2*], M. Ezzalfani[3] & C. Le Tourneau[3,4]

[1]*Biostatistics and Epidemiology Department, Gustave Roussy, Villejuif;* [2]*INSERM U1018, CESP, Paris-Sud University, Villejuif;* [3]*INSERM/Institut Curie/Mines ParisTech U900, Paris;* [4]*Department of Medical Oncology, Clinical Trial Unit, Institut Curie, Paris & Saint-Cloud, France*

The changing landscape of phase I trials in oncology

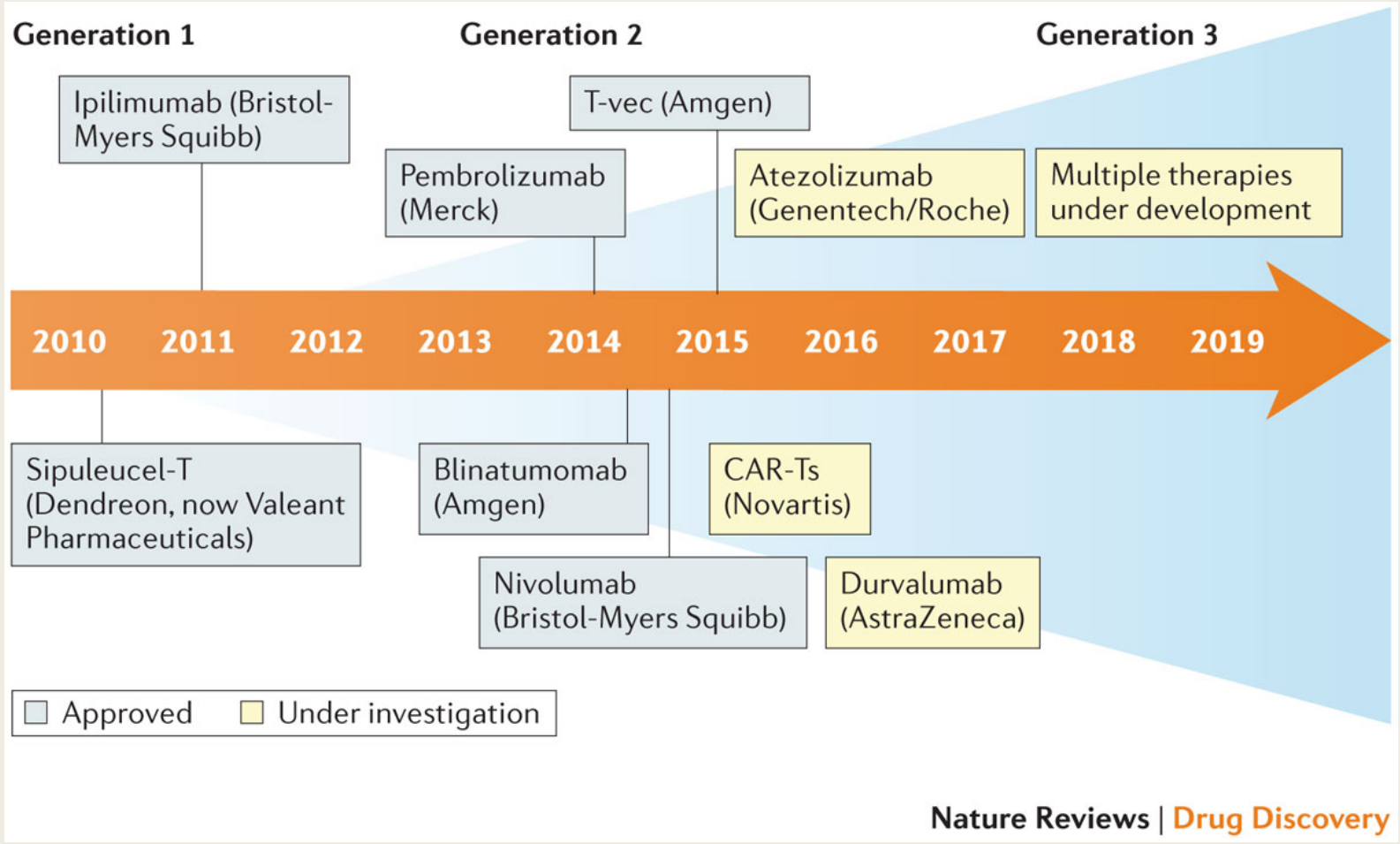
Kit Man Wong, Anna Capasso and S. Gail Eckhardt

MTAs- review of 84 studies from 2000 to 2010

- 49% used the 3+3 design
- 42% Accelerated titration design
- 7% continuous reassessment model
- 1% pharmacologically guided dose escalation

LeTourneau, PLOS ONE, e51039 (2012)

Word on immuno-oncology



Hoos, 2016

Immuno-oncology: immune checkpoint inhibitors

- 13 main phase 1 studies
  - *1 determined dose based on DLT*
  - *10 maximum feasible dose*
  - *2 PK parameters*
- imAbs have limited potential for causing acute or cumulative toxicities
- immune-related adverse events (irAEs) occur at any time later in trial, therapy usually held if grade 2 or greater
  - *affects drug exposure and thus should be considered as part of DLT definition*

Overview of trial designs

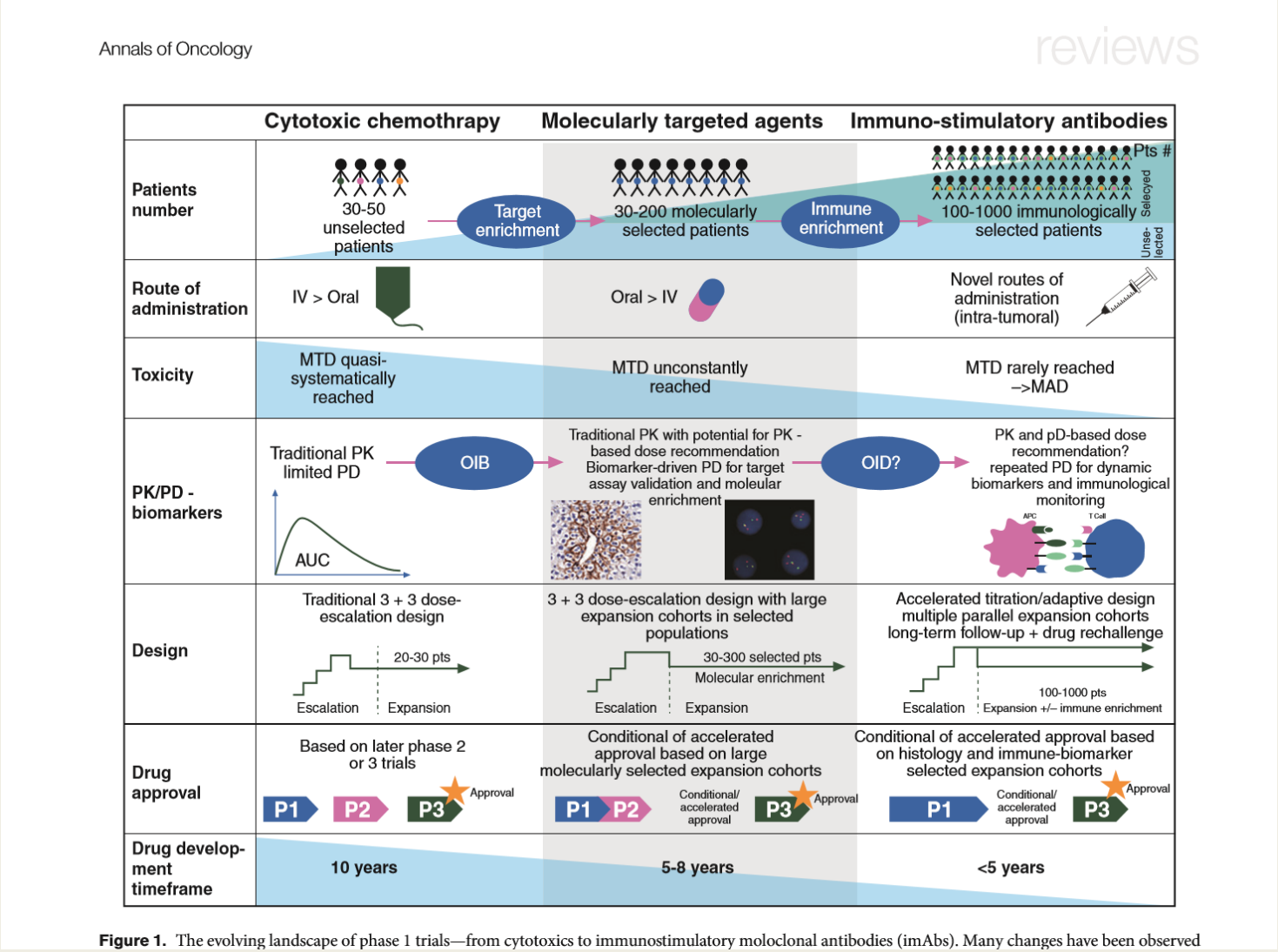


Figure 1. The evolving landscape of phase 1 trials—from cytotoxics to immunostimulatory moloclonal antibodies (imAbs). Many changes have been observed

Postel-Vinay, Annals of Oncology, 2016

Phase 1 combination studies

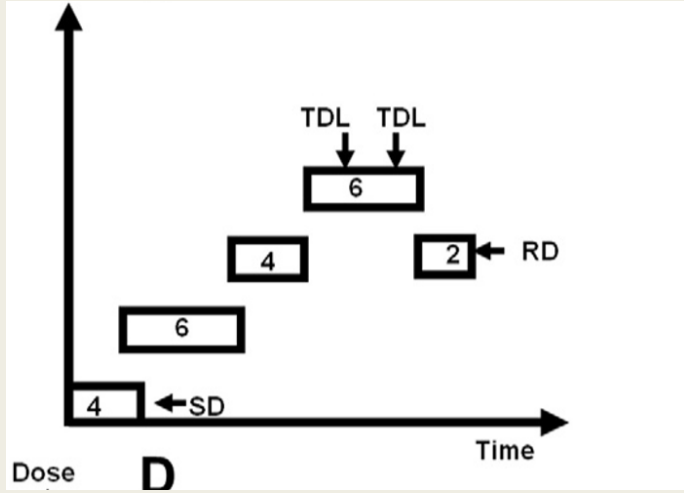
- Combination with standard chemotherapy
  - *Usually the chemotherapy is kept at a fixed dose, dose of molecularly targeted agent is varied*
- Combination of two molecularly targeted agents
  - *Testing synergistic target requires preclinical evidence supporting biological rationale*
  - *More complex because of synergistic or antagonistic PK/PD interactions*
  - *Overlapping toxicity*

Paller C. NCI recommendation.
Clinical Cancer Res. 2014

Pediatric Phase I studies

- Adult studies usually performed prior to pediatric studies, thus dose and toxicity already known
- Few toxic deaths in children
- Rare diseases with rapid progression – need to limit suspension of accrual

- Rolling six design – enrol 2 to 6 patients at a time, dose patient receives depend on number of enrolled patients, DLT rate, and number of patients who have completed the DLT window. De-escalation occurs when two or more DLT occur at a dose level, whereas escalation can be performed when 3/3, 4/4, 5/5, 5/6 or 6/6 patients are evaluated without DLT.
- CRM/Model based ensures fewer patients treated at lower doses



A. Doussau et al. / Contemporary Clinical Trials 47 (2016) 217–227

You and your site

- Multi-institutional phase I studies to expedite patient accrual
  - *To accommodate the same number of patients, a site needs*
    - More phase I studies
      - *More personnel*
      - *More resources*
      - *More conference calls*
- Greater interaction with CRO
  - *To accommodate greater study coordination*
  - *To ensure quality of data as phase 1 may lead to drug approval*
- More physicians involved in phase 1 research
  - *Molecularly targeted studies are disease specific*
  - *Large studies with dose expansion cohorts*

Wong KM, Nature Reviews. Clinical Oncology. 2016

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Thank you.
Questions?